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ORIGINAL RESEARCH

Safety of Rimegepant in Adults with Migraine and Cardiovascular Risk Factors: Analysis of a Multicenter, Long-Term, Open-Label Study

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ABSTRACT

***Introduction*:** Cardiovascular (CV) risk factors can limit treatment options for migraine. Rimegepant is an orally administered small-molecule calcitonin gene-related peptide receptor antagonist that does not induce vasoconstriction. The aim of these post hoc subgroup analyses was to assess the safety of rimegepant according to CV risk.

***Methods*:** In a multicenter, long-term, open-label, phase II/III safety study, participants with a history of 2–14 migraine attacks per month of moderate or severe pain intensity self-administered rimegepant 75 mg, orally, to treat migraine up to once daily for up to 52 weeks. Uncontrolled, unstable, or recently diagnosed CV disease was part of the exclusion criteria. Safety was assessed across subgroups according to number of CV risk factors (0, 1, or ≥ 2) and Framingham Risk Score (< 10% or ≥ 10%).

***Results*:** Of 1800 treated participants, 28.8% had one CV risk factor and 12.1% had ≥ 2 CV risk factors; 7.0% had Framingham Risk Score ≥ 10%. Across the subgroups with 0, 1, and ≥ 2 CV risk factors and Framingham Risk Score < 10% and ≥ 10%, respectively, proportions of participants reporting adverse events (AEs; 59.6%, 61.4%, 62.2%, 59.9%, 67.5%) and serious AEs (2.7%, 2.5%, 2.3%, 2.6%, 2.4%) were consistent, and AEs leading to study drug discontinuation were low (1.9%, 3.1%, 5.5%, 2.5%, 4.8%).

***Conclusions*:** Rimegepant showed favorable safety and tolerability in adults with migraine and CV risk factors, including those with moderate to high CV risk.

***Trial Registration*:** ClinicalTrials.gov NCT03266588.

PLAIN LANGUAGE SUMMARY

Older patients with migraine often have cardiovascular (CV) disease – such as a prior heart attack – or risk factors for CV disease. Examples of CV risk factors are high blood pressure, diabetes, smoking, high cholesterol, and a family history of heart disease. The choice

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of treatments for migraine is limited by safety concerns for patients who have CV risk factors. Newer treatments for migraine – including rimegepant – work differently than older drugs, by targeting calcitonin gene-related peptide. The safety of rimegepant for patients with migraine and CV risk factors can be studied in a clinical trial. In a long-term trial, patients with migraine took rimegepant tablets to treat migraine attacks, up to once a day, for up to 52 weeks. Some of the patients in the study had CV risk factors. We analyzed the results of the study by grouping the patients based on how many CV risk factors they had. We found that the side effects of rimegepant were similar across the groups. This showed that rimegepant was safe and well tolerated in adults with migraine and CV risk factors.

Keywords: Calcitonin gene-related peptide receptor antagonists; Cardiovascular; Migraine; Rimegepant; Risk factors; Safety

Key Summary Points

Why carry out the study?
Treatment options for migraine can be limited for patients with cardiovascular (CV) risk factors.
Rimegepant is an orally administered small-molecule calcitonin gene-related peptide receptor antagonist that is used for acute and preventive treatment of migraine.
Data from a long-term, open-label safety study were used to assess safety of rimegepant across subgroups according to number of CV risk factors (0, 1, or ≥ 2) and Framingham Risk Score (< 10% or ≥ 10%).
What was learned from the study?
Across the subgroups based on CV risk factors and Framingham Risk Score, proportions of participants reporting adverse events and serious adverse events were consistent, and adverse events leading to study drug discontinuation were low.
Rimegepant, administered up to once daily and for up to 1 year, showed favorable safety and tolerability in adults with migraine with CV risk factors.

INTRODUCTION

Patients with migraine frequently have cardiovascular (CV) disease or CV risk factors. A study of US administrative data found that at least 20% of patients with migraine had ischemic heart disease, cerebrovascular disease, peripheral artery disease, uncontrolled hypertension, gastrointestinal ischemia, or other significant underlying CV disease; and an additional 25% of patients had ≥ 2 CV risk factors, such as hypertension, hyperlipidemia, diabetes, obesity, increased age, and smoking [1]. The role of migraine, and especially migraine with aura, as an independent risk factor for CV disease is the subject of ongoing research [2–5]. A meta-analysis demonstrated that migraine was associated with myocardial infarction (MI) and stroke, and migraine with aura was associated with an increased risk of overall CV mortality [3]. CV safety is of paramount importance to patients with migraine and their clinicians, and migraine treatment needs to be individualized accounting for the patient's migraine symptoms as well as any CV condition or CV risk factors, other comorbidities, and concomitant medications.

Treatment options for people with migraine can be limited by the presence of CV disease or CV risk factors, particularly with advancing age. Triptans and ergot derivatives are contraindicated in patients with migraine and certain CV conditions, and use requires caution in those with CV risk factors [6, 7]. Observational studies

have reported CV risk for ergot derivatives [8]. The CV risk for triptans is the subject of ongoing research, but the risk appears low in clinical practice [8, 9]. Some of the more recently developed treatments for migraine target calcitonin gene-related peptide (CGRP) [10]. CGRP and its receptors are found in the central and peripheral nervous system, but also in blood vessels and the heart [11]. The available data support the CV safety of CGRP antagonists for patients with migraine [12–20], but longer-term data specific to each medication are needed.

