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Research Article

Keywords: Pediatric migraine, Adolescent migraine, Rimegepant, CGRP receptor antagonist, Preventive treatment, Real-world evidence

Posted Date: November 9th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11451012/v1

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Additional Declarations: No competing interests reported.

Real-world integration of rimegepant into pediatric migraine care: treatment selection, persistence, and longitudinal trajectories

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Running title: Rimegepant trajectories in pediatric migraine

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Manuscript type: Original Article

Approximate main-text word count (including abstract, excluding references/tables): 5486

Tables: 4 Figures: 2 Supplementary tables: 6

Abstract

Background: Rimegepant is increasingly entering pediatric migraine care, but little is known about how scheduled preventive use is selected, integrated with existing treatment, and subsequently adapted in routine practice. We characterized treatment selection, four-month clinical outcomes, and longitudinal treatment trajectories after initiation of scheduled rimegepant.

Methods: This multicenter retrospective real-world cohort study used data from the China Headache and Vertigo Registry Study. Within a 448-patient pediatric/adolescent source population, 109 patients were linked by original registry identifiers to clinically verified follow-up of at least four months; 64 initiated scheduled preventive rimegepant and 45 were managed without scheduled rimegepant. Potential selection into longitudinal follow-up was assessed using linked-versus-non-linked comparisons, including a center-conditioned sensitivity analysis. Among scheduled-rimegepant initiators, monthly headache days (MHD), response thresholds, background preventive treatment, treatment duration, and subsequent treatment trajectories were evaluated.

Results: Linked patients showed no major measured registry-baseline imbalance relative to non-linked patients, including in the analysis restricted to centers contributing longitudinal cases. Scheduled rimegepant was more often introduced in patients with chronic migraine and greater preventive-treatment complexity; chronic migraine (aOR 4.71, 95% CI 1.13–19.63) and concurrent amitriptyline use (aOR 3.29, 95% CI 1.40–7.75) were associated with treatment selection. Among 64 initiators, mean MHD decreased from 16.58±10.62 to 5.82±5.78 days/month, and 46/64 (71.9%) achieved a ≥50% reduction. At four months, 10/64 remained on scheduled treatment, 6/64 transitioned to as-needed (PRN) use, and 48/64

discontinued rimegepant. All 48 patients who discontinued rimegepant continued their background conventional preventive therapy. Of these discontinuations, 20 followed complete or marked improvement, 27 followed insufficient or absent effectiveness, and 1 was attributed to nausea. Improvement-associated de-escalation occurred in 26/64 (40.6%).

Conclusions: Scheduled rimegepant was preferentially integrated into more complex pediatric migraine care, while subsequent exposure was dynamically adapted within an ongoing preventive regimen. Clinical response, persistence, and therapeutic role were related but non-interchangeable dimensions of the longitudinal treatment course. These findings characterize a real-world treatment pathway rather than comparative rimegepant effectiveness.

Keywords: Pediatric migraine; Adolescent migraine; Rimegepant; CGRP receptor antagonist; Preventive treatment; Real-world evidence

Introduction

Migraine is common in children and adolescents and can adversely affect quality of life [1]. Headache-related disability can interfere with school participation and daily functioning [2]. Management encompasses acute and preventive interventions selected through shared decision-making [3]. Preventive treatment should be discussed when headaches are frequent or associated with migraine-related disability [4]. However, evidence for many conventional preventive medications in youth remains limited or inconsistent [4–6]. Acute and preventive strategies therefore require individualized selection and coordination [4,7].

Evidence implicating the calcitonin gene-related peptide (CGRP) pathway in migraine has provided a rationale for developing targeted therapies [8]. In adults, rimegepant demonstrated efficacy in randomized trials for acute [9] and preventive [10] treatment. The adult evidence base has subsequently been extended by an open-label long-term safety study [11], a phase 3 acute-treatment trial in China and South Korea [12], and a four-week prospective real-world study of patient-reported outcomes in Chinese adults [13]. Early pediatric literature included expert recommendations on anti-CGRP monoclonal antibodies [14] and retrospective experience with these agents in adolescents with refractory headache disorders [15]. More recently, a randomized trial demonstrated preventive efficacy of fremanezumab in children and adolescents with episodic migraine [16], and a multicenter chart review described preventive gepant use in youth [17]. Pediatric rimegepant evidence also includes retrospective acute-treatment experience in adolescents [18] and single-dose pharmacokinetic and safety data in children aged 6 to <12 years [19].

These studies provide an important foundation for evaluating clinical benefit and tolerability and for characterizing pediatric drug exposure to inform dose selection. A complementary question arises once such treatments enter routine care: how are they selected, incorporated into existing treatment, and subsequently adapted? This question is particularly relevant in pediatric migraine, where new therapies may be layered onto existing preventive regimens and modified as headache burden, perceived benefit, tolerability, treatment burden, and patient or family preferences evolve.

Rimegepant has demonstrated acute and preventive efficacy in adults [9,10]. Once introduced into care, its longitudinal use may involve changes in therapeutic role rather than simple continuation or discontinuation. A patient may begin with scheduled preventive dosing, later transition to PRN acute use, or discontinue after either meaningful improvement or insufficient benefit. In this setting, persistence alone may not capture the clinical meaning of treatment modification. In the Child and Adolescent Migraine Prevention (CHAMP) study, headache frequency declined most rapidly early in treatment, with individual variation in

symptom change [20]; adolescent real-world CGRP research has also incorporated persistence alongside clinical outcomes [21]. However, symptom response, treatment persistence, and therapeutic role are not necessarily equivalent.

We therefore conducted a multicenter real-world study to characterize how scheduled preventive rimegepant was selected, integrated into existing pediatric migraine care, and subsequently adapted over time. Rather than comparing efficacy between treatment regimens, we first examined the clinical context associated with scheduled-rimegepant initiation and then, among initiators, evaluated clinical response, treatment persistence, and therapeutic role as distinct longitudinal dimensions. We specifically characterized continued scheduled use, transition to PRN use, and discontinuation together with the documented reasons for treatment modification.

Methods

Study design and data source

This retrospective multicenter real-world cohort study was based on the China Headache and Vertigo Registry Study (CHRS), a clinical registry designed to capture demographic characteristics, headache and vestibular symptoms, diagnoses, treatment patterns, and longitudinal outcomes across participating centers. For the present analysis, registry recruitment and data collection spanned June 2025 through March 2026, with March 2026 serving as the data cutoff.

