TEV-48125 for the preventive treatment of chronic migraine

Efficacy at early time points

OPEN

Marcelo E. Bigal, MD,
PhD
David W. Dodick, MD
Abouch V.
Krymchantowski, MD,
PhD
Juliana H. VanderPluym,
MD
Stewart J. Tepper, MD
Ernesto Aycardi, MD
Pippa S. Loupe, PhD
Yuju Ma, MS
Peter J. Goadsby, MD

Correspondence to
Dr. Bigal:
marcelo.bigal@tevapharm.com

ABSTRACT

Objective: To evaluate the onset of efficacy of TEV-48125, a monoclonal antibody against calcitonin gene-related peptide, recently shown to be effective for the preventive treatment of chronic migraine (CM) and high-frequency episodic migraine.

Methods: A randomized placebo-controlled study tested once-monthly injections of TEV-48125 675/225 mg or 900 mg vs placebo. Headache information was captured daily using an electronic headache diary. The primary endpoint was change from baseline in the number of headache hours in month 3. Herein, we assess the efficacy of each dose at earlier time points.

Results: The sample consisted of 261 patients. For headache hours, the 675/225-mg dose separated from placebo on day 7 and the 900-mg dose separated from placebo after 3 days of therapy ($p = 0.048$ and $p = 0.033$, respectively). For both the 675/225-mg and 900-mg doses, the improvement was sustained through the second ($p = 0.004$ and $p < 0.001$) and third ($p = 0.025$ and $p < 0.001$) weeks of therapy and throughout the study (month 3, $p = 0.0386$ and $p = 0.0057$). For change in weekly headache days of at least moderate intensity, both doses were superior to placebo at week 2 ($p = 0.031$ and $p = 0.005$).

Conclusions: TEV-48125 demonstrated a significant improvement within 1 week of therapy initiation in patients with CM.

Classification of evidence: This study provides Class II evidence that for patients with CM, TEV-48125 significantly decreases the number of headache hours within 3 to 7 days of injection. *Neurology*® 2016;87:41-48

GLOSSARY

CGRP = calcitonin gene-related peptide; **CI** = confidence interval; **CM** = chronic migraine; **LSM** = least square mean; **NNT** = number needed to treat; **TNC** = trigeminal nucleus caudalis.

Chronic migraine (CM) is characterized by headaches occurring on at least 15 days per month, with at least 8 days of migraine per month.¹ It affects approximately 1% of the adult population^{2,3} and is the most frequently seen headache syndrome at major headache clinics and neurology specialty centers.^{4,5} On the basis of ictal disability alone, migraine was ranked sixth highest among specific causes of disability globally.^{6,7} Migraine-related disability is classified by the World Health Organization as more burdensome than paraplegia, deafness, or angina, and at the same level as psychosis and quadriplegia.⁸ Furthermore, relative to individuals with episodic migraine or without headaches, those with CM are significantly more likely to be unemployed or employable but not actively working for pay.⁹ Individuals with CM are also significantly more likely to be divorced and to have psychological comorbidities.⁹

Despite its enormous burden, CM is undertreated. Effective treatment, at a minimum, requires consultation with a physician, an accurate diagnosis, and receiving appropriate treatment.

From Teva Pharmaceuticals (M.E.B., E.A., P.S.L., Y.M.); Mayo Clinic (D.W.D., J.H.V.P.), Phoenix, AZ; The Headache Center of Rio (A.V.K.); American Headache Society (A.V.K.); Dartmouth Medical School (S.J.T.), Hanover, NH; and NIHR-Wellcome Trust King's Clinical Research Facility (P.J.G.), King's College London, UK.

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In the United States, less than 5% of persons with CM are able to traverse all 3 of these hurdles, and only a third of those with CM receive preventive medications.¹⁰ Furthermore, 1-year adherence to labeled or off-label migraine preventive medication among individuals with CM occurs in less than 20% of patients. The most important reasons for discontinuation of preventive medications among individuals with CM appear to be incomplete efficacy, as well as slow time to reach meaningful efficacy, and poor tolerability.^{10,11} It has been suggested that fast onset of efficacy of migraine drugs may have significant implications for patients, since it would favor compliance and improve long-term outcomes.¹²

TEV-48125 is a fully humanized monoclonal antibody that potently and selectively binds to calcitonin gene-related peptide (CGRP).¹³ Its efficacy in the preventive treatment of CM was demonstrated in a large phase 2b study, where both tested doses separated from placebo after 1 month of therapy for primary, secondary, and exploratory endpoints.¹⁴ Since statistically significant effects were seen very early in that trial, herein we conducted post hoc analyses to evaluate the efficacy of 2 doses of subcutaneous TEV-48125 within the first few weeks of therapy in patients with CM.

