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RESEARCH SUBMISSION

Effects of multiple-dose administration of zavegepant nasal spray on the single-dose pharmacokinetics of ethinyl estradiol-levonorgestrel

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Abstract

Objective: The potential for drug–drug interaction of multiple-dose intranasal zavegepant on the single-dose oral contraceptive ethinyl estradiol and levonorgestrel (EE-LNG) was evaluated.

Background: Zavegepant (as a nasal spray) is a calcitonin gene-related peptide receptor antagonist approved in the United States for treatment of acute migraine in adults.

Methods: This single-center, Phase 1, open-label, fixed-sequence study included healthy, nonsmoking females (18–45 years old). In treatment Period 1, a single oral dose of EE-LNG 0.02–0.10 mg was administered on Day 1. In treatment Period 2, intranasal zavegepant (20 mg daily; 10 mg per nostril separated by 1 h) was administered on Days 1–5; 1 oral dose of EE-LNG 0.02–0.10 mg was administered immediately after first 10 mg intranasal zavegepant dose on Day 2. Blood samples for EE-LNG concentrations were collected on Day 1, treatment Period 1, and Day 2, treatment Period 2, and zavegepant concentrations on Day 2, treatment Period 2. Noncompartmental pharmacokinetic parameters included maximum observed concentration (C_{max}), area under the concentration-time curve (AUC) from Time 0 to last non-zero concentration ($AUC_{0\text{-}t}$), and AUC from Time 0 to infinity ($AUC_{0\text{-}inf}$). The safety and pharmacokinetic sample sizes were 26 and 23, respectively.

Results: Statistical comparisons of pharmacokinetic exposure parameters after coadministration of zavegepant and EE-LNG versus EE-LNG alone showed small, but statistically insignificant, changes in either EE or LNG exposure. EE comparison ratios (90% confidence intervals [CIs]) were 109.9% (105.3%, 114.8%) for $AUC_{0\text{-}inf}$ and

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, area under the concentration-time curve from time 0 to 24 h; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time zero to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from time zero to the last non-zero concentration; CGRP, calcitonin gene-related peptide; CI, confidence interval; C_{max}, maximum observed concentration; COVID-19, Coronavirus Disease 2019; CV, coefficient of variation; CYP, cytochrome P450; CYP2C9, cytochrome P450 2C9; CYP3A4, cytochrome P450 3A4; ECG, electrocardiogram; EDTA K2, dipotassium ethylenediaminetetraacetic acid; EE, ethinyl estradiol; FDA, Food and Drug Administration; LC–MS/MS, liquid chromatography with tandem mass spectrometry; LNG, levonorgestrel; SD, standard deviation; S-STS, Sheehan Suicidality Tracking Scale; $t_{½\ el}$, elimination half-life; TEAE, treatment-emergent adverse event; t_{max}, time to maximum plasma drug concentration; UGT, UDP-glucuronosyltransferase; ULN, upper limit of normal.

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110.2% (104.6%, 116.1%) for C_{max}. LNG comparison ratios (90% CIs) were 107.0% (100.2%, 114.3%) for $AUC_{0\text{-}inf}$ and 108.8% (99.9%, 118.4%) for C_{max}. Frequently reported treatment-emergent adverse events included dysgeusia ($n=25$, 96%), throat irritation ($n=11$, 42%), headache ($n=10$, 39%), nasal discomfort ($n=7$, 27%), pharyngeal paresthesia ($n=5$, 19%), and nausea ($n=4$, 15%).

Conclusion: Co-administration of zavegepant nasal spray with a single dose of an oral contraceptive resulted in no clinically meaningful changes (<12% increase) in EE-LNG exposure.

Plain Language Summary

We studied possible interactions between the migraine medication zavegepant and an oral birth control pill. The medicines were given alone or in combination to healthy females, and we evaluated the safety of these medications as well as their concentrations in the participants' blood. We found that administering the birth control pill and zavegepant together did not change the drug concentrations in blood, and it also did not cause any safety problems compared with the birth control pill alone.

KEYWORDS
calcitonin gene-related peptide receptor antagonist, drug–drug interaction, ethinyl estradiol-levonorgestrel, nasal spray, oral contraceptive, zavegepant

INTRODUCTION

Migraine is a complex chronic neurological disorder associated with unilateral pulsating headache and frequently associated with nausea, photophobia, and/or phonophobia.[1] Notably, migraine is highly prevalent in females especially during their reproductive years, concurrent with oral contraceptives use.[2–4] Reports of migraine in females are highest during childbearing years (incidence of 18.2 cases per 1000 human years in females 20 and 24 years old).[4] More than half of emergency department visits for headache are linked to females of childbearing age.[5] Migraine is more common and burdensome for females (2- to 3-fold higher prevalence compared to men) mainly due to sex hormone differences.[4–6] Estrogen fluctuation during reproductive, perimenopausal, and postmenopausal years plays a key role in migraine.[2] The need for new therapeutic options for management of acute and preventive treatment of migraine in females of all ages remains a high priority.

