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Effectiveness of eptinezumab 300 mg dose escalation in partial responders to 100 mg among patients with difficult-to-treat migraine: A prospective, real-world study by the GRASP study group

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Abstract

Aim: This prospective real-world study aimed to evaluate the effectiveness of escalating eptinezumab to 300 mg in difficult-to-treat migraine patients with a partial response after two 100 mg cycles.

Methods: We included adults with high-frequency episodic or chronic migraine who achieved a partial response (30% to < 50% reduction in monthly headache days (MHD)) after two 100 mg eptinezumab cycles and escalated to 300 mg for two consecutive quarterly cycles. The primary outcome was the proportion of patients achieving a ≥ 50% MHD reduction from baseline after each 300 mg cycle. Secondary outcomes evaluated changes in MHDs with peak intensity > 4, monthly acute medication intake, Migraine Disability Assessment (i.e. MIDAS), and Headache Impact Test-6 (i.e. HIT-6) scores. Logistic regression assessed predictors of response.

Results: We analyzed 57 patients (87.7% female, mean ± SD age of 48.2 ± 10.8 years). Following dose escalation, 57.9% and 64.9% of partial responders achieved ≥ 50% MHD reduction after the first and second 300 mg cycles, respectively. Using generalized estimating equations models, estimated marginal mean MHDs (95% confidence interval) dropped from a baseline of 18.65 (16.93–20.37) days/month to 13.33 (11.76–14.91) days/month after two 100 mg cycles, 10.02 (8.15–11.88) days/month after one 300 mg cycle, and 8.84 (6.77–10.91) days/month after two 300 mg cycles (all $p < 0.05$ vs baseline). Across all secondary outcomes, significant cumulative improvements occurred. Multivariable analysis showed that greater MHD reduction during the 100 mg phase (odds ratio = 0.920, $p = 0.008$) and no prior erenumab exposure (odds ratio = 0.145, $p = 0.012$) independently predicted a ≥ 50% response.

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Conclusions: Escalation to eptinezumab 300 mg was associated with improved population-averaged outcomes in this selected cohort of difficult-to-treat partial responders to 100 mg, supporting, as such, dose escalation over switching therapy.

Keywords
eptinezumab, dose escalation, effectiveness, partial responders, safety

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Introduction

Achieving adequate migraine prevention can substantially improve health-related quality of life (QOL), reduce migraine-related burden and halt clinical progression in patients living with this disabling primary headache. On clinical grounds, effective migraine prophylaxis aims to reduce the attack frequency, disability, and the risk of medication overuse,[1–3] but obtaining an adequate response remains a challenge in a substantial proportion of patients.[4]

From the patients' perspective, expectations regarding preventive therapy indicate that effectiveness ranks among the most valued parameter.[5] Moreover, more than half of migraine patients consider the rapid reduction in migraine probability of occurrence even on the very first day of administration to be at least as crucial as the clinically significant reduction of migraine days over the first month.[6]

The introduction of monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway (anti-CGRP mAbs) has substantially advanced migraine prevention.[7] These targeted therapies are particularly indicated for patients failing to respond to or not tolerating traditional non-specific oral prophylactic medications in high-frequency episodic migraine (HFEM) and onabotulinumtoxinA in the case of chronic migraine (CM).[8] Clinical trials have confirmed the efficacy of these agents in reducing migraine frequency and associated disability in both HFEM and CM.[9–11]

Eptinezumab is a humanized mAb selectively targeting the CGRP ligand with high affinity and specificity. By contrast to other subcutaneously injected anti-CGRP mAbs, eptinezumab is administered intravenously at 100 mg or 300 mg doses every 3 months.[12] This route confers 100% bioavailability and rapid onset, with maximum plasma concentration reached within 30 min and clinical relief from headaches and associated symptoms often evident within hours of infusion.[13] Eptinezumab has shown a favorable benefit-risk ratio in pivotal clinical trials (PROMISE-1 and PROMISE-2) and has been approved for the prophylactic treatment of both episodic and chronic migraine.[14–16]

While real-world studies have confirmed the effectiveness and safety of eptinezumab 100 mg in difficult-to-treat migraine,[17–19] a subset of patients achieves only a partial response. Current clinical guidelines and reimbursement policies often mandate treatment discontinuation if a predefined response threshold (typically $\geq 30\%$ or $\geq 50\%$ reduction in monthly headache days (MHD)) is not met usually after a trial period of at least 6 months.[20] However, dose escalation to 300 mg can rescue partial responders. In the DELIVER trial, which focused on patients with multiple prior preventive failures, eptinezumab 300 mg demonstrated numerically higher responder rates compared to 100 mg.[21] Furthermore, recent real-world data indicate that dose escalation to 300 mg is frequently required in clinical practice and is associated with further reductions in migraine-related disability.[22] Despite these observations, prospective longitudinal data, specifically evaluating the trajectory of partial responders escalated from 100 mg to 300 mg eptinezumab, are lacking.

Two real-world studies, led by the Greek Research Alliance for the Study of headache and Pain (GRASP) study group, demonstrated that eptinezumab 100 mg exerted rapid preventive action from the first week, with sustained reductions in headache days, disability, and acute medication use in treatment-refractory patients over 6 months.[23,24] In the core study, all patients received eptinezumab 100 mg for at least two courses, while dose escalation to 300 mg was reserved for partial responders ($\geq 30\%$ MHD reduction) after treatment for 6 months.[24]

Therefore, the objective of the current study was to evaluate the clinical outcomes, longitudinal changes, and predictors of response following dose escalation to eptinezumab 300 mg in a prospectively followed cohort of difficult-to-treat migraine patients, who exhibited a partial response after two initial cycles of eptinezumab 100 mg.

