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RESEARCH SUBMISSIONS

Zavegepant nasal spray for the acute treatment of migraine: A Phase 2/3 double-blind, randomized, placebo-controlled, dose-ranging trial

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Abstract

Objective: Evaluate the efficacy, safety, and tolerability of zavegepant nasal spray in the acute treatment of migraine.

Background: Calcitonin gene-related peptide-targeting agents are a novel class of therapeutics for migraine, but none are currently available as a nonoral option for acute treatment. Zavegepant, a high-affinity, selective, and structurally unique calcitonin gene-related peptide-receptor antagonist in late-stage development, is formulated as a nasal spray for the acute treatment of migraine.

Methods: This randomized, dose-ranging, placebo-controlled, Phase 2/3 trial in adults aged ≥18 years with migraine (NCT03872453) was conducted at US study sites. Participants were randomized by an interactive web response system and treated a single attack of moderate to severe pain intensity with zavegepant nasal spray 5, 10, 20 mg, or placebo. Coprimary efficacy endpoints were pain freedom and freedom from the most bothersome symptom at 2 h postdose.

Results: Of the 1673 participants aged 18 to 79 years who were randomized, 1588 were treated with study medication, and 1581 (mean age 40.8 years, 85.5% female) were analyzed for efficacy: zavegepant 5 mg (n = 387), 10 mg (n = 391), 20 mg (n = 402), and placebo (n = 401). Zavegepant 10 and 20 mg were more effective than placebo on the coprimary endpoints of pain freedom at 2 h postdose (placebo: 15.5% [98.3% confidence interval (CI), 11.1, 19.8]; 10 mg: 22.5% [98.3% CI, 17.5, 27.6; p = 0.0113]; 20 mg: 23.1% [98.3% CI, 18.1, 28.2; p = 0.0055]) and freedom from the most bothersome symptom at 2 h postdose (placebo: 33.7% [98.3% CI, 28.0, 39.3]; 10 mg: 41.9% [98.3% CI, 36.0, 47.9; p = 0.0155]; 20 mg: 42.5% [98.3% CI, 36.6, 48.4; p = 0.0094]). Findings for the 5 mg dose were not significant. The most common treatment-emergent adverse events with zavegepant 10 and 20 mg and placebo were

Abbreviations: AE, adverse event; CGRP, calcitonin gene-related peptide; CI, confidence interval; IWRS, interactive web response system; MBS, most bothersome symptom; SAE, serious adverse event; SD, standard deviation.

dysgeusia (13.5% to 16.1% vs. 3.5%), nausea (2.7% to 4.1% vs. 0.5%), and nasal discomfort (1.3% to 5.2% vs. 0.2%). Most adverse events were mild or moderate and resolved without treatment. There was no signal of hepatotoxicity.

Conclusion: Zavegepant nasal spray, in single doses of 10 or 20 mg, was effective for the acute treatment of migraine, with a favorable safety profile. Additional research is needed to confirm its potential as a nonoral medication for the acute treatment of migraine.

KEYWORDS
acute treatment, CGRP, intranasal, migraine, nasal spray, zavegepant

INTRODUCTION

In the acute treatment of migraine, clinicians can choose from a range of medications formulated for oral, parenteral, or intranasal delivery.[1] Although oral formulations are the most widely used, of the nonoral options, nasal sprays are used 2 to 3 times more often than injectables for the acute treatment of migraine.[2] Guidelines recommend nonoral therapies for attacks that include severe nausea or vomiting or rapidly escalating headache pain, as well as for patients in whom oral forms are associated with inadequate response, slow onset of action, or poor tolerability.[1,3,4] At present, approved parenteral or intranasal medications for the acute treatment of migraine include 5-$HT_{1B/1D}$ receptor agonists (sumatriptan, zolmitriptan) and ergot alkaloids (dihydroergotamine mesylate).

Because rapid onset of treatment effect is a priority for many people with migraine and an area of unmet acute treatment need,[5–7] the route of administration influences the onset of treatment effects,[8,9] and most patients prefer nasal sprays to injectables,[2,5] intranasally administered antimigraine drugs can meet an important need in clinical practice. However, triptans are ineffective in approximately one third of those who try them,[10] and cardiovascular contraindications restrict their use in almost 10% of the total migraine population in the United States (~3.5 million people[11,12]). Dihydroergotamine nasal spray is less effective than sumatriptan nasal spray at early time points,[13,14] although new formulations are emerging[15]; it is contraindicated in patients with ischemic heart disease, coronary artery vasospasm, or uncontrolled hypertension, and coadministration with potent cytochrome P450 3A4 inhibitors may lead to potentially fatal cerebral and peripheral ischemia.[16] Gepants may be helpful in people who do not respond to triptans, cannot tolerate them, or who are unable to take them due to cardiovascular contraindications.[4] The available gepants for acute treatment are administered orally. A gepant nasal spray could be advantageous in the groups targeted in guidelines for nonoral therapy: those with gastrointestinal distress, rapidly escalating headache pain, or patients with inadequate response to oral therapy.[1,3,4]

All other things being equal, people with migraine prefer tablets to nasal sprays.[5] But all other things are not always equal. Guidelines for the acute treatment of migraine recommend nonoral agents (injections or nasal sprays) for patients who do not respond to oral agents, patients with prominent nausea or vomiting that interferes with administration or absorption of oral acute treatments, and those for whom oral therapies are intolerable due to treatment-emergent nausea or dysphagia.[1,3] While gepants have many advantages over triptans as acute treatments, including the absence of cardiovascular contraindications and precautions, favorable tolerability, and no evidence of medication-overuse headache, as of this writing there are no marketed gepants available for nonoral administration.

