

Triptans, gepants, lasmiditan, and valproate for migraine: A 24-week prospective cohort study in Iraq

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ABSTRACT

Prospective real-world data comparing all major migraine drug classes are scarce in low- and middle-income countries; Iraq offers an opportune setting given expanding access to gepants and lasmiditan. To compare 24-week efficacy, tolerability, and medication overuse headache (MOH) risk across triptans, gepants, lasmiditan, and valproate in Iraqi migraineurs, and to identify independent predictors of optimal response. This prospective cohort study (February–August 2024) enrolled 247 patients at four Baghdad tertiary headache clinics. Four primary drug groups (triptans $n=110$, gepants $n=46$, lasmiditan $n=38$, valproate $n=35$; $N=229$) were compared by ANOVA; a smaller simple-analgesics cohort ($n=18$) was analysed descriptively. Monthly migraine days (MMD), visual analogue scale (VAS), and HIT-6 were assessed at baseline, 12, and 24 weeks. Ethical approval was obtained (Approval No. 238); retrospective ISRCTN registration is in progress. At 24 weeks, gepants achieved the lowest residual MMD (3.9 ± 2.4 days/month), VAS (3.8 ± 1.4), and HIT-6 (47.8 ± 6.8), significantly better than triptans ($P < 0.05$). Two-hour pain freedom did not differ significantly among triptans, gepants, and lasmiditan after correction for multiple comparisons. Gepant use was the strongest independent predictor of optimal response ($\geq 50\%$ MMD reduction: OR=2.66, 95% CI 1.20–5.89; $\geq 30\%$: OR=2.41, 95% CI 1.12–5.19), robust across sensitivity analyses and E-value analysis at both thresholds ($E=4.25$ – 4.76). Gepants and lasmiditan showed no MOH signal. The Composite Migraine Control Score (CMCS) ranked gepants highest (76.0/100). In this first concurrent 24-week comparison of four migraine drug classes in the MENA region, gepants showed superior control, best tolerability, and lowest MOH risk. Confirmatory trials and external validation of the novel CMCS are needed.

Keywords: Migraine, Gepants, CGRP receptor antagonist, Triptans, Lasmiditan, Valproate

Introduction

Migraine is the second leading cause of years lived with disability (YLDs) globally and the primary cause among women of reproductive age, affecting approximately 1.1 billion people [1, 2]. Access to modern migraine pharmacotherapy remains

markedly inequitable across low- and middle-income countries (LMICs), including in the Middle East and North Africa (MENA) region [3, 4]. A 2024 multi-country survey found that fewer than 25% of Iraqi migraineurs had ever been prescribed a triptan and fewer than 5% had been exposed to gepants or lasmiditan [3]. The pharmacological landscape of migraine has been transformed over two decades. Triptans (5-HT_{1B/1D} receptor agonists) have been the mainstay of acute therapy, achieving 2-hour pain freedom in 40–50% of patients [5, 6]. Valproate and other preventive agents reduce monthly migraine days (MMD) by $\geq 50\%$ in approximately 40–50% of adherent patients [7–10]. The most consequential long-term complication is medication overuse headache (MOH), occurring in up to 50% of frequent simple analgesic users and 15–20% of triptan users in tertiary settings [11].

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Gepants (rimegepant 75 mg, ubrogepant 50/100 mg) and lasmiditan (5-HT_{1F} agonist) are a paradigm shift. Gepants have no vasoconstrictor properties, negligible MOH potential, and rimegepant has a dual acute/preventive licensed indication [12–15]. Despite this, no prospective study from Iraq — or the broader MENA region — has concurrently evaluated all major drug classes in a single real-world cohort with extended follow-up.

This study aims to: (1) compare 24-week effectiveness and tolerability across four drug classes (simple analgesics examined as a descriptive safety reference); (2) assess MOH risk via use-frequency correlations; (3) identify independent predictors of optimal response using dual pre-specified thresholds ($\geq 50\%$ primary, $\geq 30\%$ sensitivity); and (4) introduce the Composite Migraine Control Score (CMCS) as a novel multi-domain LMIC outcome metric.

Study framing and scope

This is an observational, hypothesis-generating study. Non-randomised treatment allocation and absence of blinding preclude causal inference. Simple analgesics ($n=18$) are examined as a descriptive safety reference cohort, not as a primary comparator; their data are summarised separately (§2.2, §4.5) to preserve the statistical integrity of the main ANOVA. All findings should be interpreted as associations to inform future confirmatory RCTs. This study followed STROBE reporting guidelines for observational research [16].

Materials and Methods

Study design, setting, ethical approval, and registration

A prospective observational cohort study was conducted at four tertiary neurology/headache clinics in Baghdad, Iraq: (1) Baghdad Teaching Hospital, (2) Al-Yarmouk Teaching Hospital, (3) Ibn Sina Teaching Hospital, and (4) Al-Kindi Teaching Hospital. Patients were enrolled from February 2024 to March 2024 and followed prospectively for 24 weeks (final assessment: August 2024). Outcomes were assessed at baseline, 12 weeks, and 24 weeks. Prospective ethical approval was granted by the Research and Ethical Committee, College of Pharmacy, Mustansiriyah University, Baghdad (Approval No. 238, 1 February 2024). As this study was a non-interventional observational cohort conducted entirely within approved institutional clinical settings, institutional ethics committee approval is the applicable and sufficient oversight mechanism under Iraqi regulatory norms for observational pharmacoepidemiology research; no additional Ministry of Health approval is required for this study category. All procedures conformed to the Declaration of Helsinki. All participants provided written informed consent.

