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ADISINSIGHT REPORT

Zavegepant: First Approval

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Abstract
Zavegepant is a third generation, small-molecule, calcitonin gene-related peptide (CGRP) receptor antagonist being developed by Pfizer, under a license from Bristol-Myers Squibb, for the prevention and treatment of chronic and episodic migraine. In March 2023, zavegepant nasal spray (ZAVZPRET™) received its first approval in the USA for the acute treatment of migraine with or without aura in adults. Clinical development of an oral formulation of zavegepant is currently underway. This article summarizes the milestones in the development of zavegepant leading to this first approval for the acute treatment of migraine with or without aura in adults.

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Zavegepant: Key Points

A CGRP receptor antagonist being developed by Pfizer, under a license from Bristol-Myers Squibb, for the prevention and treatment of chronic and episodic migraine.

Received its first approval on 9 March 2023 in the USA as a nasal spray formulation (ZAVZPRET™).

Approved for the acute treatment of migraine with or without aura in adults.

1 Introduction

Migraine is a common neurobiological disorder affecting over one billion individuals globally in 2016 [1, 2]. It is usually characterized by recurrent, moderate to severe attacks of pulsating, unilateral headache that last for 4–72 h and are accompanied by nausea, vomiting, photophobia and phonophobia [2, 3]. Release of the potent vasodilatory neuropeptide calcitonin gene-related peptide (CGRP) in the trigeminovascular system is believed to be crucial for migraine generation [2, 4]. This provided the rationale for developing CGRP-targeted therapies for the treatment of migraine, including anti-CGRP monoclonal antibodies and small molecule CGRP receptor antagonists (gepants) [2, 4].

Zavegepant is a third generation, small-molecule, CGRP receptor antagonist being developed by Pfizer, under a license from Bristol-Myers Squibb. On 9 March 2023 [5], zavegepant nasal spray (ZAVZPRET™) received its first approval in the USA for the acute treatment of migraine with or without aura in adults [6]. The recommended dose of zavegepant is 10 mg given as a single spray in one nostril, as needed. Zavegepant nasal spray is administered with a unit-dose nasal spray device, which delivers a single spray containing 10 mg zavegepant. The maximum zavegepant dose that can be administered over a 24-h period is 10 mg (one spray). The safety of treating more than 8 migraines with zavegepant over a 30-day period has not been established [6]. Clinical development of an oral formulation of zavegepant is currently underway [7].

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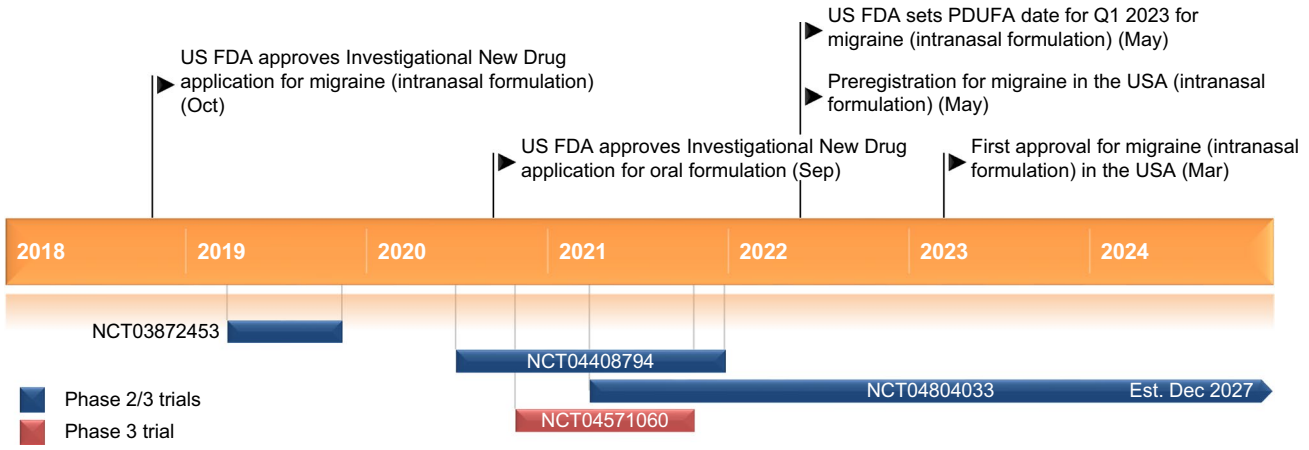


Key milestones in the development of zavegepant in the treatment of migraine. *PDUFA* Prescription Drug User Fee Act