The present analysis included children and adolescents aged ≤18 years and focused on treatment selection, clinical outcomes, and longitudinal treatment trajectories after initiation of scheduled preventive rimegepant. The study was designed to characterize a real-world treatment pathway rather than to estimate comparative causal treatment effects between preventive strategies.

The CHRS protocol was approved by the Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine and registered at ClinicalTrials.gov (NCT04939922; first posted June 25, 2021). Written informed consent was obtained from all participants and/or their legal guardians at enrollment in the registry. All analyses used de-identified data.

The longitudinal analytic cohort was derived by record linkage within the 448-patient pediatric/adolescent source registry population. The registry platform did not uniformly contain standardized four-month treatment outcomes for all participating centers; for the present study, longitudinal records were included when original registry identifiers could be linked to clinically verified follow-up extending to at least four months. A total of 109 patients met this requirement. These patients therefore represent an ID-linked subset of the source population rather than the survivors of a uniform prospective follow-up process or a randomly sampled subset.

Patients without linked longitudinal records were not classified uniformly as lost to follow-up, because absence of an eligible record could reflect center-level follow-up processes, record availability, or patient-level follow-up. Four months was selected as the common longitudinal endpoint because longer follow-up was available only in smaller and uneven subsets.

At the index-treatment stage, 64 patients initiated scheduled preventive rimegepant, whereas 45 were managed without scheduled rimegepant. The latter group included patients receiving conventional preventive treatment with or without PRN rimegepant for acute attacks. PRN rimegepant use was therefore considered an acute-treatment characteristic rather than a separate preventive-treatment strategy.

Registry baseline and index-treatment baseline

Two baseline data layers were distinguished. Registry baseline referred to information recorded at initial CHRS enrollment and was used to describe the source population and evaluate characteristics associated with inclusion in the longitudinal cohort. Index-treatment baseline referred to clinically re-verified demographic, diagnostic, headache, and treatment variables at the time the preventive-treatment strategy was established. These variables were used for analyses of treatment selection and subsequent clinical outcomes. Registry-baseline and index-treatment variables were analyzed according to their relevant assessment time points and were not treated as interchangeable.

Clinical variables and treatment-pathway classification

Migraine diagnoses were established from clinical records according to the International Classification of Headache Disorders, 3rd edition [22]. Monthly headache days (MHD) were defined as the number of days with headache during the preceding 30 days. Concurrent preventive treatment was recorded at the index-treatment stage and included conventional preventive medications and traditional Chinese medicine (TCM), where applicable. Background preventive-treatment burden was represented by the original categorical field recorded in the source dataset (1, 2, or ≥3 background preventive drugs), rather than by a reconstructed medication count. Individual background medication classes were analyzed separately.

The primary treatment-pathway classification was based on whether rimegepant was introduced on a scheduled preventive basis at the index-treatment stage. Scheduled preventive rimegepant was operationally defined as rimegepant 75 mg every other day intended for prevention at treatment initiation. Patients were classified as either scheduled preventive rimegepant or management without scheduled rimegepant. The latter category was used to characterize real-world treatment selection and baseline clinical context; it was not treated as a causal comparator for estimating the effect of rimegepant. Background preventive medications were considered components of the concurrent treatment regimen rather than mutually exclusive treatment groups.

Rimegepant treatment decisions were individualized on the basis of clinical assessment and clinician–patient/caregiver discussion. Potential benefits and treatment uncertainties were discussed before initiation, and written informed consent for rimegepant treatment was obtained from the patient and/or legal guardian according to clinical and institutional procedures.

Four-month clinical outcomes

Among patients initiating scheduled preventive rimegepant, MHD was assessed at the index-treatment baseline and at four-month follow-up. The four-month assessment reflected headache frequency during the preceding month, not an average across the entire follow-up period. Absolute MHD reduction was calculated as baseline MHD minus four-month MHD. Relative MHD reduction was calculated at the patient level as (baseline MHD − four-month MHD) / baseline MHD × 100%. Frequency-based response thresholds of ≥50%, ≥75%, and ≥90% were derived exclusively from patient-level baseline and four-month MHD values. The ≥50% threshold corresponds to the conventional responder definition described in International Headache Society guidance for pediatric preventive-treatment trials [23].

Overall clinical improvement

An overall clinical improvement percentage was also documented during routine follow-up. This non-standardized global estimate was not restricted to headache frequency and could reflect changes in headache frequency, intensity, duration, functional impact, or overall headache burden. The estimate was obtained from the patient when available or from a parent or caregiver when direct patient contact was not

feasible. Because this measure was neither standardized nor reporter-specific, it was analyzed separately as an exploratory complementary outcome and was not used to define MHD response.

Longitudinal treatment trajectories and clinical-benefit classification

Because rimegepant use could change after treatment initiation, exposure was not assumed to remain fixed throughout follow-up. Among the 64 patients who initiated scheduled preventive rimegepant, subsequent treatment status at four months was classified into three mutually exclusive trajectories: continued scheduled preventive use, transition from scheduled preventive treatment to PRN use, or discontinuation of rimegepant. Reasons for discontinuation were categorized separately, according to verified clinical documentation, as complete improvement, marked improvement, insufficient effectiveness, lack of effectiveness, or adverse-event-related discontinuation. Treatment persistence was analyzed as one component of the longitudinal treatment course rather than as a surrogate for clinical response.

Among patients who discontinued rimegepant, overall clinical improvement at the time of discontinuation was assessed during routine follow-up as a non-standardized percentage reflecting the perceived overall treatment benefit. For descriptive analyses of discontinued patients, clinical benefit at the time of discontinuation was additionally summarized as marked/complete benefit, partial benefit, or no meaningful benefit based on the corresponding clinical assessment. This measure was distinct from the documented reason for treatment discontinuation and was not used to define MHD-based response or considered an independent validation outcome.

Improvement-associated de-escalation

Improvement-associated de-escalation was defined as either transition from scheduled preventive treatment to PRN use after documented clinical improvement or discontinuation of rimegepant after complete or marked improvement. This variable was used descriptively to characterize treatment adaptation and was not treated as an independent efficacy endpoint.

