Anti-CGRP Monoclonal Antibodies and Gepant Side Effects (>2% in Clinical Trials) Per Medication Inserts

Gepants rimegepant (r), ubrogepant (u), atogepent (a), and zavegepant(z)[1-4]	**Anti-CGRP monoclonal antibodies** erenumab (er), eptinezumab (ep), galcanezumab (g), fremanezumab (f)
Nausea (a, u, r, z)	Injection site reactions (er, g, f)
Vomiting (z)	Constipation (er)
Dry mouth (u)	Cramps, muscle spasms (er)
Somnolence (u, a)	Nasopharyngitis (ep)
Decreased appetite (a)	Hypersensitivity reactions (ep)
Constipation (a)	
Nasal discomfort (z)	
Taste disorders (z)	
Dizziness (a)	

Is there a potential benefit to combining CGRP antagonists?

- CGRP mAbs do not completely block peripheral CGRP signaling
- Adding gepants can provide additional biologic effect
- CGRP plasma levels first drop and then rise with up to 36% to 55% of CGRP still circulating freely
- Modeling with galcanezumab showed minimum free CGRP is ≈22% to ≈28%, and maximum free CGRP is ≈50% to 55%[9]

1.Qulipta. Package insert. AbbVie Inc.; 2023; 2. Nurtec ODT. Package insert. Pfizer Inc.; 2023; 3. Ubrelvy. Package insert. AbbVie Inc.; 2023. 4. Zavzpret. Package insert. Pfizer Inc.; 2023; 5. Aimovig. Package insert. Amgen Inc.; 2023; 6. Vyepti. Package insert. Lundbeck Seattle BioPharmaceuticals, Inc.; 2022; 7. Emgality. Package insert. Eli Lilly and Company; 2021; 8. Ajovy. Package insert. Teva Pharmaceuticals; 2022; 9. Berman G, et al. *Headache.* 2020;60(8):1734-42.

Small Studies and Case Studies Support Safety and Tolerability When Combining CGRP Antagonists

Case 1: migraine without aura, 8 MMDs, moderate-to-severe intensity[1]

- Used rimegepant 75 mg and then added erenumab 70 mg
- MMD declined by 46% over 4 weeks
- Treated 7 breakthrough migraines with rimegepant
- No treatment-related TEAEs

Case 2: migraine without aura, 11 MMDs, moderate-to-severe intensity[1]

- Used rimegepant 75 mg and then added erenumab 140 mg
- Treated 9 breakthrough migraines with rimegepant within 30 days of starting erenumab
- No treatment-related TEAEs

Substudy[2]	Nested within a multicenter, open-label, long-term safety study; patients (n = 13) had 2-8 MMD, moderate-to-severe intensity; taking erenumab (er; n = 7), fremanezumab (fr; n = 4), galcanezumab (n = 2) and adding rimegepant 75mg for up to 12 weeks (mean = 9.6 weeks); Mean (SD) 4-week rimegepant exposure = 7.8 (5.5)[2]
On treatment adverse events	Viral gastroenteritis (fr), moderate, unlikely related; 1st-degree AV block (er), mild, possibly related; dizziness (er), possibly related; Not related: nasopharyngitis (fr, er); back pain (er); myalgia (er); sinusitis (er); contusion (er)
Serious adverse events	None; no AEs led to study drug discontinuation, no cases of ALT or AST levels >3× ULN

Pharmacokinetic interactions[2]

- Probability of pharmacokinetic interactions between gepants and anti-CGRP monoclonal antibodies is low
- mAbs are not metabolized by cytochrome P450 (CYP) enzymes and interactions with concomitant medications that are substrates, inducers, or inhibitors of CYP enzymes are unlikely

AE, adverse event; AV, atrioventricular; mAb, monoclonal antibody; MMD, monthly migraine days; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

1. Mullin K, et al. *Neurology.* 2020;94:e2121-5; 2. Berman G, et al. *Headache.* 2020;60(8):1734-42.

No Safety Concerns Were Identified When Coadministering Ubrogepant With Erenumab or Galcanezumab

Study design[1]	Multicenter, open-label, phase 1b; adults (n = 40) received either ubrogepant plus erenumab or ubrogepant plus galcanezumab			
Day	1	8	12-15	16-45
Arm 1	Ubrogepant 100 mg	Erenumab 140 mg	Ubrogepant 100 mg daily	Follow-up
Arm 2	Ubrogepant 100 mg	Galcanezumab 240 mg	Ubrogepant 100 mg daily	Follow up

TEAEs	Ubrogepant + erenumab: constipation (11%), nausea (11%), upper abdominal pain (11%); potentially clinically significant increased blood pressure (n = 1, day 13) Ubrogepant + galcanezumab: dizziness (11%)
Serious AEs	No serious TEAE, TEAEs leading to discontinuation, or clinically relevant changes in laboratory parameters or vital signs
Pharmacokinetic interactions	The pharmacokinetic profile for ubrogepant was not significantly changed when co-administered with erenumab or galcanezumab

COURAGE[2]	Real-world study; combination of ubrogepant (50 mg, 100 mg) with anti-CGRP mAb (+/- onabotulinumtoxin A) (n = 245)	
Outcomes	1st attack (n = 245)	• 61.6% and 80.4% achieved MPR at 2 h and 4 h post-dose • 34.7% and 55.5% achieved RNF at 2 h and 4 h post dose
	10 attacks (n = 1153)	• 51.3% and 73.5% achieved MPR at 2 h and 4 h post-dose • 32.2% and 53.2% achieved RNF at 2 h and 4 h post dose
	30 days (n = 231)	• 72.7% reported satisfaction using ubrogepant with anti-CGRP mAb • 79.7% achieved acute treatment optimization (moderate-maximum treatment efficiency)

AE, adverse event; COURAGE, Combining UbRogepAnt and Preventives for MiGrainE; MPR, meaningful pain relief; RNF, return to normal function; TEAE, treatment emergent AE.

1. Jakate A, et al. *Headache.* 2021;61(4):642-52; 2. Lipton RB et al. *Neuro Ther.* 2024;13(1):69-83.

Coadministering Ubrogepant With Atogepant Was Considered Safe and Well Tolerated

Study Design	Phase 1B study, multi-center, open-label, fixed sequence, adults (n = 26) with migraine for at least 1 year received ubrogepant (100mg) on day 1, atogepant (60 mg) on day 2-6, atogepant (60 mg), and ubrogepant (100 mg) every 3 days (day 7-28); primary outcome was clinically significant pharmacokinetic changes
Adverse events	Mild: constipation (51.6%), resolved without study drug discontinuation; nausea (35.5%); fatigue (25.8%); back pain (16.1%); abdominal pain (12.9%); neck pain (12.9%) Moderate: vomiting (1); not study-drug related No clinically meaningful changes in mean clinical laboratory values, vital signs, or ECG parameters; one case of palpitations, study related; no AST or ALT elevations >3x ULN
Serious adverse events	No deaths, serious AEs, or severe AE
Discontinuations	Mild, non-serious rash, not study–related (1); mild, non-serious drug eruption, possibly related to atogepant (1)
Pharmacokinetic interactions	Pharmacokinetic changes were not clinically meaningful

Conclusion: No clinically relevant pharmacokinetic drug-drug interactions between atogepant and ubrogepant. The combination was well-tolerated and no new safety concerns were identified.

AE, adverse events; ECG, electrocardiogram; TEAE, treatment emergent adverse event.

Blumenfeld Am et al. *Headache.* 2023;63(3):322-32.