1.1 Company Agreements

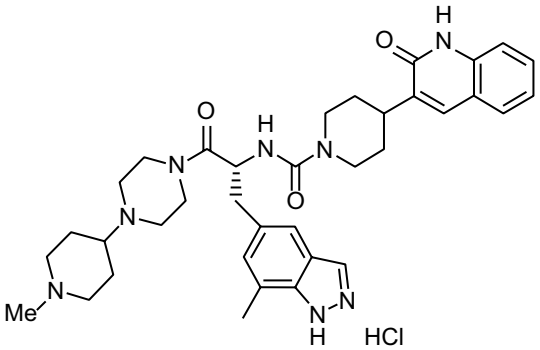
In July 2016, Biohaven Pharmaceutical Holding Company entered into an exclusive, worldwide license agreement with Bristol-Myers Squibb (BMS) for the development and commercialisation of zavegepant and rimegepant, as well as other CGRP-related intellectual property [8, 9]. In March 2018, Biohaven restructured the agreement with BMS, which permitted Biohaven to potentially license zavegepant or rimegepant to a company with a CGRP antibody program. The license agreement continued to provide Biohaven with exclusive global development and commercialisation rights to zavegepant, rimegepant and related CGRP molecules, as well as related know-how and intellectual property. Biohaven's obligations to make development and commercial milestone payments to BMS remain unchanged [10]. In November 2020, Biohaven Pharmaceutical Holding Company entered into a further amendment of the BMS agreement. Under the November 2020 BMS Amendment, certain exclusivity provisions under the BMS Agreement were waived, permitting the company to develop certain CGRP compounds licensed by Biohaven Pharmaceutical Holding Company from Heptares Therapeutics Limited [9].

In November 2021, Biohaven Pharmaceuticals and Pfizer entered into a collaboration and license agreement and related sublicense agreement. Under this agreement, Biohaven Pharmaceuticals was to continue to lead research and development for zavegepant and rimegepant, while Pfizer acquired the rights to commercialize zavegepant and rimegepant outside of the USA [11]. In January 2022, Biohaven Pharmaceutical and Pfizer announced the completion of the collaboration transaction [12]. In October 2022, Pfizer completed the acquisition of Biohaven Pharmaceutical Holding Company. The acquisition brought to Pfizer a portfolio of promising CGRP receptor antagonists including zavegepant and rimegepant [13].

2 Scientific Summary

2.1 Pharmacodynamics

Zavegepant is a highly potent, selective, competitive CGRP receptor antagonist that displays excellent aqueous solubility (allowing for nasal delivery) and oxidative stability [14]. In vitro, zavegepant displayed > 10,000-fold selectivity for CGRP over adrenomedullin receptors 1 and 2, calcitonin, and amylin receptors 1 and 3. Zavegepant exhibited potent inhibition [inhibitor constant (Ki) 23 pM] of CGRP binding to human CGRP receptor expressed in cell membranes and demonstrated potent and full reversal of CGRP-induced dilation of ex vivo human intracranial arteries [half maximal effective concentration (EC_{50}) 880 pM]. Zavegepant also displayed good intranasal bioavailability in rabbits, with



Chemical structure of zavegepant

peak plasma concentrations (C_{max}) reached within 15–20 mins [14].

In two phase 1, randomized, double-blind, single and multiple ascending dose studies in adults, intranasal zavegepant at a dose up to four times the recommended daily dose did not prolong the corrected QT interval and had no clinically relevant effect on other electrocardiogram parameters [6, 15]. Single doses of zavegepant ≥ 10 mg in these studies produced an average peak plasma drug concentration associated with ≥ 90% inhibition of CGRP signalling [16].

2.2 Pharmacokinetics

Zavegepant administered as a nasal spray is absorbed rapidly, with peak plasma concentration reached at ≈ 30 mins after a single 10 mg dose [6, 16]. The absolute bioavailability of intranasal zavegepant is ≈ 5% [6, 17]. After single dose administration, the pharmacokinetics of zavegepant nasal spray were slightly less than dose proportional up to a dose of 40 mg (approximately four times the recommended 10 dose) [6, 16]. There was no evidence of zavegepant accumulation after once daily dosing for 14 days [6]. The plasma protein binding of zavegepant is ≈ 90% and the mean apparent volume of distribution of intranasal zavegepant is ≈ 1774 L [6].