Registration

This study was not registered in a clinical trials registry prior to enrolment. Registration was not mandated by the local Iraqi regulatory or ethical framework at study commencement (February 2024); observational pharmacoepidemiology studies were not subject to mandatory registry requirements under Iraqi Ministry of Health guidelines at the time of study initiation. The study was conducted under prospective institutional ethical oversight, with a pre-specified protocol approved and dated prior to any data collection (Approval No. 238, 1 February 2024; available from the corresponding author upon request). Retrospective registration with ISRCTN (International Standard Randomised Controlled Trial Number registry, managed by Research Square/Springer Nature) is currently in progress and the registration number will be updated upon acceptance. Five transparency measures were implemented in lieu of prospective registration: (a) full adherence to STROBE reporting guidelines; [16]. (b) ethics committee-approved protocol with pre-specified primary and secondary outcomes, filed before data collection; (c) E-value analysis applied at both pre-specified response thresholds; (d) six pre-specified sensitivity analyses with results reported in full; (e) all exploratory post-hoc findings (including the disease-duration ROC analysis, §3.7.1) clearly labelled as exploratory. This approach is consistent with EQUATOR guidance for transparent reporting of observational research [16].

Participants

Inclusion criteria

Age ≥ 18 years; ICHD-3-confirmed [17] episodic (<15 headache days/month) or chronic (≥ 15 days/month for >3 months) migraine; initiation or stable use of a single oral migraine agent for the 24-week study period (any oral triptan [sumatriptan, rizatriptan, eletriptan, zolmitriptan], rimegepant 75 mg, ubrogepant 50–100 mg, lasmiditan 50–200 mg, valproate 500–1000 mg/day, ibuprofen 400 mg, or paracetamol 1000 mg); written informed consent.

Exclusion criteria

Concurrent use of >1 preventive agent; CGRP monoclonal antibody use; secondary headache; pregnancy or lactation; significant psychiatric illness impairing self-report; chronic opioid or barbiturate use (≥ 10 days/month). Valproate was analysed separately as a preventive agent and excluded from acute efficacy comparisons.

Simple analgesics group (descriptive safety cohort)

Patients using simple analgesics only (ibuprofen 400 mg $n=11$; paracetamol 1000 mg $n=7$; $n=18$ total) were enrolled for pharmacoepidemiological safety surveillance — specifically to document MOH risk in patients without access to prescription migraine agents — but are not included in any primary inferential analysis. Their complete profile is summarised in

§4.5: mean age 31.8 ± 7.7 years, 83.3% female, baseline MMD 9.3 ± 5.0 days/month, baseline VAS 7.0 ± 1.9 , baseline HIT-6 63.7 ± 7.9 , previous MOH 50.0%, and mean monthly use 11.9 ± 4.0 days. This allocation mirrors the clinical reality that the use of simple analgesics in Iraqi primary care is common, but pharmacologically distinct from active migraine-specific therapy, and that pooling this group into ANOVA would violate the assumption of homogeneous treatment comparisons.

Data collection

Trained clinical pharmacists at all four sites administered standardized structured questionnaires. Prospective headache diaries documented MMD, VAS (0–10), and HIT-6 at four weeks before enrolment (baseline), at 12 weeks, and at 24 weeks. Medication adherence: validated Arabic MMAS-4 (Cronbach's $\alpha=0.79$) [18] HIT-6: validated Arabic version (Cronbach's $\alpha=0.82$) [19] MOH: defined per ICHD-3 criteria (≥ 15 headache days/month, with ≥ 10 days/month acute medication use for >3 months). Medical records were cross-checked for accuracy at each visit.

Drug groups

Four primary ANOVA groups: triptans ($n=110$; sumatriptan $n=40$, rizatriptan $n=30$, eletriptan $n=26$ [regression reference], zolmitriptan $n=14$); gepants ($n=46$; rimegepant $n=24$, ubrogepant $n=22$); lasmiditan ($n=38$; 200 mg $n=30$, 100 mg $n=8$); valproate ($n=35$). Descriptive safety group: simple analgesics ($n=18$; ibuprofen $n=11$, paracetamol $n=7$) — summarised in §4.5. Total enrolled: $N=247$.

Outcomes

Primary

MMD, VAS, HIT-6 at 24 weeks across four ANOVA groups; $\geq 50\%$ MMD reduction from baseline (primary optimal response definition).

Sensitivity optimal response

$\geq 30\%$ MMD reduction — pre-specified before data unblinding to confirm independence of primary findings from threshold choice, consistent with ICON task force recommendations for flexible responder analysis.

Secondary

2-hour pain freedom; adverse events; probable MOH prevalence; CMCS.

CMCS

Composite Migraine Control Score (0–100): $\geq 50\%$ MMD reduction (30 pts), 2-hour pain freedom (25 pts), AE rate $\leq 20\%$ (20 pts), MOH risk $\leq 10\%$ (15 pts), HIT-6 < 50 at 24 weeks (10 pts). Domain weights assigned a priori before data unblinding.

The CMCS is proposed as a hypothesis-generating composite metric and requires external validation in independent LMIC cohorts before routine use.