Rimegepant is an orally administered small-molecule CGRP receptor antagonist that does not induce vasoconstriction [14, 21]. Rimegepant is indicated for the acute treatment of migraine and the preventive treatment of episodic migraine in the United States, European Union, and United Kingdom. The efficacy and safety of rimegepant for the acute treatment of migraine [22–25] and the preventive treatment of episodic migraine [26] have been established in randomized controlled trials.

The safety and tolerability of rimegepant during longer-term treatment (up to 52 weeks) in participants with migraine was investigated in a multicenter open-label study [27, 28]. The aim of the current subgroup analyses of that study was to assess the safety of rimegepant according to CV risk.

METHODS

Study Design

This prospective, phase II/III, 1-year open-label safety study of rimegepant in the acute treatment of migraine (Study 201, NCT03266588) was conducted across 103 sites in the United States between August 30, 2017, and July 15, 2019. The study comprised a screening visit and 30-day observation period before participants were provided with study medication and commenced a long-term treatment period of up to 52 weeks. There was a final follow-up visit 14 ± 2 days after the end of treatment. Full methodology for the study has been published previously [28].

Ethical Approval

The study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation, Good Laboratory Practice, the Declaration of Helsinki, and all applicable regulations. All participants provided written informed consent prior to participation in the study. The protocol was approved by Institutional Review Boards (Advarra IRB [IRB00000971], Schulman Associates IRB [IRB00007642; acquired by Advarra], and Biomedical Research Alliance New York [BRANY] IRB [IRB00000080]) before the start of the study.

Participants

Eligible for the study were males and females aged 18 years or older, with at least a 1-year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition, beta version [29]. Migraine onset had to be prior to age 50 years, and participants had to have 2–14 migraine attacks of moderate or severe pain intensity per month within the last 3 months prior to screening, with average duration of untreated attacks 4–72 h, and be able to distinguish migraine attacks from tension or cluster headaches. Key exclusion criteria were a history of basilar or hemiplegic migraine; current evidence of uncontrolled, unstable, or recently diagnosed CV disease (such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia); MI, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke or transient ischemic attack during the 6 months prior to screening; uncontrolled hypertension (>150 mmHg systolic or 100 mmHg diastolic after 10 min of rest) or uncontrolled diabetes (hypertension and/or diabetes that was stable for 3 months prior to screening was permitted); body mass index ≥ 30 kg/m^2; glycated hemoglobin (HbA1c) ≥ 6.5%; and history of human immunodeficiency virus (HIV) disease. Individuals with contraindications for use of triptans could be included provided they

met all other study entry criteria. Concomitant preventive treatments for migraine were permitted if the dose had been stable at least 2 months prior to the baseline visit and the regimen was not likely to change during the study.

Participants were assigned to 1 of 3 sequentially enrolled, nonrandomized treatment groups, as described below.

Intervention

The first group (PRN [as needed] 2–8) comprised participants with a history of 2–8 moderate or severe migraine attacks/month who were assigned to take rimegepant 75 mg as needed up to once daily to treat migraine attacks of any severity, for up to 52 weeks. Participants in the second group (PRN 9–14), with a history of 9–14 moderate or severe migraine attacks/month, were assigned to take rimegepant 75 mg as needed up to once daily to treat migraine attacks of any severity, for up to 52 weeks. Participants in the third group (scheduled EOD [every other day] + PRN) had a history of 4–14 moderate or severe migraine attacks/month and were assigned to take rimegepant 75 mg every other day, irrespective of migraine attacks, as well as when needed up to once daily on other days to acutely treat migraine attacks of any severity, for up to 12 weeks. For all three enrolment groups, the maximum daily dose of rimegepant was 75 mg (1 oral tablet). Rimegepant 75-mg tablets for oral self-administration were provided by Biohaven Pharmaceuticals.

Safety Outcomes

Primary safety endpoints included the frequency and severity of adverse events (AEs), serious AEs, AEs leading to study drug discontinuation, and clinically significant laboratory abnormalities. Serious AEs were reported by investigators, based on pre-specified criteria, and were not subject to independent adjudication. On-treatment AEs were those with AE start dates in the on-treatment safety analysis period, from the time after the first dose of rimegepant through the last dose of rimegepant (plus 7 days). Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 was used. For laboratory tests at baseline, week 4, week 24, and at the end of the study (week 12 or week 52) or end of treatment, participants were requested to fast for at least 8 h beforehand, if possible, whereas at other time points samples were not preceded by fasting.

Prespecified CV AEs were identified from Standardized MedDRA Queries (SMQs) based on narrow preferred terms: conditions associated with central nervous system hemorrhages and cerebrovascular accidents SMQ; ischemic central nervous system vascular conditions SMQ; ischemic colitis SMQ; ischemic heart disease SMQ, comprising MI SMQ and other ischemic heart disease SMQ; and embolic and thrombotic events, arterial SMQ, comprising peripheral arterial occlusive disease, peripheral arterial reocclusion, peripheral artery angioplasty, peripheral artery bypass, peripheral artery occlusion, peripheral artery stent insertion, and peripheral artery thrombosis.