Methods

Study design and patient selection

This was a prospective, multicenter, open-label, real-world observational study conducted across dedicated headache centers. We enrolled adult patients (aged 18–70 years) with a confirmed diagnosis of HFEM (8–14 migraine days/month) or CM (≥ 15 headache days/month), with or without medication-overuse headache (MOH). The migraine diagnoses were established according to the International Classification of Headache Disorders, 3rd edition (ICHD-3).[25] The MOH diagnosis was based on patient-

reported acute medication use, as documented in headache diaries and clinical records, and was defined per ICHD-3 criteria, as headache occurring on ≥ 15 days per month arising from the regular overuse of acute headache medications for more than 3 months.[25]

Without performing an apriori formal power analysis, the current analysis is focused on a specific sub-cohort of consecutive patients with either HFEM or CM, with or without MOH, who had a history of difficult-to-treat migraine, defined as inadequate response or intolerance to at least three previous preventive treatments; and onabotulinumtoxinA in CM patients. Patients initially received intravenous eptinezumab administered quarterly at a dose of 100 mg for two consecutive sessions (6 months).

Patients demonstrating a partial response were offered dose escalation to 300 mg for the subsequent two quarterly cycles. In this real-world setting, "partial response" was defined clinically by the treating physician as an inadequate, but detectable overall improvement. While this boadly corresponded to an approximate 30% to < 50% mathematical reduction in MHDs, real-world clinical decision-making occasionally replaced strict mathematical diary thresholds when deciding to escalate, taking into account subjective reductions in headache severity and duration, as well as the efficacy of acute medication.

Eptinezumab (Vyepti®, C/S.Sol.In 100 mg/ml vial; Lundbeck A/S) 300 mg (vials of 100 mg/ml, 3 × 1) was administered as a 30-min intravenous infusion in accordance with standard clinical practice. The decision to escalate was made jointly by the treating physician and the patient based on routine clinical practice. Concomitant use of other preventive medications for migraine, including topiramate, onabotulinumtoxinA, or gepants, was not allowed throughout the 12-month observation period.

Eligibility was verified using a protocol-specific STROBE checklist, written informed consent was obtained from all participants, and the study was approved by the principal investigator's Institutional Review Board in accordance with the Declaration of Helsinki. While our core publication described the broader cohort's initial response to 100 mg,[24] this pre-planned longitudinal sub-analysis focuses exclusively on partial responders, escalating to 300 mg. As part of the GRASP study group's ongoing migraine registry, which operates under institutional ethics committee approval with standardized data collection and steering committee oversight, the core study[24] and this subanalysis were not listed in any public clinical trial registry and carries no formal public or internal registry identifier.

Exclusion criteria included major psychiatric disorders (i.e. schizophrenia, severe uncontrolled obsessive–compulsive disorder), illicit substance use disorders, and any contraindication to eptinezumab according to the Summary of Product Characteristics.[26]

Effectiveness evaluation

Patients maintained a daily headache diary from baseline (T0, the trimester before eptinezumab initiation) and throughout the treatment period of 12 months. Clinical follow-ups were conducted after two cycles of 100 mg eptinezumab (T1), after one cycle of 300 mg (T2), and after two cycles of 300 mg (T3). To be compliant, patients had to complete their headache diaries for at least 80% of total days to document changes in all primary and secondary objectives, throughout the study period.

The primary objective was to determine the proportion of patients achieving a ≥ 50% reduction in MHDs (responder rate) at T2 and T3, compared to T1. Secondary objectives included the longitudinal evaluation of changes across the four timepoints (T0, T1, T2, T3) in: (i) overall MHDs; (ii) MHDs with peak pain intensity > 4 (MHDVAS > 4) on a 0–10 visual analog scale (VAS), ranging from 0 to 10[27,28]; and (iii) monthly acute medication intake (MAI). Furthermore, patients were also assessed at T2 and T3 for migraine freedom (no MMDs), optimal control (< 4 MMDs), modest control (4–6 MMDs), and insufficient control (> 6 MMDs), as recently outlined by the International Headache Society (HIS).[29]

Migraine-related disability was assessed longitudinally using the Migraine Disability Assessment (MIDAS) and the Headache Impact Test-6 (HIT-6) questionnaires.[30,31] Patients' self-perceived impact of disease management and satisfaction were investigated using the Patient Global Impression of Change (PGIC) and a binary question (yes/no) regarding satisfaction and intent to continue treatment. PGIC is a 7-point scale, where scores ≥ 5 indicate a clinically significant benefit.[32] Safety was evaluated by recording any adverse events, occurring during or after the infusions.

Statistical analysis

Descriptive statistics were conducted to summarize demographic and clinical characteristics. Continuous variables are presented as the mean ± SD or medians with interquartile range (IQR), depending on data distribution. Categorical variables were presented as frequencies and percentages. Longitudinal changes in continuous effectiveness variables (MHD, MHDVAS > 4, MAI, MIDAS, and HIT-6) between timepoints were analyzed using generalized estimating equations (GEE) models with an exchangeable working correlation matrix to account for within-patient correlation across repeated observations. Estimated marginal means (EMMs) with 95% confidence intervals (CIs) were derived for each timepoint. Pairwise contrasts between timepoints were estimated from the GEE models and p values were Bonferroni-adjusted for the six within-outcome pairwise comparisons.

Changes in MIDAS and HIT-6 are presented descriptively and were assessed using paired Wilcoxon signed-rank tests. Medians and 95% CIs for the differences were estimated using bootstrap resampling. Response rates (≥ 50% reduction in MHDs) were calculated at T2 and T3 and changes in responder status between these timepoints were assessed using the McNemar test.

To identify factors independently associated with a ≥ 50% reduction in MHDs after two cycles of eptinezumab 300 mg (T3), univariable analyses were performed using the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. A multivariable logistic regression model was then constructed with definition of a ≥ 50% MHD reduction at T3 as the binary dependent variable. To reduce the risk of overfitting in this modest sample, the model was restricted a priori to three clinically selected covariates: MHD after the 100 mg phase, percentage change in MHD during the 100 mg phase, and prior erenumab exposure. Results are reported as odds ratios (ORs) with 95% CIs. Unless otherwise stated, all statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS, release 27.0 (IBM Corp.).

