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Effectiveness and tolerability of atogepant in the prevention of migraine: A real life, prospective, multicentric study (the STAR study)

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Abstract

Background: Focusing on calcitonin gene-related peptide (CGRP) as a specific target has changed and improved migraine management. After the positive results of monoclonal antibodies directed to the CGRP pathway (anti-CGRP mAbs), randomized controlled trials also demonstrated the efficacy of gepants in migraine prevention. The present study aimed to assess the effectiveness of atogepant in preventing migraine after a 12-week treatment in clinical practice.
Methods: Adult patients with a clinical indication for atogepant 60 mg daily were screened for participation in this multicentric prospective observational cohort study. At baseline (T0) and after 12 weeks (T3) since the first atogepant administration, monthly migraine days (MMDs), monthly headache days (MHDs) and monthly acute medications (MAMs) were assessed. The co-primary endpoints were the changes in MMDs from T0 to T3 and the percentage of T3 Responders (those with a reduction of MMDs ≥50%, i.e. 50% response rate (RR)). At T0 and T3, we also collected the Headache Impact Test (HIT-6), the Migraine Disability Assessment (MIDAS) questionnaire, the Migraine Treatment Optimization Questionnaire-6 (mTOQ-6), the Migraine-Specific Quality-of-Life Questionnaire (MSQ), the 12-item Allodynia Symptom Checklist (ASC-12) and the Migraine Interictal Burden Scale (MIBS-4).
Results: One hundred and six patients (56/106 (52.8%) with chronic migraine (CM), 93/106 (87.7%) female, aged 50.6 ± 13.2 years) from 10 Italian centers completed the 12-week observation since the first atogepant tablet intake. From

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baseline to T3, a reduction of 6.9 MMDs (SD 9.7; $p < 0.001$) was achieved in the whole group and, specifically, of −4.9 (SD 6.6; $p < 0.001$) in episodic migraine (EM) and of −8.6 (SD 11.7; $p < 0.001$) in CM patients. Overall, 60/106 (56.6%) of patients were Responders (60.0% in the EM and 46.4% in the CM group). Non-Responders previously experienced more ineffective treatments than Responders with anti-CGRP mAbs (65.2% vs. 43.3%, respectively, $p = 0.031$) and with onabotulinumtoxinA (56.5% vs. 28.3%, $p = 0.005$), and presented more medication overuse at baseline (55.7% vs. 44.3%, $p = 0.003$). However, no baseline characteristics were significantly associated with the Responder status in the multiple regression analysis. For T0 to T3, MAMs, MIDAS, ASC-12 and mTOQ-6 reduced ($p \leq 0.001$ consistently), and MSQ role-function restriction increased ($p = 0.026$), whereas HIT-6 and MIBS-4 did not change. Only seven subjects (7/106, 6.6%) dropped out of atogepant treatment: four for lack of effectiveness and three for adverse events or poor tolerability.

Conclusions: The STAR study demonstrates the effectiveness and tolerability of atogepant 60 mg at 12 weeks in a real-world setting. Previous ineffective anti-CGRP mAbs were not a relevant prognostic factor.

Trial Registration: The study was preregistered on clinicaltrial.gov, NCT06414044.

Keywords

atogepant, migraine prevention, real-world studies

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Introduction

The discovery of calcitonin gene-related peptide (CGRP) as a specific target for migraine therapies has changed the rules of treating this common neurological disorder (1). Monoclonal antibodies against CGRP or its receptor (anti-CGRP mAbs) have been proven highly effective both in randomized controlled trials (RCTs) and real-world studies. They should be now be considered as the first-line therapies for the prevention of high-frequency episodic or chronic migraine (CM) (2,3). Gepants comprise the new class of selective CGRP-targeted therapies that are going to play an important role in the treatment of migraine patients (1,4). While anti-CGRP mAbs are large molecules with a typical molecular weight of around 150 kDa, gepants are small-molecule drugs with a simpler structure and a molecular weight generally below 500 Da. Gepants act by antagonizing the CGRP receptor, such that they block the capability of CGRP to bind its receptor within the trigemino-vascular system, aborting the migraine attack and/or preventing it from occurring (1).