Sample size

Meta-analyses of published triptans [6] suggested that 210 patients were needed to detect a 15% absolute difference in $\geq 50\%$ MMD reduction with 80% power (two-sided $\alpha=0.05$). Power is $>85\%$ for the main comparison with 247 enrolled (229 in ANOVA groups). The lasmiditan group ($n=38$) has $\geq 75\%$ power for the primary endpoint. The small sample sizes for lasmiditan ($n=38$) and valproate ($n=35$) limit the precision of estimates for these groups and increase the risk of type II error for subgroup comparisons; results should be interpreted with appropriate caution. The simple analgesics group ($n=18$) is too small for ANOVA and its role is purely descriptive safety surveillance.

Statistical analysis

SPSS v28.0 and R v4.2. Significance: $P < 0.05$. Benjamini–Hochberg FDR correction ($q < 0.05$) was applied to all pairwise comparisons across **Tables 2–4**.

Baseline/ANOVA

One-way ANOVA (or Kruskal–Wallis) and chi-square across four primary groups only. Simple analgesics excluded from all inferential analyses. Normality was assessed using the Shapiro–Wilk test ($P > 0.05$ for all groups) and homogeneity of variances using Levene's test ($P > 0.05$), confirming the assumptions of parametric ANOVA.

Within-group $SD(\Delta)$

$SD(\Delta) = \sqrt{(SD_{er}^2 + SD_{most}^2 - 2r \cdot SD_{er} \cdot SD_{most})}$, $r=0.70$ (conservative estimate from migraine diary ICC literature). Paired t-tests or Wilcoxon signed-rank for significance. Sensitivity analysis using $r=0.60$ and $r=0.80$ did not materially alter the $SD(\Delta)$ estimates (maximum change $\pm 8\%$), confirming robustness of the primary $r=0.70$ assumption.

Multivariate logistic regression

Outcome: $\geq 50\%$ MMD reduction (primary) and $\geq 30\%$ (sensitivity, same covariates). Covariates: age, sex, chronic migraine, disease duration ≥ 10 years, drug group (eletriptan reference), prior MOH, adherence, monthly drug use days. Diagnostics: Hosmer–Lemeshow, Nagelkerke R^2 .

Six pre-specified sensitivity analyses

(1) Excluding chronic migraine ($n=166$); (2) excluding poor adherers (Morisky ≥ 3); (3) leave-one-out logistic regression; (4) MICE multiple imputation (10 datasets) [20]; (5) mixed-effects logistic regression (centre as random effect); (6) model including monthly drug use days as additional covariate.

E-value analysis

Gepant vs. eletriptan in the full cohort, calculated at both pre-specified response thresholds ($\geq 50\%$: OR=2.66, lower CI=1.20; $\geq 30\%$: OR=2.41, lower CI=1.12). Formula: $E = OR + \sqrt{[OR \times (OR - 1)]}$ [21].

Post-hoc exploratory

A ROC analysis examining disease duration as a predictor of optimal response was conducted post-hoc and is reported in §3.7.1 for transparency. This post-hoc exploratory analysis was not pre-specified and requires independent prospective validation. It does not inform any primary or secondary conclusion of this study and must not be used to guide clinical decision-making.

Results and Discussion

Enrolment and baseline characteristics

Of 268 eligible patients, 21 (7.8%) declined and were excluded. A total of 247 patients were enrolled: 229 in the four primary ANOVA groups and 18 in the descriptive analgesics safety cohort. Demographics of primary groups: 82.5% female, mean age 33.9 ± 8.4 years, median disease duration 8 years (IQR 4–16). Chronic migraine: 63/229 (27.5%); aura: 58/229 (25.3%). Baseline: MMD 9.6 ± 5.1 days/month, VAS 7.4 ± 1.6 , HIT-6 65.0 ± 7.7 . Groups were well balanced except chronic migraine prevalence ($P=0.044$; higher in valproate group), adjusted for in all analyses (**Table 1**). Full data for the descriptive analgesics safety cohort ($n=18$) are summarised in §4.5.

Table 1. Baseline characteristics — four primary ANOVA groups (N=229; the n=18 simple-analgesics safety cohort is summarised in §4.5)

P value	Valproate (n=35)	Lasmiditan (n=38)	Gepants (n=46)	Triptans (n=110)	Characteristic
0.58	34.7 ± 9.1	33.5 ± 7.9	32.9 ± 8.6	34.2 ± 8.1	Age, years (mean $\pm$ SD)
0.97	29 (82.9)	31 (81.6)	39 (84.8)	91 (82.7)	Female sex, n (%)
0.41	27.1 ± 4.3	26.3 ± 3.8	25.8 ± 4.0	26.7 ± 4.1	BMI, kg/m ² (mean $\pm$ SD)
0.044*	15 (42.9)	8 (21.1)	12 (26.1)	28 (25.5)	Chronic migraine, n (%)
0.82	10 (28.6)	9 (23.7)	10 (21.7)	29 (26.4)	Migraine with aura, n (%)
0.10	10 (5–18)	7 (3–13)	6 (3–12)	9 (5–16)	Disease duration, yrs (median, IQR)
0.37	10.4 ± 5.4	9.3 ± 4.8	9.0 ± 5.2	9.7 ± 5.0	Baseline MMD (days/month, mean $\pm$ SD)
0.44	7.6 ± 1.7	7.4 ± 1.5	7.3 ± 1.6	7.5 ± 1.5	Baseline VAS (0–10, mean $\pm$ SD)
0.53	66.0 ± 8.3	64.0 ± 7.9	64.7 ± 8.1	65.5 ± 7.5	Baseline HIT-6 score (mean $\pm$ SD)
0.05	9 (25.7)	17 (44.7)	20 (43.5)	—	Previous triptan use, n (%)
0.042†	10 (28.6)	4 (10.5)	6 (13.0)	22 (20.0)	Previous MOH, n (%)
0.47	25 (71.4)	30 (78.9)	38 (82.6)	83 (75.5)	Good adherence (Morisky 0–1), n (%)

* $P=0.044$ chronic migraine higher in valproate group; adjusted in all subsequent analyses. † $P=0.042$ prior MOH. P values from one-way ANOVA or chi-square across four primary groups. MMD=monthly migraine days; VAS=visual analogue scale; HIT-6=Headache Impact Test-6; MOH=medication overuse headache.

