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CLINICAL TRIAL REPORT

Safety of Rimegepant in Patients Using Preventive Migraine Medications: A Subgroup Analysis of a Long-Term, Open-Label Study Conducted in the United States

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Purpose: To evaluate the safety and tolerability of rimegepant 75 mg for the acute treatment of migraine in participants concurrently using a preventive migraine medication.

Patients and Methods: This long-term, open-label safety study (NCT03266588) enrolled adults with a history of 2–14 moderate or severe migraine attacks per month. Participants self-administered rimegepant 75 mg (1) up to once daily as needed for 52 weeks to treat attacks of any pain intensity or (2) every other day plus as needed for 12 weeks. Preventive migraine medications were allowed if dosing was stable for ≥2 months prior to the baseline visit.

Results: Of 1800 rimegepant-treated participants, 243 (13.5%) took a concomitant preventive medication. The most common preventive medication was topiramate (26.3%). Rimegepant exposure was comparable in both groups (mean [SD] number of doses per 4 weeks was 7.8 [4.5] in those taking preventives and 7.7 [4.7] in those not taking preventives). The proportion of participants experiencing ≥1 on-treatment adverse event (AE) was 68.7% among those using preventive medication and 59.2% among those not using preventives. Serious AEs occurred in 4.5% of those using preventive medication and 2.3% of those who were not using preventives. AEs leading to study drug discontinuation occurred in 4.5% of those taking preventive medication and 2.4% of those not taking preventives. AEs occurring in ≥5% of participants in either cohort (with preventives vs without preventives) were upper respiratory tract infection (7.4% vs 9.0%), nasopharyngitis (7.8% vs 6.6%), sinusitis (7.0% vs 4.8%), urinary tract infection (5.3% vs 3.6%), and back pain (5.3% vs 2.8%).

Conclusion: Acute treatment of migraine with rimegepant 75 mg for up to 52 weeks was well tolerated and had a favorable safety profile in adults who were concomitantly using preventive migraine medication.

Keywords: rimegepant, migraine, preventive, concomitant, safety, clinical trial

Introduction

Migraine is a complex debilitating neurological disorder characterized by recurring, typically moderate to severe, unilateral head pain that may be accompanied by other symptoms such as nausea, photophobia, or phonophobia.[1] There is great variation in migraine attacks in terms of both frequency (from a few times a month to daily) and severity (from mildly disabling to requiring bedrest). Migraine therapies aim to alleviate pain and other symptoms and are often classified as either acute (ie, taken after a migraine attacks starts) or preventive (ie, taken at regular intervals to reduce the frequency and/or severity of future attacks in people with frequent attacks). Preventive treatments for migraine reduce attack frequency but rarely eliminate all attacks, with successful response often defined as a decrease in attack frequency of at least 50%.[2–4] Therefore, many patients using preventive medication still require acute treatment.[2,4]

Preventive medications have included propranolol, timolol, divalproex sodium, topiramate, beta-blockers, calcium channel antagonists, antidepressants, anticonvulsants, non-steroidal anti-inflammatory drugs, and botulinum toxin.[2]

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These medications, however, can be associated with significant adverse events and/or increased rates of treatment discontinuation.[5] A key role for calcitonin gene-related peptide (CGRP) has been established in the pathophysiology of migraine.[6] As a result, several migraine therapies have been recently developed that target CGRP or its receptor. These therapies have demonstrated improved safety profiles over older migraine treatments.[5,7,8]

Rimegepant is an oral small molecule CGRP receptor antagonist indicated in the United States, European Union, United Kingdom, and other regions for the acute treatment of migraine with or without aura and for the preventive treatment of episodic migraine in adults.[9,10] Currently, rimegepant is the only migraine medication approved for both acute and preventive treatment.[9] The efficacy and safety of a single dose of rimegepant 75 mg for the acute treatment of migraine has been established in three previous randomized placebo-controlled trials in the United States.[11,12] In these three US-based studies, approximately 15% (n = 547) of treated participants (rimegepant or placebo; n = 3507) used concomitant preventive medications.[13–15] The repeated, long-term use of rimegepant for the acute treatment of migraine has also been assessed in an open-label safety study (NCT03266588).[16] However, the long-term safety of rimegepant in patients taking concomitant preventive migraine medication has not been assessed. The purpose of this subgroup analysis was to assess long-term safety of rimegepant in adults receiving concomitant preventive migraine medication during study NCT03266588.