Treatment-selection analysis

To characterize factors associated with real-world selection of scheduled preventive rimegepant, an exploratory multivariable logistic regression model was fitted in the 109-patient longitudinal cohort. The model included baseline MHD (per 5-day increase), chronic migraine, and concurrent amitriptyline use. A 5-MHD change has also been used as a longitudinal migraine-progression threshold [24]. Results were reported as adjusted odds ratios (aORs) with 95% confidence intervals. The model was intended to characterize treatment selection and clinical channeling rather than to estimate treatment effects or identify predictors of rimegepant response.

Statistical analysis

Continuous variables were summarized as mean±SD or median [interquartile range], as appropriate, and categorical variables as counts and percentages. Between-group comparisons used t tests, Welch tests, Mann–Whitney U tests, Kruskal–Wallis tests, χ^2 tests, Fisher exact tests, or Fisher–Freeman–Halton exact tests, as appropriate. Absolute standardized mean differences (SMDs) were used to assess covariate imbalance.

Exploratory multivariable logistic regression models were used to examine factors associated with longitudinal linkage and selection of scheduled preventive rimegepant; center-clustered robust standard errors were applied to linkage models. The treatment-selection model included baseline MHD (per 5-day increase), chronic migraine, and concurrent amitriptyline use, with adjusted odds ratios (aORs) and 95%

confidence intervals reported. The 5-MHD scale is consistent with previous longitudinal migraine research [24]. Spearman rank correlation was used for associations between continuous clinical measures. Analyses were based on available cases without imputation. All tests were two-sided, with $P<0.05$ used for exploratory inference. Reporting followed STROBE recommendations [25].

Results

Source population and longitudinal cohort

Among the 448 children and adolescents in the source registry population, 109 were successfully linked by original registry identifiers to clinically verified longitudinal follow-up extending to at least four months and constituted the ID-linked longitudinal analytic cohort. Center information was identifiable for 447/448 patients in the source population and for all 109 patients in the longitudinal cohort. The source population represented 53 identifiable contributing centers, whereas the longitudinal cohort represented 28 identifiable contributing centers (Figure 1; Supplementary Table S3).

At registry baseline, the ID-linked longitudinal cohort was broadly similar to the source population across major measured demographic and clinical characteristics. Mean age was 13.2 years in the linked cohort and 12.9 years in the source population, and female patients accounted for 58.7% and 56.9%, respectively. Among patients with evaluable registry-baseline headache data, chronic migraine was present in 20/73 (27.4%) patients in the linked cohort and 79/288 (27.4%) in the source population. In the formal mutually exclusive comparison of the 109 linked patients with the remaining 339 source-population patients, SMDs were generally small, with only modest imbalance in age, headache burden, and documented previous preventive-treatment exposure (Supplementary Tables S1–S2).

The 28 centers that contributed at least one longitudinal case contained 397/448 (88.6%) source-registry patients; 109 were linked and 288 were not. Within this center-conditioned population, measured registry-baseline characteristics remained closely balanced: all displayed absolute SMDs were ≤0.111, including 0.067 for age, 0.071 for sex, 0.111 for MHD, and 0.020 for chronic migraine (Supplementary Table S4). In exploratory center-clustered logistic models, age, sex, chief-complaint category, MHD availability, MHD, and chronic migraine were not clearly associated with successful linkage. Model discrimination was we\ak (area under the receiver-operating-characteristic curve 0.548 in the full center-conditioned model and 0.546 in the MHD/chronic-migraine available-case model), indicating limited ability of these measured patient-level variables to distinguish linked from non-linked patients (Supplementary Table S5).

Baseline clinical burden, treatment complexity, and selection of scheduled preventive rimegepant

At the index-treatment stage, 64/109 patients (58.7%) initiated scheduled preventive rimegepant, whereas 45/109 (41.3%) were managed without scheduled rimegepant (Table 1). Patients initiating scheduled rimegepant had greater baseline headache burden, with higher median MHD (15.0 [IQR, 6.8–30.0] vs 7.0 [4.0–12.5] days/month; $P=0.002$) and a higher prevalence of chronic migraine (28/64 [43.8%] vs 5/45 [11.1%]; $P<0.001$). Age, sex, weight, headache duration, MIDAS score, aura, and prior analgesic use did not differ clearly between treatment pathways.

Background preventive-treatment complexity also differed between pathways. The distribution of the original one-, two-, and ≥3-drug background preventive categories differed overall ($P=0.005$), with three or more background preventive drugs more frequent among scheduled-rimegepant initiators (15/64 [23.4%] vs 1/45 [2.2%]). Concurrent amitriptyline use was also more common in the scheduled-rimegepant pathway (43/64 [67.2%] vs 16/45 [35.6%]; $P=0.002$), whereas TCM was less common (16/64 [25.0%] vs 24/45

[53.3%]; P=0.004). Erenumab use was uncommon in both pathways (5/64 [7.8%] vs 2/45 [4.4%]; P=0.697).

In the exploratory multivariable treatment-selection model, chronic migraine was associated with higher odds of initiating scheduled preventive rimegepant (aOR, 4.71; 95% CI, 1.13–19.63; P=0.033), as was concurrent amitriptyline use (aOR, 3.29; 95% CI, 1.40–7.75; P=0.006). Baseline MHD, modeled per 5-day increase, was not independently associated with treatment selection (aOR, 1.06; 95% CI, 0.79–1.42; P=0.697) (Table 1, Panel B). These associations characterize real-world treatment selection and clinical channeling within this cohort and should not be interpreted as predictors of rimegepant response.

Four-month clinical outcomes following scheduled-rimegepant initiation

Among the 64 patients who initiated scheduled preventive rimegepant, mean MHD decreased from 16.58±10.62 days/month at baseline to 5.82±5.78 days/month at four months. The mean absolute reduction was 10.76±7.82 days/month (95% CI, 8.80–12.71) (Table 2). The mean patient-level relative reduction in MHD was 64.5%, with a median reduction of 67.7% [IQR, 43.8–81.7]. A ≥50% reduction in MHD was observed in 46/64 patients (71.9%); 26/64 (40.6%) achieved a ≥75% reduction and 11/64 (17.2%) achieved a ≥90% reduction.

Baseline headache frequency was strongly associated with the magnitude of absolute improvement. Baseline MHD correlated with absolute MHD reduction (Spearman ρ=0.888, P<0.001), but not with proportional MHD reduction (ρ=0.033, P=0.799).