Elevated blood levels of calcitonin gene-related peptide (CGRP), an inflammatory mediator and a potent vasodilator, can trigger migraine attacks.[7] CGRP is a key target for both acute and preventive migraine treatment.[8,9] Small-molecule CGRP receptor antagonists (gepants) are relatively new treatment options for acute and preventive treatment for migraine.[10–14] There is general consensus that gepants avoid the cardiovascular effects caused by active vasoconstriction associated with some available migraine therapies.[15–18] Accordingly, gepants offer a new approach for patients with cardiovascular risk factors or risk factors which may contraindicate triptan use.

Zavegepant is a high-affinity, selective, and structurally unique, small-molecule CGRP receptor antagonist and is the first and only approved CGRP receptor antagonist intranasal spray for the acute treatment of migraine with or without aura in adults.[19,20] The efficacy and safety profile of zavegepant nasal spray for the acute treatment of migraine was demonstrated in two randomized, placebo-controlled Phase 2/3 trials involving approximately 3000 participants.[21,22] Zavegepant 10 mg and 20 mg demonstrated statistical superiority to placebo for freedom from pain and the most bothersome symptom (nausea, photophobia, or phonophobia),[21,22] as well as rapid onset of pain relief (15 min, the earliest measured time point), and sustained benefits through 48 h after a single intranasal dose.[22] Non-oral formulations may benefit patients with acute migraine when attacks are associated with severe nausea or vomiting, rapidly intensifying headache pain, or when orally administered medications take too long to relieve symptoms, are not reliably effective, or cause tolerability issues.[23]

Following single and multiple doses administered to healthy adult volunteers, zavegepant nasal spray in doses up to 40 mg was rapidly absorbed, with a median time to maximum plasma drug concentration (t_{max}) ranging from 0.5 to 1.0 h after single-dose administration.[24] The effective elimination half-life ($t_{½\ el}$) is 6.6 h (range 5.0 to 7.6 h) with little accumulation following multiple daily doses, and the drug is excreted primarily via the biliary/fecal route.[20,24] Zavegepant is not a time-dependent inhibitor of cytochrome P450 (CYP) 3A4 (CYP3A4) nor an inducer of metabolism[20,25]; thus, it is not expected to cause CYP-mediated interactions at exposures commensurate with clinical exposures. Furthermore, zavegepant is not an inhibitor of P-glycoprotein.[20]

Oral contraceptive hormones, typically a combination of estrogen and progestin, are primarily metabolized by the hepatic CYP system. Ethinyl estradiol (EE) is metabolized by hydroxylation via the isoenzymes CYP3A4 and cytochrome P450 2C9 (CYP2C9) and by conjugation via sulfation and glucuronidation via

UDP-glucuronosyltransferase (UGT) 1A1.[26] Levonorgestrel (LNG) is mainly metabolized via CYP3A4.[26] Although zavegepant is not a known inducer or inhibitor of CYP3A4 or UGT1A1 and is not expected to be an inducer of drug metabolism at clinically relevant concentrations,[25] it remains vital to assess whether any clinically meaningful drug–drug interactions occur when zavegepant and EE-LNG are administered concomitantly.

The primary aim of this study was to evaluate the effect of multiple-dose administration of zavegepant nasal spray (20 mg daily) on the single-dose pharmacokinetic profiles of the combination oral contraceptive containing EE and LNG. The secondary objective was to evaluate the safety and tolerability of co-administering zavegepant nasal spray and EE-LNG in healthy females. We tested the hypothesis that multiple-dose administration of zavegepant nasal spray (20 mg daily) would not significantly alter the single-dose pharmacokinetic profiles of the combination oral contraceptive containing EE and LNG in healthy females.

METHODS

Study design

This was a Phase 1, open-label, multiple-dose, fixed-sequence, two-period, drug–drug interaction study in healthy female participants. A total of 32 participants were enrolled and 26 participants received at least 1 dose of study drug. A sample size of up to 26 healthy females for participation and receipt of the study drug treatments in this study was planned, which was deemed sufficient to provide a reliable estimate of the magnitude and variability of pharmacokinetic parameters.[27] This study was conducted at a single center (Syneos Health, Quebec, Canada).

In treatment Period 1, a single oral dose of EE-LNG 0.02–0.10 mg (Alesse® 21) was administered on Day 1. A washout period of ≥7 days was required prior to the start of treatment Period 2. In treatment Period 2, on Days 1–5, participants received 2 intranasal sprays of zavegepant (10 mg in each nostril separated by 1 h [± 2 min]) (Biohaven Pharmaceuticals, Inc., New Haven, CT, USA) for a total dose of 20 mg daily. On Day 2 of treatment Period 2, participants received a single oral dose of EE-LNG 0.02–0.10 mg just after the first 10 mg intranasal spray of zavegepant. The oral contraceptive was co-administered with intranasal zavegepant on the second day of dosing and was judged sufficient to study the steady-state effects of zavegepant, if any, on the pharmacokinetic profile of EE-LNG. Furthermore, zavegepant dosing was continued during the time period the EE-LNG pharmacokinetic profile was studied (i.e., until 96 h post-EE-LNG administration) to maintain any interactive effect during the washout of the EE-LNG combination. EE-LNG and intranasal zavegepant were administered under fasted conditions and at approximately the same time daily in both treatment periods.