Material and Methods

Study Design

Data were from a multicenter, open-label, long-term, safety study of rimegepant (NCT03266588) conducted in the United States. The study included a screening visit/observation period of 30 days, a long-term treatment period of 12 or 52 weeks (depending on treatment group), and a follow-up safety visit 14 ± 2 days after the end of treatment. Full study details have already been described.[16]

Participants

Eligible participants were aged ≥18 years with a ≥1 year history of migraine (with or without aura) according to criteria of the International Classification of Headache Disorders, 3rd edition, beta version,[1] migraine attacks lasting 4–72 hours if untreated, age of migraine onset <50 years, and 2–14 moderate or severe migraine attacks per month within the 3 months before screening.

Participants were excluded if they had a history of migraine with brainstem aura or hemiplegic migraine; human immunodeficiency virus disease; Gilbert's syndrome or active hepatic or biliary disease; alanine aminotransferase, aspartate aminotransferase, or serum bilirubin >1 × upper limit of normal; diseases or conditions causing malabsorption; alcohol or drug abuse within the past 12 months; uncontrolled, unstable or recently diagnosed cardiovascular disease; uncontrolled hypertension; uncontrolled diabetes; body mass index ≥30 kg/m^2; unstable medical conditions; diagnosis of major depressive disorder, pain syndromes, psychiatric conditions or significant neurological disorders; current diagnosis of schizophrenia, major depressive disorder requiring treatment with atypical antipsychotics, bipolar disorder or borderline personality disorder; and medically significant positive drug screen for drugs of abuse.

Treatment

Participants self-administered rimegepant 75 mg oral tablet 1) up to once daily as needed to treat attacks of any pain intensity upon the onset of migraine (PRN) for 52 weeks or 2) every other day plus PRN on non-scheduled days (EOD +PRN) for 12 weeks. Standard-of-care medications (aspirin, ibuprofen, acetaminophen up to 1000 mg/day for a maximum of 2 consecutive days at a time, nonsteroidal anti-inflammatory drugs, antiemetics, or muscle relaxants) were also permitted as needed. Use of triptans by participants without a contraindication was allowed only during the 30-day screening visit/observation period; use was prohibited during the long-term treatment phase. Concomitant use of strong cytochrome P450 3A4 inhibitors or inducers with rimegepant was prohibited during the study. Preventive migraine medications were permitted if dosing was stable for ≥2 months prior to the baseline visit and was not expected to change during the study. Site investigators identified which specific medications were used by participants for the preventive treatment of migraine

and documented such use in the case report form. Following initiation of the study, a protocol amendment was implemented to enroll a small subgroup of participants with a history of 2–8 moderate-to-severe migraine attacks per month and receiving stable, FDA-approved CGRP antagonist biologics to evaluate the safety of rimegepant in combination with these agents. These participants received rimegepant PRN for up to 12 weeks and findings from this subgroup have been presented previously.[17]

Assessments

In the current analysis, assessment of rimegepant safety was based upon the number and percentage of participants with on-treatment adverse events (AEs) and laboratory test abnormalities. On-treatment was defined as occurring after rimegepant initiation (ie, date of first use) through 7 days after rimegepant cessation (ie, date of last use + 7 days). AE severity and relationship to study drug were determined by site investigators. AEs with study drug relationships of "related", "possibly related", "unlikely related", or "not reported" were classified as treatment-related AEs. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v21.1. In analyses of AEs by severity, if a participant had an AE with different severities over time on treatment, then only the greatest severity was selected. Laboratory test values were graded according to numeric laboratory test criteria in Common Terminology Criteria for Adverse Events Version 5.0 (2017) if available, or Division of Acquired Immunodeficiency Syndrome Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 (2017). If a participant had a laboratory test abnormality with different toxicity grades over time on treatment, then only the highest toxicity grade was selected.

AEs were assessed during study visits occurring at screening, baseline (day 1), approximately every 2 weeks during the first month of treatment, and then every 4 weeks until week 12 (for the EOD+PRN group) or week 52 (for the PRN groups). Clinical laboratory testing was performed at screening, baseline, week 4, and week 12 (EOD+PRN group) or weeks 24 and 52 (PRN groups). For clinical laboratory test evaluations, participants were instructed to fast for a minimum of 8 hours prior to blood draws. If a participant had not fasted before a given visit, the blood draw was still performed.