Results

Baseline characteristics

During the study period, a total of 150 patients started eptinezumab 100 mg within the parent GRASP registry. Of these, 57 patients met the clinical definition of partial responder after 6 months. The current cohort comprised of 57 consecutive partial responders who jointly decided with their physician to undergo dose escalation to 300 mg and successfully completed the subsequent two quarterly cycles with > 80% of total days diary compliance.

The cohort was predominantly female (87.7%), with a mean ± SD age of 48.2 ± 10.8 years. CM was present in 56.1% of patients, and 56.1% had comorbid MOH. The population was highly refractory, with a median migraine duration of 22.0 years and a median of four prior preventive treatment failures (IQR = 4–6). Among participants, 28.1% ($n = 16$) had previously failed the anti-CGRP receptor mAb erenumab and 47.4% ($n = 27$) had failed an anti-CGRP ligand mAb. Notably, these categories were not mutually exclusive because 11 patients had been exposed to both classes. Psychiatric comorbidities were common, affecting 59.6% of the cohort.

At T0, patients experienced a high disease burden, with a median of 17.0 days/month for MHDs, 14.0 days/month for MHDVAS > 4 and 15.0 days/month, for MAIs. Disability scores were high as well, with a median MIDAS score of 93.0 and a median HIT-6 score of 66.0. Following the initial two cycles of 100 mg eptinezumab (T1), the median MHDs had decreased to 11.0 days/month, representing a median percentage reduction of 30.0% (IQR = 16.7–37.5) to confirm the required status of participants as partial responders. The baseline demographic and clinical characteristics of our cohort are summarized in Table 1.

Longitudinal changes across four timepoints

Using GEE longitudinal modelling to account for intra-subject repeated measures, it was evident that the dose escalation to eptinezumab 300 mg resulted in significant and cumulative improvements across all effectiveness and disability outcomes. For MHD, the EMM (95% CI) decreased from 18.65 (16.93–20.37) days/month at baseline (T0) to 13.33 (11.76–14.91) days/month after two 100 mg cycles (T1), 10.02 (8.15–11.88) days/month after one 300 mg cycle (T2), and 8.84 (6.77–10.91) days/month after two 300 mg cycles (T3). Relative to T1, MHD decreased by an estimated 3.32 days/month at T2 (95% CI = −4.38 to −2.25; Bonferroni-adjusted; $p < 0.001$) and by 4.49 days/month at T3 (95% CI = −5.74 to −3.24; adjusted $p < 0.001$). A further, smaller reduction was observed between T2 and T3 (ΔEMM = −1.18 days/month, 95% CI = −1.83 to −0.52; adjusted $p = 0.003$). Likewise, MAI decreased from an EMM (95% CI) of 17.25 (15.63–18.86) days/month at T0 to 12.39 (10.84–13.94) days/month at T1, 9.40 (7.49–11.31) days/month at T2, and 8.16 (6.18–10.14) days/month at T3. Compared with T1, MAI was reduced by 2.98 days/month at T2 (95% CI = −4.01 to −1.96; adjusted $p < 0.001$) and by 4.23 days/month at T3 (95% CI = −5.50 to −2.96; adjusted $p < 0.001$), with a further reduction from T2 to T3 (ΔEMM = −1.25 days/month days/month, 95% CI = −2.06 to −0.44; adjusted $p = 0.015$). Similar beneficial changes were observed for severe headache days (MHDVAS > 4). The longitudinal EMM changes and pairwise comparisons in MHD frequency, MHD with VAS > 4 severity, and MAI across timepoints are described in Tables 2 and 3.

Migraine-related disability also significantly improved. The median MIDAS score decreased from 93.0 at baseline to 75.0 after 100 mg, dropping substantially to 39.0 after two cycles of 300 mg (T1 vs T3: Δmedian = −32.0, 95% CI = −40.0 to −23.0; Bonferroni-corrected $p < 0.001$). HIT-6 scores followed the latter improvement, decreasing from 66.0 to 54.0 by the end of the observation period. The longitudinal changes in MIDAS and HIT-6 scores across timepoints are depicted in Figure 1.

Response rates and patient satisfaction

Following dose escalation to 300 mg, a substantial proportion of these initial partial responders achieved a ≥ 50% reduction in MHDs, compared to baseline. After the first 300 mg cycle (T2), 57.9% (33/57) met the ≥ 50% responder threshold. This proportion increased to 64.9% (37/57) after the second 300 mg cycle. The shift in responder status

Table 1. Baseline demographic and clinical characteristics ($N = 57$).

Variable	Value
Demographics	
Female, *n* (%)	50 (87.7%)
Age (years), mean ± SD (range)	48.2 ± 10.8 (23–67)
Clinical history	
Migraine type, *n* (%)	
Episodic migraine (HFEM)	25 (43.9%)
Chronic migraine (CM)	32 (56.1%)
Migraine duration (years), median (interquartile range (IQR))	22.0 (15.0–28.0)
Prior preventive treatments, median (IQR)	4.0 (4.0–6.0)
Prior anti-calcitonin gene-related peptide (CGRP) receptor Mab (erenumab), *n* (%)	16 (28.1%)
Prior anti-CGRP ligand monoclonal antibody (mAb), *n* (%)	27 (47.4%)
Migraine with aura, *n* (%)	13 (22.8%)
Medication overuse headache (MOH), *n* (%)	32 (56.1%)
Any psychiatric comorbidity, *n* (%)	34 (59.6%)
Anxiety disorder	14 (24.6%)
Depression	9 (15.8%)
Baseline disease burden (median, IQR)	
Monthly headache days (MHD)	17.0 (12.0–25.0)
MHD with intensity VAS > 4	14.0 (10.0–19.0)
Monthly acute medication intake (MAI)	15.0 (12.0–22.0)
MIDAS score	93.0 (80.0–137.0)
HIT-6 score	66.0 (66.0–72.0)

HIT-6: Headache Impact Test-6; MIDAS: Migraine Disability Assessment.

between the first and second 300 mg cycles was not statistically significant (McNemar test $p = 0.344$), although a trend to improvement was seen. When analyzing specific response categories after two 300 mg cycles, 45.6% (26/57) of patients achieved a super-response (≥ 75% reduction), 19.3% (11/57) achieved a 50–74% reduction, 14.0% (8/57) maintained a 30–49% reduction, and 21.1% (12/57) experienced < 30% reduction. The response rate categories at T2 and T3 are depicted in Figure 2.