The protocol was reviewed and approved by an independent ethics committee (Advarra IRB, Aurora, ON, Canada). The study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonization and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). All participants provided written informed consent.

Participants

Healthy female participants of childbearing potential and/or non-menopausal females with tubal ligation who ranged in age from ≥18 to ≤45 years, with a body mass index between ≥18.5 and ≤30.0 kg/m^2 and a body weight of ≥45.0 kg, were eligible to enroll in the study. Additional inclusion criteria were that females were nonlactating, had regular menstrual cycles, were nonsmokers (no use of tobacco products within 3 months prior to screening), and had a score of 0 on the Sheehan Suicidality Tracking Scale (S-STS) at the screening visit.[28,29]

Females who met any of the following criteria were excluded from study participation: clinically significant history of nasal conditions that may affect the administration or absorption of the nasal product (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); positive test for hepatitis B antigen, hepatitis C virus, or human immunodeficiency virus during medical screening; significant history of seizure disorder; current or recent (within 3 months of study drug administration) gastrointestinal disease including gastrointestinal surgery that interferes with physiological absorption and motility; use of medication other than topical products without significant systemic absorption; and positive test for Coronavirus Disease 2019 (COVID-19) within 3 days prior to first study drug administration. In addition, participants with any clinically significant deviation from normal in physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory determinations beyond what was consistent with the target (migraine) population were excluded from enrollment in the study.

Sample collection

On Day 1 in treatment Period 1 and Day 2 in treatment Period 2, 14 blood samples were collected for EE and LNG concentration analysis at predose and 0.75, 1.25, 1.75, 2.5, 4, 6, 8, 12, 24, 36, 48, 72, and 96 h postdose. On Day 2 in treatment Period 2 only, 19 blood samples were obtained for determination of zavegepant concentration at predose and 0.083, 0.25, 0.5, 0.75, 1 (predose second spray), 1.083, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 h (predose Day 3) postdose.

Bioanalytical methods

EE was measured in human dipotassium ethylenediaminetetraacetic acid (EDTA K2) plasma over a concentration range of 1 to 200 pg/mL

using a validated high-performance liquid chromatography with tandem mass spectrometry (LC–MS/MS) assay with automated liquid–liquid extraction and derivatization. LNG was measured in human EDTA K2 plasma over a concentration range of 10 to 10,000 pg/mL using a validated high-performance LC–MS/MS assay with automated liquid–liquid extraction.

Zavegepant was quantitatively determined in human EDTA K2 plasma using a validated LC–MS/MS assay with automated solid-phase extraction (Syneos Health [formerly inVentiv Health Clinique, Inc.] Quebec, Canada). The quantifiable range was 0.02 ng/mL to 50 ng/mL. The internal standard was BHV3500-d_8. Validation was performed using an API 5000 LC–MS/MS system with Analyst software, version 1.6.3 (SCIEX, Framingham, MA, USA). The precision of zavegepant calibration standards ranged from −7.87% to 4.02%; the between-run accuracy and precision bias ranged from 0.85% to 3.47%; and the within-run accuracy and precision bias ranged from −2.20% to 6.39%. The accuracy and precision of quality control samples was ≤15%, and the calibration curves for the LC–MS/MS bioanalytical assay were within acceptable limits.

Outcomes

Pharmacokinetic assessments

Pharmacokinetic parameters for EE-LNG and zavegepant were assessed by standard noncompartmental methods using validated Phoenix® WinNonlin® (version 6.4, Certara, USA).

The pharmacokinetic endpoints calculated for EE and LNG included area under the concentration-time curve (AUC) from Time 0 to 24 h ($AUC_{0\text{-}24}$), AUC from Time 0 to the last non-zero concentration ($AUC_{0\text{-}t}$), AUC from Time 0 to infinity ($AUC_{0\text{-}inf}$), maximum observed concentration (C_{max}), t_{max}, and $t_{½\ el}$. For zavegepant, the following pharmacokinetic parameters were calculated: $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, C_{max}, t_{max}, and $t_{½\ el}$.

Safety

Participants were carefully observed for adverse events for the study duration. The incidence of adverse events was determined, and all adverse events were reviewed for their relation to EE-LNG and intranasal zavegepant and their clinical importance.