The non-standardized overall clinical improvement estimate had a mean of 66.5% and a median of 75.0% [IQR, 40.0–85.0]. It was strongly correlated with MHD-derived relative improvement (Spearman ρ=0.902, P<0.001), although the two measures were not identical (Supplementary Table S6).

Longitudinal treatment trajectories and improvement-associated de-escalation

Treatment status changed substantially during follow-up. At four months, 10/64 patients (15.6%) remained on scheduled preventive rimegepant, 6/64 (9.4%) had transitioned from scheduled treatment to PRN use, and 48/64 (75.0%) had discontinued rimegepant. Subsequent treatment status did not correspond directly to the magnitude of headache-frequency improvement. Mean relative MHD reductions were 57.0%, 69.2%, and 65.5%, respectively, across the continued-scheduled, scheduled-to-PRN, and discontinued trajectories (P=0.673). Similarly, ≥50% MHD reduction was observed in 6/10 (60.0%), 6/6 (100%), and 34/48 (70.8%), respectively (Figure 2; Table 3).

Discontinuation was clinically heterogeneous. Among the 48 patients who discontinued rimegepant, the documented reason was complete improvement in 1 patient, marked improvement in 19, insufficient effectiveness in 21, lack of effectiveness in 6, and nausea in 1. Thus, 20 discontinuations followed complete or marked improvement, whereas 27 followed insufficient or absent effectiveness. Clinical improvement had already been documented at the time of rimegepant withdrawal in the 20 improvement-associated discontinuations. All 48 patients who discontinued rimegepant continued their background conventional preventive therapy through the four-month assessment; discontinuation therefore represented withdrawal of rimegepant rather than cessation of preventive treatment as a whole. Together with six patients who transitioned to PRN use after improvement, improvement-associated de-escalation was documented in 26/64 patients (40.6%).

When discontinued patients were considered according to the separately documented clinical-benefit category, 21 were classified as having marked or complete benefit, 20 as having partial benefit, and 7 as having no meaningful benefit. Mean relative MHD reductions were 80.8%, 56.0%, and 46.9%,

respectively, while ≥50% MHD reduction was observed in 21/21 (100%), 11/20 (55.0%), and 2/7 (28.6%). Because the clinical-benefit category and reason for discontinuation were distinct fields arising from routine follow-up, these findings were interpreted descriptively rather than as independent validation of MHD response (Table 4).

Discussion

This study adds a treatment-pathway perspective to the emerging pediatric CGRP-targeted literature. Recent pediatric reports have described preventive gepant use [17], acute rimegepant treatment [18], and rimegepant pharmacokinetics and single-dose safety [19]. Building on these reports, the present analysis focused on how scheduled rimegepant was selected, layered into existing care, and subsequently adapted. Three findings were most informative. First, scheduled preventive rimegepant was preferentially introduced in children and adolescents with greater migraine burden and more complex preventive-treatment backgrounds. Second, substantial reductions in MHD were frequently observed after initiation. Third, treatment use subsequently evolved in heterogeneous ways: some patients continued scheduled prevention, some transitioned to PRN use, and others discontinued for either improvement, insufficient benefit, or intolerance. Together, these observations support viewing scheduled rimegepant use in pediatric migraine as a longitudinal treatment pathway rather than a fixed exposure state.

The first finding concerns treatment selection. Patients entering the scheduled-rimegepant pathway more often had chronic migraine and greater background preventive-treatment complexity, and exploratory multivariable analysis identified associations with chronic migraine and concurrent amitriptyline use rather than with baseline MHD alone. This pattern is compatible with clinical channeling, whereby newer targeted treatments may be introduced when disease burden or treatment complexity is greater. In a recent multicenter pediatric gepant chart review, youths receiving preventive rimegepant had substantial previous preventive-treatment exposure [17], while a US cross-sectional survey of adults prescribed galcanezumab also found substantial patient-reported experience with conventional preventive treatments [26]. Our cohort, however, should not be characterized as a uniformly refractory population. Beyond the structured variables available for analysis, routine clinical decision-making also considered the degree of headache-related burden and disability, previous treatment experience, patient and caregiver expectations for symptom control, concerns regarding adverse effects or long-term use of conventional preventive medications, and acceptance of a migraine-specific targeted therapy. These preference- and decision-related factors were not captured as standardized registry variables and therefore cannot be quantified or modeled in the present study. The observed treatment-selection pattern should consequently be interpreted as individualized real-world integration rather than as evidence for a refractory-migraine threshold or an earlier-line treatment recommendation.

The second finding is that scheduled rimegepant was usually integrated into existing care rather than introduced as a uniform replacement therapy. Many initiators remained on conventional preventive medications, indicating that rimegepant entered an already established therapeutic structure. This pattern has precedent in adult rimegepant practice: in a subgroup analysis of the long-term open-label safety study [11], 243 of 1,800 rimegepant-treated participants used a concomitant preventive medication, with topiramate the most common [27]. A US survey of patients prescribed anti-CGRP monoclonal antibodies also documented recent and past use of other preventive treatments [28]. In our cohort, the integrated nature of treatment remained evident after rimegepant withdrawal: all 48 patients who discontinued rimegepant continued their background conventional preventive therapy through the four-month assessment. These observations support interpreting rimegepant as one dynamically adjustable component

within a broader preventive regimen rather than as an isolated replacement therapy. They should not be interpreted as evidence of pharmacologic synergy, and our observational design cannot determine the contribution of any individual component to the observed clinical improvement.

The observed four-month clinical change was substantial: mean MHD decreased from 16.58 to 5.82 days/month, the mean absolute reduction was 10.76 days/month, and 71.9% of patients achieved a ≥50% MHD reduction. Randomized evidence in adults demonstrates that scheduled rimegepant reduces monthly migraine days compared with placebo [10]. However, the present study assessed MHD within a changing, multicomponent treatment pathway, precluding direct comparison of effect sizes. In the 52-week adult open-label extension, preventive exposure was protocol-defined as rimegepant 75 mg every other day, with additional PRN dosing permitted on nonscheduled days [29]. In our cohort, by contrast, scheduled exposure frequently changed before the four-month assessment, while background preventive treatment continued. The four-month outcome should therefore be understood as the clinical course of an integrated preventive pathway following scheduled-rimegepant initiation, not as the isolated pharmacologic effect of four months of uninterrupted rimegepant exposure or as evidence of a persistent drug effect after withdrawal.