Statistics

For the current post hoc subgroup analyses, participants receiving ≥ 1 dose of rimegepant were grouped according to the number of CV risk factors (0, 1 or ≥ 2) and Framingham 10-year risk of developing a CV condition (< 10% [low] or ≥ 10% [moderate or high]). CV risk factors were collected at screening and included uncontrolled hypertension, treatment for hypertension, history of diabetes, current smoker, treatment with a statin, and family history of coronary artery disease. Framingham Risk Score was based on age, sex, baseline systolic blood pressure, baseline total cholesterol, baseline high-density lipoprotein (HDL) cholesterol, treatment for hypertension, history of diabetes, and current smoker.

Table 1 Demographics and clinical characteristics of the study population, according to number of cardiovascular risk factors and Framingham Risk Score

	Number of CV risk factors			Framingham Risk Score		Overall[a]
	0 (*n* = 1065)	1 (*n* = 518)	≥ 2 (*n* = 217)	< 10% (*n* = 1673)	≥ 10% (*n* = 126)	(*N* = 1800)
Age, mean (SD), years	41.0 (11.66)	44.4 (12.38)	49.9 (10.97)	41.9 (11.63)	58.5 (7.44)	43.1 (12.15)
< 40 years, *n* (%)	512 (48.1)	201 (38.8)	46 (21.2)	758 (45.3)	0	759 (42.2)
≥ 40 years, *n* (%)	553 (51.9)	317 (61.2)	171 (78.8)	915 (54.7)	126 (100.0)	1041 (57.8)
< 65 years, *n* (%)	1041 (97.7)	491 (94.8)	202 (93.1)	1632 (97.5)	101 (80.2)	1734 (96.3)
≥ 65 years, *n* (%)	24 (2.3)	27 (5.2)	15 (6.9)	41 (2.5)	25 (19.8)	66 (3.7)
Female, *n* (%)	958 (90.0)	467 (90.2)	184 (84.8)	1542 (92.2)	66 (52.4)	1609 (89.4)
Male, *n* (%)	107 (10.0)	51 (9.8)	33 (15.2)	131 (7.8)	60 (47.6)	191 (10.6)
Race, *n* (%)						
White	870 (81.7)	431 (83.2)	174 (80.2)	1369 (81.8)	106 (84.1)	1475 (81.9)
Black or African American	150 (14.1)	62 (12.0)	38 (17.5)	232 (13.9)	17 (13.5)	250 (13.9)
American Indian or Alaska Native	6 (0.6)	4 (0.8)	0	10 (0.6)	0	10 (0.6)
Asian	20 (1.9)	11 (2.1)	1 (0.5)	31 (1.9)	1 (0.8)	32 (1.8)
Native Hawaiian or Other Pacific Islander	2 (0.2)	3 (0.6)	0	4 (0.2)	1 (0.8)	5 (0.3)
Multiple	17 (1.6)	7 (1.4)	4 (1.8)	27 (1.6)	1 (0.8)	28 (1.6)
Ethnicity, *n* (%)						
Hispanic or Latino	118 (11.1)	45 (8.7)	14 (6.5)	173 (10.3)	4 (3.2)	177 (9.8)
Not Hispanic or Latino	947 (88.9)	473 (91.3)	203 (93.5)	1500 (89.7)	122 (96.8)	1623 (90.2)
Body mass index, mean (SD), kg/m^2 [b]	28.73 (7.182)	29.36 (7.412)	32.75 (8.107)	29.24 (7.525)	31.32 (6.271)	29.40 (7.471)
Systolic blood pressure, mean (SD), mmHg	116.9 (12.21)	118.6 (12.66)	124.4 (12.89)	117.3 (12.27)	130.7 (10.81)	118.3 (12.64)
Total cholesterol, mean (SD), mg/dl[c]	186.1 (34.85)	192.7 (38.72)	191.4 (39.96)	187.2 (35.80)	207.1 (43.70)	188.6 (36.75)
HDL cholesterol, mean (SD), mg/dl[c]	58.1 (16.26)	56.9 (17.19)	51.9 (14.93)	57.6 (16.44)	49.3 (15.14)	57.0 (16.49)

Table 1 continued

	Number of CV risk factors			Framingham Risk Score		Overall[a]
	0 ($n = 1065$)	1 ($n = 518$)	≥ 2 ($n = 217$)	< 10% ($n = 1673$)	≥ 10% ($n = 126$)	($N = 1800$)
CV risk factors, *n* (%)						
Uncontrolled hypertension	0	0	2 (0.9)	0	2 (1.6)	2 (0.1)
Treatment for hypertension	0	81 (15.6)	130 (59.9)	155 (9.3)	56 (44.4)	211 (11.7)
History of diabetes	0	12 (2.3)	42 (19.4)	30 (1.8)	24 (19.0)	54 (3.0)
Current smoker	0	113 (21.8)	75 (34.6)	148 (8.8)	39 (31.0)	188 (10.4)
Treatment with a statin	0	43 (8.3)	107 (49.3)	104 (6.2)	46 (36.5)	150 (8.3)
Family history of coronary artery disease	0	269 (51.9)	156 (71.9)	382 (22.8)	42 (33.3)	425 (23.6)