Zavegepant nasal spray—a third-generation, high-affinity, selective and structurally unique, small molecule calcitonin gene-related peptide (CGRP) receptor antagonist—is the first CGRP receptor antagonist for intranasal administration in late-stage development for the acute treatment of migraine. A previous single ascending dose study found that doses of zavegepant nasal spray ranging from 5 to 40 mg were rapidly absorbed (T_{max} ~ 30 min) and produced potentially therapeutic systemic exposures.[17] In vitro evaluations have demonstrated that zavegepant has low potential for drug–drug interactions.[18,19] The objective of this study was to evaluate the efficacy, safety, and tolerability of zavegepant nasal spray at dose levels of 5, 10, and 20 mg for the acute treatment of migraine.

METHODS

Ethics

This study was conducted in accordance with the principles of Good Clinical Practice and Good Laboratory Practice as referenced in the International Council for Harmonisation guidelines, as well as all applicable regulations, including the Federal Food, Drug, and Cosmetic Act; Title 21 of the Code of Federal Regulations; and any institutional review board requirements relevant to clinical studies. The study also complied with the recommendations in the most recent version of the Declaration of Helsinki. Participants provided written informed consent before any study-related procedures were undertaken. The protocol was approved by a central institutional review board (Advarra IRB, Cincinnati, OH, USA) and two local institutional review boards (North Kansas City Hospital, North Kansas City, MO, USA; Biomedical Research Alliance of New York Institutional Review Board, Lake Success, NY, USA). The study was prospectively registered at clinicaltrials.gov (NCT03872453).

Design

This double-blind, randomized, placebo-controlled, dose-ranging study evaluated the efficacy, safety, and tolerability of three different dose levels of zavegepant nasal spray (5, 10, and 20 mg) relative to placebo in the acute treatment of migraine. The study was also designed to identify at least one dose level of zavegepant that was safe, well tolerated, and suggestive of efficacy in adults with migraine.

The study, which was conducted at academic medical centers, private practices, and independent research facilities, included a screening period (3 to 28 days), a treatment phase (up to 45 days) during which the participants could treat a single qualifying migraine attack, and an end-of-treatment visit (7 days, plus two days if necessary, after dosing of study medication). At the baseline visit, participants who met all eligibility criteria were randomized (1:1:1:1) to zavegepant 5 mg, zavegepant 10 mg, zavegepant 20 mg, or placebo. The total duration of the study was approximately 11 weeks.

Participants were identified from the investigators' clinical practices, by referrals to investigators from other healthcare providers, through advertising via radio and social media, and through searches of patient databases. Randomization was managed by an interactive web response system (IWRS), which investigators contacted to enroll participants into a centralized database. At the time of enrollment, immediately after written informed consent was obtained and before any study-related procedures were undertaken, the IWRS assigned each participant a unique, sequential 4-digit participant number for identification throughout the study. After completion of all screening evaluations, including the diagnosis of migraine by investigators or a qualified designee at each trial site, eligible participants returned to the study site for the baseline (randomization) visit and were randomized to the zavegepant 5, 10, or 20 mg or placebo treatment groups stratified by the use of preventive migraine medications (yes or no). The randomization schedules were generated and kept by the IWRS vendor in a secure network folder with access limited to unblinded team members.

To record migraine symptoms and response to study treatment, participants were provided with an electronic clinical outcome assessment handheld device (Clario, Bridgewater, NJ, USA). Study personnel instructed the participants on the proper use of the handheld device to ensure proper understanding and use of the tool. Participants were dispensed one liquid spray device (Unidose [UDS] system, Aptar Pharma, Crystal Lake, IL, USA) containing a single dose of zavegepant or matching placebo. Study personnel also trained each participant on the proper use of the liquid spray device using printed instructions for use, which were provided to each participant. They were instructed to take study medication only if they had a migraine attack with headache pain of moderate or severe intensity and only after answering questions about their current pain and symptoms and after identifying their current most bothersome symptom (MBS) in the handheld device. Before participants left the site, study personnel ensured proper understanding and usage of the handheld device and the liquid spray device. Participants completed assessments for 48 h after taking study medication.

Participants

Men and women aged 18 years and older (no upper limit) with at least a 1-year history of migraine (with or without aura) consistent with the criteria set forth in the International Classification of Headache Disorders, 3rd edition,[20] were eligible. To participate, they had to meet all of the following criteria: age of migraine onset prior to age 50; migraine attacks, on average, lasting about 4 to 72 h if untreated; not more than 8 migraine attacks of moderate or severe intensity per month within the last 3 months prior to the screening visit[21]; the ability to distinguish an attack of migraine from those of tension-type headache and cluster headache; at least 2 consistent migraine attacks of moderate or severe intensity in each of the 3 months prior to the screening visit and throughout the screening phase (participant self-report); and fewer than 15 days with headaches (migraine or nonmigraine) per month in each of the 3 months prior to the screening visit and throughout the screening phase (participant self-report). Participants taking medication for the preventive treatment of migraine were permitted to remain on therapy if they were on a stable dose for at least 3 months prior to the screening visit and if the dose was not expected to change during the course of the study. Participants could not have been involved in any clinical trial of nonbiological investigational agents, such as gepants, within 30 days before the baseline visit. The use of CGRP antagonist biologics must have been discontinued 6 months prior to screening and was prohibited during the study. Participants with contraindications for use of triptans could be included as long as they met all other study entry criteria. Use of opioids or barbiturate-containing products was prohibited during the treatment period.