When treatment outcomes were re-grouped into optimal control (< 4 MMDs), moderate response (4–6 MMDs), and insufficient control (> 6 MMDs), just 7 (12.3%) patients achieved optimal control at T2. While a significant proportion of patients achieved the traditional ≥ 50% response threshold at both T2 (57.9%) and T3 (64.9%), only a minority (12.3%) obtained optimal control (< 4 MMDs), particularly when the assessment was made at T2. At T3, the optimal migraine control rates significantly elevated to 35.1%.

Patient satisfaction was generally high, with 87.7% expressing satisfaction and intention to continue treatment after the first 300 mg cycle and 64.9% after the second cycle. The median PGIC score was 5.0 (IQR = 5.0–6.0) after one 300 mg cycle and 6.0 (IQR = 4.0–6.0) after two cycles. A clinically significant benefit (PGIC ≥ 5) was reported by 75.4% and 70.2% of patients at T2 and T3, respectively.

Predictors of response after 300 mg escalation

To identify factors associated with achieving a ≥ 50% response after two cycles of 300 mg, univariate and multivariable analyses were performed. In univariate analysis, responders had a significantly shorter migraine duration (median = 20.0 vs 26.0 years, $p = 0.001$), fewer prior preventive treatments (median = 4.0 vs 6.0, $p = 0.016$), and lower MHDs after the 100 mg phase (median = 10.0 vs 16.5, $p = 0.002$). A greater initial percentage reduction in MHDs during the 100 mg phase was strongly associated with eventual response to 300 mg (median = −31.8% vs −18.3%, $p = 0.009$). Prior exposure to erenumab was significantly less common among responders (16.2% vs 50.0%, OR = 0.19, $p = 0.012$).

To both prevent overfitting and ensure statistical stability as a result of the modest sample size, the multivariable logistic regression model was strictly limited to three core clinical covariates, and included lower MHDs after the 100 mg phase, percentage change in MHDs during the 100 mg phase, and prior exposure to erenumab. This simplified model confirmed that a greater percentage MHD reduction during the 100 mg phase (OR = 0.920, 95% CI = 0.865–0.978, $p = 0.008$; note that more negative values represent greater reduction) and the absence of prior erenumab exposure (OR = 0.145, 95% CI = 0.032–0.654; $p = 0.012$) remained independent predictors of achieving a ≥ 50% response following dose escalation.

Subgroup analysis: HFEM vs CM

Although migraine type was not an independent predictor in the multivariable model, clinical outcomes differed slightly between subgroups. Figure 3 shows that among the 25 HFEM patients, median MHDs decreased from 12.0 days/month at baseline to 4.0 days/month after two 300 mg cycles, with 76.0% (19/25) achieving a ≥ 50% response. Among the 32 CM patients, median MHDs decreased from 25.0 days/month to 7.5 days/month, with 56.2% (18/32) achieving a ≥ 50% response. Notably, of the 29 patients with CM and comorbid MOH at baseline, 21 patients (72.4%) reverted to non-MOH status at T3. The difference in response rates between EM and CM remained statistically insignificant (Fisher's exact OR = 2.46, $p = 0.165$).

Safety

Dose escalation to eptinezumab 300 mg was generally safe and well tolerated. Adverse events were mild, transient, and

Table 2. Estimated marginal means (EMMs) in core efficacy outcomes, across study timepoints.

Outcome	T0: baseline EMM (95% CI)	T1: after 2 × 100 mg EMM (95% CI)	T2: after 1 × 300 mg EMM (95% CI)	T3: after 2 × 300 mg EMM (95% CI)
MHD	18.65 (16.93–20.37)	13.33 (11.76–14.91)	10.02 (8.15–11.88)	8.84 (6.77–10.91)
MHDVAS > 4	15.14 (13.70–16.58)	11.77 (10.30–13.25)	8.39 (6.60–10.17)	7.51 (5.68–9.34)
MAI	17.25 (15.63–18.86)	12.39 (10.84–13.94)	9.40 (7.49–11.31)	8.16 (6.18–10.14)

Bonferroni-adjusted $p < 0.05$ for all comparisons.
Abbreviations: CI: confidence interval; EMM, estimated marginal mean; MHD, monthly headache days; MHDVAS > 4, monthly headache days with peak pain intensity > 4 on a 0–10 visual analogue scale; MAI, monthly acute medication intake.

Table 3. Pairwise comparisons in core efficacy variables derived from the GEE models.