The following assessments were performed during the study: vital sign measurements at screening, Day −1 in treatment Period 1, Day 1 to Day 5 in treatment Period 2, and at study exit; supine ECG at screening, Day −1 in treatment Period 1, predose on Days 1 to 5 in treatment Period 2, and at study exit; physical examination at screening, Day −1 of each treatment period and at study exit; nasal cavity examination at screening, Day −1 of each treatment period, predose on Days 1 to 5 in treatment Period 2, and at study exit; S-STS[28,29] at screening and at study exit; routine laboratory tests (biochemistry, serology, hematology, coagulation, urinalysis) at screening, Day −1 of each treatment period, and at study exit; serology at screening; and COVID-19 at screening window within 3 days prior to the first dosing, and before the first study drug administration in treatment Period 2.

Statistical analysis

The safety population included participants who received at least 1 dose of EE-LNG or intranasal zavegepant; safety data were described descriptively. The pharmacokinetic population included all participants who completed both EE-LNG dosing (treatment Periods 1 and 2) and intranasal zavegepant dosing up to Day 2 in treatment Period 2 and for whom the pharmacokinetic profiles of EE-LNG and zavegepant were adequately characterized.

Samples with no reportable concentration value occurring prior to dosing were replaced by "0"; otherwise, they were set to missing for tabulation, graphical representation, and calculation purposes.

Mean plasma concentration-time curves for EE-LNG were presented as both linear and semilogarithmic scales. Descriptive statistics were presented for EE, LNG, and zavegepant pharmacokinetic parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}inf}$, C_{max}, t_{max}, and $t_{½\ el}$) including the number of observations and geometric mean (% coefficient of variation [CV]) except for t_{max}, which is presented as median (minimum, maximum), and $t_{½\ el}$, which is presented as mean standard deviation (SD).

The effect of multiple-dose administration of intranasal zavegepant on the single-dose pharmacokinetics of EE-LNG was evaluated by performing analysis of variance using generalized linear model procedures with SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) for EE and LNG, with treatment as fixed effect and subject as random effect on ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. 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. The ratio (EE-LNG + zavegepant [on Day 2 in treatment Period 2] versus EE-LNG [on Day 1 in treatment Period 1]) of geometric means and 90% confidence interval (CI) for the ratios of geometric means were calculated for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. Intra- and inter-subject CVs were also estimated for these parameters. The 90% CIs for the ratios of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} were used to quantify the extent of the potential drug–drug interaction between EE-LNG and intranasal zavegepant.

RESULTS

Study population

Of the 57 females screened for study entry, 23 (40%) were considered screen failures. Thirty-two (56%) participants were enrolled in the study (Figure S1). Two additional females were not enrolled;

despite being judged eligible, these two participants decided not to participate or were not selected to participate in the study since there was already a sufficient number of participants enrolled. As planned, 26 participants received at least 1 dose of study drug and were included in the safety population. The first participant was enrolled on December 10, 2020, and the last participant completed the study on March 4, 2021. Twenty-three participants comprised the pharmacokinetic population; three of the 26 participants were excluded for the following reasons: no quantifiable EE and LNG concentrations for samples collected on Days 1 to 5; nasal leakage of zavegepant (1 drop) on Day 2 of treatment Period 2; and discontinuation from the study (after receiving 1 dose of EE-LNG) due to an adverse event of COVID-19. This is the primary analysis of this study, which was based on a preplanned statistical analysis.

The demographic characteristics of the pharmacokinetic population were similar to those of the safety population (Table 1). Female participants were mostly white with a median age ranging from 32 to 34 years.

Pharmacokinetics

EE-LNG

Mean linear scale and semilogarithmic scale plasma concentration-time profiles of EE are shown in Figure 1A and of LNG in Figure 1B with and without zavegepant. Following co-administration of intranasal zavegepant with EE-LNG on Day 2 of treatment Period 2, no apparent differences in the concentration-time profiles of EE and LNG were observed when compared to those following the treatment of EE-LNG alone on Day 1 of treatment Period 1 (Figure 1A,B).

A comparison of descriptive statistics for EE and LNG pharmacokinetic parameters with and without intranasal zavegepant are shown in Table 2. Single-dose pharmacokinetic parameters of EE-LNG were comparable when given alone and when co-administered with intranasal zavegepant.

Co-administration of multiple-dose intranasal zavegepant with single-dose EE-LNG versus EE-LNG alone showed no clinically meaningful changes in exposure (<12% increases in EE exposure and <10% increases in LNG exposure) (Table 3).

TABLE 1 Demographics.

Parameter	Safety population (*N* = 26)	Pharmacokinetic population (*N* = 23)
Age (years)		
Mean	33.3 (5.8)	34.1 (5.4)
Median (range)	32.5 (21–44)	34.0 (23–44)
Race, *n* (%)		
White	25 (96)	22 (96)
Black	1 (4)	1 (4)
Ethnicity		
Not Hispanic or Latino	22 (85)	19 (83)
Hispanic or Latino	4 (15)	4 (17)
Weight (kg), median	67.1	68.3
BMI (kg/m^2), median	24.3	24.3

Abbreviations: BMI, body mass index; *N*, number of participants dosed; *n*, number of participants with data.