CV Cardiovascular, *HDL* high-density lipoprotein, *SD* standard deviation

[a]Some of the data for the overall population were published previously [28]

[b]Sample size $n = 1061$, $n = 516$, $n = 217$, $n = 1667$, $n = 126$, and $N = 1794$ across the groups, respectively

[c]Sample size $n = 1065$, $n = 518$, $n = 216$, $n = 1673$, $n = 126$, and $N = 1799$ across the groups, respectively

RESULTS

Demographics and Clinical Characteristics

Of 1800 participants treated with ≥ 1 dose of rimegepant, 1033 were enrolled in the PRN 2–8 group, 481 were enrolled in the PRN 9–14 group, and 286 were enrolled in the scheduled EOD + PRN group. The mean age of the study population was 43.1 years and 89.4% were female (Table 1). Historically, the median number of moderate or severe migraine attacks per month was 6.0 overall and was as expected across the assigned enrolment groups (5.0, 10.0, and 6.0 across the three enrolment groups, respectively), and the primary migraine type was without aura (66.7%).

A small proportion of study participants had a history of CV disease, including 0.2% with a history of ischemic coronary artery disease and 1.9% with other significant underlying CV disease: Wolf–Parkinson–White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders (0.2%) or other arrhythmias (1.5%), stroke or transient ischemic attack (0.4%), peripheral vascular disease (0.2%), uncontrolled hypertension (0.1%), and ischemic bowel disease (0%).

Known CV risk factors included family history of coronary artery disease (23.6%), treatment for hypertension (11.7%), current smoker (10.4%), treatment with a statin (8.3%), and history of diabetes (3.0%). Of the 1800 participants, 59.2% ($n = 1065$) had no CV risk factors, 28.8% ($n = 518$) had one CV risk factor, and 12.1% ($n = 217$) had ≥ 2 CV risk factors. Overall, 7.0% of participants ($n = 126$) had a Framingham Risk Score ≥ 10% (Table 1).

Table 2 Exposure to rimegepant during 1-year study, according to number of cardiovascular risk factors and Framingham Risk Score

	Number of CV risk factors			Framingham Risk Score		Overall[a]
	0 ($n = 1065$)	1 ($n = 518$)	≥ 2 ($n = 217$)	< 10% ($n = 1673$)	≥ 10% ($n = 126$)	($N = 1800$)
Time on rimegepant, weeks						
Mean (SD)	33.8 (19.11)	33.4 (19.39)	35.0 (19.10)	33.6 (19.24)	36.7 (18.35)	33.9 (19.18)
Median	47.3	46.4	48.7	47.1	48.5	47.3
Minimum, maximum	0.1, 55.3	0.1, 54.9	0.4, 52.9	0.1, 55.3	0.3, 52.9	0.1, 55.3
Average rimegepant exposure, tablets per 4 weeks						
Mean (SD)	7.8 (4.74)	7.3 (4.38)	8.0 (4.66)	7.7 (4.58)	7.4 (5.26)	7.7 (4.63)
Median	6.4	6.3	6.8	6.5	6.0	6.5
Minimum, maximum	0.2, 27.6	0.3, 25.5	0.3, 24.2	0.2, 27.2	0.3, 27.6	0.2, 27.6
Participants taking ≥ 8 tablets, *n* (%)	411 (38.6)	198 (38.2)	89 (41.0)	659 (39.4)	39 (31.0)	698 (38.8)
Cumulative rimegepant exposure, tablets						
Mean (SD)	62.8 (48.91)	58.8 (45.11)	67.8 (52.97)	61.9 (47.54)	66.8 (58.93)	62.2 (48.42)
Median	50.0	47.0	52.0	49.0	54.0	50.0
Minimum, maximum	1.0, 359.0	1.0, 255.0	2.0, 314.0	1.0, 355.0	2.0, 359.0	1.0, 359.0

CV Cardiovascular, *SD* standard deviation

[a]Some of the data for the overall population were published previously [28]

Table 3 On-treatment adverse events during 1-year study, according to number of cardiovascular risk factors and Framingham Risk Score

	Number of CV risk factors			Framingham Risk Score		Overall[a]
	0 ($n=1065$)	1 ($n=518$)	≥2 ($n=217$)	<10% ($n=1673$)	≥10% ($n=126$)	($N=1800$)
Participants with any AE, *n* (%)						
AE	635 (59.6)	318 (61.4)	135 (62.2)	1002 (59.9)	85 (67.5)	1088 (60.4)
Mild AE	437 (41.0)	241 (46.5)	98 (45.2)	713 (42.6)	62 (49.2)	776 (43.1)
Moderate AE	373 (35.0)	186 (35.9)	83 (38.2)	592 (35.4)	50 (39.7)	642 (35.7)
Severe AE	48 (4.5)	19 (3.7)	12 (5.5)	75 (4.5)	4 (3.2)	79 (4.4)
Serious AE	29 (2.7)	13 (2.5)	5 (2.3)	44 (2.6)	3 (2.4)	47 (2.6)
AE related to study drug	217 (20.4)	108 (20.8)	35 (16.1)	331 (19.8)	29 (23.0)	360 (20.0)
Serious AE related to study drug	5 (0.5)	4 (0.8)	1 (0.5)	10 (0.6)	0	10 (0.6)
AE leading to study drug discontinuation	20 (1.9)	16 (3.1)	12 (5.5)	42 (2.5)	6 (4.8)	48 (2.7)
Participants with CV AE, *n* (%)[b]	1 (0.1)	0	3 (1.4)	2 (0.1)	2 (1.6)	4 (0.2)