Acute efficacy — 2-hour pain freedom

Eletriptan 40 mg showed the highest observed 2-hour pain freedom (46.2%), followed by rimegepant 75 mg (45.8%) and

ubrogepant (45.5%). After FDR correction, pairwise differences among triptans, gepants, and lasmiditan were not statistically significant (all adjusted $P>0.05$), consistent with network meta-analysis evidence (**Table 2**) [5].

Table 2. Acute efficacy: 2-hour pain freedom — primary groups (N=229; simple-analgesics data summarised in §4.5)

Mean VAS Reduction $\pm$ SD	2-h Pain Relief (≥ 2 -pt VAS drop) n (%)	2-h Pain Freedom n (%)	N	Drug (dose)
-2.9 ± 1.3	26 (65.0)	16 (40.0)	40	Sumatriptan 100 mg
-3.1 ± 1.4	21 (70.0)	13 (43.3)	30	Rizatriptan 10 mg
-3.4 ± 1.2	20 (76.9)	12 (46.2)	26	Eletriptan 40 mg (reference)
-3.1 ± 1.3	10 (71.4)	6 (42.9)	14	Zolmitriptan 5 mg
-3.3 ± 1.2	19 (79.2)	11 (45.8)	24	Rimegepant 75 mg
-3.2 ± 1.3	16 (72.7)	10 (45.5)	22	Ubrogepant 50–100 mg
-3.2 ± 1.1	23 (76.7)	13 (43.3)	30	Lasmiditan 200 mg
-2.5 ± 1.2	5 (62.5)	3 (37.5)	8	Lasmiditan 100 mg

After Benjamini–Hochberg FDR correction: no significant pairwise differences among triptans, gepants, and lasmiditan (all adjusted $P>0.05$). Valproate excluded (preventive indication). Simple-analgesics data summarised in §4.5.

Effectiveness at 24 weeks and within-group change from baseline

Gepant users showed the greatest reductions from baseline and the lowest residual values at 24 weeks across all outcome

measures. Valproate was analysed as a preventive agent and is not directly comparable to acute treatments in efficacy outcomes; it is included in ANOVA for exploratory purposes only. ANOVA (four groups): MMD $F(3,225)=5.14$, $P=0.002$; VAS $F(3,225)=5.47$, $P=0.001$; HIT-6 $F(3,225)=7.02$, $P<0.001$. On

Tukey post-hoc testing, gepants were independently associated with superior MMD, VAS, and HIT-6 outcomes compared to triptans (all $P<0.05$); (**Table 3**). Lasmiditan was also associated with better VAS outcomes than triptans ($P=0.042$). Among individual triptans, eletriptan showed the lowest residual MMD (5.1 ± 2.8 days) and the highest $\geq 50\%$ MMD reduction rate (65.4%).

All four primary groups showed statistically significant and clinically meaningful improvements from baseline to 24 weeks. Gepants achieved the greatest within-group reductions: Δ MMD -5.1 ± 3.9 days and Δ HIT-6 -16.9 ± 7.8 points (>6 -fold above MCID of 2.5 points) [22] $SD(\Delta)$ was computed directly using $r=0.70$, providing conservative estimates avoiding systematic underestimation from the commonly assumed $r=0.5$.

Table 3. Twenty-four-week effectiveness outcomes and within-group change from baseline — four ANOVA groups (N=229)

$\geq 30\%$ MMD n (%)	$\geq 50\%$ MMD n (%)	Δ HIT-6, SD(Δ)	HIT-6	Δ VAS, SD(Δ)	Residual VAS	Δ MMD, SD(Δ)	Residual MMD (d/mo)	N	Group
77 (70.0)	59 (53.6)	-9.7 ± 6.1	55.8 ± 7.3	-2.6 ± 1.7	4.9 ± 1.7	-3.4 ± 3.6	6.3 ± 3.1	110	Triptans (n=110)
39 (84.8)*	33 (71.7)*	-16.9 ± 7.8	$47.8\pm6.8^{*\dagger}$	-3.5 ± 1.9	$3.8\pm1.4^{*\dagger}$	-5.1 ± 3.9	$3.9\pm2.4^{*\dagger}$	46	Gepants (n=46)
28 (73.7)	22 (57.9)	-12.8 ± 7.0	51.2 ± 6.8	-3.2 ± 1.6	$4.2\pm1.5^*$	-4.7 ± 3.5	$4.6\pm2.7^*$	38	Lasmiditan (n=38)
23 (65.7)	19 (54.3)	-8.5 ± 7.1	57.5 ± 7.9	-3.0 ± 1.7	4.6 ± 1.5	-4.6 ± 3.9	5.8 ± 3.0	35	Valproate (n=35, preventive)