Zavegepant

Following co-administration of intranasal zavegepant 20 mg (10 mg in each nostril separated by 1 h) with EE-LNG 0.02–0.10 mg on Day 2 of treatment Period 2, the geometric mean (%CV) of $AUC_{0\text{-}t}$ and C_{max}, and the mean (SD) $t_{½\ el}$ of zavegepant were 71.8 h•ng/mL(67.9%), 24.1 ng/mL (58.0%), 6.9 hours (0.9 hours), respectively (Table 4). The median t_{max} was 1.5 hours (range of 0.3 to 2.0 hours).

Safety and tolerability

No deaths or serious adverse events were reported in this Phase 1 study of healthy adult females (Table 5). One participant discontinued from the study (after receiving 1 dose of EE-LNG) due to an adverse event of COVID-19.

All 26 (100%) participants experienced ≥1 treatment-emergent adverse events (TEAEs) including 25 of 25 (100%) while receiving EE-LNG concomitantly with intranasal zavegepant, 11 of 26 (42%) following a single dose of EE-LNG, and 24 of 25 (96%) following daily doses of intranasal zavegepant (Table 5). Overall, the most frequently reported TEAEs were dysgeusia (25 [96%]), throat irritation (11 [42%]), headache (10 [39%]), nasal discomfort (7 [27%]), pharyngeal paresthesia (5 [19%]), and nausea (4 [15%]); the remaining TEAEs were reported in ≤3 participants each. All reported TEAEs were mild or moderate in severity. Among the 248 reported TEAEs, 239 TEAEs were considered related to the study drugs, with the majority related to intranasal zavegepant and the minority related to EE-LNG. All TEAEs were recovered or resolved by the end of the study except for events of menstrual disorder and alopecia in one participant; both events were mild in severity.

No subject participant had elevated aspartate aminotransferase or alanine transaminase levels (>3 × upper limit of normal [ULN]), total bilirubin (>2 × ULN), or alkaline phosphatase (>1.5 × ULN). Clinically meaningful changes from baseline in laboratory values, vital signs, ECGs, or the S-STS were not observed in this study.

DISCUSSION

In females of child-bearing age, headache is the third leading cause of visits to the emergency department.[5] Approximately 40% of females experience migraine at some point during their reproductive