Analysis and Data Presentation

Safety data were summarized descriptively for the subgroup of participants who used concomitant preventive migraine medications, the subgroup who did not use concomitant preventive migraine medications, and for the overall study population. Concomitant medications were defined as those taken on or after rimegepant initiation. These subgroup analyses were pre-specified in the statistical analysis plan.

The proportion of patients in each cohort with an AE (of any severity), with a severe AE, with a serious AE, and with an AE leading to discontinuation were presented. Also presented were the most common (occurring in ≥2% of all treated participants) AEs, the most common (occurring in >1 participant in any cohort) serious AEs, and the most common (occurring in >1 participant in any cohort) AEs leading to discontinuation. Finally, the most common (occurring in ≥1% of all treated participants) lab abnormalities deemed clinically relevant (pre-specified in the study protocol as Grade 3 or 4 events according to the Common Terminology Criteria for Adverse Events v5.0) were presented.

Results

Participants and Exposure

A total of 1800 participants received treatment with rimegepant. Most participants were female (89.4%) and most were white (81.9%; Table 1). The proportion of participants using preventive medication during long-term treatment with rimegepant was 13.5% (n = 243). The mean historical migraine attack frequency (number of moderate or severe migraine attacks per month) was 7.1 in the cohort using preventives and 6.7 in the cohort not using preventives. The mean historical duration of untreated migraine attacks was 36.9 hours in the cohort using preventives and 33.4 hours in the cohort not using preventives. The mean (SD) number of rimegepant doses administered per 4 weeks was 7.8 (4.5) in the cohort taking preventives and 7.7 (4.7) in the cohort not taking preventives. Among the 243 participants using preventives, the most common preventive medication used was topiramate (26.3%; Table 2).

Table 1 Demographics, Migraine History, and Exposure to Rimegepant

	Using Preventives (N = 243)	Not Using Preventives (N = 1557)	Total (N = 1800)
Age, years			
Mean (SD)	45.5 (13.0)	42.7 (12.0)	43.1 (12.2)
Median (min, max)	45.8 (18, 84)	42.6 (18, 77)	43.0 (18, 84)
Sex, n (%)			
Female	225 (92.6)	1384 (88.9)	1609 (89.4)
Male	18 (7.4)	173 (11.1)	191 (10.6)
Race, n (%)			
White	207 (85.2)	1268 (81.4)	1475 (81.9)
Black or African American	23 (9.5)	227 (14.6)	250 (13.9)
Other[a]	13 (5.3)	62 (4.0)	75 (4.2)
BMI, kg/m^2			
Mean (SD)	29.0 (6.6)	29.5 (7.6)	29.4 (7.5)
Median (min, max)	27.6 (17.7, 56.4)	28.1 (14.7, 73.7)	28.0 (14.7, 73.7)
Primary migraine type, n (%)[b]			
Without aura	171 (70.4)	1029 (66.1)	1200 (66.7)
With aura	72 (29.6)	528 (33.9)	600 (33.3)
Number of moderate or severe migraine attacks per month[b]			
Mean (SD)	7.1 (3.2)	6.7 (3.1)	6.7 (3.1)
Median (min, max)	7.0 (2, 14)	6.0 (2, 14)	6.0 (2, 14)
Duration of untreated migraine attacks, hours[b]			
Mean (SD)	36.9 (23.3)	33.4 (22.1)	33.9 (22.3)
Median (min, max)	36.0 (4, 72)	24.0 (4, 72)	24.0 (4, 72)
Time on rimegepant 75 mg, weeks			
Mean (SD)	33.2 (19.8)	34.0 (19.1)	33.9 (19.2)
Median (min, max)	47.0 (0.1, 54.6)	47.3 (0.1, 55.3)	47.3 (0.1, 55.3)
Number of rimegepant 75 mg tablets taken per 4 weeks			
Mean (SD)	7.8 (4.5)	7.7 (4.7)	7.7 (4.6)
Median (min, max)	6.5 (0.3, 26.0)	6.4 (0.2, 27.6)	6.5 (0.2, 27.6)
Cumulative number of rimegepant 75 mg tablets taken during the study			
Mean (SD)	61.8 (48.3)	62.3 (48.4)	62.2 (48.4)
Median (min, max)	49.0 (1.0, 339.0)	50.0 (1.0, 359.0)	50.0 (1.0, 359.0)

