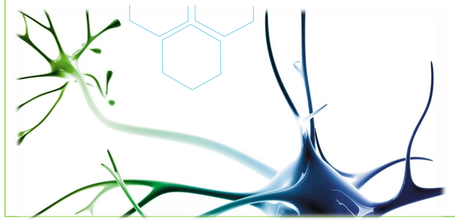

Rimegepant for the Acute Treatment of Migraine With and Without a History of Triptan Failure

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Background

- For the acute treatment of migraine, the use of sumatriptan and other 5-HT$_{1B/1D}$ receptor agonists (triptans) has been associated with an inadequate response in one-third of patients and a recurrence of symptoms in up to 40% of patients; the clinical utility of triptans may also be limited by adverse events (AEs), some of which lead to discontinuation, medication-overuse headache, and cardiovascular contraindications[1]
- Rimegepant is an orally administered small-molecule calcitonin gene-related peptide receptor antagonist that has demonstrated efficacy in 3 Phase 3 trials in the acute treatment of migraine and a Phase 2/3 trial for the preventive treatment of migraine[2-5]

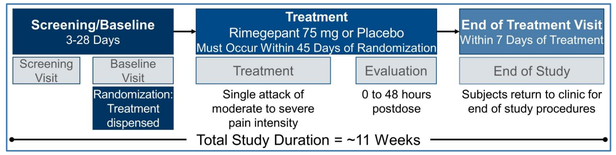
Purpose

- Compare the efficacy of rimegepant with that of placebo in the acute treatment of migraine among subjects with a history of treatment failure with 1 or ≥2 triptans and those with no history of triptan treatment failure

Methods

- Three double-blind, placebo-controlled, multicenter trials of similar design (Figure 1) randomized adults with migraine to rimegepant 75-mg tablet (NCT03235479, NCT03237845), orally dissolving tablet (NCT03461757), or placebo
- Subjects used an eDiary to record data from predose through 48 hours post dose

Figure 1. Study Design



Subjects

- Aged ≥18 years, with ≥1-year history of migraine with or without aura
- Two to 8 monthly migraine attacks with moderate or severe pain; <15 monthly headache days (migraine or nonmigraine) over the past 3 months
- Preventive migraine medication use permitted if stable for ≥3 months

Assessments

- Coprimary efficacy endpoints: pain freedom at 2 hours post dose and freedom from the most bothersome symptom (MBS) at 2 hours post dose

Statistical Analysis

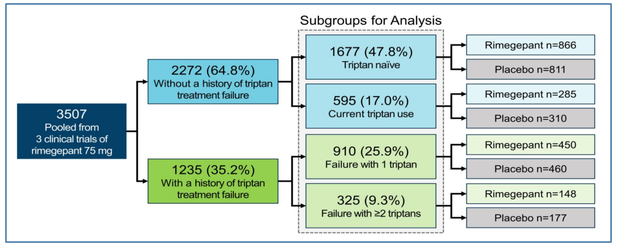
- Efficacy analyses were performed on the modified intent-to-treat population: randomized subjects who had a qualifying migraine attack, took study medication, and provided ≥1 evaluable postbaseline efficacy data point
- Efficacy endpoints were evaluated using Cochran-Mantel-Haenszel tests and stratified by the use of preventive medication at randomization
- Subjects who (1) were missing data at the time point or (2) took rescue medication at or before the time point were considered to have failed treatment
- In this post hoc analysis, the subgroups assessed for efficacy included subjects with a history of treatment failure with 1 or ≥2 triptans and those without a history of triptan failure, including a triptan-naïve group and a group currently using triptans at the time of study enrollment
- Triptan treatment failure was defined as a self-reported history of ≥1 triptan discontinuation due to inadequate efficacy or tolerability, or both, and included any medication in the triptan class

Results

Subjects

- Of the 3507 subjects in the 3 trials (rimegepant n=1749, placebo n=1758), 2272 (64.8%) had no history of triptan treatment failure, and 1235 (35.2%) had a history of treatment failure with 1 or ≥2 triptans (Figure 2)

Figure 2. Triptan Use Subgroups



- Demographics and migraine history of subjects with and without a history of treatment failure with triptans are shown in Table 1