Baseline burden further influenced how improvement should be interpreted. Higher baseline MHD was strongly associated with a larger absolute reduction in headache days but was essentially unrelated to proportional MHD improvement. Absolute change should therefore be interpreted in relation to starting burden, whereas proportional response provides a complementary perspective that is less directly determined by the number of headache days available to improve.

The most distinctive finding concerned the relationship between clinical response and persistence. At four months, 10 patients remained on scheduled preventive treatment, six had transitioned to PRN use, and 48 had discontinued rimegepant, yet the magnitude of MHD improvement showed no clear gradient across these groups. CHAMP trajectory analyses found early reductions in headache frequency and individual variation, but no clear differences in response trajectories between active medication and placebo [20]. PRIME-Teen evaluated persistence and migraine-frequency response both separately and within a composite outcome [21], while the Migraine Signature study assessed persistence alongside patient-reported effectiveness, function, and quality of life [28]. The divergence was particularly apparent among our responders: of the 46 patients achieving a ≥50% MHD reduction, only six remained on scheduled treatment, whereas six transitioned to PRN use and 34 discontinued. Because background preventive therapy was maintained after rimegepant withdrawal, low rimegepant persistence did not represent low persistence with preventive care as a whole. Persistence of one treatment component should therefore not be used as a surrogate for either clinical response or continuation of the broader preventive regimen.

Discontinuation was also clinically heterogeneous rather than a single endpoint with a uniform meaning. Twenty of the 48 discontinuations followed complete or marked improvement, and clinical improvement had already been documented when rimegepant was withdrawn; 27 discontinuations followed insufficient or absent effectiveness. Importantly, background conventional preventive therapy was maintained after rimegepant withdrawal in all 48 patients. For improvement-associated discontinuations, this pattern is most appropriately viewed as selective de-escalation of rimegepant within an ongoing preventive regimen rather than cessation of preventive treatment. A prior pediatric gepant chart review also reported rimegepant discontinuation for insufficient benefit and, less frequently, headache improvement [17]. Similar distinctions have been considered in longer-term CGRP real-world research. In a three-year Japanese cohort of anti-CGRP monoclonal-antibody users, 12 of 50 patients (24%) underwent planned treatment completion after prespecified goal attainment rather than discontinuation for treatment failure [30]. In a separate multicenter cohort, a uniform three-month interruption of anti-CGRP monoclonal antibodies after

one year of treatment was followed by increases in migraine frequency and disability [31]. These monoclonal-antibody studies did not directly compare stopping strategies and cannot establish outcomes after pediatric rimegepant withdrawal. They underline the need to interpret cessation in relation to its reason and subsequent clinical course.

The treatment pattern observed in our cohort may therefore be conceptualized, cautiously, as response-guided, time-limited treatment intensification within an ongoing preventive regimen, followed in some patients by selective de-escalation of rimegepant. Pediatric guidance supports discussing preventive-medication withdrawal once migraine is well controlled [4], and earlier anti-CGRP monoclonal-antibody recommendations also considered withdrawal after treatment goals were reached [14]. These principles do not establish a rimegepant-specific protocol. In our cohort, monthly response was not assessed at fixed intervals, and withdrawal timing was individualized. However, for patients who stopped rimegepant after improvement, benefit was documented at the time of withdrawal, and background preventive therapy was subsequently maintained. Routine clinical discussions also allowed for reduction or discontinuation of rimegepant after substantial improvement; treatment cost could be a practical consideration, although the relative contribution of cost, preference, and clinical response was not systematically recorded. The scheduled-to-PRN trajectory is additionally relevant for a dual-purpose gepant. In adults, a long-term extension study evaluated every-other-day preventive dosing with PRN dosing permitted on nonscheduled days [29]. This combined regimen differs from the transition to PRN-only use observed here, which represents a change in therapeutic role rather than simple treatment cessation. We use the term improvement-associated de-escalation rather than successful discontinuation because post-withdrawal follow-up was not standardized sufficiently to establish durable remission. This treatment-pathway interpretation is descriptive and hypothesis-generating and should not be regarded as an established pediatric treatment protocol.

The non-standardized overall clinical improvement measure provided a complementary, although exploratory, perspective. It was strongly correlated with MHD-derived improvement but was not identical to it, consistent with the possibility that children and caregivers integrate headache frequency with intensity, duration, functional interference, school participation, and overall burden when judging whether treatment has helped. IHS pediatric preventive-trial guidelines include disability and functioning as outcomes in addition to headache frequency [23]. PedIMMPACT recommendations likewise support evaluating function and global treatment assessments alongside pain outcomes [32]. The Migraine Signature study similarly assessed treatment persistence alongside patient-reported effectiveness, function, and quality of life [28]. Our global improvement estimate was neither standardized nor reporter-specific and should therefore be interpreted as a contextual measure rather than a validated patient-reported outcome. Its main value here is to reinforce that symptom-frequency change and perceived clinical benefit overlap but are not identical constructs.

Several limitations define the boundaries of inference. First, treatment selection was non-random, precluding causal comparison between scheduled rimegepant and management without scheduled rimegepant. Second, the 109-patient analytic cohort was an ID-linked subset of the 448-patient source population rather than the result of a uniform prospective follow-up protocol. Although both the full-source comparison and the center-conditioned sensitivity analysis showed little major imbalance in measured registry-baseline characteristics, availability of clinically verifiable longitudinal records remained selective even within contributing centers. The exploratory linkage models likewise had weak discrimination, which argues against strong selection on the measured patient-level variables but does not exclude selection related to unmeasured disease features, clinician follow-up practices, family engagement, treatment access,

record completeness, or other center-level processes. Third, contributing centers were heterogeneous in volume, and the longitudinal cohort was concentrated within a subset of the source centers. Fourth, exposure changed during follow-up, so four-month MHD cannot be interpreted as the effect of uninterrupted scheduled treatment. Although improvement was documented at the time of rimegepant withdrawal in improvement-associated discontinuations, efficacy was not assessed at standardized monthly intervals; the precise temporal course of improvement before withdrawal therefore cannot be reconstructed. Information on treatment persistence and medication use was reconstructed from routine clinical follow-up rather than prospective electronic dosing records. Headache adherence research has highlighted the limitations of self-reported medication use and the value of objective, multimethod assessment [33]. Patient/caregiver preferences, concerns regarding conventional preventive therapy, treatment cost, and the reasons for maintaining background therapy were not captured as standardized variables. Fifth, adverse events were collected from routine records rather than through structured trial surveillance, so the observation of only one nausea-related discontinuation cannot establish pediatric safety or adverse-event incidence. Finally, the clinical-benefit and global-improvement measures were non-standardized and should be interpreted only as contextual descriptors.