Notes: [a]Includes American Indian or Alaska Native, Asian, Multiple, and Native Hawaiian or Other Pacific Islander. [b]Historical data assessed at screening.
Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2 Most Common (>3%) Preventive Migraine Medications Used During Treatment with Rimegepant[a]

N (%) of Participants[b]	
Any preventive medication	243 (100)
Topiramate	64 (26.3)
Amitriptyline	24 (9.9)
Botulinum toxin type A	19 (7.8)
Erenumab-aooe	13 (5.3)
Magnesium	14 (5.8)
Propranolol	12 (4.9)
Nortriptyline	11 (4.5)
Metoprolol	11 (4.5)

Notes: [a]Non-study medications were recorded on the case report form. Investigators were required to indicate on the form whether the medication was a prophylactic migraine medication (yes or no). [b]Percentages based on the 243 participants who used preventive medications.

AEs

The proportion of participants experiencing at least 1 on-treatment AE during long-term treatment with rimegepant was 68.7% for the cohort using preventive medications and 59.2% for the cohort not using preventive medications (Table 3). AEs occurring in >5% of participants using preventive medications included nasopharyngitis (7.8%), upper respiratory tract infection (7.4%), sinusitis (7.0%), urinary tract infection (5.3%), and back pain (5.3%).

Table 3 Summary of On-Treatment AEs

n (%) of Participants	Using Preventives (N = 243)	Not Using Preventives (N = 1557)	Total (N = 1800)
Any AE	167 (68.7)	921 (59.2)	1088 (60.4)
Severe AE	16 (6.6)	63 (4.0)	79 (4.4)
Serious AE	11 (4.5)	36 (2.3)	47 (2.6)
Discontinued treatment due to AE	11 (4.5)	37 (2.4)	48 (2.7)
Most common AEs[a]			
Upper respiratory tract infection	18 (7.4)	140 (9.0)	158 (8.8)
Nasopharyngitis	19 (7.8)	103 (6.6)	122 (6.8)
Sinusitis	17 (7.0)	75 (4.8)	92 (5.1)
Urinary tract infection	13 (5.3)	56 (3.6)	69 (3.8)
Influenza	7 (2.9)	52 (3.3)	59 (3.3)
Back pain	13 (5.3)	43 (2.8)	56 (3.1)

(*Continued*)

Table 3 (Continued).

n (%) of Participants	Using Preventives (N = 243)	Not Using Preventives (N = 1557)	Total (N = 1800)
Bronchitis	11 (4.5)	42 (2.7)	53 (2.9)
Nausea	8 (3.3)	43 (2.8)	51 (2.8)
Dizziness	8 (3.3)	34 (2.2)	42 (2.3)
Arthralgia	5 (2.1)	31 (2.0)	36 (2.0)
Most common serious AEs[b]			
Appendicitis	1 (0.4)	2 (0.1)	3 (0.2)
Osteoarthritis	1 (0.4)	2 (0.1)	3 (0.2)
Pulmonary embolism	1 (0.4)	2 (0.1)	3 (0.2)
Accidental overdose	0	3 (0.2)	3 (0.2)
Constipation	0	2 (0.1)	2 (0.1)
Sepsis	0	2 (0.1)	2 (0.1)
Pneumonia	0	2 (0.1)	2 (0.1)
Most common AEs leading to discontinuation[b]			
Dizziness	1 (0.4)	4 (0.3)	5 (0.3)
Anxiety	2 (0.8)	0	2 (0.1)
Depression	0	2 (0.1)	2 (0.1)
Suicidal ideation	0	2 (0.1)	2 (0.1)
Alanine aminotransferase increased	0	3 (0.2)	3 (0.2)
Aspartate aminotransferase increased	0	3 (0.2)	3 (0.2)
Blood creatine phosphokinase increased	0	2 (0.1)	2 (0.1)
Hot flush	0	2 (0.1)	2 (0.1)
Constipation	0	2 (0.1)	2 (0.1)
Arthralgia	0	2 (0.1)	2 (0.1)
Vertigo	0	2 (0.1)	2 (0.1)

Notes: [a]Occurring in ≥2% of all treated participants. [b]Occurring in >1 participant in any cohort.
Abbreviation: AE, adverse event.