Table 1. Baseline Demographics and Migraine History

	Without a History of Treatment Failure With Triptans		History of Treatment Failure With	
	Triptan Naïve	Current Triptan Use	1 Triptan	≥2 Triptans
	n=1677	n=595	n=910	n=325
DEMOGRAPHICS				
Age, years, mean (SD)	38.3 (12.1)	43.5 (12.0)	42.2 (11.7)	44.1 (10.8)
Sex, n (%)				
Female	1372 (81.8)	528 (88.7)	823 (90.4)	302 (92.9)
Male	305 (18.2)	67 (11.3)	87 (9.6)	23 (7.1)
Race, n (%)				
White	1110 (66.2)	512 (86.1)	757 (83.2)	292 (89.8)
Black or African American	473 (28.2)	63 (10.6)	121 (13.3)	25 (7.7)
Other[a]	93 (5.5)	20 (3.4)	31 (3.4)	8 (2.5)
MIGRAINE HISTORY				
Time since migraine onset, years, mean (SD)	16.3 (11.9)	21.6 (13.2)	22.6 (12.1)	24.3 (11.5)
Moderate-severe attacks/month, mean (SD)	4.6 (1.7)	4.7 (1.8)	4.7 (1.9)	4.7 (1.8)
Duration of untreated attacks, hours, mean (SD)	26.7 (20.8)	33.5 (21.8)	33.7 (22.2)	35.9 (22.6)
Primary migraine type, n (%)				
Without aura	1171 (69.8)	406 (68.2)	579 (63.6)	218 (67.1)
With aura	506 (30.2)	189 (31.8)	331 (36.4)	107 (32.9)
Preventive medication use, n (%)	95 (5.7)	137 (23.0)	211 (23.2)	104 (32.0)

[a]Includes American Indian or Alaskan native, Asian, Hawaiian native or other Pacific Islander, or subjects of multiple races.

Prior Triptan Response

- The most commonly failed triptans (all formulations) were sumatriptan and rizatriptan (Table 2); reasons for sumatriptan and rizatriptan failure are shown in Table 3

Table 2. Prior Failed Triptans

	History of Treatment Failure With 1 Triptan, n (%)			History of Treatment Failure With ≥2 Triptans, n (%)		
	Rimegepant 75 mg	Placebo	Overall	Rimegepant 75 mg	Placebo	Overall
	n=450	n=460	N=910	n=148	n=177	N=325
Sumatriptan	327 (72.7)	337 (73.3)	664 (73.0)	123 (83.1)	145 (81.9)	268 (82.5)
Rizatriptan	71 (15.8)	69 (15.0)	140 (15.4)	89 (60.1)	115 (65.0)	204 (62.8)
Eletriptan	14 (3.1)	27 (5.9)	41 (4.5)	65 (43.9)	64 (36.2)	129 (39.7)
Zolmitriptan	25 (5.6)	14 (3.0)	39 (4.3)	46 (31.1)	63 (35.6)	109 (33.5)
Naratriptan	3 (.7)	6 (1.3)	9 (1.0)	14 (9.5)	19 (10.7)	33 (10.2)
Frovatriptan	0 (0)	3 (.7)	3 (.3)	14 (9.5)	20 (11.3)	34 (10.5)
Almotriptan	4 (.9)	4 (.9)	8 (.9)	9 (6.1)	13 (7.3)	22 (6.8)
Sumatriptan-naproxen	6 (1.3)	0 (0)	6 (.7)	6 (4.1)	4 (2.3)	10 (3.1)

Table 3. Reason for Triptan Discontinuation

	History of Treatment Failure With			
	1 Triptan n (%)		≥2 Triptans n (%)	
	Rimegepant 75 mg	Placebo	Rimegepant 75 mg	Placebo
Sumatriptan oral	n=301	n=308	n=119	n=134
Took too long to relieve pain	203 (67.4)	206 (66.9)	84 (70.6)	94 (70.1)
Pain returned within 24 hours	138 (45.8)	148 (48.1)	72 (60.5)	72 (53.7)
Did not relieve other symptoms	171 (56.8)	183 (59.4)	76 (63.9)	79 (59.0)
Inconsistent relief	213 (70.8)	216 (70.1)	84 (70.6)	102 (76.1)
Treatment caused side effects	141 (46.8)	131 (42.5)	73 (61.3)	58 (43.3)
None of the above	25 (8.3)	28 (9.1)	7 (5.9)	9 (6.7)
Rizatriptan oral	n=68	n=65	n=85	n=112
Took too long to relieve pain	28 (41.2)	42 (64.6)	56 (65.9)	72 (64.3)
Pain returned within 24 hours	28 (41.2)	33 (50.8)	49 (57.6)	60 (53.6)
Did not relieve other symptoms	30 (44.1)	38 (58.5)	56 (65.9)	72 (64.3)
Inconsistent relief	35 (51.5)	44 (67.7)	60 (70.6)	86 (76.8)
Treatment caused side effects	25 (36.8)	25 (38.5)	37 (43.5)	46 (41.1)
None of the above	22 (32.4)	11 (16.9)	6 (7.1)	12 (10.7)