Outcome	Pairwise comparisons	ΔEMM (days/month) (95% CI)	Bonferroni-adjusted *p* value
MHD	T0 vs T1	−5.32 (−7.07 to −3.56)	< 0.001
	T0 vs T2	−8.63 (−10.47 to −6.80)	< 0.001
	T0 vs T3	−9.81 (−11.90 to −7.71)	< 0.001
	T1 vs T2	−3.32 (−4.38 to −2.25)	< 0.001
	T1 vs T3	−4.49 (−5.74 to −3.24)	< 0.001
	T2 vs T3	−1.18 (−1.83 to −0.52)	0.003
MHDVAS > 4	T0 vs T1	−3.37 (−5.22 to −1.52)	0.002
	T0 vs T2	−6.75 (−8.79 to −4.72)	< 0.001
	T0 vs T3	−7.63 (−9.77 to −5.50)	< 0.001
	T1 vs T2	−3.39 (−4.37 to −2.40)	< 0.001
	T1 vs T3	−4.26 (−5.35 to −3.18)	< 0.001
	T2 vs T3	−0.88 (−1.43 to −0.32)	0.012
MAI	T0 vs T1	−4.86 (−6.82 to −2.90)	< 0.001
	T0 vs T2	−7.84 (−9.93 to −5.76)	< 0.001
	T0 vs T3	−9.09 (−11.37 to −6.81)	< 0.001
	T1 vs T2	−2.98 (−4.01 to −1.96)	< 0.001
	T1 vs T3	−4.23 (−5.50 to −2.96)	< 0.001
	T2 vs T3	−1.25 (−2.06 to −0.44)	0.015

Abbreviations: CI: confidence interval; EMM, estimated marginal mean; GEE, generalized estimating equations; MAI, monthly acute medication intake; MHD, monthly headache days; MHDVAS > 4, monthly headache days with peak pain intensity > 4 on a 0–10 visual analogue scale.

infrequent. During the 300 mg phase, the most commonly reported adverse events were fatigue ($n = 4$) and intense dreams ($n = 2$). No infusion-related adverse events or safety-related discontinuations occurred.

Discussion

Prospective longitudinal data, specifically examining the clinical course of partial responders who undergo dose escalation from eptinezumab 100 mg to 300 mg, remain quite limited. Our real-world study provides prospective evidence that dose escalation to eptinezumab 300 mg is clinically effective in difficult-to-treat migraine patients, who exhibit only a partial response to the standard 100 mg dose.

In this highly refractory cohort with a median of four prior preventive treatment failures, escalation to eptinezumab 300 mg was associated with clinically relevant reductions/improvements in MHD, severe headache days, MAI, and patient-reported disability measures. For the diary-derived efficacy outcomes, repeated-measures GEE analysis confirmed significant population-averaged reductions across the four study timepoints. A substantial proportion of patients achieved the traditional ≥ 50% response threshold at T2 (57.9%); 64.9% achieved a ≥ 50% reduction in MHDs at T3, and 45.6% achieved a ≥ 75% MHD reduction. However, the optimal migraine-control rate (< 4 MMDs) was 12.3% at T2 and 35.1% at T3. This pattern overall, demonstrates a clinically-relevant mismatch between conventional trial metrics (≥ 50% MMD reduction) and the higher threshold of optimal control, as recently set by the IHS (29). Nonetheless, our results at T3 showed that the dose escalation can drive significant clinical improvements even in patients who initially exhibit a modest or insufficient control at T2.

These results are consistent with and even extend upon recent clinical trial and real-world data. In the DELIVER trial, which also focused on patients with multiple prior preventive failures, eptinezumab 300 mg was highly effective, and post-hoc analyses revealed that approximately one-third

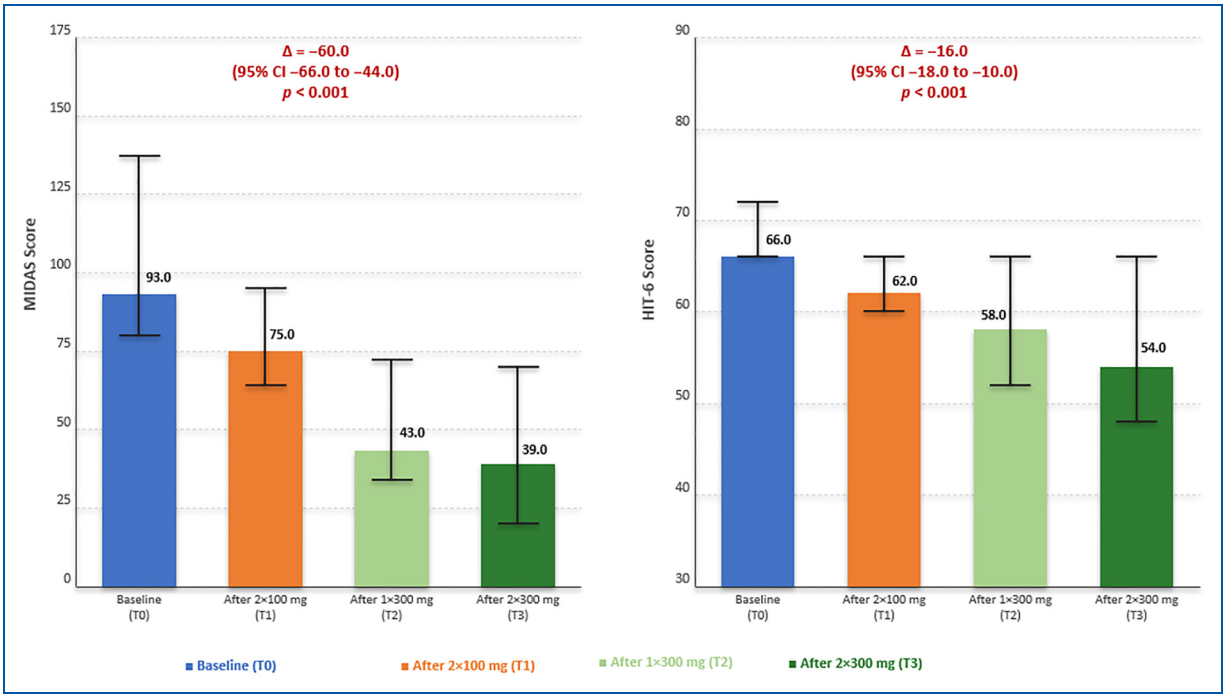


Figure 1. Longitudinal disability and headache impact during eptinezumab treatment. MIDAS (left) measures migraine-limited days over the prior 3 months; HIT-6 (right) measures headache impact. Bars show median scores (labeled) with IQR (25th to 75th percentiles). Numeric labels identify medians and vertical axes are scores. CI: confidence interval; HIT-6: Headache Impact Test-6; MIDAS: Migraine Disability Assessment

of initial non-responders became responders after a second infusion.[21] Our study demonstrates that in a real-world setting, extending treatment and escalating the dose can rescue a large proportion of partial responders. However, the findings of the 48-week EMBRACE III study cautioned against attributing clinical improvements solely to dose escalation because patients maintained on the 100 mg dose also demonstrated continued, time-dependent improvements.[22]