* $P<0.05$ vs. triptans (Tukey HSD). $\dagger P<0.05$ vs. valproate. ANOVA: MMD $F(3,225)=5.14$, $P=0.002$; VAS $F(3,225)=5.47$, $P=0.001$; HIT-6 $F(3,225)=7.02$, $P<0.001$. Δ columns: paired within-group change, $P<0.001$ for all groups (paired t-test; Wilcoxon where non-normal); $SD(\Delta)$ computed directly as $SD(\Delta)=\sqrt{(SD_{\text{et}}^2+SD_{\text{most}}^2-2rSD_{\text{et}}SD_{\text{most}})}$, $r=0.70$. MCID HIT-6=2.5 points [22] Simple analgesics (n=18): all within-group changes clinically marginal and not statistically significant (Δ MMD -1.4 , Δ VAS -1.2 , Δ HIT-6 $+0.1$); summarised in §4.5.

Sensitivity analysis — $\geq 30\%$ optimal response

Using the $\geq 30\%$ MMD reduction threshold, response rates were: gepants 84.8% (39/46), lasmiditan 73.7% (28/38), triptans 70.0% (77/110), valproate 65.7% (23/35). The gepant advantage persisted (OR=2.41; 95% CI 1.12–5.19; $P=0.024$), confirming independence from threshold definition.

Preventive subgroup: rimegepant vs. valproate

At 24 weeks, those on rimegepant (preventively every other day, n=16) vs. valproate (n=35) had lower residual MMD (3.8 ± 2.3

vs. 5.8 ± 3.0 ; $P=0.03$), lower HIT-6 (47.5 ± 6.5 vs. 57.5 ± 7.9 ; $P=0.001$), and fewer adverse events (12.5% vs. 40.0%; $P=0.02$).

Adverse events and tolerability

Gepants had the best tolerability: 19.6% any AE, 2.2% discontinuation. Valproate had the highest AE rate (40.0%) and discontinuation (14.3%, $P=0.028$). Lasmiditan caused dizziness in 26.3% of patients ($P<0.001$ vs. triptans and gepants). Triptans: 22.7% AEs, 5.5% discontinued (chest tightness) (**Table 4**). Tolerability of the simple analgesics cohort (n=18) is summarised in §4.5.

Table 4. Adverse events and tolerability — four primary ANOVA groups

P value	Valproate (n=35)	Lasmiditan (n=38)	Gepants (n=46)	Triptans (n=110)	Adverse Event
0.006*	14 (40.0)	15 (39.5)	9 (19.6)	25 (22.7)	Any AE, n (%)
0.12	8 (22.9)	5 (13.2)	4 (8.7)	12 (10.9)	Nausea/vomiting
<0.001	2 (5.7)	10 (26.3)*	1 (2.2)	5 (4.5)	Dizziness/vertigo
0.13	6 (17.1)	5 (13.2)	3 (6.5)	8 (7.3)	Fatigue/somnolence
0.05	0	0	0	5 (4.5)	Chest tightness
<0.001	6 (17.1)	0	0	0	Weight gain
0.001	4 (11.4)	0	0	0	Tremor/hair loss
0.028	5 (14.3) $\dagger$	3 (7.9)	1 (2.2)	6 (5.5)	Discontinued, n (%)

* $P<0.05$ vs. triptans and gepants (lasmiditan dizziness). $\dagger P<0.05$ vs. all other groups (valproate discontinuation). P values from chi-square; Fisher's exact for cells $n<5$. Simple-analgesics data summarised in §4.5.

Medication overuse headache (moh) risk

Among the four primary groups, triptans showed a significant positive correlation between monthly use frequency and headache severity ($r=+0.30$; 95% CI 0.11–0.47; $P=0.002$), consistent with MOH risk at high use frequency. Gepants ($r=-0.12$; $P=0.43$) and lasmiditan ($r=-0.19$; $P=0.25$) showed

no positive correlation, consistent with their known MOH-sparing pharmacology [23]. Valproate (preventive): probable MOH in 22.9%, attributable to underlying chronification rather than drug overuse (**Table 5**). The MOH signal for simple analgesics ($r=+0.54$; 50% probable MOH) is summarised below and discussed in §4.5.

Table 5. Correlation between monthly drug use frequency and headache severity — four primary groups

Probable MOH n (%)	P value	Pearson r (95% CI)	Mean Monthly Use (days) ± SD	N	Group
20 (18.2)	0.002	+0.30 (0.11–0.47)	8.0±3.2	110	Triptans
1 (2.2)	0.43	−0.12 (−0.40 to 0.18)	6.2±2.6	46	Gepants
2 (5.3)	0.25	−0.19 (−0.50 to 0.16)	5.7±2.3	38	Lasmiditan
8 (22.9)	—	N/A	Preventive only	35	Valproate

Fisher's r-to-z: gepants significantly lower than triptans ($P=0.012$). MOH prevalence across four primary groups: $\chi^2=18.3$, $P<0.001$. Valproate: MOH attributed to underlying chronification, not drug overuse. Simple-analgesics data ($r=+0.54$, 95% CI 0.13–0.79, $P=0.020$; 50.0% probable MOH) summarised in §4.5.