The efficacy of gepants in treating attacks was first demonstrated in 2004 by a double-blind, randomized trial showing that intravenous olcegepant significantly alleviated migraine symptoms (5). Evidence of efficacy for the acute treatment of migraine was shown later also for oral telcagepant (6). Unfortunately, the clinical development of those first-generation gepants in migraine was stopped due to a few cases of liver toxicity. Subsequently, a second generation of oral gepants has been developed and is currently approved for clinical use. No severe cases of liver disease were reported in clinical trials or the drug agencies' safety repository, and no case met the criteria for potential Hy's law. Hy's law states that a patient is at high risk of serious liver injury if all three of the following criteria are met: (i) elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST), ≥3 times the upper limit of normal (ULN); (ii) elevated total bilirubin ≥2 times the ULN, without initial findings of significant cholestasis; and (iii) no other reason can be found to explain the combination of liver enzyme and bilirubin elevations.

Ubrogepant (7) and rimegepant (8), both orally administered, and, more recently, zavegepant (9), for intranasal administration, are approved and available for acute treatment of migraine.

Rimegepant 75 mg taken every other day has been investigated with positive results (10) and has also been approved for the preventive treatment of episodic migraine (EM) in adults. Moreover, the first head-to-head study comparing two CGRP-targeted therapies, galcanezumab vs. rimegepant, for the prevention of EM failed to demonstrate that the mAb was superior to the gepant in achieving a ≥50% reduction from baseline in migraine headache days per month (62% vs. 61%, respectively) (11).

Given the robust evidence from randomized trials, atogepant 60 mg or 10 mg taken once daily was approved by the Food and Drug Administration (FDA) on September 2021 for EM prevention. The efficacy, safety and tolerability of atogepant in EM were previously shown in a first phase 2–3 trial (12), in a phase 3 trial (ADVANCE) (13) and finally in a 52-week, open-label long-term safety trial (14).

The PROGRESS study (15) demonstrated the efficacy, safety and tolerability of atogepant also for the preventive

treatment of chronic migraine (CM). Thus, in April 2023, atogepant was approved by the FDA also for CM prevention. In August 2023, atogepant became the first oral gepant approved by the European Medicine Agency (EMA) for the preventive treatment of both chronic and episodic migraine.

Finally, atogepant was found safe, well tolerated, and showed significant and clinically relevant mean monthly migraine day reductions compared to placebo across 12 weeks in patients with EM who had previously experienced an inadequate response to two to four classes of conventional oral preventive treatments (16).

The clinical benefit of atogepant demonstrated by RCTs has not yet been replicated in real-world practice. The present study aimed to evaluate the effectiveness, safety, and tolerability of atogepant in preventing, over 12 weeks, EM and CM in a real-life setting in Italy.

Methods

Study design

STAR is a real-world, prospective, multicenter, investigator-initiated and independent study conducted in Italy, considering all consecutive outpatients treated with atogepant 60 mg orally for EM or CM. The study has a pre-planned two-year follow-up. In this study, we included all patients with potential 12 weeks of follow-up, taking at least one atogepant 60 mg tablet regardless of discontinuation for any reason from June to December 2024. The study was preregistered on clinicaltrials.gov (NCT06414044).

The local Ethics committee approved the study as part of the *Registro Italiano Cefalee* (RICe) study (Studio RICe, 14591_oss CEAVC Studio RICe, 14591_oss and subsequent amendments). Other information on the RICe study is reported elsewhere (17,18). All patients provided their written informed consent before starting treatment with atogepant. The open online database Research Electronic Data Capture (REDCap) and the *Empedocle* electronic platform (developed for the RICe study) have been used for data collection.

When the STAR study started, atogepant was not subsidized by the Italian National Health Service. Therefore, patients received the drug under an agreement among the Italian Medicines Regulatory Agency (AIFA), regional healthcare systems and the manufacturing company that provided the drug at no cost.

Patient features

Inclusion criteria were: (i) individuals aged 18 years or older; (ii) diagnosis of migraine without aura, migraine with aura or CM according to International Classification of Headache Disorders, 3rd edition (ICHD-3) (19); (ii) at least four monthly migraine days (MMDs) in the three months before enrollment; (iii) good compliance to study procedures; (iv) availability of headache diaries over least one month before enrollment; and (v) clinical indication for prescription of atogepant 60 mg.