Participants with a history of migraine with brainstem aura ("basilar migraine" in the protocol) or hemiplegic migraine were excluded, as were those with a history or current evidence of any significant and/or unstable medical condition(s) that might expose them to undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial. Participants using over-the-counter or prescribed nasal sprays were also excluded unless they stopped using them for at least 14 days before the screening visit and refrained from use throughout the study. The complete list of exclusion criteria is presented in the study protocol (see the Supplement in the Supporting Information).

Treatments

Study treatments included zavegepant nasal spray (5, 10, or 20 mg) or matching placebo.

Zavegepant and matching placebo were provided in single-use liquid spray devices fully prepared and ready for administration.

Participants were instructed to self-administer a single intranasal spray of study medication from the liquid spray device at the time of moderate or severe migraine headache pain onset.

Outcomes

Efficacy

The coprimary efficacy endpoints were pain freedom and freedom from the MBS associated with migraine (i.e., phonophobia, photophobia, or nausea) at 2 h postdose.

Secondary efficacy endpoints included pain relief at 2 h postdose; return to normal function at 2 h postdose; rescue medication use within 24 h postdose; freedom from photophobia at 2 h postdose; freedom from phonophobia at 2 h postdose; pain relief at 60 min postdose; return to normal function at 60 min postdose; pain relief at 30 min postdose; return to normal function at 30 min postdose; sustained pain relief from 2 to 24 h postdose; sustained pain freedom from 2 to 24 h postdose; sustained pain relief from 2 to 48 h postdose; sustained pain freedom from 2 to 48 h postdose; freedom from nausea at 2 h postdose; and pain relapse from 2 to 48 h postdose.

Participants used the handheld device to record the intensity of migraine pain and the presence or absence of migraine-associated symptoms. Pain freedom was assessed using ratings of pain intensity on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Freedom from the MBS was assessed using the presence or absence of the symptom identified by participants as the MBS (selected from among photophobia, phonophobia, or nausea) for the treated attack. The MBS was identified before participants used the study medication.

Secondary endpoints were assessed as follows. Pain relief was assessed using the percentage of participants with baseline pain of moderate or severe intensity who had pain levels of none or mild at 30 min, 60 min, and 2 h postdose. Return to normal function was measured as the proportion of participants reporting normal function at 30 min, 60 min, and 2 h postdose in the subset of participants with functional disability (mildly impaired, severely impaired, or requires bedrest) at the time of dosing. Rescue medication use within 24 h postdose was assessed using the percentage of participants that took rescue medication within 24 h after administration of study medication; participants with rescue medication start date on or before the study drug start date +1 day and missing rescue medication start time were excluded. Freedom from photophobia, phonophobia, and nausea were assessed using the percentage of participants with photophobia, phonophobia, or nausea absent at 2 h postdose in the subset of participants with photophobia, phonophobia, or nausea, respectively, present at the time of dosing. Sustained pain freedom was assessed using the percentage of participants with pain levels of none at all time points from 2 to 24 h postdose or 2 to 48 h postdose. Pain relapse was assessed using the percentage of participants with a pain level of mild, moderate, or severe at any time point after 2 through 48 h postdose in the subset of participants with pain freedom at 2 h postdose.

Safety and tolerability

Safety variables included AEs, serious AEs (SAEs), clinical laboratory evaluations (including liver function tests), vital sign measurements, physical examinations, and electrocardiograms. Adverse events were spontaneously reported or elicited during open-ended questioning, examination, or evaluation of participants. To prevent reporting bias, participants were not questioned regarding the specific occurrence of events.

Measures of interest

Other prospectively defined endpoints included participants' preference of medication compared with their usual acute treatment, migraine pain and associated symptoms, and migraine-related quality of life; participants recorded them using the handheld device. Nasal passages and turbinates were visually inspected with a nasal speculum or otoscope at the screening, baseline, and end of treatment visits. Nasal findings were recorded per protocol.

Sample size and blinding

Assuming 380 participants per group and true response rates for pain freedom at 2 h postdose of 22% in a zavegepant group and 12% in the placebo group, a chi-square test at the Bonferroni-corrected alpha level of 0.0167 had 90% power to detect a difference between the treatments. Similarly, with 380 participants per group, if the true response rates for MBS freedom at 2 h postdose were 45% in a zavegepant group and 32% in the placebo group, then a chi-square test ($\alpha = 0.0167$) had 90% power to detect a difference between the treatments. Under the assumption that the 2-h pain freedom and MBS freedom endpoints were independent, the power to detect a difference between the treatments for both endpoints jointly was roughly 80% (81%).

Participants and all study personnel were blinded by having enrollment, randomization, and treatment assignments centralized and automated, as well as by providing study medications in ready-to-use liquid spray devices that were identical in appearance.

Statistical analysis

Populations

The efficacy population consisted of modified intent-to-treat participants, which included randomized participants who were treated, had moderate to severe pain at the onset of the treated attack, and

had any postbaseline efficacy data. Safety and tolerability were analyzed in the safety population, which included all treated participants.