Multivariate logistic regression — dual-threshold analysis

Complete data available for 205/229 patients (89.5%); 24 patients (10.5%) were excluded due to incomplete diary entries or missed follow-up visits. Baseline comparison between complete-case participants and excluded patients showed no significant differences in age, sex, or any baseline clinical variable ($P>0.05$ for all), suggesting a missing-at-random (MAR)

mechanism. Primary model ($\geq 50\%$ MMD reduction): $\chi^2=34.1$, $P<0.001$; Hosmer–Lemeshow $P=0.58$; Nagelkerke $R^2=0.31$. Gepant use was the strongest independent predictor (OR=2.66; 95% CI 1.20–5.89; $P=0.016$). Disease duration ≥ 10 years independently predicted non-response (OR=0.54; $P=0.030$). Sensitivity analysis ($\geq 30\%$ threshold): gepant OR=2.41 (95% CI 1.12–5.19; $P=0.024$) (**Table 6**). The convergent direction and statistical significance across both thresholds establishes threshold-independence of the gepant association.

Table 6. Multivariate logistic regression — $\geq 50\%$ (primary) and $\geq 30\%$ (sensitivity) optimal response (n=205 complete cases)

P	95% CI	OR ($\geq 30\%$)	P	95% CI	OR ($\geq 50\%$)	β	Predictor
0.024	1.12–5.19	2.41	0.016	1.20–5.89	2.66	0.98	Gepant use (vs. eletriptan)
0.067	0.95–4.69	2.11	0.058	0.97–5.42	2.29	0.83	Lasmiditan use (vs. eletriptan)
0.047	0.36–0.99	0.60	0.030	0.31–0.94	0.54	−0.61	Disease duration ≥ 10 yrs
0.31	0.97–1.09	1.03	0.28	0.97–1.11	1.04	0.04	Monthly drug use days
0.08	0.35–1.07	0.61	0.053	0.31–1.03	0.57	−0.57	Prior MOH
0.58	0.48–1.50	0.85	0.52	0.44–1.51	0.82	−0.20	Chronic migraine
0.72	0.97–1.04	1.01	0.64	0.97–1.05	1.01	0.01	Age (continuous)
0.73	0.54–2.38	1.14	0.67	0.54–2.63	1.19	0.17	Sex (female vs. male)
0.38	0.73–2.29	1.29	0.35	0.72–2.48	1.34	0.29	Good adherence

Model diagnostics ($\geq 50\%$ endpoint): $\chi^2=34.1$, $P<0.001$; Hosmer–Lemeshow $P=0.58$; Nagelkerke $R^2=0.31$. Both threshold models use identical covariate structure. OR=odds ratio; CI=confidence interval. Gepant use is the primary predictor of interest.

Sensitivity analyses and e-value

Six sensitivity analyses ($\geq 50\%$): (1) Excluding chronic migraine: OR=2.88 (1.30–6.38); (2) excluding poor adherers: OR=2.79 (1.26–6.17); (3) leave-one-out range: 2.75–3.04; (4) MICE imputation (n=229 primary): pooled OR=2.83 (1.30–6.15); (5) mixed-effects + centre: OR=2.82 (1.31–6.10); (6) adjusted for monthly use days: OR=2.58 (1.18–5.64). All consistent with primary finding.

E-value: Gepant E-values were calculated at both pre-specified response thresholds: full-cohort gepant vs. eletriptan at the $\geq 50\%$ threshold (OR=2.66) yielded $E=4.76$ (lower-CI $E=1.69$); at the $\geq 30\%$ threshold (OR=2.41), $E=4.25$ (lower-CI $E=1.49$). These consistent E-values across both thresholds indicate that, to fully account for the gepant association, an unmeasured confounder would need to have OR >4.76 in both exposed and unexposed groups — a threshold far exceeding any known migraine prognostic factor [21]. For context, the simple-analgesics MOH use-frequency correlation ($r=+0.54$) is descriptive only and not amenable to E-value analysis.

Post-hoc exploratory analysis: disease duration threshold

Important caveat: this post-hoc analysis was not pre-specified and does not contribute to any primary or secondary conclusion of this manuscript. It is reported here solely for scientific transparency, consistent with EQUATOR guidance that post-hoc exploratory analyses be clearly disclosed rather than omitted. This analysis must be interpreted with extreme caution and requires independent prospective validation before any clinical relevance can be attributed.

A post-hoc ROC analysis was performed to explore whether baseline disease duration could predict $\geq 50\%$ MMD reduction at 24 weeks. The Youden-index optimal cut-off was identified at ≤ 8.5 years (apparent AUC=0.71; 10-fold cross-validated AUC=0.69±0.06; sensitivity 72%, specificity 64%). This threshold was derived from the current dataset and is subject to optimism bias even after cross-validation. Subgroup analysis showed a numerically larger gepant effect in patients with disease duration ≤ 8.5 years (OR=3.42; 95% CI 1.52–7.70) than in

those with >8.5 years (OR=1.87; P=0.20), which — if confirmed externally — would be consistent with the hypothesis that gepants are most effective earlier in the disease course before extensive central sensitisation develops.

This threshold is a discovered candidate, not a validated clinical tool. External prospective validation in an independent Iraqi or MENA cohort is required before this finding can inform clinical decision-making. We propose it as a hypothesis for a future, pre-registered, adequately powered validation study.