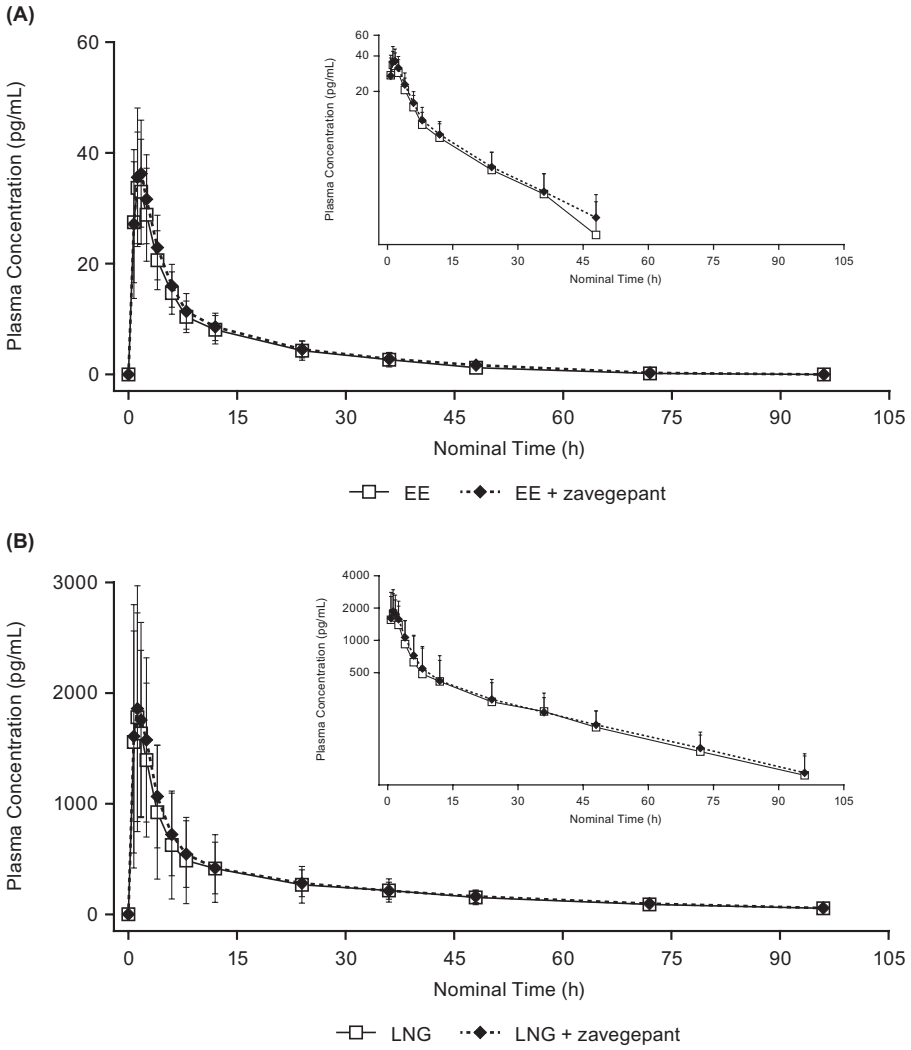

FIGURE 1 Mean ± SD plasma EE (A) and LNG (B) linear and semilogarithmic concentration-time profiles following the treatment of EE-LNG + intranasal zavegepant or EE-LNG alone. EE, ethinyl estradiol; LNG, levonorgestrel.

TABLE 2 EE and LNG pharmacokinetic parameters with and without intranasal zavegepant ($N = 23$).

Group (N)	C_{max} (pg/mL)	t_{max} (h)	$AUC_{0\text{-}t}$ (h•pg/mL)	$AUC_{0\text{-}24}$ (h•pg/mL)	$AUC_{0\text{-}inf}$ (h•pg/mL)	$t_{½\ el}$ (h)
EE						
EE + zavegepant	36.7 (29.5)	1.2 (0.7, 2.5)	360.2 (29.2)	286.7 (24.9)	395.4 (28.8)	16.6 (4)
EE alone	33.3 (28.2)	1.3 (0.7, 2.6)	322.9 (33.9)	264.6 (26.6)	359.7 (32.3)	14.9 (3)
LNG						
LNG + zavegepant	1926.0 (47.2)	1.2 (0.7, 6.0)	23381.8 (39.3)	13525.2 (48.5)	25202.0 (38.8)[a]	34.2 (14)
LNG alone	1770.8 (47.3)	1.3 (0.7, 2.6)	21353.8 (51.6)	12063.2 (63.4)	24121.9 (49.4)[b]	36.0 (19.0)

Note: All pharmacokinetic parameters are presented as geometric mean (%CV), except for t_{max}, which is presented as median (minimum, maximum), and $t_{½\ el}$, which is presented as mean (SD).

Abbreviations: %CV, percent coefficient of variation; AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, AUC from time zero to 24 h; $AUC_{0\text{-}inf}$, AUC from time zero to infinity; $AUC_{0\text{-}t}$, AUC from time zero to the last non-zero concentration; C_{max}, maximum observed concentration; EE, ethinyl estradiol; h, hour; LNG, levonorgestrel; N, number of participants dosed; n, number of participants with data; SD = standard deviation; $t_{½\ el}$, elimination half-life; t_{max}, time to maximum plasma drug concentration.

[a] $n = 20$.

[b] $n = 19$.

life cycle often necessitating therapeutic intervention.[30] Zavegepant is the first and only intranasally administered gepant approved for the acute treatment of migraine with or without aura in adults.[20,31] This intranasal formulation provides pain relief in as little as 15 min and which persists through 48 h after a single dose.[22] This study evaluated whether intranasal zavegepant when taken concomitantly with a frequently prescribed oral contraceptive altered either drug's pharmacokinetic profile.

Multiple-dose administration of intranasal zavegepant (total dose up to 20 mg), twice the approved dose,[20] did not show a clinically meaningful increase in the exposure of a commonly used oral contraceptive (EE 0.02 mg/LNG 0.10 mg). Because the $AUC_{0\text{-}inf}$ of EE and LNG was only increased by 9.9% and 7.0%, respectively, after co-administration with multiple doses of intranasal zavegepant compared with EE-LNG alone, these small changes in magnitude are not anticipated to alter the contraceptive efficacy of EE-LNG or alter the oral contraceptive's safety.[26,32] In addition, the 90% CIs for the comparison of EE and LNG with and without zavegepant were 105.3 to 114.8 and 100.2 to 114.3, respectively, which are within the range of what the Food and Drug Administration (FDA) considers bioequivalent (i.e., ≥0.80- to ≤1.25-fold).[33] Furthermore, in the current study, intranasal zavegepant exposure ($AUC_{0\text{-}24}$) at steady state on Day 2 (total 20 mg dose) was similar to the mean $AUC_{0\text{-}24}$ value reported in a previous Phase 1 study in fasted, non-smoking adult participants after 14 days of daily dosing of intranasal zavegepant 20 mg.[24]

Co-administration of zavegepant with the combination oral contraceptive EE-LNG in this study did not result in a clinically important drug–drug interaction for either contraceptive drug. EE is metabolized by hydroxylation via CYP3A4 and CYP2C9 and by conjugation via sulfation and glucuronidation via UGT1A1.[26] LNG is primarily metabolized via CYP3A4.[26,34] Because zavegepant is not a time-dependent inhibitor of CYP3A4, nor a strong inducer of metabolism,[20] it was not unexpected that the pharmacokinetics of EE and LNG were minimally changed by zavegepant.