Efficacy

For each of the three zavegepant dose groups, the percentages of participants with pain freedom at 2 h postdose and the percentages of participants with MBS freedom at 2 h postdose were compared pairwise with placebo using Cochran–Mantel–Haenszel tests stratified by preventive migraine medication use at randomization (yes, no). In these analyses, participants who had missing data at the time of efficacy evaluation or who took rescue medication at or before the evaluation of the endpoints were imputed as failures.

To correct for multiple testing, the alpha level of 0.05 was split among the three zavegepant dose groups using a Bonferroni correction. The coprimary endpoints for each dose group were tested against placebo at an alpha level of 0.0167. If the coprimary endpoints within a dose group were statistically significant, then the secondary endpoints in that dose group were tested using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at an alpha level of 0.0167. Secondary endpoints were tested in the order listed above under Outcomes. If a test in the hierarchy was not significant, then any further tests on endpoints in the sequence had nominal *p*-values, which are presented for descriptive purposes. Consistent with the Bonferroni correction for multiple testing, point estimates are reported with 98.3% confidence intervals (CIs).

Safety

Investigators determined the severity of AEs and the relationship of AEs to study treatments. The investigators' terms were coded and grouped by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (version 21.1). If a participant had an AE with different severities over time, only the greatest severity was reported. Laboratory tests were analyzed using results from a central laboratory (LabConnect, Johnson City, TN, USA) and local laboratories.

RESULTS

The study enrolled 2154 participants at 82 sites in the United States between March 25, 2019 and September 6, 2019. Of the 1673 participants aged 18 to 79 years who were randomized, 1588 were in the safety population, and 1581 were in the efficacy population (zavegepant 5 mg [$n = 387$], 10 mg [$n = 391$], 20 mg [$n = 402$], placebo [$n = 401$]). As shown in Figure 1, 481 (22.3%) of enrolled participants discontinued the study before randomization, mainly for screening failure due to eligibility criteria (20.6%). After randomization, 2 participants discontinued the study and did not take study medication due to a clavicle fracture and clostridium difficile colitis in 1 participant each.

The efficacy population had a mean (standard deviation [SD]) age of 40.8 (12.7) years. Participants were predominantly female (85.5%)