Table 7. Composite Migraine Control Score (CMCS) — 24-week outcomes, a priori-weighted five domains

CMCS (/100)	HIT-6<50 (10 pts)	MOH ≤10% (15 pts)	Low AE ≤20% (20 pts)	2-h PF (25 pts)	≥50% MMD (30 pts)	Group
76.0*	8.0	15	20	11.5	21.5	Gepants (n=46)
55.7	4.5	15	8	10.8	17.4	Lasmiditan (n=38)
48.7	3.0	7	11	11.6	16.1	Triptans (n=110)
31.8†	2.5	7	6	—	16.3	Valproate (n=35)

CMCS domain weights assigned a priori before data unblinding: ≥50% MMD reduction=30 pts; 2-h pain freedom=25 pts; AE rate ≤20%=20 pts; MOH risk ≤10%=15 pts; HIT-6<50=10 pts. *Gepants significantly outperformed triptans (P<0.05). †Valproate excluded from acute 2-h PF (preventive agent; shown as ‘—’). Simple analgesics not included in CMCS (descriptive safety cohort).

Principal findings

This 24-week prospective cohort study — the first to concurrently compare four major migraine drug classes across four Baghdad tertiary centres in 247 patients — demonstrates four principal findings: (1) equivalent acute 2-hour pain freedom among triptans, gepants, and lasmiditan after FDR correction; (2) gepants were independently associated with superior MMD and HIT-6 control at 24 weeks, with this association robust across two pre-specified optimal response thresholds (≥50% and ≥30%), six sensitivity analyses, and E-value analysis; causal inference cannot be drawn due to the observational design; (3) no MOH signal for gepants or lasmiditan, with a clinically important MOH risk for triptans and a prominent MOH signal for the simple-analgesics safety cohort; and (4) gepant use and shorter disease duration as independent predictors of optimal response.

Acute efficacy in context of global evidence

The observed 2-hour pain freedom rates — eletriptan 46.2%, rimegepant 45.8%, lasmiditan 43.3% — align with the 2024 Karlsson *et al.* network meta-analysis of 137 RCTs (89,445 patients), which ranked eletriptan highest among oral triptans and found gepants and lasmiditan 200 mg to have comparable acute efficacy [5]. The efficacy of lasmiditan was confirmed in the 2025 DART real-world prospective study, irrespective of prior triptan failure [35].

The absence of statistically meaningful acute efficacy differences supports basing prescribing decisions on tolerability, MOH risk profile, cost, and patient comorbidities.

Extended follow-up and gepant independent association

Composite migraine control score (CMCS)

At 24 weeks, gepants ranked highest on the CMCS (76.0/100), reflecting superior performance across all five domains: highest ≥50% MMD reduction rate, competitive 2-hour pain freedom, best tolerability, lowest MOH risk, and most favourable HIT-6 threshold achievement. Lasmiditan ranked second (55.7) and triptans third (48.7) (**Table 7**) [24-34].

The 24-week design — extending beyond the standard 12-week assessment common in LMIC observational studies — is a key methodological strength. The gepant advantage in overall MMD reduction (Δ MMD -5.1 ± 3.9 days) and HIT-6 improvement (-16.9 ± 7.8 points; $>6 \times$ the MCID [22]) grew in absolute magnitude compared to 12-week interim data, suggesting accumulating preventive carry-over benefit consistent with rimegepant’s approved every-other-day preventive indication [36]. The 7.8-point residual HIT-6 advantage of gepants over triptans at 24 weeks (47.8 vs. 55.8) substantially exceeds the MCID, confirming that the difference is not only statistically but also clinically meaningful.

Dual-threshold robustness: a methodological contribution

Pre-specifying both ≥50% (primary) and ≥30% (sensitivity) MMD reduction thresholds represents a novel methodological contribution to LMIC migraine research, directly addressing a common critique of single-threshold comparative studies. The convergent gepant association across both thresholds (OR=2.66 and OR=2.41, respectively), six sensitivity analyses, and E-value analysis at both thresholds demonstrates that the independent association is not an artefact of threshold selection, model specification, or missing data handling. This dual-threshold pre-specification approach, combined with the CMCS composite metric, represents the most rigorous statistical framework applied to migraine pharmacotherapy research in Iraq to date and should be adopted as standard practice in future pharmacoepidemiology research in LMIC settings.

Simple analgesics: a descriptive safety cohort

The decision to analyse simple analgesics (n=18) separately from the primary ANOVA reflects both statistical necessity (insufficient power for ANOVA cell size) and conceptual clarity:

simple analgesics represent a non-migraine-specific safety reference cohort rather than a genuine treatment comparator. This cohort (ibuprofen 400 mg $n=11$; paracetamol 1000 mg $n=7$) had baseline MMD 9.3 ± 5.0 days/month, VAS 7.0 ± 1.9 , and HIT-6 63.7 ± 7.9 , with 50.0% (9/18) reporting previous MOH. At 24 weeks, residual MMD was 7.7 ± 3.4 days (Δ MMD -1.4 days, non-significant, $P=0.18$), residual VAS 5.8 ± 1.6 , and HIT-6 63.8 ± 7.0 , with only 16.7% achieving $\geq 50\%$ MMD reduction and 22.2% achieving 2-hour pain freedom. Probable MOH was present in 50.0% (9/18) at 24 weeks, and monthly use frequency correlated positively with headache severity (Pearson $r=+0.54$; 95% CI 0.13–0.79; $P=0.020$), descriptive only with no causal inference. Any adverse event occurred in 11.1% (2/18) and no patients discontinued. This clinically negligible improvement and high MOH prevalence are consistent with MENA-wide analgesic overuse data from Egypt [37] and Saudi Arabia [38]. This evidence supports the clinical recommendation to restrict simple analgesic monotherapy for any patient using acute migraine medications >8 days/month, consistent with ICHD-3 and European Headache Federation guidance [17].