AE adverse event, *CV* cardiovascular, *SMQ* Standardized MedDRA Query

[a]Some of the data for the overall population were published previously [28]

[b]Prespecified CV AEs were identified from SMQs based on narrow preferred terms: conditions associated with central nervous system hemorrhages and cerebrovascular accidents SMQ; ischemic central nervous system vascular conditions SMQ; ischemic colitis SMQ; ischemic heart disease SMQ, comprising myocardial infarction SMQ and other ischemic heart disease SMQ; and embolic and thrombotic events, arterial SMQ, comprising peripheral arterial occlusive disease, peripheral arterial reocclusion, peripheral artery angioplasty, peripheral artery bypass, peripheral artery occlusion, peripheral artery stent insertion, peripheral artery thrombosis

Rimegepant Exposure

Mean rimegepant exposure ranged from 7.3 to 8.0 doses per participant per month (4 weeks) across the subgroups (Table 2).

Adverse Events

During the year-long study, 60.4% of participants overall reported ≥1 AE (Table 3). The proportion of participants reporting AEs was consistent across subgroups: 59.6, 61.4 and 62.2% of participants in the 0, 1, and ≥2 CV risk factor subgroups, 59.9% of participants with Framingham Risk Score <10%, and 67.5% of participants with Framingham Risk Score ≥10%. The most common AE was upper respiratory tract infection, occurring in <10% of participants across all subgroups (Table 4). The majority of AEs were mild or moderate in intensity (Table 3). The proportion of participants reporting severe AEs was consistent across subgroups: 4.5, 3.7, and 5.5% of participants in the 0, 1, and ≥2 CV risk factor subgroups, 4.5% of participants with Framingham Risk Score <10%, and 3.2% of participants with Framingham Risk Score ≥10%.

There were no deaths during the study. The proportion of participants reporting serious AEs was consistently low across subgroups: 2.7, 2.5, and 2.3% of participants in the 0, 1, and ≥2 CV risk factor subgroups, 2.6% of participants with Framingham Risk Score <10%, and 2.4% of participants with Framingham Risk Score ≥10% (Table 3). In the overall

Table 4 Participants with on-treatment adverse events reported in ≥ 2% of participants in any subgroup during 1-year study, according to number of cardiovascular risk factors and Framingham Risk Score

	Number of CV risk factors			Framingham Risk Score		Overall[a]
	0 (*n* = 1065)	1 (*n* = 518)	≥ 2 (*n* = 217)	< 10% (*n* = 1673)	≥ 10% (*n* = 126)	(*N* = 1800)
Participants with preferred term, *n* (%)						
Upper respiratory tract infection	98 (9.2)	39 (7.5)	21 (9.7)	150 (9.0)	8 (6.3)	158 (8.8)
Nasopharyngitis	71 (6.7)	42 (8.1)	9 (4.1)	112 (6.7)	10 (7.9)	122 (6.8)
Sinusitis	58 (5.4)	28 (5.4)	6 (2.8)	89 (5.3)	2 (1.6)	92 (5.1)
Urinary tract infection	38 (3.6)	25 (4.8)	6 (2.8)	66 (3.9)	3 (2.4)	69 (3.8)
Influenza	27 (2.5)	25 (4.8)	7 (3.2)	51 (3.0)	8 (6.3)	59 (3.3)
Back pain	34 (3.2)	12 (2.3)	10 (4.6)	49 (2.9)	7 (5.6)	56 (3.1)
Bronchitis	17 (1.6)	25 (4.8)	11 (5.1)	46 (2.7)	7 (5.6)	53 (2.9)
Nausea	30 (2.8)	13 (2.5)	8 (3.7)	49 (2.9)	2 (1.6)	51 (2.8)
Dizziness	25 (2.3)	12 (2.3)	5 (2.3)	39 (2.3)	3 (2.4)	42 (2.3)
Arthralgia	20 (1.9)	9 (1.7)	7 (3.2)	26 (1.6)	10 (7.9)	36 (2.0)
Diarrhea	18 (1.7)	10 (1.9)	6 (2.8)	33 (2.0)	1 (0.8)	34 (1.9)
Constipation	11 (1.0)	12 (2.3)	6 (2.8)	26 (1.6)	3 (2.4)	29 (1.6)
Gastroenteritis viral	8 (0.8)	11 (2.1)	6 (2.8)	23 (1.4)	2 (1.6)	25 (1.4)
Rash	16 (1.5)	6 (1.2)	1 (0.5)	20 (1.2)	3 (2.4)	23 (1.3)
Neck pain	12 (1.1)	7 (1.4)	3 (1.4)	18 (1.1)	4 (3.2)	22 (1.2)
Nephrolithiasis	8 (0.8)	8 (1.5)	4 (1.8)	17 (1.0)	3 (2.4)	20 (1.1)
Ligament strain	8 (0.8)	6 (1.2)	6 (2.8)	18 (1.1)	2 (1.6)	20 (1.1)
Vertigo	12 (1.1)	5 (1.0)	3 (1.4)	16 (1.0)	4 (3.2)	20 (1.1)
Pain in extremity	10 (0.9)	3 (0.6)	5 (2.3)	16 (1.0)	2 (1.6)	18 (1.0)
Muscle strain	7 (0.7)	5 (1.0)	6 (2.8)	15 (0.9)	3 (2.4)	18 (1.0)
Contusion	3 (0.3)	8 (1.5)	5 (2.3)	13 (0.8)	3 (2.4)	16 (0.9)
Insomnia	6 (0.6)	7 (1.4)	3 (1.4)	13 (0.8)	3 (2.4)	16 (0.9)
Pneumonia	5 (0.5)	5 (1.0)	3 (1.4)	10 (0.6)	3 (2.4)	13 (0.7)
Viral infection	5 (0.5)	5 (1.0)	2 (0.9)	9 (0.5)	3 (2.4)	12 (0.7)
Toothache	4 (0.4)	6 (1.2)	2 (0.9)	9 (0.5)	3 (2.4)	12 (0.7)
Hyperlipidemia	2 (0.2)	1 (0.2)	2 (0.9)	2 (0.1)	3 (2.4)	5 (0.3)