Exclusion criteria were: (i) subjects with any contraindications to gepants according to the EMA summary of product characteristics; (ii) concomitant diagnosis of medical diseases and/or comorbidities that could undermine the study according to clinicians; and (iii) pregnancy and breastfeeding.

Participants were enrolled regardless of the number of prior ineffective or non-tolerated preventive treatments, if any, according to clinical practice. We have defined "lack of efficacy" as no meaningful improvement in the frequency of headaches after the administration of drugs for ≥6 weeks at the appropriate dose for oral standard of care and two cycles (24 weeks) for onabotulinumtoxinA (OBT-A) and at least three months for CGRP mAbs according to the European Headache Federation (EHF) criteria (3).

We also considered "lack of efficacy" patients presenting a loss of effectiveness for ≥6 weeks at the appropriate dose for oral standard of care and one cycle (12 weeks) for OBT-A and at least three months for CGRP mAbs.

Collected variables

Clinicians diagnosed migraine and collected clinical and demographic features: concomitant and previous preventive treatments, MMDs, monthly headache days (MHDs) and number of monthly acute medications (MAMs) before atogepant first intake (i.e. baseline). Triptan self-reported effectiveness was also collected. We defined triptan as effective if the patient reported pain freedom or relief within two hours. We defined, as patients with medication overuse (MO) or medication overusers, regardless of the diagnosis of CM, those subjects with overuse of acute or symptomatic headache medication (on 10 or more days per month for triptans and combination analgesics or 15 or more days per month for non-opioid analgesics) for more than three months (19).

Finally, a panel of questionnaires was administered at baseline and after 12 weeks of therapy (T3): the Headache Impact Test (HIT-6) (20), the Migraine Disability Assessment (MIDAS) questionnaire (21), the Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) (22), the Migraine-Specific Quality-of-Life Questionnaire (MSQ) (23), the 12-item Allodynia Symptom Checklist (ASC-12) (24) and the Migraine Interictal Burden Scale (MIBS-4) (25). The Patient's Global Impression of Change (PGIC) (26) was administered at T3.

A headache day was defined as any day on which a patient recorded any type of headache, and an MMD was defined as any day with a headache with the characteristics of migraine or use of triptans. Adverse events (AEs) were

collected and reported to the Italian Drug Agency (AIFA) according to the Italian normative.

Outcomes and analysis

According to the guidelines of the International Headache Society (IHS), the co-primary effectiveness outcomes of the STAR study were: (i) changes in MMDs after 12 weeks of treatment compared to baseline and (ii) the percentage of Responders (namely patients who presented a reduction of MMDs ≥50%, i.e. 50% response rate (RR), compared to baseline) after 12 weeks of treatment. We associated the assessment of the occurrence of treatment-emergent side effects (TEAEs) to evaluate the safety of the drug in a real-world population.

Secondary outcomes included from baseline to T3:

(i) The percentage of patients with MO reverted during treatment;
(ii) Changes in MAMs;
(iii) Changes in MIBS4 questionnaire scores (0–12 scale);
(iv) Changes in MSQ role function restrictive questionnaire scores (0–100 scale);
(v) Changes in ASC-12 questionnaire scores (0–24 scale);
(vi) Changes in mTOQ-6 questionnaire scores (6–24 scale);
(vii) Changes in HIT-6 questionnaire scores (36–78 scale);
(viii) Changes in MIDAS questionnaire (0–270 scale);
(ix) Patient satisfaction measured with the Patient Global Impression of Change (PGIC) questionnaire; and
(x) Percentage of adverse events (AE).