Most AEs were mild or moderate in severity; severe AEs occurred in 6.6% of participants using preventive medications and 4.0% of those not using preventives (Table 3). Serious AEs occurred in 4.5% of participants using preventive medications and in 2.3% of those not using preventives, though no individual AE was classified as serious in >1 participant (0.4%) in the cohort using preventives.

AEs leading to study drug discontinuation occurred in 4.5% of participants using preventive medications and 2.4% of those not using preventives (Table 3). However, among the 42 AEs that led to study drug discontinuation across both cohorts, most did not lead to discontinuation in more than 1 participant. AEs leading to study drug discontinuation in the cohort using preventives included anxiety (n = 2), pulmonary embolism (n = 1), colitis ischemic (n = 1), deep vein

thrombosis (n = 1), dizziness (n = 1), invasive ductal breast carcinoma (n = 1), osteoarthritis (n = 1), patella fracture (n = 1), somnolence (n = 1), and transaminases increased (n = 1).

Treatment-Related AEs

The rate of on-treatment AEs classified as related to rimegepant was 22.2% in the cohort using preventives and 19.7% in the cohort not using preventives (Table 4). Only dizziness (1.5%), nausea (1.3%), constipation (1.1%), and somnolence (1.1%) occurred in ≥1% of all treated participants, and the rates of each of these AEs were comparable across cohorts. Serious treatment-related AEs occurred in 1.6% of participants (n = 4) in the cohort using preventive medications and in 0.4% of the cohort not using preventives (n = 6). No individual serious treatment-related AE occurred in >1 participant in any cohort, and most (9 of 10) were considered to be "unlikely related" to rimegepant; 1 event (colitis ischemic) was considered "possibly related" to rimegepant.

Table 4 Summary of On-Treatment AEs Classified as Related to Rimegepant[a]

n (%) of Participants	Using Preventives (N = 243)	Not Using Preventives (N = 1557)	Total (N = 1800)
Any AE	54 (22.2)	306 (19.7)	360 (20.0)
Severe AE	6 (2.5)	12 (0.8)	18 (1.0)
Serious AE	4 (1.6)	6 (0.4)	10 (0.6)
Most common AEs[b]			
Dizziness	3 (1.2)	24 (1.5)	27 (1.5)
Nausea	2 (0.8)	21 (1.3)	23 (1.3)
Constipation	2 (0.8)	18 (1.2)	20 (1.1)
Somnolence	4 (1.6)	15 (1.0)	19 (1.1)
All serious AEs[c]			
Cellulitis	1 (0.4)	0	1 (0.1)
Deep vein thrombosis	1 (0.4)	0	1 (0.1)
Headache	0	1 (0.1)	1 (0.1)
Hemiplegic migraine	0	1 (0.1)	1 (0.1)
Invasive ductal breast carcinoma	1 (0.4)	0	1 (0.1)
Suicidal ideation	0	1 (0.1)	1 (0.1)
Migraine	0	1 (0.1)	1 (0.1)
Colitis ischemic	1 (0.4)	0	1 (0.1)
Constipation	0	1 (0.1)	1 (0.1)
Nephrolithiasis	0	1 (0.1)	1 (0.1)

Notes: [a]Treatment-related AEs represent AEs that were considered by site investigators to have study drug relationship of "unlikely related", "possibly related", "related", or not reported. [b]Occurring in ≥ 1% of all treated participants. [c]All serious treatment-related AEs were deemed "unlikely related" to rimegepant by site investigators except for colitis ischemic, which was deemed "possibly related" to rimegepant.
Abbreviation: AE, adverse event.

Table 5 Summary of On-Treatment Grade 3 to 4 Clinical Laboratory Test Abnormalities Occurring in ≥1% of All Treated Participants

Grade 3 to 4 Abnormality, Number of Participants with Abnormality/Number of Participants with Data (%)	Using Preventives (N = 243)	Not Using Preventives (N = 1557)	Total (N = 1800)
LDL cholesterol (fasting)[a]	2/93 (2.2)	25/720 (3.5)	27/813 (3.3)
LDL cholesterol	6/214 (2.8)	42/1332 (3.2)	48/1546 (3.1)
LDL cholesterol (non-fasting)	4/143 (2.8)	19/760 (2.5)	23/903 (2.5)
Creatine kinase	3/238 (1.3)	26/1492 (1.7)	29/1730 (1.7)
Urine glucose	0/180	12/1048 (1.1)	12/1228 (1.0)

Note: [a]Fasting for ≥8 hours.
Abbreviation: LDL, low-density lipoprotein.