METHODS Study design and patients. The current study represents post hoc analyses conducted as part of a phase 2b trial assessing the efficacy of TEV-48125 in the preventive treatment of CM in adults.¹⁴ The randomized, double-blind, placebo-controlled, phase 2b study was conducted at 62 sites in the United States (headache centers, neurology clinics, and primary care facilities) and an independent clinical research organization, NCGS, monitored the study, assessing for appropriate patient eligibility, protocol adherence, and completeness and accuracy of case report entries. Eligible study participants were men or women aged 18 to 65 years with a history of CM as per the *International Classification of Headache Disorders*, 3rd edition (beta version).¹ Headache and migraine frequencies were confirmed during a prospective 28 days run-in period. Participants could continue to use up to 2 different standard migraine preventive medications, if on stable doses for at least 3 months before study onset. They were allowed to treat their acute migraine attacks as usual and had to show higher than 80% compliance in completing the electronic headache diary during the 28-day run-in phase to participate in this study. Patients were excluded if they had received onabotulinumtoxinA during the 6 months before study entry or if 3 or more preventive medications failed because of lack of efficacy.

Standard protocol approvals, registrations, and patient consents. The study was conducted in accordance with the principles of Good Clinical Practice and the US Food and Drug Administration guidelines for safety monitoring. All patients

provided written informed consent before enrollment. The study protocol was approved by the institutional review boards for each site, and the trial is registered at clinicaltrials.gov (NCT02021773).

Randomization and treatment procedures. After the run-in period, participants were randomized (1:1:1) via an electronic interactive web response system, which was accessible through the eClinical Operating System Portal. Randomization was stratified independently by sex and preventive medication use. The randomization sequence was developed centrally by staff at NCGS who had no further role in the study. Study sites had 2 blinded study coordinators at clinic visits, one for clinical assessments and one for treatment administration, and participants were masked to treatment allocations. Participants randomized to the 900-mg arm received 4 active injections of 225 mg/1.5 mL once monthly. Those in the 675/225-mg arm received an initial loading dose of 675 mg (3 active injections of 225 mg and one placebo injection), followed by maintenance doses of 225 mg (one active and 3 placebo injections) for the second and third monthly treatments. Patients receiving placebo received 4 placebo injections monthly. Adverse events, laboratory findings, ECG, and concomitant drugs were captured monthly at every visit.

Outcomes. As described previously,¹⁴ the primary endpoint for the study was the mean change from baseline in the number of headache hours of any severity during the 28-day posttreatment period ending with month 3. The secondary endpoint was the mean change from baseline in the number of headache days of at least moderate severity during month 3. Here, we analyzed the weekly cumulative headache hours and headache days of at least moderate severity in the first month by week and further analyzed accumulative headache hours in the first 7 days after the first dose of study medication.

Statistical analyses. Similar to the analyses conducted for the primary and secondary endpoints, the mixed-effects model repeated measurement analysis method was used for the post hoc analyses reported herein of the weekly change-from-baseline values for the number of headache hours and moderate/severe headache days in first 4 weeks. We used analysis of covariance for the post hoc intraweekly assessments. For each given period (e.g., first week after treatment, or 3 days after treatment), baseline values were calculated using the original monthly baseline value multiplied by a factor to match the time period (in the examples given above, first week or first 3 days, baseline value was the original monthly baseline multiplied by 7/28, or 3/28). In additional post hoc analyses, we calculated the absolute risk reduction and the number needed to treat (NNT) in the proportion of patients with at least a 50% reduction from baseline headache hours and moderate/severe headache days in the first few weeks.

All statistical tests were 2-sided at α level of 0.05. All efficacy variables were analyzed by the intent-to-treat principle, which included all randomized participants who received at least one dose of study drug and provided at least one endpoint measurement. Overall compliance for baseline and first month posttreatment was 92%. For the analyses presented herein, all *p* values presented are nominal without multiplicity adjustment. Analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS Eligibility screening for the phase 2 study began in January 2014 and the last patient visit

occurred in December 2014. The sample consisted of 261 patients randomized to receive placebo ($n = 89$), 675/225 mg ($n = 87$), or 900 mg ($n = 85$) (figure 1). Demographics and clinical disease characteristics were similar across groups and are described in table 1. Mean overall age was 41 years, 86% of participants were women, 83% were white, and 40% of participants used preventive medications at the time of the study.