Response heterogeneity between the first and second 300 mg cycles also warrants consideration. Regarding the increase in the proportion of patients with $<30\%$ response (from 10.5% to 21.1%), it should be discussed that between the first and second 300 mg cycles, all six patients classified as poor responders ($<30\%$ MHD reduction) at T2 remained in that category at T3, confirming that this subset represents a refractory group for whom dose escalation was insufficient regardless of the number of cycles. The six additional patients entering the $<30\%$ category at T3 had been in borderline response categories at T2 (30% to $<50\%$), with individual trajectories consistent with the natural intra-individual variability of migraine frequency.[33] As such, the apparent doubling of the $<30\%$ responder category at T3 does not indicate pharmacological failure after the second 300 mg cycle, but rather reflects the persistence of an already-established refractory subgroup (six patients unchanged) combined with the natural intra-individual variability of migraine frequency in other six borderline cases.

The GEE models showed significant further reductions from T2 to T3 in MHD ($\Delta EMM = -1.18$ days/month; Bonferroni-adjusted $p = 0.003$), MHDVAS >4 ($\Delta EMM = -0.88$ days/month; adjusted $p = 0.012$), and MAI ($\Delta EMM = -1.25$ days/month; adjusted $p = 0.015$). These GEE trajectories indicate attenuation rather than cessation of benefit during the 300 mg escalation phase. The most marked reductions were observed before or after the first 300 mg cycle as MHD decreased by 3.32 days/month from T1 to T2 (adjusted $p < 0.001$), MHDVAS >4 by 3.39 days/month (adjusted $p < 0.001$), and MAI by 2.98 days/month (adjusted $p < 0.001$). Additional reductions from T2 to T3 were smaller, but remained statistically significant for each endpoint. Thus, the available data are compatible with an emerging therapeutic ceiling or diminishing marginal benefit after the initial 300 mg infusion and do not support a definitive response plateau, because the population-averaged trajectories continued to improve. In parallel, the $\geq 50\%$ responder proportion increased from 57.9% to 64.9%, although this change did not reach statistical significance by the exact McNemar test ($p = 0.344$). Taken together, these results suggest that continued 300 mg treatment may augment response in some patients, whereas others show stable or fluctuating disease activity. The intravenous administration of eptinezumab provides 100% bioavailability and immediate maximal concentration, which may facilitate a more profound blockade of