Taken together, the principal contribution of this study is not a comparative estimate of rimegepant efficacy, but a description of how a dual-purpose CGRP receptor antagonist is selected, layered into existing pediatric preventive care, and subsequently adapted. In this cohort, rimegepant functioned as a dynamically adjustable component of an ongoing preventive regimen: clinical improvement could be followed by continued scheduled treatment, transition to PRN use, or selective rimegepant withdrawal while background preventive therapy was maintained. The clinically important observation was that symptom response, medication persistence, and therapeutic role did not move in parallel. These dimensions were related but not interchangeable. Future prospective pediatric studies should capture treatment-selection rationale, serial symptom response, adherence, treatment cost and preference, longitudinal exposure, reasons for de-escalation, standardized patient-reported outcomes, and post-withdrawal follow-up alongside conventional headache-frequency endpoints.

Conclusions

In this multicenter real-world cohort, scheduled rimegepant was preferentially integrated into more complex pediatric migraine care, and substantial MHD reductions were frequently observed after initiation. Subsequent management was dynamic: rimegepant could be continued, transitioned to PRN use, or selectively withdrawn while background conventional preventive therapy was maintained. Clinical response, persistence of rimegepant, and therapeutic role should therefore be interpreted as distinct dimensions of the longitudinal treatment course. These findings describe individualized real-world treatment selection and adaptation rather than comparative effectiveness or a standardized pediatric treatment protocol.

List of abbreviations

CHRS, China Headache and Vertigo Registry Study

ICHD-3, International Classification of Headache Disorders, 3rd edition

IHS, International Headache Society

MIDAS, Migraine Disability Assessment Scale

MHD, monthly headache days

aOR, adjusted odds ratio

OR, odds ratio

SD, standard deviation

CI, confidence interval

SMD, standardized mean difference

CGRP, calcitonin gene-related peptide

IQR, interquartile range

TCM, traditional Chinese medicine

PRN, as needed

Declarations

Ethics approval and consent to participate: This study used data from the China Headache and Vertigo Registry Study (CHRS), an observational registry registered at ClinicalTrials.gov (NCT04939922; first posted June 25, 2021). The CHRS protocol was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine. Written informed consent was obtained from all participants and/or their legal guardians at registry enrollment.

Consent for publication: All authors authorize publication of this manuscript.

Funding: This study was supported by the Key Research and Development Program of Zhejiang Province (Grant No. 2024C03007). The funder had no role in the study design, conduct, analysis, interpretation, or publication decisions.

Data availability: The data presented in this study are available from the corresponding author upon reasonable request, subject to applicable institutional and ethical requirements.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process: During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with language editing, manuscript organization, literature identification, and reference checking. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement: Zexian Zhao: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. Jingxin Fu: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. Jinyi Song, Mengting Zhou, Feifan Liu, Yuhui Xia, Mengna Yang, Han Xiao Pan, Linli Gao, and Jiahuan He: Investigation, Data curation. Xiaodong Yuan: Writing – review & editing. Kaiming Liu: Conceptualization, Supervision, Writing – review & editing. All authors approved the final version for submission.

Declaration of competing interest: The authors declare that they have no competing interests.

Acknowledgments

We thank Zhejiang University and The Second Affiliated Hospital, Zhejiang University School of Medicine, for their technical and equipment support. We are grateful to the headache specialists and clinical teams who contributed to diagnostic verification, longitudinal follow-up, and registry data collection, and to all participants and investigators of the CHRS program.

Participating centers represented in the pediatric/adolescent source registry population were: The Second Affiliated Hospital, Zhejiang University School of Medicine; Ningbo Medical Center Lihuili Hospital; Huzhou Central Hospital; Linhai First People's Hospital; The First Affiliated Hospital of Wenzhou Medical University; Zhongshan Hospital, Fudan University; Jiaxing Hospital of Traditional Chinese Medicine; Nanjing Drum Tower Hospital; Taizhou Municipal Hospital; The Fourth Affiliated Hospital, Zhejiang University School of Medicine; The First Affiliated Hospital of Xi'an Jiaotong University; Tongxiang Second People's Hospital; Sir Run Run Shaw Hospital, Zhejiang University School of Medicine; Jiaxing Second Hospital; Nanjing Brain Hospital; Quzhou People's Hospital; Affiliated Hospital of Shaoxing University; The First Affiliated Hospital of Ningbo University; Jiangsu Province Hospital of Chinese Medicine; Tongde Hospital of Zhejiang Province; Wenling First People's Hospital; Ninghai County First Hospital; Sichuan Provincial People's Hospital; Hangzhou First People's Hospital; Ruijin Hospital, Shanghai Jiao Tong University School of Medicine; Jinhua Central Hospital; Lishui Hospital of Traditional Chinese Medicine; Hangzhou Third People's Hospital; Tiantai County People's Hospital, Zhejiang Province; Zhoushan Hospital, Zhejiang Province; Guiyang Second People's Hospital; People's Hospital Affiliated to Ningbo University; Jinshan Branch of Shanghai Sixth People's Hospital; The First Affiliated Hospital of Anhui Medical University; Zhejiang Provincial People's Hospital; Wenzhou Hospital of Traditional Chinese Medicine; Yuhuan Second People's Hospital; Northern Jiangsu People's Hospital; Shanghai General Hospital; Yongkang First People's Hospital; Zhejiang Provincial Hospital of Chinese Medicine; Shanghai Shidong Hospital, Yangpu District; The First People's Hospital of Yunnan Province; Taizhou First People's Hospital; Changzhou First People's Hospital; Affiliated Hospital of Yangzhou University; The First Affiliated Hospital of Kunming Medical University; Yongkang Hospital of Traditional Chinese Medicine; Rui'an People's Hospital; The First Affiliated Hospital of Soochow University; General Hospital of Xiangshan County Traditional Chinese Medicine Medical and Health Group; Zhejiang Hospital; Shaanxi Provincial People's Hospital.