Planned analyses recap. A priori analyses have been published.¹⁴ In brief, at baseline, participants had a mean of 162 headache hours per month and a mean of 22 headache days and 17 migraine days per month. For the primary endpoint, least square mean (LSM) change from baseline to month 3 in the number of headache hours was -37.1 (SE 8.4) for placebo, -59.8 (8.6) for 675/225 mg ($p = 0.039$, LSM difference -22.7 , and 95% confidence interval [CI]:

-44.28 to -1.21), and -67.5 (8.6) for 900 mg ($p = 0.006$, LSM difference -30.4 , and 95% CI: -51.88 to -8.95). At 1 month of therapy, the number of headache hours decreased from baseline for placebo was -18.1 (7.1), 675/225 mg = -44.1 (7.3; $p = 0.003$); 900 mg = -56.82 (7.3; $p < 0.001$). At 2 months of therapy, the number of hours decreased from baseline for placebo was -34.1 (8.0), 675/225 mg = -58.3 (8.1; $p = 0.018$); and 900 mg = -66.2 (8.1; $p = 0.002$).

Early time points: Headache hours. There were significant decreases in the mean number of headache hours after 1 week of therapy for both treatment doses relative to placebo. The LSM change from baseline to 1 week was -2.85 (2.21) hours for placebo, -9.08 (2.25) for 675/225 mg ($p = 0.031$, LSM difference -6.22 , and 95% CI: -11.86 to -0.59), and -11.37 (2.26) for 900 mg ($p = 0.003$, LSM

Figure 1 Patient disposition

*Patients were considered screen failures for the chronic migraine study if they (1) had fewer than 15 days of headaches per month for 3 months before screening, (2) they had at least 15 days of headache per month for 3 months before screening but did not have 15 days of headaches or evidence of migraines during the 28-day run-in period, (3) they met the headache criteria but did not qualify for one or more of the other inclusion/exclusion criteria, (4) they were less than 80% compliant with diary entry during the 28-day run-in period and other miscellaneous reasons such as site closure, subject withdraws consent, and the subject was lost to follow-up. AE = adverse event. Modified from Lancet Neurol, 14, Bigal ME, Edvinsson L, Rapoport AM, et al., Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study, 1081-1090, 2015, with permission from Elsevier.¹⁴

Table 1 Patient characteristics

Characteristic	Placebo (n = 89)	TEV-48125, 675/225 mg (n = 88)	TEV-48125, 900 mg (n = 86)
Age, y	40.7 (11.5) 20-63	40.0 (11.6) 18-63	41.5 (12.9) 18-65
Height, cm	166.4 (8.1) 153-188	165.4 (8.3) 146-187	165.7 (7.6) 152-185
Body weight, kg	71.3 (13.1) 46-107	74.2 (17.0) 50-119	73.0 (15.6) 50-118
Body mass index, kg/cm ²	25.7 (4.5) 18-37	27.0 (5.2) 18-37	26.6 (5.3) 18-38
Sex			
Male	13 (14.6)	12 (13.6)	12 (13.8)
Female	76 (85.4)	76 (86.4)	75 (86.2)
Ethnic origin			
White	76 (85.4)	70 (79.6)	73 (83.9)
Black/African American	9 (10.1)	12 (13.6)	9 (10.3)
Asian	1 (1.1)	0 (0)	0 (0)
Other	3 (3.4)	6 (6.8)	5 (5.8)
Hours of headaches of any severity per month	169.1 (13.9) 42-672	159.1 (9.73) 29-431	157.7 (11.73) 37-672
Headache days of at least moderate severity per month	13.9 (5.6) 1-28	13.8 (6.3) 1-28	13.1 (5.9) 2-28
Days of acute medication use	15.7 (6.2) 0-28	15.1 (7.0) 0-28	16.2 (6.7) 0-28
Years of migraines	20.4 (13.1) 1-58	15.8 (11.2) 1-45	18.8 (12.2) 0-48
Preventive medicine use			
Yes	38 (42.7)	35 (39.7)	33 (37.9)
No	51 (57.3)	53 (60.2)	54 (62.1)

Data are mean (SD) minimum–maximum, or n (%).