MOH risk: a public health priority

The divergent MOH risk profiles — gepants and lasmiditan showing neutral-to-negative use-frequency correlations vs. triptans showing $r=+0.30$ — are consistent with preclinical evidence that CGRP antagonists do not induce neuroplastic changes associated with MOH, [23, 39] while triptans and simple analgesics produce central sensitisation with chronic exposure [11]. For Iraqi policymakers, these data provide direct evidence supporting prescribing guidelines that prioritise gepants for patients already showing early signs of analgesic overuse.

Confounding robustness and transparency of conduct

Reporting E-values at both pre-specified response thresholds (full cohort $\geq 50\%$, full cohort $\geq 30\%$) is a feature of this study's transparent reporting. The consistent E-values (4.25–4.76) across both thresholds provide a stringent convergent validity test: [21] an unmeasured confounder would need to achieve $OR>4.76$ in both exposed and unexposed groups — simultaneously — to fully account for the observed gepant association. No known migraine prognostic factor approaches this effect size. Regarding trial registration: the absence of prospective registration reflects the fact that Iraq's regulatory framework did not mandate registration for observational pharmacoepidemiology studies at study commencement (February 2024), consistent with LMIC norms at that time. The study was conducted under prospective institutional ethics oversight (protocol pre-specified and filed before enrolment). Compensatory transparency measures implemented include: (a) full adherence to STROBE reporting guidelines; (b) all primary and sensitivity analyses pre-specified; (c) E-value analysis at both pre-specified response thresholds; (d) all post-hoc findings

explicitly labelled; (e) retrospective ISRCTN registration in progress. These measures are consistent with EQUATOR and COPE guidance [16]. Future Iraqi prospective observational studies should register prospectively with WHO ICTRP or ISRCTN.

Regional context

Our findings are consistent with MENA headache epidemiology [3, 4, 40, 41]. MOH prevalence in analgesic users (50% in the descriptive cohort) mirrors rates of 38–50% reported in Egypt [37] and Saudi Arabia [38]. Preventive pharmacotherapy guidelines, including valproate, are broadly consistent across the region [7]. The gepant independent association is biologically plausible given the CGRP pathway's role in trigeminovascular sensitisation, [42] which is unlikely to differ fundamentally across ethnic groups absent specific pharmacogenomic data.

Strengths and limitations

Strengths

(1) 24-week follow-up — longest prospective LMIC migraine pharmacotherapy comparison; (2) four Baghdad tertiary centers; (3) prospective diary design eliminating recall bias; (4) validated Arabic instruments; (5) rigorous statistical framework — FDR, MICE, E-value analysis at both response thresholds, six sensitivity analyses; (6) $SD(\Delta)$ computed directly; (7) dual optimal response thresholds; (8) analgesics appropriately separated as a descriptive safety cohort; (9) CMCS as a novel composite metric; (10) complete STROBE-guided reporting.

Limitations

(1) Non-randomised allocation — causal inference cannot be drawn due to the observational design; residual confounding by indication persists despite E-value analysis; (2) absence of blinding; (3) no prospective registry registration (mitigation described in §4.7); (4) small sample sizes for lasmiditan ($n=38$) and valproate ($n=35$) limit precision of estimates and increase the risk of type II error for subgroup comparisons; (5) simple analgesics cohort ($n=18$) underpowered for ANOVA — descriptive only; (6) single-country design limits external generalisability; (7) 24-week follow-up, while longer than most LMIC studies, insufficient for long-term safety conclusions; (8) no socioeconomic or educational covariate; (9) $r=0.70$ assumption for $SD(\Delta)$ — sensitivity analyses using $r=0.60$ – 0.80 showed maximum change of $\pm 8\%$, confirming robustness; (10) the CMCS is proposed as a hypothesis-generating composite metric and requires external validation in independent LMIC cohorts before routine use; (11) no propensity-score matching or other formal confounder-matching technique was performed for the gepant-vs-eletriptan comparison in this analysis, so residual confounding by indication cannot be excluded beyond what the multivariable regression and E-value sensitivity analysis address.

Future directions

(1) Prospective RCTs comparing gepants vs. eletriptan in Iraqi/MENA populations; (2) long-term (≥ 12 months) gepant and lasmiditan safety studies; (3) cost-effectiveness analysis in LMIC settings; (4) multi-city expansion to Basra, Mosul, Erbil; (5) pharmacogenomics of CGRP pathway variants in Iraqi population; (6) CMCS external validation in multicenter LMIC study; (7) all future Iraqi prospective studies to register prospectively with WHO ICTRP.

Conclusion

In this 24-week prospective cohort study from four Baghdad tertiary headache clinics ($N=247$), gepants were independently associated with superior MMD and HIT-6 outcomes, best tolerability, and lowest MOH risk — with acute 2-hour pain freedom equivalent across triptans, gepants, and lasmiditan. The gepant association was robust across dual optimal response thresholds ($\geq 50\%$: OR=2.66; $\geq 30\%$: OR=2.41), six sensitivity analyses, and E-value analysis at both thresholds ($E=4.25-4.76$). Simple analgesics were examined as a descriptive safety cohort; their data documented high MOH risk (50%) and negligible therapeutic benefit (\$4.5). The Composite Migraine Control Score (CMCS) ranked gepants highest (76.0/100) and is proposed as a standardised multi-domain outcome framework for LMIC migraine comparative effectiveness research. Prospective registration of future Iraqi observational studies is strongly recommended.

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