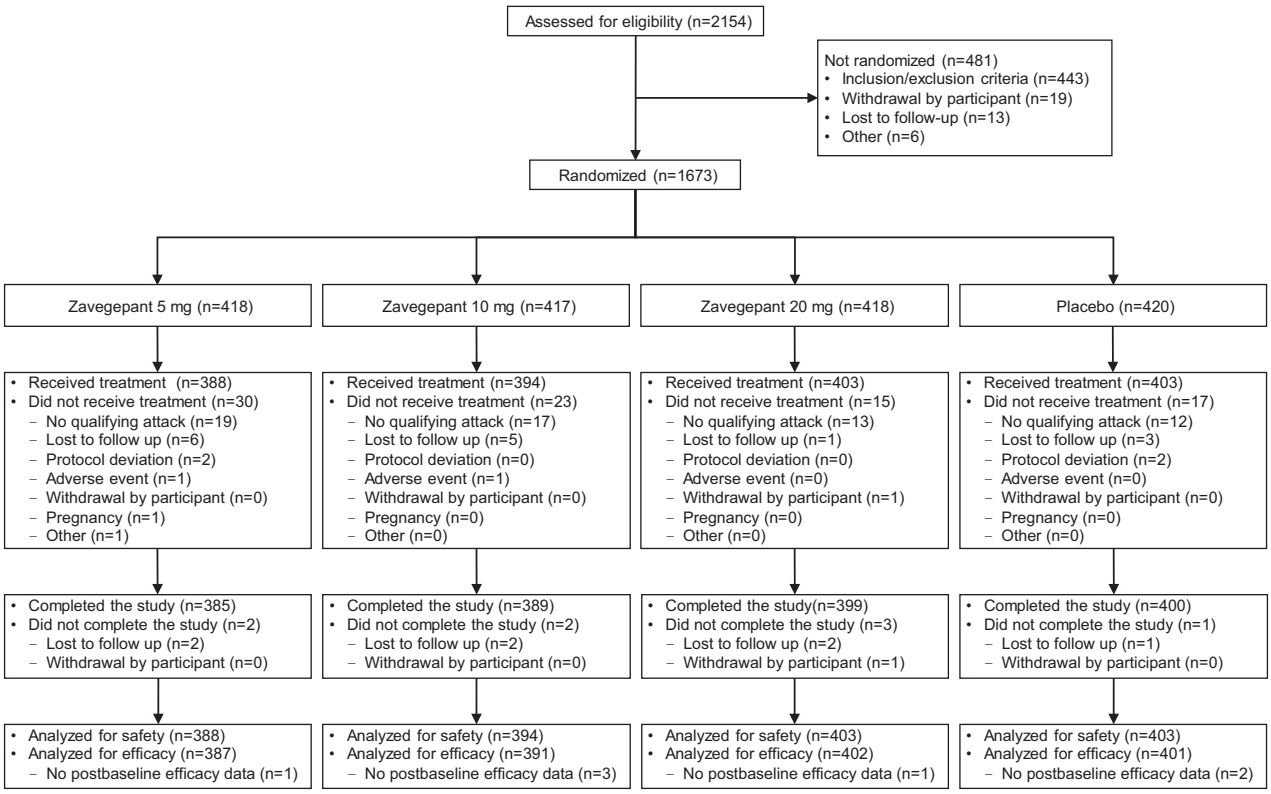

FIGURE 1 Disposition of participants

TABLE 1 Demographics and baseline characteristics of the efficacy population

	Zavegepant				
	5 mg (n = 387)	10 mg (n = 391)	20 mg (n = 402)	Placebo (n = 401)	Overall (N = 1581)
Age, years, mean (SD)	41.9 (12.6)	41.4 (12.9)	40.0 (13.0)	39.9 (12.0)	40.8 (12.7)
Sex, *n* (%)					
Female	336 (86.8)	333 (85.2)	344 (85.6)	338 (84.3)	1351 (85.5)
Male	51 (13.2)	58 (14.8)	58 (14.4)	63 (15.7)	230 (14.5)
Race, *n* (%)					
White	299 (77.3)	296 (75.7)	315 (78.4)	328 (81.8)	1238 (78.3)
Black or African-American	65 (16.8)	72 (18.4)	62 (15.4)	58 (14.5)	257 (16.3)
American Indian or Alaska Native	2 (0.5)	0	3 (0.7)	1 (0.2)	6 (0.4)
Asian	17 (4.4)	13 (3.3)	15 (3.7)	13 (3.2)	58 (3.7)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)	0	0	1 (0.1)
Multiple	4 (1.0)	9 (2.3)	7 (1.7)	1 (0.2)	21 (1.3)
Ethnicity, *n* (%)					
Hispanic or Latino	64 (16.5)	69 (17.6)	72 (17.9)	81 (20.2)	286 (18.1)
Not Hispanic or Latino	323 (83.5)	322 (82.4)	330 (82.1)	320 (79.8)	1295 (81.9)
Height, cm, mean (SD)	165.3 (7.9)	166.0 (8.3)	165.4 (8.4)	166.3 (8.9)	165.7 (8.4)
Weight, kg, mean (SD)	75.2 (15.9)	75.5 (14.6)	74.8 (14.3)	76.4 (15.3)	75.5 (15.0)
Body mass index, kg/m^2, mean (SD)	27.4 (4.8)	27.4 (4.5)	27.3 (4.5)	27.5 (4.5)	27.4 (4.6)
Preventive migraine medication use[a], *n* (%)					
Yes	54 (14.0)	50 (12.8)	57 (14.2)	54 (13.5)	215 (13.6)
No	333 (86.0)	341 (87.2)	345 (85.8)	347 (86.5)	1366 (86.4)
Cardiovascular risk factors					
Diabetes	7 (1.8)	6 (1.5)	10 (2.5)	8 (2.0)	31 (2.0)
Treatment with a statin	27 (7.0)	27 (6.9)	23 (5.7)	14 (3.5)	91 (5.8)
Treatment for hypertension	37 (9.6)	41 (10.5)	32 (8.0)	23 (5.7)	133 (8.4)
Current smoker	39 (10.1)	29 (7.4)	30 (7.5)	37 (9.2)	135 (8.5)
Family history of coronary artery disease	66 (17.1)	74 (18.9)	64 (15.9)	69 (17.2)	273 (17.3)

[a]At randomization.

and White (78.3%), with a mean (SD) body mass index of 27.4 (4.6) kg/m^2. Preventive migraine medications were being used by 13.6% of participants at randomization. Demographic and baseline characteristics of the efficacy population, including cardiovascular risk factors, are presented in Table 1.

Efficacy

As Figure 2 shows, zavegepant 10 mg and zavegepant 20 mg were more effective than placebo for the coprimary endpoints of pain freedom at 2 h postdose (placebo: 15.5% [98.3% CI, 11.1, 19.8]; 10 mg: 22.5% [98.3% CI, 17.5, 27.6; p = 0.0113]; 20 mg: 23.1% [98.3% CI, 18.1, 28.2; p = 0.0055]) and freedom from the MBS at 2 h postdose (placebo: 33.7% [98.3% CI, 28.0, 39.3]; 10 mg: 41.9% [98.3% CI, 36.0, 47.9; p = 0.0155]; 20 mg: 42.5% [98.3% CI, 36.6, 48.4; p = 0.0094]). Findings for the 5 mg dose were not significant.

Results for secondary efficacy endpoints are presented in Table 2. The percentages of participants who had pain relief at 2 h postdose were 53.6% (98.3% CI, 47.7, 59.6) for placebo, 60.6% (98.3% CI, 54.7, 66.5) for zavegepant 10 mg (p = 0.0439), and 61.2% (98.3% CI, 55.4, 67.0) for zavegepant 20 mg (p = 0.0302). In the absence of a significant difference between the active treatments and placebo on this endpoint, p-values reported for all of the secondary efficacy endpoints are nominal. However, response to zavegepant was greater than placebo on multiple secondary endpoints (nominal $p \leq 0.05$), including return to normal function at 30 min postdose with zavegepant 20 mg and sustained pain freedom from 2 to 48 h postdose with zavegepant 5, 10, and 20 mg.