Modified from Lancet Neurol, 14, Bigal ME, Edvinsson L, Rapoport AM, et al., Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study, 1081-1090, 2015, with permission from Elsevier.¹⁴

difference -8.52 , and 95% CI: -14.27 to -2.87), a benefit that was extended through the second and third weeks of therapy (figure 2A). The 900-mg dose first separated from placebo after 3 days of therapy (-3.08 hours vs $+0.36$ for placebo, $p = 0.0331$). The lower dose separated from placebo on day 7 (placebo = -1.59 hours, 675/225 mg = -7.28 , $p = 0.0486$, 900 mg = -9.76 , $p = 0.0048$) (figure 2B).

As shown in table 2, the percent of patients with a 50% reduction from baseline in the number of headache hours increased in the TEV-48125 groups relative to the placebo group in weeks 1 to 3, although the NNTs at these early time points were high.

Early time points: Moderate to severe headache days. For moderate to severe headache days, the lower dose, 675/225 mg, nonsignificantly reduced the number of days with moderate severity headaches in week 1 and week 3 (LSM change from baseline -1.12 vs placebo -0.77 , $p = 0.167$ for week 1, and -1.13 vs -0.74 , $p = 0.142$ for week 3). The 900 mg showed separation after 1 week (-1.26 vs -0.77 for placebo, $p < 0.054$). Both doses separated from placebo after 2 weeks' LSM change from baseline (SE): -0.79 (0.19) for placebo, -1.34 (0.20) for 675/225 mg ($p = 0.031$, LSM difference -0.55 , and 95% CI: -1.06 to -0.05), and -1.51 (0.20)

for 900 mg ($p = 0.005$, LSM difference 0.73 , and 95% CI: -1.23 to -0.22) ($p = 0.005$) (figure 3). The 900-mg dose continued to separate from the placebo group in week 3 (-1.39 vs -0.74 , $p = 0.016$).

The percent of patients with a 50% reduction from baseline in the number of moderate to severe headache days also increased in the TEV-48125 groups during weeks 1 to 3, although the NNTs, as seen for headache hours, were also high (table 2).

DISCUSSION It has been previously demonstrated that both doses of TEV-48125 were superior to placebo in the preventive treatment of CM, validating for the first time CGRP as a therapeutic target in this disease. Since benefit was seen as early as 1 month after starting therapy, we explored the earliest time point at which efficacy began. The new analysis demonstrated a significant decrease in the number of headache hours starting as soon as 3 days after the highest dose (900 mg) was given, and 7 days after the lower dose (675/225 mg) was given. For moderate or severe headache days, a significant decrease was seen during the second week of treatment for the 675/225-mg and 900-mg doses. These data offer a glimpse of how quickly

Figure 2 Effect of TEV-48125 at early time points

(A) Change in number of headache hours in the first 3 weeks of TEV-48125 treatment. (B) Change in headache hours in the first 7 days of TEV-48125 treatment. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

preventive treatment effects may occur for CGRP monoclonal antibodies in CM.

The new analysis of the data demonstrates that TEV-48125 can have an effect in some patients within a week of therapy initiation. Regarding clinical meaningfulness, it is not the purpose of summary measures to provide such information, but rather to offer the insight that some patients may benefit relatively rapidly from a new therapy. The early onset of effect is certainly of interest for at least 2 reasons. First, perceived early efficacy may be a reinforcing factor for compliance to therapy, especially in the context of well-tolerated medications. Second, the timing of the onset of action provides important

insights on the relevance of CGRP in the pathophysiology of migraine.

Fast onset of headache improvement is a highly desirable attribute for migraine medications.¹⁵ Oral preventive medications must be titrated over weeks to effective doses, and then administered daily for approximately 3 months to establish efficacy.^{16,17} Although some patients respond quickly to onabotulinumtoxinA, the only approved CM preventive treatment, response is often delayed.¹⁸ Clinical experience also suggests that in many cases, adverse events with migraine preventive medications are perceived nearly immediately while efficacy requires time to be noticed. Early onset of efficacy may provide positive

Table 2 Percent of patients with 50% reduction from baseline in headache hours and moderate to severe headache days in the first few weeks of TEV-48125 treatment