Clinical Laboratory Test Findings

Most on-treatment clinical laboratory test results were normal (Grade 0, data not shown) and few participants experienced Grade 3 to 4 laboratory test abnormalities (Table 5). The only Grade 3 to 4 abnormalities that occurred in ≥2% of all treated participants were for low-density lipoprotein (LDL) cholesterol. Grade 3 to 4 abnormalities of creatine kinase and urine glucose occurred in ≥1% of all treated participants. All other Grade 3 to 4 abnormalities occurred in <1% of all treated participants.

Discussion

This study demonstrates that long-term use of rimegepant 75 mg (up to once per day) was well tolerated and exhibited a favorable safety profile in adults using concomitant preventive migraine medications. This conclusion is based on the observation that most on-treatment AEs were mild to moderate in severity, few participants discontinued treatment due to an AE, and few lab abnormalities were Grade 3 to 4.

The overall rate of all AEs (68.7% vs 59.2%) and treatment-related AEs (22.2% vs 19.7%) were comparable among participants receiving preventive medications and those not using preventive medications. Likewise, the rates of severe AEs (6.6% vs 4.0%), serious AEs (4.5% vs 2.4%), and discontinuations of study treatment due to AEs (4.5% vs 2.4%) were low in both cohorts. There were only minor differences in the rates of common AEs (those occurring in ≥2% of all treated participants) between cohorts.

Most on-treatment clinical laboratory results were normal, there were few Grade 3 to 4 laboratory test abnormalities, and there were no obvious differences noted between participants using preventive medications and those not using preventives. The only Grade 3 to 4 laboratory test abnormalities occurring in ≥2% of all treated participants were for LDL cholesterol. However, the proportion of participants with an LDL cholesterol abnormality was low in the overall study population (2.5–3.3% depending on fasting status), the proportion was comparable across cohorts, and no trends of worsened lipids on treatment relative to baseline were observed in the overall study population.[16] It is likely these results were a result of the protocol not requiring fasting blood collections or controlling for fasting status.

Overall, no new safety concerns were identified in this study among participants using preventive migraine medications concurrently with rimegepant. Strengths of the study include the enrollment of a diverse population of individuals receiving typical preventive treatments for migraine. Additionally, the ability to use rimegepant as needed with up to daily dosing provides important, clinically relevant safety data. Limitations of this study include the relatively small number of participants using preventive medications (n = 243) relative to those not using preventives (n = 1557). Accordingly, it is unlikely that rare safety events would be identified in the cohort using preventive medications. Lastly, biologic CGRP antagonists for the preventive treatment of migraine had only just begun to receive regulatory approval

during the conduct of this study and, as a result, there are limited safety data on the concomitant use of rimegepant with these agents.

Conclusion

Long-term (up to 1 year) acute treatment of migraine with oral rimegepant 75 mg (up to once per day) was well tolerated and had a favorable safety profile in adults who were concurrently using preventive migraine medications.

Abbreviations

AE, adverse events; CGRP, calcitonin gene-related peptide; EOD, every other day; LDL, low-density lipoprotein; PRN, as needed.

Data Sharing Statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Pursuant 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.

Ethics Approval and Informed Consent

The study protocol was approved by an Institutional Review Board or Independent Ethics Committee for each participating investigational center. All participants provided written informed consent. The study was conducted in compliance with ethical principles of the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice Guidelines. Table S1 lists all ethics committees approving the protocol.

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Disclosure

Gary Berman was paid by Clinical Research Institute, partially, from funds received to conduct this clinical trial. Dr. Berman has received consulting funds from Pfizer. Alexandra Thiry was an employee of Biohaven Pharmaceuticals, owns stock in Biohaven Ltd, is currently a full-time employee of Pfizer, and owns stock/options in Pfizer. 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, Aptose Biosciences Inc., Manistee Therapeutics, and Vida Ventures Management Co. In addition, Dr Robert Croop reports a patent regarding CGRP antagonists, originally assigned to Biohaven Pharmaceuticals and now owned by Pfizer Inc.

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