This study in young healthy premenopausal females generally mirrors the findings observed in a previous study with atogepant conducted in healthy postmenopausal or oophorectomized females.[35] Co-administration of atogepant and a single dose of EE-LNG did not significantly alter the pharmacokinetics of EE, and the ~19% increase in plasma $AUC_{0\text{-}inf}$ of LNG is not considered to be clinically significant.[35] Another study explored whether rimegepant 75 mg daily affected the pharmacokinetics of an oral contraceptive containing EE/norgestimate (0.035 mg/0.25 mg) in healthy, young females with migraine.[36] Only modest, but clinically irrelevant, elevations in overall EE and norgestimate exposures (changes to 20% and 46%, respectively) were observed after multiple doses of rimegepant.

The current study also found that the co-administration of multiple intranasal doses of zavegepant and a single dose of EE-LNG was well tolerated. No deaths, serious adverse events, clinically significant laboratory results, or pregnancies were reported during the treatment period. The majority of adverse events were considered related to intranasal zavegepant including the most commonly reported event of dysgeusia. The observed adverse event profile following multiple-dose intranasal zavegepant in

TABLE 3 Statistical comparison of plasma EE and LNG pharmacokinetic exposure parameters with and without intranasal zavegepant.

	Geometric LSM		Comparison (EE-LNG + Zavegepant versus EE-LNG)	
Parameter	EE-LNG + Zavegepant	EE-LNG	Ratio (%)	90% CI
EE				
$AUC_{0\text{-}t}$ (h•pg/mL)	366.5	328.5	111.6	106.3, 117.1
$AUC_{0\text{-}inf}$ (h•pg/mL)	401.9	365.7	109.9	105.3, 114.8
C_{max} (pg/mL)	37.4	33.9	110.2	104.6, 116.1
LNG				
$AUC_{0\text{-}t}$ (h•pg/mL)	23,746.3	21,686.8	109.5	103.5, 115.9
$AUC_{0\text{-}inf}$ (h•pg/mL)	25,202.0	23,551.4	107.0	100.2, 114.3
C_{max} (pg/mL)	1952.7	1795.4	108.8	99.9, 118.4

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}t}$, AUC from time zero to the last non-zero concentration; $AUC_{0\text{-}inf}$, AUC from time zero to infinity; CI, confidence interval; C_{max}, maximum observed concentration; EE, ethinyl estradiol; h, hour; LNG, levonorgestrel; LSM, least squares mean.

TABLE 4 Steady-state zavegepant pharmacokinetic parameters following co-administration with EE-LNG.[a]

Group (*N*)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}t}$ (h•ng/mL)	$AUC_{0\text{-}24}$ (h•ng/mL)	$t_{½\ el}$ (h)
EE-LNG + zavegepant (*N* = 23)	24.1 (58.0)	1.5 (0.3, 2.0)	71.8 (67.9)	73.6 (67.1)[b]	6.9 (0.9)[b]

Abbreviations: %CV, percent coefficient of variation; AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, AUC from time zero to 24 h; $AUC_{0\text{-}t}$, AUC from time zero to the last non-zero concentration; C_{max}, maximum observed concentration; EE, ethinyl estradiol; h, hour; LNG, levonorgestrel; *N*, number of participants dosed; *n*, number of participants with data; SD, standard deviation; $t_{½\ el}$, elimination half-life; t_{max}, time to maximum plasma drug concentration.

[a]All pharmacokinetic parameters are presented as geometric mean (%CV), except for t_{max}, which is presented as median (minimum, maximum), and $t_{½\ el}$, which is presented as mean (SD).

[b]*n* = 22.

TABLE 5 Summary of adverse events per treatment (safety population).