	No. (%) patients			ARR, % (NNT)	
	Placebo (n = 89)	TEV-48125, 675/225 mg (n = 87)	TEV-48125, 900 mg (n = 85)	TEV-48125, 675/225 mg vs placebo	TEV-48125, 900 mg vs placebo
Patients with $\geq 50\%$ reduction in headache hours from baseline					
Week 1	27 (30)	28 (32)	33 (39)	2 (50)	9 (11.1)
Week 2	18 (20)	37 (43)	41 (48)	23 (4.3)	28 (3.6)
Week 3	27 (30)	33 (38)	40 (47)	8 (12.5)	17 (5.9)
Patients with $\geq 50\%$ reduction in moderate to severe headache days from baseline					
Week 1	34 (38)	41 (47)	40 (47)	9 (11)	9 (11.1)
Week 2	33 (37)	42 (48)	50 (59)	11 (9.1)	22 (4.5)
Week 3	36 (40)	44 (51)	45 (53)	11 (9.1)	13 (7.7)

Abbreviations: ARR = absolute risk reduction; NNT = number needed to treat.

reinforcement for migraineurs and increase adherence to therapy.

Other CGRP monoclonal antibodies when studied in episodic migraine have shown fast onset of efficacy.^{19,20} It is known that circulating CGRP levels are increased in CM relative to episodic migraine and in episodic migraine relative to controls.²¹ CGRP-containing peripheral nerve cells in the trigeminal ganglion act as polymodal nociceptors, innervating peripheral tissues and in response to stimuli, release CGRP sending primary afferent sensory transmissions to neurons in dorsal horn of the spinal cord, the trigeminal nucleus caudalis (TNC), and the nucleus of the solitary tract. These neurons in turn project sensory inputs to the amygdala, hypothalamus, brainstem, and thalamus, which relay these inputs to the insular cortex.^{22–25} Monoclonal antibodies are large molecules that mostly do not cross the

blood–brain barrier with immunoglobulin G plasma to CSF ratio of 0.1%.²⁶ As a result, it has been suggested that modulation of CGRP outside the blood–brain barrier induces nearly immediate modulation of central pathways. This probable mechanism is supported by previous work suggesting that in humans, IV administration of CGRP, which does not cross the blood–brain barrier, induces migraine attacks in individuals with migraine.²⁷ Antibodies could bind to the CGRP released at trigeminal nerve endings, thereby avoiding the peripheral events of migraine and consequent sensory transmission to central second-order neurons in the TNC, thus avoiding the secondary central sensitization that would follow.²⁸ Reduced afferent input into central second-order neurons within the TNC could modulate neuronal activity and subsequent central trigeminal sensory transmission.

The study has important limitations that should be considered. First, the analyses reported in this article had not been a priori defined. Nonetheless, post hoc analyses have an important role in further defining the benefits of any drug, including subsets of patients experiencing particular benefit^{29,30} or, as in our case, providing preliminary evidence for future rigorous assessments. Second, and most important, we have not interviewed patients to check whether the effect size at early time points was clinically meaningful, and we do not suggest that they were for the early time points, although they certainly are for what is seen after 1 month of therapy, as the therapeutic gain (placebo-subtracted difference) seems to suggest so. In the pooled analyses of the onabotulinumtoxinA pivotal trials, the therapeutic gain for moderate or severe headache days after 6 months of therapy was -1.9 .³¹ In the present study, after 1 month of therapy, 900-mg and 675/225-mg doses yielded a therapeutic gain of values of respectively -2.8 and -2.0 days. Since clinical benefit may be a function of absolute response rather than placebo-adjusted response, future studies should incorporate patients' subjective assessment of improvement.

Figure 3 Change from baseline in the number of headache days of at least moderate severity

* $p < 0.05$, ** $p < 0.01$.

AUTHOR CONTRIBUTIONS

M.E.B. designed the study, interpreted data, and drafted, edited, and submitted the final article. D.W.D., A.V.K., J.H.V.P., S.J.T., E.A., and P.J.G. contributed to overseeing the data, discussed contents of the article, and participated in the writing of the article. Y.M. created the statistical analysis plan for the study and analyzed data. P.S.L. interpreted data, prepared tables and figures, and participated in writing and editing of the article.