All preferred terms reported in ≥ 2% of participants in any subgroup are shown, listed in descending order of frequency in the overall population

AE adverse event, *CV* cardiovascular

[a]Some of the data for the overall population were published previously [28]

population, serious AEs reported by > 1 participant included appendicitis ($n = 3$), osteoarthritis ($n = 3$), pulmonary embolism ($n = 3$), constipation ($n = 2$), pneumonia ($n = 2$), sepsis ($n = 2$), and three cases of accidental overdose of rimegepant (up to 1 extra tablet per day). CV events are described below.

The incidence of AEs leading to study drug discontinuation was low across all subgroups (Table 3), reported by 1.9, 3.1, and 5.5% of participants in the 0, 1, and ≥ 2 CV risk factor subgroups, 2.5% of participants with Framingham Risk Score < 10%, and 4.8% of participants with Framingham Risk Score ≥ 10%.

The incidence of hypertension AE was low across all subgroups: 0.8% ($n = 9$), 1.2% ($n = 6$), and 1.8% ($n = 4$) of participants in the 0, 1, and ≥ 2 CV risk factor subgroups, 1.0% ($n = 17$) of participants with Framingham Risk Score < 10%, and 1.6% ($n = 2$) of participants with Framingham Risk Score ≥ 10%.

Cardiovascular Adverse Events

There was no death or MI in any subgroup. There were a total of four prespecified CV AEs during the on-treatment period, including two serious AEs reported in four (0.2%) participants, including one participant each with angina pectoris, hemiparesis, hemiplegia, and ischemic colitis. Of the four CV AEs, one occurred in a participant in the subgroup with no CV risk factors, none were in the subgroup with one CV risk factor, and three occurred in the subgroup with ≥ 2 CV risk factors; two were in the subgroup with Framingham Risk Score < 10% and 2 were in the subgroup with Framingham Risk Score ≥ 10% (Table 3). The four CV AEs are described below.

Angina pectoris AE was reported in one participant in the PRN 2–8 group, with two baseline CV risk factors (treatment with a statin, treatment for hypertension) and a baseline Framingham Risk Score of 13.3%. The 53-year-old White male had hypercholesterolemia, and his medical history included angina pectoris that was ongoing at the time of enrolment in the study. Approximately 7 months after the first dose of rimegepant, and 2 days after a dose of rimegepant, the participant experienced worsening of angina pectoris (severe), which was treated with nitroglycerin (glyceryl trinitrate). The participant was discontinued from the study due to an AE of angina pectoris, which was assessed by the investigator as not being related to rimegepant.

Hemiparesis was reported in one participant in the PRN 2–8 group, with 0 baseline CV risk factors and a baseline Framingham Risk Score of 0.8%. The 30-year-old White female was taking several concomitant medications (trazodone, lithium, ethinylestradiol/norgestimate, ibuprofen, sertraline, and naproxen) and had a history of anaphylaxis from ziprasidone. Approximately 2 weeks after the first dose of rimegepant, and on the same day as a dose of rimegepant, the participant experienced lightheadedness and left-sided weakness, which were reported as AEs of dizziness (moderate) and hemiparesis (mild), respectively. Four days after the onset of the AEs of dizziness and hemiparesis, the participant took a dose of rimegepant, and the hemiparesis was considered resolved on that day; a final dose of rimegepant was taken 4 days later. The AEs were temporary and did not result in hospitalization; the hemiparesis was not treated with any medication. Rimegepant was permanently discontinued as a result of the AEs of dizziness and hemiparesis. The investigator assessed both AEs as unlikely to be related to rimegepant. During a subsequent psychiatric hospital admission for a serious AE of post-traumatic stress disorder (severe), the participant was found to have concealed extensive psychiatric history from the investigator at screening.