In vitro zavegepant is largely metabolized by CYP3A4 and to a lesser extent by CYP2D6 [6]. After a single intravenous dose of radiolabelled zavegepant 5 mg, unchanged zavegepant was the most prevalent (≈ 90%) circulating component in the human plasma and no major (> 10%) metabolites of zavegepant were detected [6, 18]. Zavegepant is primarily eliminated by biliary/faecal excretion and to a minor extent by renal excretion. After a single intravenous dose of radiolabelled zavegepant 5 mg, approximately 80% and 11% of the dose was recovered unchanged in the faeces and urine, respectively [6, 18]. After a single 10 mg dose of the nasal spray, the effective half-life of zavegepant is 6.55 h. The mean apparent clearance of intranasal zavegepant is 266 L/h [6].

Age, sex, race, ethnicity, body weight [6, 17] and moderate hepatic impairment (Child-Pugh B) [6, 19] do not affect the pharmacokinetics of zavegepant to a clinically significant extent. The effect of severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of zavegepant has not been assessed [6]. As renal excretion plays a minor role in the clearance of zavegepant, mild or moderate renal impairment [estimated creatinine clearance (CLcr) ≥ 30 mL/min] is not expected to have a clinically significant effect on the pharmacokinetics of zavegepant [6, 17]. In patients with CL_{cr} of 15–29 mL/min, accumulation of uremic solutes may inhibit OATP transporters, resulting in increased exposure to zavegepant. Zavegepant pharmacokinetics have not been assessed in patients with CL_{cr} < 15 mL/min [6].

Zavegepant is a substrate of the organic anion transporting polypeptide 1B3 (OATP1B3) and sodium taurocholate co-transporting polypeptide (NTCP) transporters in vitro [6]. Coadministration of zavegepant with inhibitors of OATP1B3 or NTCP transporters (e.g. rifampin, an OATP1B3 and NTCP inhibitor and a strong CYP3A inducer [20]) may significantly increase zavegepant exposure, while coadministration with inducers of OATP1B3 and NTCP transporters may decrease zavegepant exposure [6]. Therefore, concomitant use of zavegepant with inhibitors or inducers of OATP1B3 and NTCP transporters should be avoided [6]. Zavegepant is also a substrate of P-gp, MATE1, and MATE2-K transporters within in vitro studies; however, given the minor contribution of renal excretion in the clearance of zavegepant, coadministration of zavegepant with these transporters is not expected to affect the pharmacokinetics of zavegepant to a clinically significant extent. Zavegepant is not a substrate for BCRP, OATP1B1, OAT1, OAT3, OCT2, BSEP, MRP2, MRP3, and MRP4, and not an inhibitor of P-gp, BCRP, OAT1, OAT3, OATP1B1, and OATP1B3 within in vitro studies. Zavegepant is an inhibitor of OCT2, MATE1, and MATE2-K, but at clinically relevant concentrations, no drug interactions are expected between zavegepant and inhibitors of these transporters [6].

Within in vitro studies, zavegepant is a substrate of CYP3A4 and to a lesser extent CYP2D6 [6]. At clinically relevant concentrations, zavegepant is not an inducer of CYP1A2, 2B6, or 3A4, or an inhibitor of CYP1A2, CYP2C9, 2C19, 2B6, 2D6, 2C8, or 3A4 [6]. Coadministration of a single dose of zavegepant with a strong CYP3A4 and P-gp inhibitor (itraconazole) at steady state did not affect the pharmacokinetics of zavegepant to a clinically significant extent [6, 21].

Although the effect of coadministered intranasal decongestants on the pharmacokinetics of zavegepant has not been evaluated, concomitant use of these agents may decrease systemic exposure of zavegepant and potentially reduce the efficacy of zavegepant [6]. There were no significant pharmacokinetic interactions between coadministered zavegepant and oral contraceptives (ethinyl oestradiol) [6, 22] or sumatriptan [6, 23].

Features and properties of zavegepant

Alternative names	BHV 3500; BMS-742413; BMS-742413-03; Vazegepant; Vazegepant - Pfizer; Zavegepant hydrochloride; ZAVZPRET
Class	Anti-infectives; antiallergics; antimigraines; indazoles; piperazines; piperidines; quinolines; small molecules
Mechanism of action	CGRP receptor antagonist
Route of administration	Intranasal, oral
Pharmacodynamics	Highly potent, selective, competitive CGRP receptor antagonist
	Demonstrated potent and full reversal of CGRP-induced dilation of ex vivo human intracranial arteries
	Does not prolong the corrected QT interval or have a clinically relevant effect on other ECG parameters
	Single doses of ≥ 10 mg produced an average C_{max} associated with ≥ 90% inhibition of CGRP signalling
Pharmacokinetics (after an intranasal 10 mg dose)	C_{max} reached at ≈ 30 mins after a single dose; absolute bioavailability ≈ 5%;
	Mean apparent volume of distribution ≈ 1774 L
	Effective half-life 6.55 h; mean apparent clearance 266 L/h
Adverse events (after a single dose)	
Most frequent	Dysgeusia, nausea, nasal discomfort, vomiting
Rare	Hypersensitivity, including facial swelling and urticaria
ATC codes	
WHO ATC code	J05A-X (other antivirals); N02C (antimigraine preparations); R03 (drugs for obstructive airway diseases)
EphMRA ATC code	J5 (antivirals for systemic use); N2C (anti-migraine preparations); R3 (anti-asthma and COPD products)
Chemical name	(R)-N(3-(7-methyl-1H-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl) piperazin-1-yl)-1-oxopropan-2-yl)4-(2-oxo-1,2-dihydroquinolin-3-yl) piperidine-1-carboxamide hydrochloride