STUDY FUNDING

The protocol was designed and the study was conducted by the funder with input from all authors. The funder was responsible for data collection, data analysis, data interpretation, and writing the article. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

DISCLOSURE

M. Bigal is an employee of Teva Pharmaceuticals Research and Development team. D. Dodick within the past 3 years has served on advisory boards and/or has consulted for Allergan, Amgen, Alder, Alcobra, Arteaus, Pfizer, CoLucid, Merck, ENeura, NuPathe, Eli Lilly and Company, Autonomic Technologies, Ethicon J&J, Zogenix, Supernus, Labrys, Boston Scientific, MAP, Novartis, Tonix, Teva, and Trigemina and has received funding for travel, speaking, editorial activities or royalty payments from IntraMed, SAGE Publishing, Sun Pharma, Allergan, Oxford University Press, HealthLogix, Universal Meeting Management, WebMD, UpToDate, Starr Clinical, Decision Resources, and Synergy. A. Krymchantowski and J. VanderPluym report no disclosures relevant to the manuscript. S. Tepper received grants/research support from Alder, Allergan, Amgen, ATI, ElectroCore, eNeuro, GSK, Teva, Pernix, and OptiNose/Avanir/Otsuka. These grants do not go to him personally. S.T. has served as a consultant for Acorda, Allergan, Amgen, ATI, Avanir, Depomed, ElectroCore, Impax, Pfizer, Scion Neurostim, Teva, and Zosana and has been on the speakers bureau for Allergan, Depomed, Impax, Pernix, and Teva. In the last 12 months, he served on advisory boards for Allergan, Amgen, ATI, Avanir, Dr. Reddy's, Merck, Pfizer, and Teva. He is editor-in-chief of *Headache Currents*, American Headache Society, receives royalties for books published by University of

Mississippi Press and Springer, and has stock options in ATI. E. Aycardi is an employee of Teva Pharmaceuticals Research and Development team. P. Loupe is an employee of Teva Pharmaceuticals Research and Development team. Y. Ma is an employee of Teva Pharmaceuticals Research and Development team. P. Goadsby reports grants and personal fees from Allergan, eNeura, Autonomic Technologies Inc., Amgen, and personal fees from AlderBio, Pfizer, Dr. Reddy's, Zosana, CoLucid, Eli Lilly, Avanir, Gore, Heptares, NuPathe, Teva, Cipla, Ajinomoto, Akita, Wells Fargo, Ethicon, EMKinetix, Promius, Medico-Legal, UpToDate, and Journal Watch. In addition, Dr. Goadsby has a patent magnetic stimulation for headache pending. Go to Neurology.org for full disclosures.

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Comment: Monoclonal antibodies in chronic migraine—Are early effects meaningful?

Chronic migraine affects approximately 1% of the adult population and is defined as headache on ≥ 15 d/mo with ≥ 8 days of migraine-type headache. Since treatment often remains frustrating for both the patient and physician, new treatment strategies are highly welcome.

No doubt, monoclonal antibodies (mAbs) against calcitonin gene-related peptide (CGRP) for the preventive treatment of episodic and chronic migraine deserve to be called a breakthrough—not because they cure headache, but rather because they are effective for relatively refractory headaches and were developed based on the pathophysiologic concept that the trigeminovascular system and CGRP have a key role in the development of migraine pain; this was not a serendipitous discovery.

Recently, the authors presented convincing evidence that TEV-48125 reduced headache hours over 9 to 12 weeks.¹ Here, they present data on early effects, suggesting a reduction of headache hours within the first few weeks.² But statistical significance notwithstanding—how clinically meaningful is a reduction of a few headache hours per week? A valid answer to this question is not given here and would require multiple measurements and evidence to determine the benefit for patients' lives.

Are these data still important? Most definitely: first, there is a biological effect with relatively quick onset, whether clinically meaningful or not. Second, unlike with many established drugs, we do not see the early onset of adverse events and later onset of clinical benefit, which often challenges patient adherence. Third, mAbs do not cross the blood-brain barrier, hence the critical therapeutic target is, rather, located peripherally and not in the brain.³ This reasoning, together with the demonstrated rapid onset, strongly supports an important concept toward improved understanding of migraine mechanisms and guidance of future drug discovery. Finally, this study reinvigorates an attractive objective, namely, to treat other chronic-refractory craniofacial pain syndromes with CGRP-neutralizing mAbs, such as trigeminal neuropathic pain, chronic temporomandibular joint pain, and, certainly, cluster headaches.

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Volker Limmroth, MD, PhD

From the Klinik für Neurologie und Palliativmedizin Köln-Merheim, Cologne, Germany.

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