Hemiplegia was reported in one participant in the PRN 2–8 group, with three baseline CV risk factors (treatment with a statin, treatment for hypertension, current smoker) and a baseline Framingham Risk Score of 10.6%. The 46-year-old White female had a history of migraine with aura and was hospitalized (approximately 7 months after the first dose of rimegepant, and 9 days after a dose of rimegepant) for serious AEs of hemiplegia (moderate) and migraine with aura (moderate), with unilateral headache on the right side; a dose of rimegepant was taken on the same day,

Table 5 Participants with on-treatment grade 3 or 4 blood lipid test abnormalities during 1-year study, according to number of cardiovascular risk factors and Framingham Risk Score

	Number of CV risk factors			Framingham Risk Score		Overall
	0 (*n* = 1065)	1 (*n* = 518)	≥ 2 (*n* = 217)	< 10% (*n* = 1673)	≥ 10% (*n* = 126)	(*N* = 1800)
Total cholesterol (overall, regardless of fasting status)						
n with data	921	448	177	1435	110	1546
n (%) with abnormality grade 3 or 4	0	0	0	0	0	0
LDL cholesterol						
n with data	921	448	177	1435	110	1546
n (%) with abnormality grade 3 or 4	20 (2.2)	14 (3.1)	14 (7.9)	39 (2.7)	9 (8.2)	48 (3.1)
LDL cholesterol (fasting ≥ 8 h)						
n with data	491	229	93	749	64	813
n (%) with abnormality grade 3 or 4	14 (2.9)	8 (3.5)	5 (5.4)	24 (3.2)	3 (4.7)	27 (3.3)
LDL cholesterol (not fasting ≥ 8 h)						
n with data	530	268	105	844	58	903
n (%) with abnormality grade 3 or 4	7 (1.3)	6 (2.2)	10 (9.5)	17 (2.0)	6 (10.3)	23 (2.5)
Triglycerides (overall, regardless of fasting status)						
n with data	921	448	177	1435	110	1546
n (%) with abnormality grade 3 or 4	3 (0.3)	2 (0.4)	0	5 (0.3)	0	5 (0.3)
Triglycerides (fasting ≥ 8 h)						
n with data	491	229	93	749	64	813
n (%) with abnormality grade 3 or 4	1 (0.2)	1 (0.4)	0	2 (0.3)	0	2 (0.2)
Triglycerides (not fasting ≥ 8 h)						
n with data	531	268	104	844	58	903
n (%) with abnormality grade 3 or 4	2 (0.4)	1 (0.4)	0	3 (0.4)	0	3 (0.3)

Highest toxicity grade on treatment. Toxicity scale: common terminology criteria for adverse events (CTCAE) version 5.0; and division of AIDS (DAIDS) version 2.1 for LDL cholesterol. *n* with data are participants with non-missing data at an on-treatment visit. Because triglycerides and LDL cholesterol may be sensitive to the degree of fasting, these were each assessed as 3 separate laboratory tests according to 8-h fasting status: (1) overall, regardless of fasting status; (2) fasting ≥ 8 h; and (3) not fasting ≥ 8 h (i.e., fasting < 8 h or not fasting). Total cholesterol was assessed regardless of fasting status

AE Adverse event, *CV* cardiovascular, *LDL* low-density lipoprotein

at an unknown time. A computed tomography (CT) scan of the brain showed no acute findings, a CT angiography of the neck and head showed no stenosis or aneurysm, and magnetic resonance imaging of the brain without contrast showed no definite acute territorial infarct or intracranial hemorrhage. After excluding cerebrovascular accident, the neurologic symptoms were suspected to be due to the migraine, and hemiplegia was assessed by the investigator as not related

to rimegepant. The participant was treated with sumatriptan, and on the day after admission, the serious AEs of hemiplegia and migraine with aura were considered resolved and the participant was discharged. No action was taken with rimegepant as a result of the serious AEs of hemiplegia and migraine with aura. The participant continued in the study and completed the 52-week treatment period with an overall average use of rimegepant of 5.1 tablets per 4 weeks.

Ischemic colitis was reported in one participant in the PRN 9–14 group, with two baseline CV risk factors (treatment with a statin and family history of coronary artery disease) and a baseline Framingham Risk Score of 4.3%. The 64-year-old White female had a medical history including hypercholesterolemia and a 30-year history of Crohn's disease. Approximately 3 months after the first dose of rimegepant, and 1 day after a dose of rimegepant, the participant was hospitalized due to ischemic colitis, which was reported as a serious AE of severe intensity. A CT scan showed colitis involving a contiguous segment of the mid to distal transverse, descending and proximal sigmoid colon, and colonoscopy findings were felt to be consistent with ischemic colitis. Following treatment with hydration, ciprofloxacin, and metronidazole, the serious AE was resolved. Rimegepant was permanently discontinued as a result of the serious AE, which the investigator assessed as being possibly related to rimegepant due to the temporal relationship between the serious AE and the start of rimegepant dosing.

None of these CV AEs were in participants in the scheduled EOD + PRN enrolment group, which received rimegepant every other day and as needed, up to once daily. Of the four CV AEs, the only one assessed by the investigator as being possibly related to rimegepant was the AE of transient ischemic colitis. A definitive determination could not be made in the context of a 64-year-old woman with a history of hypercholesterolemia and a 30-year history of Crohn's disease.