Statistical analysis

The present study is an *a priori* analysis. Based on the results of atogepant clinical trials and real-world data on mAbs targeting the CGRP pathway, we calculated a sample size of at least 90 subjects to achieve a power of 80% and a significance level of 5% (two-sided) for detecting an effect size of 0.30 between paired variables (i.e. changes in MMDs). The interval variables between groups were compared with an independent *t*-test (expressed as the mean (SD)) or Mann–Whitney *U*-test (medians with interquartile range as between-subject factors) and Duncan's multiple range test was applied for multiple comparisons. The McNemar test for proportions of paired samples was applied to assess changes in the frequency of MO and CM over the evaluation times. We initially investigated which clinical baseline characteristics were associated with the Responder status (considering $p < 0.1$). These variables (i.e. age, sex, previous CGRP targeted therapy and OBT-A, and MO) were entered as independent variables in binary logistic regression (forced entry) to confirm the association with Responder status (dependent variable). Bonferroni correction was applied for multiple comparisons. Contingency tables (chi-squared tests) and unadjusted odds ratios (OR) with their 95% confidence intervals (CI) were run to compare frequencies between groups. All tests were two-tailed. $p < 0.05$ (two-tailed) was considered statistically significant. We included only subjects with complete information regarding the primary studied variables (MMDs). We declared data availability and ran the analysis only in patients with usable data for the secondary variables. Statistical analyses were performed using SPSS, version 27.0 (IBM Corp.).

Results

The present analysis was carried out in a cohort of the first 106 patients (87.7% female, aged 50.6 ± 13.2 years, range 18–80 years) enrolled in the STAR study from 10 participating Italian centers and completing the 12 weeks of observation (T3) since the first atogepant tablet intake (Figure 1). Table 1 summarizes baseline demographic and clinical profiles in EM and CM patients. In the case of missing data, the number of available data is reported. The MMDs and MHDs were fully available at baseline and T3 for the entire cohort.

In the whole sample, 56 patients (52.8%; 56/106) were previously in treatment with other CGRP-targeting therapies: 42 with erenumab, 23 with galcanezumab, 10 with fremanezumab and one with eptinezumab. Some of them took more than one mAb anti-CGRP. Of these, 19 patients have been previously treated with erenumab (anti-CGRP receptor) and other mAb anti-CGRPs. Of the 56 patients experiencing ineffective mAbs, 32 (32.1% of the whole cohort) have also been previously treated with OBT-A.

Seven subjects (6.6%) dropped out of the treatment with atogepant: four for lack of effectiveness and three for adverse events or poor tolerability. Although these subjects had stopped the treatment, they were included in the analysis as MMDs were available at baseline and T3.

Primary endpoints

From baseline to T3, a reduction of 6.9 MMDs (SD 9.7; $p < 0.001$) was achieved in the whole group and, specifically, of −4.9 (SD 6.6; $p < 0.001$) in EM and of −8.6 (SD 11.7; $p < 0.001$) in CM patients.

Similarly, MHD decreased by 7.6 (SD 9.7; $p < 0.001$) in the whole group, by 6.7 (SD 8.2; $p < 0.001$) in EM, and by 9.2 (SD 10.9; $p < 0.001$) in CM patients.

Figure 2 shows MMD 50%, 75% and 100% RR in the whole cohort of 106 patients (56.6%, 31.1% and 6.6%, respectively) and compared for EM and CM. Moreover,