Efficacy

- Rimegepant was superior to placebo for pain freedom and MBS freedom at 2 hours post dose among participants who were current triptan users and those with a history of triptan treatment failure with 1 or ≥2 triptans; among triptan-naïve subjects, rimegepant was superior to placebo for pain freedom (Figure 3)
- No differences in coprimary endpoints were found in pairwise comparisons of the triptan-naïve, current triptan use, and triptan failure subgroups in rimegepant-treated subjects (Table 4)

Figure 3. Coprimary Efficacy Endpoints at 2 Hours Post Dose in Subjects With and Without a History of Triptan Treatment Failure

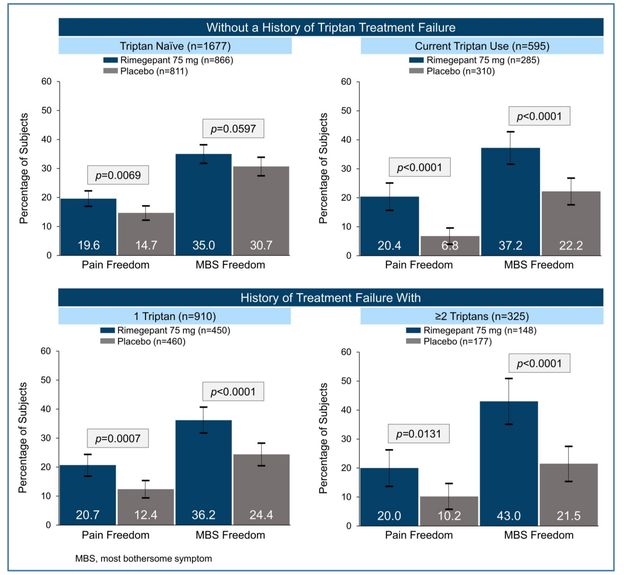


Table 4. Coprimary Efficacy Endpoints Compared Pairwise Between Triptan Subgroups in Rimegepant-Treated Subjects

	Triptan Naïve vs			Current Triptan Use vs		Failed 1 Triptan vs
	Current Triptan Use	Failed 1 Triptan	Failed ≥2 Triptans	Failed 1 Triptan	Failed ≥2 Triptans	Failed ≥2 Triptans
Pain freedom, 2 h						
Odds ratio	.96	.94	.97	.98	1.01	1.03
95% CI	.68,1.35	.70,1.26	.62,1.51	.68,1.42	.61,1.65	.65,1.63
P-value	.8116	.6799	.8803	.9169	.9776	.9101
MBS freedom, 2 h						
Odds ratio	.91	.94	.70	1.04	.78	.74
95% CI	.68,1.20	.74,1.20	.49,1.01	.77, 1.42	.52,1.16	.51,1.09
P-value	.4898	.6419	.0558	.7891	.2190	.1256

MBS, most bothersome symptom.
Comparisons used logistic regression models in rimegepant-treated subjects; models included class predictors variables for current triptan use/historical use of discontinued triptans (4 levels: triptan naïve, current triptan use, failed 1 triptan, failed ≥2 triptans) and preventive migraine medication use (yes, no).

Conclusions

- A single oral dose of rimegepant 75 mg was effective for the acute treatment of migraine in subjects with and without a history of triptan treatment failure
- Efficacy of rimegepant was consistent among those with 1 or ≥2 triptan failures and those who were triptan naïve or currently using triptans
- Rimegepant may represent a novel treatment option for patients who do not respond to, cannot tolerate, or have contraindications to triptans

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