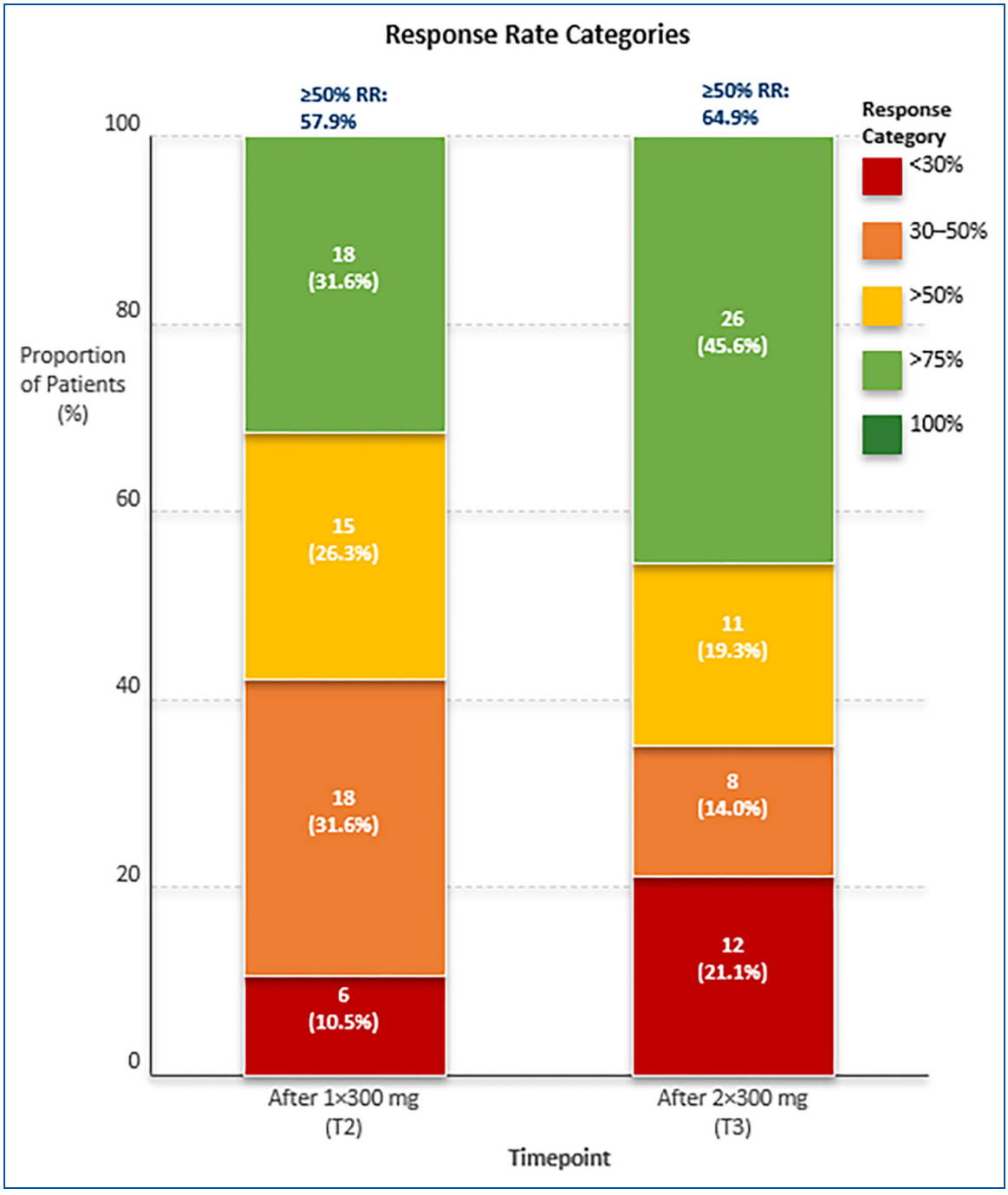


Figure 2. Monthly headache days (MHD) response category distribution after 300 mg cycles. Each stacked bar represents all 57 patients and sums to 100%. Segments show the number and percentage of patients in mutually exclusive categories of MHD reduction from baseline: < 30%, 30 to < 50%, 50 to < 75%, 75 to < 100%, and 100%. The exact McNemar test for change in ≥ 50% responder rate (RR) change between T2 and T3 was non-significant ($p = 0.344$)

the CGRP pathway when the dose is increased.[34,35] This pharmacokinetic profile could explain why patients who experience a partial, but insufficient, response at 100 mg can achieve a clinically meaningful response at 300 mg.

Multivariable logistic regression revealed two key independent predictors of successful dose escalation. First, the degree of initial response during the 100 mg phase was highly predictive. Patients who experienced a greater percentage reduction in MHDs (even if < 50%) were significantly more likely to be classified as full responders upon escalation to 300 mg. This suggests that an even modest early signal of biological responsiveness to CGRP ligand

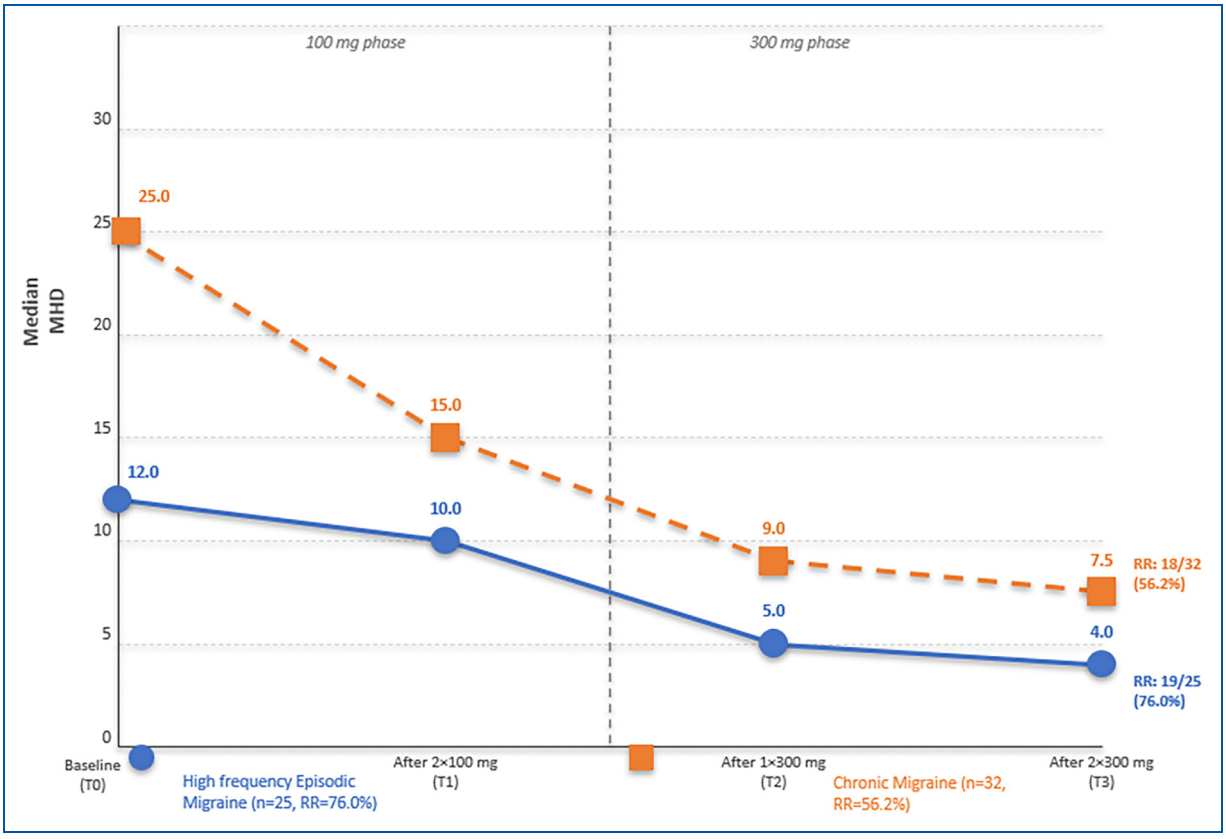


Figure 3. Descriptive monthly headache days (MHD) outcomes by migraine subtype. Subgroup medians for high-frequency episodic migraine (HFEM; $n = 25$, solid blue/circles) and chronic migraine (CM; $n = 32$, dashed orange/squares). These lines are descriptive connections between observed subgroup medians and are not regression lines or model-fitted estimates. Vertical dashed line indicates transition from 100 mg to 300 mg phase. At T3, the ≥ 50% responder rate (RR) was 76.0% (19/25) in HFEM and 56.2% (18/32) in CM (Fisher's exact test $p = 0.165$)

blockade justifies dose escalation rather than treatment discontinuation. Second, prior treatment failure with erenumab, an anti-CGRP receptor mAb, was a strong negative predictor of response to eptinezumab 300 mg. The odds of achieving a ≥ 50% response were substantially lower in patients with prior erenumab failure (OR = 0.145, 95% CI = 0.032–0.654) compared to erenumab-naïve patients. However, cautious interpretation of this finding is needed because of the wide confidence interval likely resulting from the limited sample size.