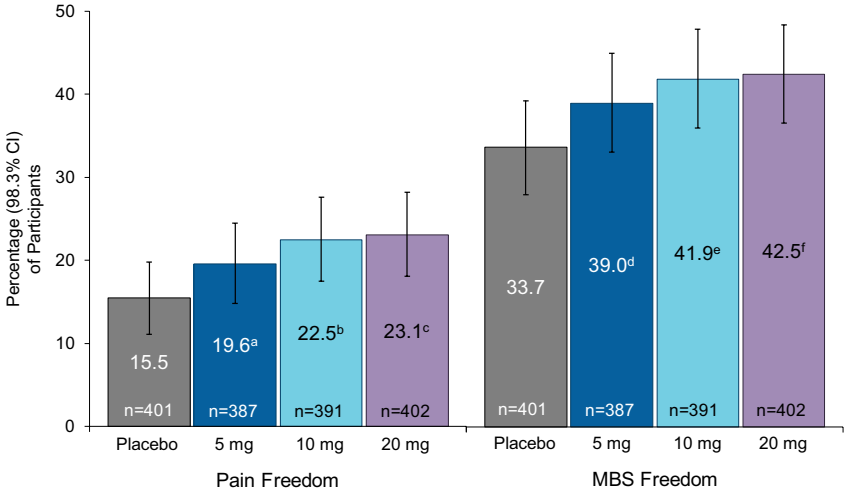

FIGURE 2 Efficacy of 5, 10, 20 mg zavegepant nasal spray versus placebo on the coprimary efficacy endpoints of pain freedom and MBS freedom at 2 h postdose. CI, confidence interval; MBS, most bothersome symptom. [a]$p = 0.1214$ versus placebo. [b]$p = 0.0113$ versus placebo. [c]$p = 0.0055$ versus placebo. [d]$p = 0.1162$ versus placebo. [e]$p = 0.0155$ versus placebo. [f]$p = 0.0094$ versus placebo

Safety

Table 3 shows that the most common treatment-emergent AEs in participants who were treated with zavegepant were dysgeusia (13.5% to 16.1% with zavegepant vs. 3.5% with placebo); nausea (2.6% to 4.1% with zavegepant vs. 0.5% with placebo); and nasal discomfort (1.3% to 5.2% with zavegepant vs. 0.2% with placebo). The majority of AEs were mild or moderate. Five participants experienced an SAE, no SAE was considered related to treatment, and only two of these participants had been treated with blinded study medication. The only SAE in any zavegepant group was thrombosis (blood clot in the leg), which was reported for 1 participant in the 10 mg group; the event occurred 13 days after the single dose of zavegepant and was attributed by the investigator to trauma from a motor vehicle accident. One participant in the placebo group had an SAE of vestibular migraine. One SAE of clostridium difficile colitis was reported after randomization in 1 participant in the zavegepant 10 mg group who was not treated. In addition, 2 participants who were neither randomized nor treated experienced SAEs, 1 with post lumbar puncture syndrome and back pain, the other with pulmonary embolism. There was no signal of hepatotoxicity.

DISCUSSION

This Phase 2/3 double-blind, randomized, placebo-controlled, dose-ranging trial was conducted to evaluate the safety and efficacy of zavegepant nasal spray in the acute treatment of migraine and to identify an optimal dose to support Phase 3 clinical trials. The 10 and 20 mg doses of zavegepant were more effective than placebo for the coprimary endpoints of freedom from pain at 2 h postdose and freedom from the MBS at 2 h postdose. Although the hierarchical testing for statistical significance was stopped at the first secondary endpoint of pain relief at 2 h postdose, evidence of therapeutic benefit was observed on multiple secondary endpoints of importance to patients with migraine, including return to normal function at 30 min postdose in zavegepant 20 mg; sustained pain relief from 2 to 24 h postdose in zavegepant 5, 10, and 20 mg; sustained pain freedom from 2 to 24 h and from 2 to 48 h postdose in zavegepant 5, 10, and 20 mg; and sustained pain relief from 2 to 48 h postdose in zavegepant 5 and 10 mg.

These results suggest that zavegepant may have a therapeutic role in the acute treatment of migraine as an effective alternative to oral and parenteral agents. Patients most likely to benefit from the use of zavegepant will be adults seeking a rapid onset of action (e.g., people regularly awakened by attacks) and those whose attacks typically involve marked gastrointestinal distress. The nasal spray formulation may be a particularly advantageous nonoral, needle-free approach to avoid exacerbations of nausea or vomiting, facilitate drug administration, and eliminate the effects of gastroparesis on drug absorption.

In the acute treatment of migraine, nausea and vomiting are reported to delay the use of oral medication and may be associated with slowed absorption.[22] There is evidence that oral triptans cause treatment-emergent nausea[23] and that a nasal form of sumatriptan caused less nausea than sumatriptan tablets in a head-to-head study.[24] A gepant nasal spray may lead to a greater willingness to treat early and a reduced risk of treatment-emergent nausea and vomiting. Subsequent trials may provide additional data to address this question.