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Figure legends

Figure 1. Source registry population, ID linkage, and analytic framework.

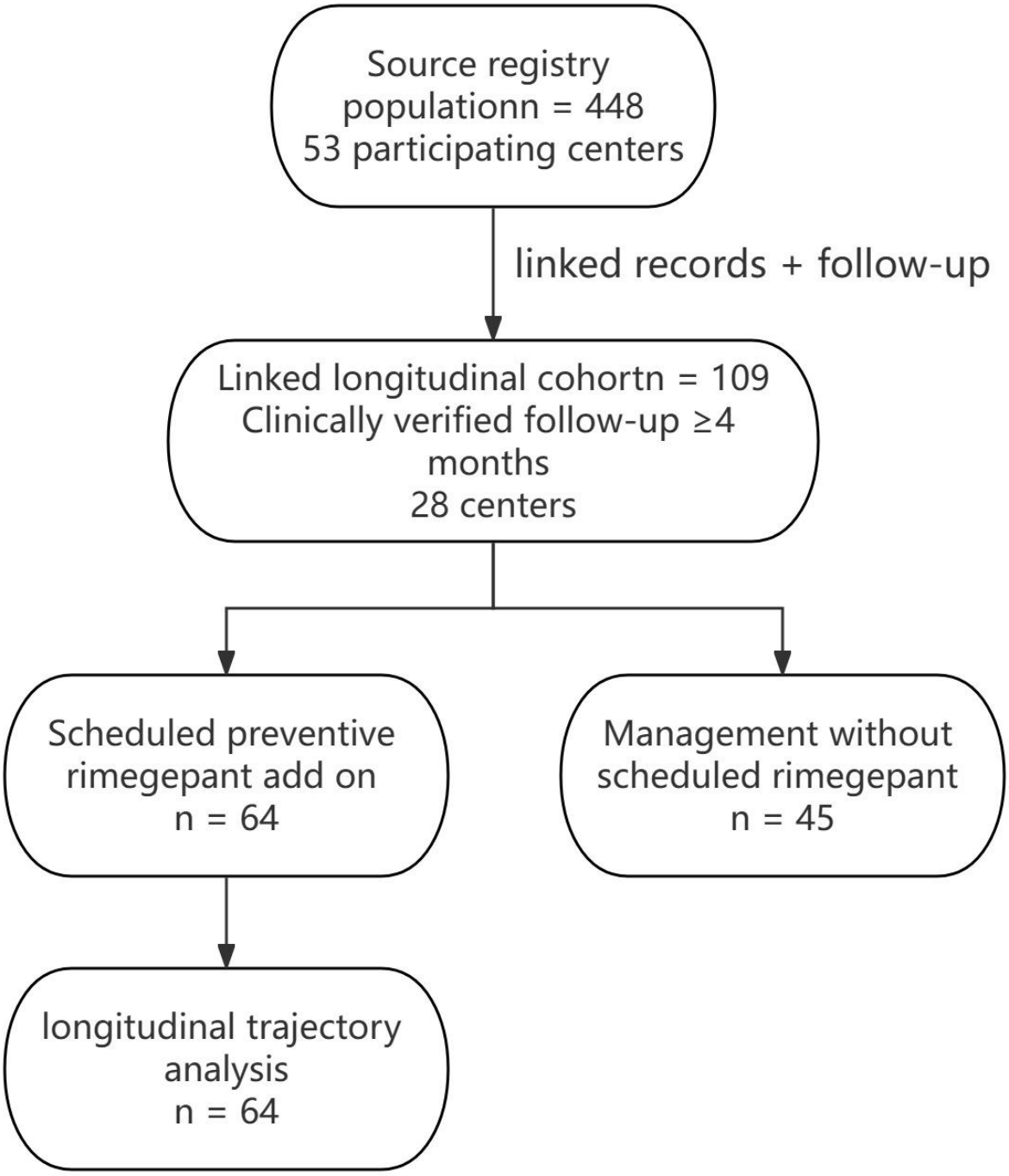
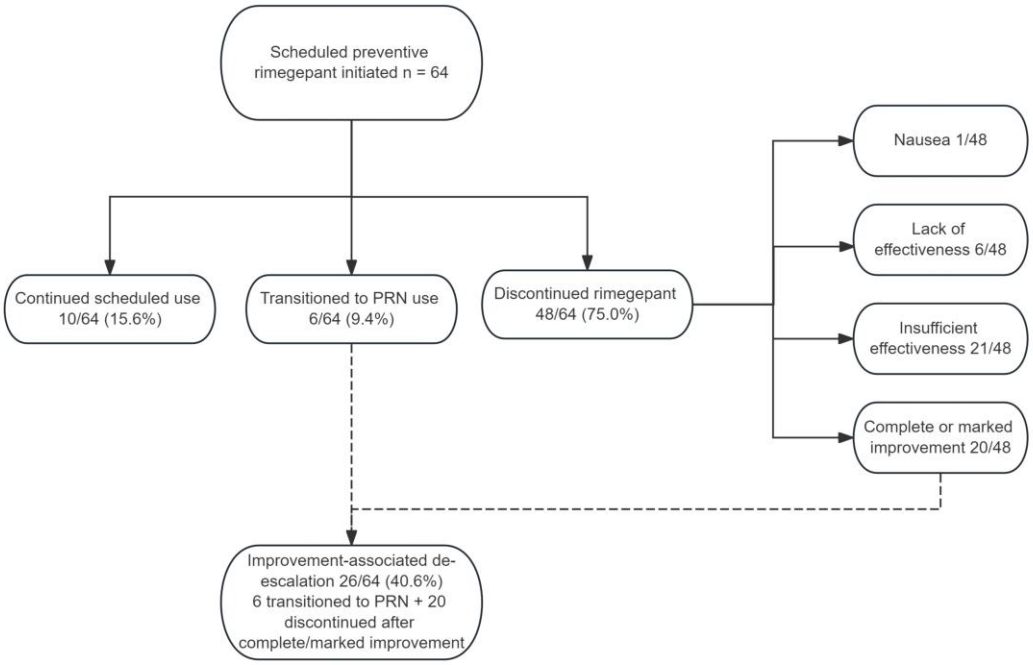


Figure 2. Longitudinal treatment trajectories after initiation of scheduled preventive rimegepant.