2.3 Therapeutic Trials

2.3.1 Phase 3 Study

Zavegepant 10 mg nasal spray was effective in the acute treatment of migraine in adults participating in a randomized, double-blind, multicentre, placebo-controlled, phase 3 study (NCT04571060) [24]. Eligibility criteria included adults 18 years and older with two to eight migraine attacks of moderate or severe intensity per month, ≥ 1-year history of migraine with or without aura [according to the criteria of the International Classification of Headache Disorders, 3rd edition (ICHD 3)], migraine onset before age 50 years, and < 15 days per month with migraine or a non-migraine headache within 3 months before screening. Participants were randomized to zavegepant 10 mg nasal spray ($n = 703$) or matching placebo ($n = 702$) and they self-treated a single migraine attack of moderate to severe pain intensity. The coprimary endpoints were freedom from pain (score of 0 on a four-point scale) and freedom from the most bothersome symptom (score of 0 on a binary scale) associated with migraine (selected from phonophobia, photophobia or nausea) at 2 h after the first dose [24].

The efficacy analysis set included 1269 participants, 623 in the zavegepant and 646 in the placebo group [24]. At baseline, the mean age of participants was 40.8 years and 65.8% had a history of migraine without aura as their primary migraine type. Participants had a mean of 4.7 moderate or severe migraine attacks per month and their untreated attacks lasted a mean of 30.8 h. The most commonly occurring most bothersome symptom was photophobia (historically 60.4% and for treated attacks 55.3% of patients) [24], and 13.4% of patients were taking preventive medications for migraine [6].

At 2 h after the first treatment dose, significantly more patients in the zavegepant group than in the placebo group had pain freedom [24% vs 15%; risk difference (RD) 8.8%; 95% CI 4.5–13.1; $p < 0.0001$] and freedom from the most bothersome symptom (40% vs 31%; RD 8.7%; 95% CI 3.4–13.9; $p = 0.0012$) [coprimary endpoints]. In addition, significantly more patients taking zavegepant than placebo had pain relief at 15 mins (15.9% vs 8.0%), 30 mins (30.5% vs 20.3%), 1 h (43.3% vs 37.3%) and 2 h (58.7% vs 49.7%) post dose (all $p < 0.03$) and sustained pain freedom from 2 to 48 h (12.4% vs 8.7%; $p = 0.013$). Significantly more zavegepant than placebo recipients also reported a return to normal function at 30 mins (10.5% vs

Key clinical trials of zavegepant sponsored by Biohaven Pharmaceuticals

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Zavegepant, placebo	Migraine	3	Completed	USA	NCT04571060; BHV3500-301
Zavegepant, placebo	Migraine	2/3	Completed	USA	NCT03872453; BHV3500-201
Zavegepant	Migraine	2/3	Completed	USA	NCT04408794; BHV3500-202
Zavegepant, placebo	Migraine	2/3	Recruiting	USA	NCT04804033; BHV3500-302

6.1%), 1 h (20.2% vs 15.5%) and 2 h (36% vs 26%) post dose (all $p < 0.05$) [24].

2.3.2 Phase 2/3 Study

Single-dose zavegepant 10 or 20 mg was effective for the acute treatment of migraine in adults participating in a randomized, double-blind, placebo-controlled, dose-ranging, phase 2/3 study (NCT03872453) [25]. Eligibility criteria included adults 18 years and older with a ≥ 1-year history of migraine (with or without aura) consistent with ICHD 3 criteria, migraine onset before age 50 years, migraine attacks lasting about 4 to 72 h if untreated, no more than 8 migraine attacks of moderate or severe intensity per month within the last 3 months, ≥ 2 migraine attacks of moderate or severe intensity in each of the 3 months prior to screening and throughout screening, and < 15 days with headaches (migraine or nonmigraine) per month in each of the 3 months prior to screening and throughout screening. Participants were randomized to zavegepant 5 mg ($n = 418$), 10 mg ($n = 417$) or 20 mg ($n = 418$) or placebo ($n = 420$) and they self-treated a single migraine attack of moderate or severe pain intensity. Coprimary endpoints were freedom from pain and freedom from most bothersome symptoms at 2 h post dose. To correct for multiple testing, the coprimary endpoints for each dose group were tested against placebo at an alpha level of 0.0167, and the same alpha level was used to test secondary endpoints in a hierarchical manner [25].