One reason nasal formulations are developed is the hope that the medication will have a short T_{max}, a feature thought to predict rapid onset of action.[25] Zavegepant nasal spray has a T_{max} of approximately 30 min for doses ranging from 5 to 40 mg, which compares favorably with other drugs in the gepant class. The rapid absorption of zavegepant nasal spray shows promise for translating into a rapid onset of action. In a dose-ranging study, power to separate active drug from placebo at early time points can be diminished by

TABLE 2 Efficacy of zavegepant nasal spray on the secondary efficacy endpoints (all times are postdose and all *p*-values are nominal)

	Zavegepant			
	5 mg (*n* = 387)	10 mg (*n* = 391)	20 mg (*n* = 402)	Placebo (*n* = 401)
Pain relief at 2 h				
n/*N* (%)	224/387 (57.9)	237/391 (60.6)	246/402 (61.2)	215/401 (53.6)
Percentage difference[a]	4.2	7.1	7.5	
p-value	0.2296	0.0439	0.0302	
Return to normal function at 2 h[b]				
n/*N* (%)	115/363 (31.7)	122/354 (34.5)	129/372 (34.7)	101/369 (27.4)
Percentage difference[a]	4.3	7.1	7.3	
p-value	0.2039	0.0389	0.0305	
Rescue medication use within 24 h[c]				
n/*N* (%)	96/385 (24.9)	101/388 (26.0)	80/397 (20.2)	109/400 (27.3)
Percentage difference[a]	−2.4	−1.1	−7.1	
p-value	0.4502	0.7154	0.0172	
Photophobia freedom at 2 h[d]				
n/*N* (%)	118/337 (35.0)	121/340 (35.6)	134/354 (37.9)	109/358 (30.4)
Percentage difference[a]	4.6	5.1	7.4	
p-value	0.1986	0.1494	0.0352	
Phonophobia freedom at 2 h[d]				
n/*N* (%)	115/260 (44.2)	107/239 (44.8)	114/263 (43.3)	94/276 (34.1)
Percentage difference[a]	10.1	10.8	9.3	
p-value	0.0161	0.0115	0.0249	
Pain relief at 60 min				
n/*N* (%)	182/387 (47.0)	180/391 (46.0)	200/402 (49.8)	168/401 (41.9)
Percentage difference[a]	5.1	4.2	7.8	
p-value	0.1495	0.2274	0.0259	
Return to normal function at 60 min[b]				
n/*N* (%)	82/363 (22.6)	67/354 (18.9)	70/372 (18.8)	63/369 (17.1)
Percentage difference[a]	5.5	1.8	1.7	
p-value	0.0624	0.5222	0.5517	
Pain relief at 30 min				
n/*N* (%)	103/387 (26.6)	117/391 (29.9)	107/402 (26.6)	99/401 (24.7)
Percentage difference[a]	1.9	5.3	1.9	
p-value	0.5359	0.0953	0.5398	
Return to normal function at 30 min[b]				
n/*N* (%)	32/363 (8.8)	27/354 (7.6)	37/372 (9.9)	20/369 (5.4)
Percentage difference[a]	3.4	2.1	4.5	
p-value	0.0753	0.2445	0.0216	
Sustained pain relief from 2 to 24 h				
n/*N* (%)	169/387 (43.7)	166/391 (42.5)	179/402 (44.5)	143/401 (35.7)
Percentage difference[a]	8.0	6.8	8.9	
p-value	0.0205	0.0495	0.0098	
Sustained pain freedom from 2 to 24 h				
n/*N* (%)	55/387 (14.2)	59/391 (15.1)	63/402 (15.7)	36/401 (9.0)
Percentage difference[a]	5.3	6.1	6.7	
p-value	0.0210	0.0081	0.0036	

TABLE 2 (Continued)

	Zavegepant			
	5 mg (n = 387)	10 mg (n = 391)	20 mg (n = 402)	Placebo (n = 401)
Sustained pain relief from 2 to 48 h				
n/*N* (%)	155/387 (40.1)	155/391 (39.6)	156/402 (38.8)	131/401 (32.7)
Percentage difference[a]	7.4	7.0	6.2	
p-value	0.0297	0.0404	0.0676	
Sustained pain freedom from 2 to 48 h				
n/*N* (%)	50/387 (12.9)	54/391 (13.8)	53/402 (13.2)	30/401 (7.5)
Percentage difference[a]	5.5	6.3	5.7	
p-value	0.0111	0.0038	0.0075	
Nausea freedom at 2 h[d]				
n/*N* (%)	126/237 (53.2)	131/243 (53.9)	145/265 (54.7)	122/239 (51.0)
Percentage difference[a]	1.8	2.9	3.7	
p-value	0.6987	0.5279	0.4092	
Pain relapse from 2 to 48 h[e]				
n/*N* (%)	24/76 (31.6)	29/88 (33.0)	35/93 (37.6)	31/62 (50.0)
Percentage difference[a]	−18.9	−17.0	−12.5	
p-value	0.0221	0.0366	0.1242	

[a]Stratified by preventive migraine medication use at randomization with Cochran–Mantel–Haenszel weighting.

[b]Among participants with functional disability at time of dosing.

[c]Participants with rescue medication start date on or before the study drug start date plus 1 day and missing rescue medication start time were excluded.

[d]Among participants with the symptom present at time of dosing.

[e]Among participants with pain freedom at 2 h postdose.