Mechanistically, prolonged erenumab receptor blockade may induce compensatory trigeminovascular neuroplasticity and upregulate CGRP synthesis.[36,37] This increased CGRP burden could render standard doses of subsequent CGRP-ligand inhibitors insufficient for effective neutralization, if the effective CGRP burden has been amplified by prior receptor blockade. Regarding ligand mAbs (47.4% in our cohort), the fact that prior ligand mAb failure did not negatively predict response is an interesting finding with mechanistic hypotheses extending beyond our clinical data and requiring validation in larger, dedicated switching studies. Nonetheless, the latter finding is also of particular interest in the context of switching strategies. Previous real-world studies have reported mixed results when switching between CGRP mAbs, with response rates generally ranging from 30% to 50%.[38–40] A recent retrospective study evaluated eptinezumab in patients who had failed both erenumab and at least one subcutaneous ligand mAb, reporting a modest 29.7% response rate even with 300 mg escalation.[41] Based on our own data, we might assume that while switching to an intravenous ligand mAb, such as eptinezumab, can be highly effective for many refractory patients, a history of receptor mAb (erenumab) failure specifically identifies a highly refractory phenotype that is less responsive to subsequent CGRP pathway manipulation, regardless of the dose or route of administration.

Another issue that certainly merits discussion concerns the results of our subgroup analysis comparing patients with HFEM ($n = 25$) and CM ($n = 32$). A 20% absolute gap in ≥ 50% response rates (76.0% vs 56.2%) appears clinically meaningful, although Fisher's exact test yielded a non-significant difference of $p = 0.165$. This result should not be interpreted as evidence that migraine subtype does not influence treatment response, although this subgroup

analysis, being underpowered, must be regarded as a hypothesis-generating finding, warranting confirmation in much larger cohorts.

This study has several strengths including its prospective design, the focus on a specifically defined and clinically challenging subpopulation (partial responders to 100 mg), and the comprehensive longitudinal assessment across four distinct timepoints, providing a clear view of the dose escalation effect. Furthermore, the inclusion of validated patient-reported outcomes (MIDAS, HIT-6, and PGIC) confirms that the numerical reductions in MHDs translate into meaningful improvements in QOL and disability.

A major limitation of our applied open-label observational design is the absence of a parallel control arm of partial responders maintained on 100 mg without escalation. Consequently, we cannot definitively exclude that the observed clinical improvements following dose escalation are partly attributable to the delayed therapeutic effect of prolonged eptinezumab exposure, expectation bias, natural disease fluctuation or placebo effect. Regression to the mean is another inherent limitation as our patients were escalated because of insufficient response, and without a control arm, spontaneous improvement cannot be fully distinguished from true drug effect. Placebo reductions in PROMISE-2 (5.6–6.2 days) and DELIVER (2.1 days) confirm that non-specific effects can occur at some degree even in refractory populations.[15,16,21] The magnitude of improvement in our cohort with a median MHD reduction of 6 days/month, and 64.9% $\geq$ 50% responders (45.6% achieving $\geq$ 75% reduction), substantially exceeds expected natural fluctuation given our cohort's long duration of disease and refractoriness. As such, the magnitude of improvement exceeds typical placebo responses observed in trials like PROMISE-2 and DELIVER.[15,16,21] The sample size of 57 patients, although sufficient for the primary analyses, may limit the statistical power to detect smaller differences in subgroup analyses, such as the comparison between HFEM and CM; as discussed in detail above. Moreover, the study was conducted in specialized headache centers, and our cohort was characterized by highly refractory disease, long migraine duration, and multiple prior preventive failures. Therefore, the generalizability of these findings to routine neurological practice, where patients typically present with less refractory phenotypes, remains uncertain. Finally, we should acknowledge that our cohort represents a highly selected subgroup of partial responders to eptinezumab 100 mg and therefore the robust responder rates observed after escalation (64.9% achieving $\geq$50% response) to the 300 mg dose cannot be generalized to the overall migraine population, to primary non-responders to 100 mg, or to patients receiving 300 mg as a first-line therapy.

In conclusion, escalation to eptinezumab 300 mg was associated with improved population-averaged outcomes in this selected cohort of difficult-to-treat partial responders to 100 mg. The GEE trajectories show that the principal mean improvement occurred by the first 300 mg cycle, with smaller but statistically significant additional reductions after the second cycle. Given the uncontrolled observational design, heterogeneity of individual response trajectories, and 6-month follow-up after escalation, a causal dose effect and the durability of benefit require confirmation in controlled studies with extended observation at 12- to 24-month follow-ups.

Article highlights

- Escalation converted partial 100 mg responders: 57.9% and 64.9% achieved $\geq$ 50% MHD reduction after first and second 300 mg cycles.
- After two 300 mg cycles, MHD decreased from 17 to 5, MIDAS scores dropped from 93 to 39 and MAI from 15 to 4.
- Greater 100 mg MHD reduction and no prior erenumab exposure independently predicted $\geq$50% response, supporting escalation before switching treatment.

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Ethical considerations

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of General Clinic, Thessaloniki and "Agios Andreas" General Hospital of Patras.

Consent to participate

All participants completed an informed consent process and signed informed consent forms approved by the above Institutional Review Boards.

Author contributions

Conceptualization: EVD, AAA, MV; Methodology: EVD, AAA, MV; Formal analysis: EVD, AAA, MV; All authors equally contributed to data curation, and writing – reviewing & editing original draft. Supervision: AAA, MV.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

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