The efficacy population included 1581 participants taking zavegepant 5 mg ($n = 387$), 10 mg ($n = 391$), 20 mg ($n = 402$) or placebo ($n = 401$). At baseline, the mean age of participants was 40.8 years and 13.6% of patients were taking preventive medications for migraine. At 2 h post dose, significantly more patients in the zavegepant 10 mg and 20 mg groups had freedom from pain (22.5% and 23.1% vs 15.5%; $p = 0.0113$ and $p = 0.0055$, respectively) and freedom from most bothersome symptoms (41.9% and 42.5% vs 33.7%; $p = 0.0155$ and $p = 0.0094$) than patients in the placebo group. Zavegepant 5 mg and placebo groups did not differ significantly in terms of freedom from pain (19.6% vs 15.5%) or freedom from the most bothersome symptoms (39.0% vs 33.7%). There was no significant difference between the zavegepant 5, 10 or 20 mg and placebo groups in the percentage of patients with pain relief at 2 h post dose (57.9%, 60.6% and 61.2% vs 53.6%; first secondary endpoint tested) [25].

2.4 Adverse Events

Pooled data from the phase 3 (NCT04571060) and phase 2/3 (NCT03872453) pivotal studies showed that zavegepant 10 mg (approved dose) had a favourable safety profile for the acute treatment of migraine in adults [6]. Data were pooled from 1023 patients taking zavegepant and 1056 patients taking placebo in the two studies. The most common adverse reactions occurring in ≥ 2% of patients treated with zavegepant and at a frequency greater than placebo were taste disorders (including dysgeusia and ageusia; 18% vs 4% with placebo), nausea (4% vs 1%), nasal discomfort (3% vs 1%) and vomiting (2% vs < 1%). Less than 1% of patients treated with zavegepant had hypersensitivity reactions, including facial swelling and urticaria [6].

Results from the individual studies were similar to those in the pooled analysis. The most common (incidence ≥ 2% and more common than with placebo) treatment-emergent adverse events (AEs) with zavegepant 10 mg in the phase 3 study were dysgeusia (21% vs 5% with placebo), nasal discomfort (4% vs 1%) and nausea (3% vs 1%) [24] and in the phase 2/3 study were dysgeusia (13% vs 3%) and nausea (4% vs 0.5%) [25].

Zavegepant 10 mg also had a favourable tolerability profile during longer-term treatment in a 1-year, phase 2/3 open-label safety study (NCT04408794) [26]. The study enrolled adults (aged ≥ 18 years) with a history of two to eight moderate to severe migraine attacks per month. Participants ($n = 603$ evaluable) self-administered a single dose of zavegepant 10 mg nasal spray per day as needed to treat migraine attacks of any severity up to eight times per month for 52 weeks. At baseline, participants had a mean of 5 migraine attacks per month and 18.1% used preventive medication for migraine. Over the 52-week treatment period, participants used a mean of 3.1 zavegepant doses

per month. The most common (incidence ≥ 5%) treatment-emergent AEs with zavegepant were dysgeusia (39.1%), nasal discomfort (10.3%), COVID-19 (7.5%), nausea (6.1%), nasal congestion (5.5%), throat irritation (5.5%) and back pain (5.3%). Most AEs with zavegepant were mild or moderate in severity. A total of 6.8% of patients discontinued zavegepant because of AEs, with 1.5% of patients discontinuing because of dysgeusia. Serious AEs occurred in seven patients, none of which were considered treatment related. Aminotransferase increases of more than three times the upper limit of normal (ULN) were reported in 2.6% of patients, none of whom had concurrent elevations in bilirubin of more than two times the ULN [26].

2.5 Ongoing Clinical Trials

A 12-week, randomized, double-blind, placebo-controlled phase 2/3 study (NCT04804033) is recruiting ≈ 1440 adults to assess the efficacy of oral zavegepant versus placebo as a preventive treatment for migraine. The primary outcome measure is the number of migraine days per month over the 12-week double-blind treatment period.

3 Current Status

Zavegepant received its first approval on 9 March 2023 in the USA [5] for the acute treatment of migraine with or without aura in adults [6].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-023-01885-6.

Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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