TABLE 3 Treatment-emergent adverse events following treatment with a single dose of zavegepant nasal spray or placebo

	Zavegepant			
	5 mg (n = 388)	10 mg (n = 394)	20 mg (n = 403)	Placebo (n = 403)
Participants with ≥1 adverse event, *n* (%)	88 (22.7)	97 (24.6)	126 (31.3)	62 (15.4)
Reported in ≥1% in any treatment group, *n* (%)				
Dysgeusia	54 (13.9)	53 (13.5)	65 (16.1)	14 (3.5)
Nausea	10 (2.6)	16 (4.1)	11 (2.7)	2 (0.5)
Nasal discomfort	5 (1.3)	5 (1.3)	21 (5.2)	1 (0.2)
Urinary tract infection	3 (0.8)	4 (1.0)	8 (2.0)	5 (1.2)
Throat irritation	4 (1.0)	4 (1.0)	9 (2.2)	0
Vomiting	1 (0.3)	7 (1.8)	7 (1.7)	1 (0.2)
Nasal edema	3 (0.8)	4 (1.0)	4 (1.0)	3 (0.7)
Somnolence	2 (0.5)	6 (1.5)	2 (0.5)	3 (0.7)
Nasal congestion	1 (0.3)	1 (0.3)	8 (2.0)	2 (0.5)
Rhinorrhea	1 (0.3)	2 (0.5)	7 (1.7)	0
Nasal mucosal disorder	0	1 (0.3)	3 (0.7)	5 (1.2)
Upper-airway cough syndrome	4 (1.0)	2 (0.5)	2 (0.5)	1 (0.2)
Upper respiratory tract infection	0	0	4 (1.0)	1 (0.2)

the statistical penalty for multiple comparisons and the high randomization ratio of active drug to placebo, which historically inflates placebo response rates.[26–29] Clear and statistically significant separations between zavegepant nasal spray and placebo were achieved at 2 h postdose for pain freedom and freedom from the MBS, and there were nominal indications for a rapid onset of action, including the results for pain relief at 60 min and return to normal function at 30 min. The results of a fully powered Phase 3 clinical trial are needed to determine if zavegepant nasal spray delivers on the possibility of rapid onset of action suggested by the 30-min T_{max}, as well as on the apparent long duration of action suggested by positive results on the sustained pain freedom and sustained pain relief endpoints from 2 to 24 h and 2 to 48 h postdose.

The 5, 10, and 20 mg doses of zavegepant nasal spray were well tolerated and demonstrated a favorable safety profile. Events of dysgeusia, and AEs such as nausea, nasal discomfort, throat irritation, nasal edema, and nasal congestion, were mostly mild and resolved without intervention.

This study has strengths and limitations. Strengths include being the first investigation of an anti-CGRP treatment delivered in intranasal form and enrollment of a large trial population that represents the general migraine population. Limitations include the single-attack design, which is required for regulatory review but prevents evaluation of longer-term tolerability and safety and provides no information about the consistency of zavegepant's treatment effects over time. The use of an active comparator would have enabled a comparison of efficacy relative to currently available treatments.

CONCLUSION

Zavegepant nasal spray, in single doses of 10 or 20 mg, was effective for the acute treatment of migraine, with a favorable safety profile. Additional research is needed to delineate onset of action and benefit to patients who are not able to take oral medications due to nausea or vomiting.

AUTHOR CONTRIBUTIONS

Study concept and design: Robert Croop, Jennifer Madonia, David A. Stock, Alexandra Thiry, Micaela Forshaw, Vladimir Coric, Richard B. Lipton. *Acquisition of data*: Robert Croop, Jennifer Madonia, David A. Stock, Alexandra Thiry, Micaela Forshaw, Abigail Murphy, Vladimir Coric. *Analysis and interpretation of data*: Robert Croop, Jennifer Madonia, David A. Stock, Alexandra Thiry, Micaela Forshaw, Vladimir Coric, Richard B. Lipton. *Drafting of the manuscript*: Robert Croop, Jennifer Madonia, David A. Stock, Alexandra Thiry, Micaela Forshaw, Abigail Murphy, Vladimir Coric, Richard B. Lipton. *Revising it for intellectual content*: Robert Croop, Jennifer Madonia, David A. Stock, Alexandra Thiry, Micaela Forshaw, Abigail Murphy, Vladimir Coric, Richard B. Lipton. *Final approval of the completed manuscript*: Robert Croop, Jennifer Madonia, David A. Stock, Alexandra Thiry, Micaela Forshaw, Abigail Murphy, Vladimir Coric, Richard B. Lipton.

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CONFLICT OF INTEREST

Robert Croop, MD, is employed by and holds stock/stock options in Biohaven Pharmaceuticals. Jennifer Madonia, MS, PA-C, is employed by and holds stock/stock options in Biohaven Pharmaceuticals. Alexandra Thiry, PhD, is employed by and holds stock/stock options in Biohaven Pharmaceuticals. Micaela Forshaw, MPH, is employed by and holds stock/stock options in Biohaven Pharmaceuticals. David A. Stock, PhD, is employed by and holds stock/stock options in Biohaven Pharmaceuticals. Abigail Murphy, BA, is employed by and holds stock/stock options in Biohaven Pharmaceuticals. Vladimir Coric, MD, is employed by and holds stock/stock options in Biohaven Pharmaceuticals. Richard B. Lipton, MD, serves on the editorial board of *Neurology and Cephalalgia* and as senior advisor to *Headache* but is not paid for his roles on these journals. He has received research support from the NIH. He also receives support from the National Headache Foundation. He receives research grants from Allergan/AbbVie, Amgen, Dr. Reddy's Laboratories, and Novartis. He has reviewed for the NIA and NINDS and serves as consultant, advisory board member, or has received honoraria from Allergan/AbbVie, Amgen, Biohaven, Dr. Reddy's Laboratories, electroCore, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Teva, and Vedanta. He receives royalties from *Wolff's Headache* (8th edition, Oxford University Press, 2009) and Informa. He holds stock options in Biohaven Pharmaceuticals and Manistee.

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