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624 Tables

625 Table 1. Baseline clinical characteristics, preventive-treatment background, and factors associated with
626 selection of scheduled preventive rimegepant

627 Panel A. Baseline clinical characteristics and preventive-treatment background

Characteristic	Overall (n=109)	Scheduled rimegepant (n=64)	Management without scheduled rimegepant (n=45)	Absolute SMD	P value
Age, y	15.0 [13.0–17.0]	15.0 [13.8–16.0]	14.0 [13.0–17.0]	0.009	0.833
Age <12 y	12/109 (11.0%)	9/64 (14.1%)	3/45 (6.7%)	0.243	0.352
Female sex	61/109 (56.0%)	33/64 (51.6%)	28/45 (62.2%)	0.215	0.329
Weight, kg	55.0 [45.0–63.5]	55.0 [44.5–62.5]	55.0 [45.0–67.0]	0.117	0.609
Monthly headache days	10.0 [5.0–22.0]	15.0 [6.8–30.0]	7.0 [4.0–12.5]	0.646	0.002
Chronic migraine	33/109 (30.3%)	28/64 (43.8%)	5/45 (11.1%)	0.732	<0.001
Headache duration, y	2.0 [1.0–4.0]	2.0 [1.0–4.0]	2.0 [1.0–4.0]	0.128	0.296
MIDAS score	26 [5–74]	31 [6–80]	21 [5–55]	0.355	0.242
Aura	15/109 (13.8%)	8/64 (12.5%)	7/45 (15.6%)	0.088	0.779
Prior analgesic use	36/109 (33.0%)	22/64 (34.4%)	14/45 (31.1%)	0.070	0.837
Prior Failed Preventive Drug	17/109 (15.6%)	11/64 (17.2%)	6/45 (13.3%)	0.107	0.789
Background preventive-drug category					0.005
1 drug	58/109 (53.2%)	30/64 (46.9%)	28/45 (62.2%)	0.308	
2 drugs	35/109 (32.1%)	19/64 (29.7%)	16/45 (35.6%)	0.125	
≥3 drugs	16/109 (14.7%)	15/64 (23.4%)	1/45 (2.2%)	0.634	
TCM	40/109 (36.7%)	16/64 (25.0%)	24/45 (53.3%)	0.580	0.004
Amitriptyline	59/109 (54.1%)	43/64 (67.2%)	16/45 (35.6%)	0.633	0.002
Antiseizure medication	27/109 (24.8%)	18/64 (28.1%)	9/45 (20.0%)	0.190	0.375
Calcium-channel blocker	13/109 (11.9%)	7/64 (10.9%)	6/45 (13.3%)	0.073	0.769
Erenumab	7/109 (6.4%)	5/64 (7.8%)	2/45 (4.4%)	0.140	0.697

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629 Panel B. Exploratory multivariable treatment-selection model

Variable	Adjusted OR	95% CI	P value
Baseline MHD, per 5-day increase	1.06	0.79–1.42	0.697
Chronic migraine, yes vs no	4.71	1.13–19.63	0.033
Concurrent amitriptyline use, yes vs no	3.29	1.40–7.75	0.006

630

631 Data are median [IQR] or n/N (%). Weight data were available for 108/109 participants (63/64 in the
632 scheduled-rimegepant group). SMD: Standardized Mean Difference; MHD: Monthly Headache Days;
633 MIDAS: Migraine Disability Assessment; TCM: Traditional Chinese Medicine; OR: Odds Ratios; CI:
634 Confidence Interval.

635

636 Table 2. Four-month clinical outcomes following scheduled preventive rimegepant initiation

Outcome	Result
Baseline MHD, mean ± SD	16.58 ± 10.62
4-month MHD, mean ± SD	5.82 ± 5.78
Absolute MHD reduction, mean ± SD	10.76 ± 7.82 days/month
Absolute MHD reduction, 95% CI	8.80–12.71 days/month
Relative MHD reduction, mean	64.5%
Relative MHD reduction, median [IQR]	67.7% [43.8–81.7]
≥50% MHD reduction	46/64 (71.9%)
≥75% MHD reduction	26/64 (40.6%)
≥90% MHD reduction	11/64 (17.2%)
Overall clinical improvement, mean	66.5%
Overall clinical improvement, median [IQR]	75.0% [40.0–85.0]
Scheduled-rimegepant duration, median [IQR]	2.5 [1.5–3.5] months

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638 MHD: Monthly Headache Days; SD, Standard Deviation; IQR: Interquartile Range; PRN: As needed.

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641 Table 3. Four-month outcomes according to subsequent rimegepant treatment trajectory

Outcome	Continued scheduled (n=10)	Scheduled→PRN (n=6)	Discontinued (n=48)	Overall P
Baseline MHD, mean	16.05	19.17	16.36	0.820
4-month MHD, mean	5.98	5.19	5.87	0.786
Absolute MHD reduction, mean	10.07	13.98	10.50	0.713

Relative MHD reduction, mean	57.0%	69.2%	65.5%	0.673
≥50% MHD reduction	6/10 (60.0%)	6/6 (100%)	34/48 (70.8%)	0.235

Trajectory represents post-initiation management state rather than treatment success or failure. MHD: Monthly Headache Days; PRN: As needed.

Table 4. Four-month outcomes among patients who discontinued rimegepant, according to clinical context of discontinuation

Outcome	**Marked/complete clinical benefit (n=21)**	**Partial clinical benefit (n=20)**	**No meaningful clinical benefit (n=7)**
Baseline MHD, mean ± SD	15.60 ± 9.53	17.40 ± 11.45	15.71 ± 11.29
4-month MHD, mean ± SD	2.84 ± 3.18	8.63 ± 7.62	7.06 ± 5.45
Absolute MHD reduction, mean ± SD	12.75 ± 7.81	8.78 ± 6.09	8.66 ± 8.32
Relative MHD reduction, mean ± SD	80.8 ± 13.9%	56.0 ± 19.5%	46.9 ± 21.4%
≥50% MHD reduction	21/21 (100%)	11/20 (55.0%)	2/7 (28.6%)

SD: Standard Deviation; MHD: Monthly Headache Days; IQR: Interquartile Range.

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