Category	EE-LNG (*N* = 26)	Zavegepant (*N* = 25)	EE-LNG + Zavegepant (*N* = 25)
Number of participants with at least one treatment-emergent AE (TEAE), *n* (%)	11 (42)	24 (96)	25 (100)
Number of deaths, *n* (%)	0	0	0
Number of serious TEAEs	0	0	0
Number of participants who discontinued due to TEAEs	0	0	0
Number of TEAEs	27	57	164
Number of related TEAEs[a]	21	55	163
Number of severe TEAEs	0	0	0
Frequency of participants experiencing TEAEs[b]			
MedDRA® System Organ Class MedDRA® Preferred Term, *n* (%) number of TEAEs			
Nervous system symptoms	8 (31) 10	23 (92) 29	25 (100) 104
Dysgeusia	0	23 (92) 26	24 (96) 94
Headache	7 (27) 8	0	4 (16) 5
Paresthesia	0	2 (8) 2	2 (8) 5
Presyncope	1 (4) 1	0	0
Sciatica	1 (4) 1	0	0
Somnolence	0	1 (4) 1	0
Respiratory, thoracic and mediastinal symptoms	0	16 (64) 21	15 (60) 42
Throat irritation	0	6 (24) 8	9 (36) 16
Nasal discomfort	0	5 (20) 6	3 (12) 8
Pharyngeal paresthesia	0	2 (8) 2	5 (20) 11
Rhinorrhea	0	2 (8) 2	1 (4) 1
Oropharyngeal pain	0	0	2 (8) 3
Nasal congestion	0	2 (8) 2	0
Nasal pruritus	0	0	2 (8) 2
Epistaxis	0	1 (4) 1	0
Nasal dryness	0	0	1 (4) 1
Gastrointestinal symptoms	5 (19) 7	3 (12) 3	7 (28) 9
Nausea	1 (4) 1	1 (4) 1	2 (8) 2
Constipation	1 (4) 1	1 (4) 1	1 (4) 1
Abdominal pain lower	1 (4) 1	0	1 (4) 1
Diarrhea	1 (4) 1	0	1 (4) 1
Vomiting	2 (8) 2	0	0
Oral discomfort	0	1 (4) 1	1 (4) 1
Abdominal distension	1 (4) 1	0	0
Abdominal pain	0	0	1 (4) 1
Feces soft	0	0	1 (4) 1
Stomatitis	0	0	1 (4) 1
Musculoskeletal and connective tissue symptoms	2 (8) 2	1 (4) 1	2 (8) 3
Musculoskeletal stiffness	1 (4) 1	0	2 (8) 3
Arthralgia	0	1 (4) 1	0
Pain in extremity	1 (4) 1	0	0

Abbreviations: EE, Ethinyl Estradiol; LNG, Levonorgestrel; MedDRA®, Medical Dictionary for Regulatory Activities, Version 23.1.

[a]Includes all remotely related, possibly related, and probably related relationships; relationships to either Zavegepant or EE-LNG.

[b]Data reported for MedDRA System Organ Class where events for overall/total number of participants were ≥3.

this study was similar to that reported in larger Phase 2/3 clinical trials.[21,22]

Strengths and limitations

The two-treatment period fixed-sequence design of this study ensured that the potential interaction of intranasal zavegepant with the oral contraceptive EE-LNG was assessed after steady-state zavegepant exposure had been achieved. However, fixed-sequence designs can introduce period effects, where the outcome may be influenced by the order of treatments rather than the treatments themselves. Single doses of EE-LNG were selected based on the FDA guidance on drug–drug interactions for combined contraceptives and FDA guidance for CYP enzyme- and transporter-mediated drug interactions.[27] A single dose of EE-LNG is likely sufficient to determine this drug–drug interaction because of the linear pharmacokinetics with minimal accumulation following multiple doses of EE-LNG.[37] Multiple doses of intranasal zavegepant were given to represent the worst case scenario on CYP enzyme inhibition.

The study design employed only single doses of EE-LNG; thus, the effect of steady-state pharmacokinetics of EE-LNG on intranasal zavegepant pharmacokinetics were not evaluated. While this study was not designed to assess the effect of EE-LNG on zavegepant, the steady-state pharmacokinetics of intranasal zavegepant reported in this study were similar to previous publications.[20,24] Furthermore, because zavegepant is not extensively metabolized,[38] and significant metabolites have not been observed,[38] we did not expect an interaction of EE-LNG on zavegepant. After completion of this study, we compared zavegepant pharmacokinetics with historical data[24] and did not see any meaningful change when zavegepant was co-administered with EE-LNG.

CONCLUSIONS

Co-administration of multiple doses of zavegepant nasal spray at a total dose of 20 mg with a single dose of an oral contraceptive (EE-LNG 0.02–0.10 mg) resulted in no clinically meaningful changes (<12%) in exposure of EE and LNG. Furthermore, no dose adjustment is recommended for zavegepant nasal spray when co-administered to females taking EE-LNG for oral contraception. No new or untoward safety events for zavegepant were observed following co-administration of multiple daily doses of intranasal zavegepant with a single dose of EE-LNG in healthy, young females.

AUTHOR CONTRIBUTIONS

Rajinder Bhardwaj: Conceptualization; formal analysis; methodology; writing – original draft; writing – review and editing. **Julie Collins:** Formal analysis; funding acquisition; writing – review and editing. **Jennifer Madonia:** Conceptualization; writing – review and editing. **Kyle Matschke:** Formal analysis; funding acquisition; writing – review and editing. **Richard Bertz:** Conceptualization; formal analysis; project administration; supervision; writing – original draft; writing – review and editing. **Jing Liu:** Project administration; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Rajinder Bhardwaj is an employee of Certara who was a paid consultant to Biohaven, asset acquired by Pfizer in October 2022, for this study. **Jennifer Madonia** and **Richard Bertz** are current or former employees of Biohaven, asset acquired by Pfizer in October 2022, for this study. **Julie Collins, Kyle Matschke,** and **Jing Liu** are employed by and hold 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 subject data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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SUPPORTING INFORMATION

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

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