Laboratory Tests

The incidence of grade 3 or 4 blood lipid test abnormalities in fasted participants was low across all subgroups (Table 5).

DISCUSSION

These analyses showed that rimegepant was safe and well tolerated when administered for up to 1 year for the acute treatment of migraine in adults with CV risk factors, including those at moderate or high CV risk, and including those participants in the scheduled EOD + PRN enrolment group, who received rimegepant every other day and as needed, up to once daily.

The incidences of AEs, serious AEs, and AEs leading to study drug discontinuation in participants with migraine and CV risk factors were comparable to those observed in the subgroup without CV risk factors and the overall population. The observation that the proportion of participants with AEs leading to study drug discontinuation were numerically higher in the subgroups with CV risk would require investigation with an appropriately larger sample size and statistical testing to confirm. The subgroups with CV risk factors included participants with a history of diabetes, current smokers, treatment with a statin, uncontrolled hypertension, treatment for hypertension, and family history of coronary artery disease. The possibility that the comorbidities and/or polypharmacy in the subgroups with CV risk might contribute to the discontinuation rates cannot be excluded. Exclusion criteria for the study were uncontrolled, unstable or recently diagnosed CV disease, uncontrolled hypertension, uncontrolled diabetes, and body mass index ≥ 30 kg/m^2. No deaths or MI occurred in any subgroup during the study, and three of the four CV-related AEs were assessed as unlikely to be or not related to rimegepant.

These longer-term safety data for rimegepant extend the knowledge base of the CV safety of CGRP antagonists. Data for atogepant are currently limited, but for ubrogepant the data include analyses of single-dose trials according to CV risk and inclusion of participants with CV disease in a real-world study [13, 27, 30]. The tolerability and safety of ubrogepant did not differ by CV risk status [13]. Data specific to the CV safety of the CGRP monoclonal antibodies include an analysis of clinical trial

participants using fremanezumab for up to 12 weeks according to CV risk [18], and CV outcomes in pooled analyses of clinical trial populations using galcanezumab for up to 6 months [17] and eptinezumab for up to 1 year [16]. The vascular safety of erenumab has been analyzed according to CV risk and assessed in four double-blind, placebo-controlled studies with extensions of up to 5 years [19, 20] and administered as a single intravenous infusion to a population with stable angina before an exercise treadmill test [31]. There was no increased risk of hypertension with erenumab compared with placebo in clinical trials, and rates of hypertension AE reported with erenumab in the postmarketing setting were generally low [32]. Across the class of CGRP antagonists, there are no contraindications regarding CV conditions or risk factors [15]. Further longer-term data are needed with respect to the CV safety of all agents in the class, and these may further differentiate between the intermittent or repeated administration of the small-molecule gepants and the continuous CGRP antagonism associated with the monoclonal antibodies.

The current study population was predominantly female, representative of the real-world migraine patient population [33, 34], ethnically diverse, and varied in age. As might be expected, the participants in the subgroups with ≥ 2 CV risk factors and moderate or high CV risk were more likely to be older, male, and to have a higher body mass index compared with the other subgroups.

Limitations

This study has limitations, including the inherent risk of bias associated with open-label studies, and the limited study duration which precluded collection of longer-term data. As with many clinical trials in migraine populations, uncontrolled, unstable, or recently diagnosed CV disease was part of the exclusion criteria, and the safety of rimegepant for such patients cannot be extrapolated from the current data. The sample sizes for the subgroups with CV risk factors were small compared with the size of the subgroup without CV risk. The data reflect a study population which volunteered to participate in a clinical trial with an investigational drug and may not be wholly generalizable to the real-world migraine population, who may differ in underlying CV disease and/or CV risk factors, as well as sociodemographics and migraine characteristics.

CONCLUSIONS

Rimegepant, administered up to once daily and for up to 1 year, showed favorable safety and tolerability in adults with migraine with CV risk factors, including those with a moderate or high 10-year risk of developing a CV condition.

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

Declarations

Conflict of interest. The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. David True has served as a principal investigator for headache trials for Allergan, AbbVie, electroCore, Eli Lilly, Teva, Theranica, Ionis, Avanir, Amgen, Aeon, Alder, Lundbeck, Axsome, Mayo Clinic, Nocira, Satsuma, Zosano, Tonix, and Pfizer. Kathleen Mullin serves as a consultant or advisory board member for or has received honoraria from Amgen, Biohaven, electroCore, and Eli Lilly. Robert Croop was an employee of Biohaven Pharmaceuticals, owns stock in Biohaven Ltd, was an employee of Pfizer, has received research payments from Pfizer, and provides services to Collima LLC, which has had consulting agreements with Pfizer, Actio Biosciences, Inc., Aptose Biosciences Inc., Biohaven Pharmaceuticals, Inc., Manistee Therapeutics, and Vida Ventures Management Co., LLC.

Ethical Approval. The study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation, Good Laboratory Practice, the Declaration of Helsinki, and all applicable regulations. All participants provided written informed consent prior to participation in the study. The protocol was approved by Institutional Review Boards (Advarra IRB [IRB00000971], Schulman Associates IRB [IRB00007642; acquired by Advarra], and Biomedical Research Alliance New York [BRANY] IRB [IRB00000080]) before the start of the study.

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