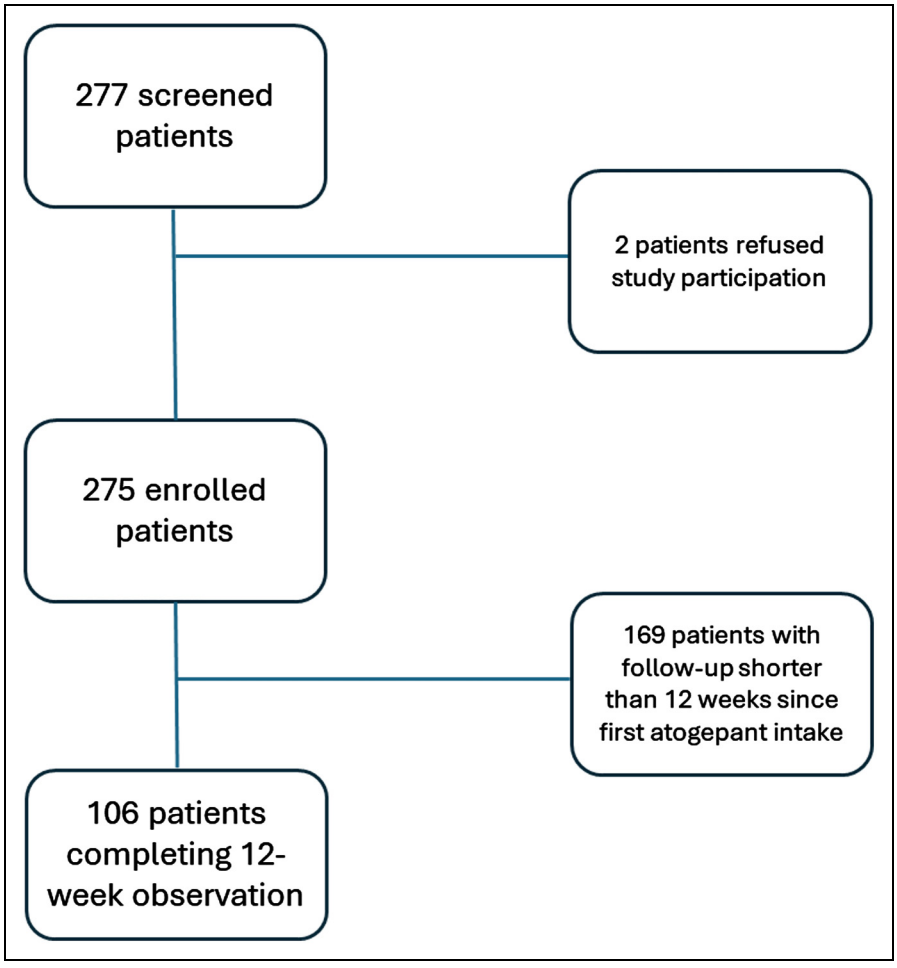

Figure 1. Flow chart showing patients' screening and enrollment.

in CM, MHD 50% RR was 46.6%, MHD 75% RR was 17.9% and MHD 100% RR was 1.8%.

Table 2 compares baseline clinical characteristics in the 50%RR Responder and Non-Responder groups. Responders less frequently presented baseline medication overuse (OR = 0.28; 95% CI = 0.12–0.66) and previously experienced ineffective treatment with anti-CGRP mAbs (OR = 0.41; 95% CI = 0.18–0.90) and OBT-A (OR = 0.30; 95% CI = 0.13–0.68).

Logistic regression did not confirm the association between Non-Responder status and previous failure of preventive treatment with CGRP-targeted therapies and OBT-A or medication overuse (see supplemental material). Figure 3 shows MMDs at T0 and T3 (A) and the response rates (B) in the naïve group compared to those with previous ineffective treatment with anti-CGRP mAbs.

Secondary endpoints

From baseline to T3, MAMs (available for 95 subjects) reduced from 16.3 (SD 18.9) to 8.8 drugs (SD 16.0; $p < 0.001$) in the whole cohort, in CM from 27.9 (SD 24.7) to 10.9 (SD 7.2; $p < 0.001$) and in EM from 8.7 (7.5; $p < 0.001$) to 5.3 (6.7). Accordingly, medication overusers decreased from 61/106 (57.5% of the cohort) to 33/106 patients (31.1%; $p < 0.001$).

Of the initial 56 patients with CM, 33/56 (58.9%) reverted to EM. However, 10 patients with EM at baseline (20.0%) had a chronic frequency at T3. In the cohort, CM reduced from 56/106 (52.8%) to 33/106 (31.1%l $p < 0.001$).

Because disability and functioning scale scores did not differ at baseline between CM and EM, we analyzed their variation as a whole group. Table 3 displays score variations, highlighting the number of available data for the paired analysis.

Figure 4 shows the distribution of responses to the PGIC questionnaire: 50.9% of patients replayed they felt "much better" or "very much better" after the 12-week treatment, and 66.0% of the whole cohort stated that had a worth noting improvement from atogepant.

Adverse events and tolerability

Forty-seven patients (47/106; 44.3%) reported AEs related to atogepant. The most common events were constipation

Table 1. Comparison of baseline characteristics between patients with episodic (EM) and chronic (CM) migraine.

	Cohort (n = 106)	EM (n = 50)	CM (n = 56)	*p*
Age (years), mean (SD)	50.6 (13.2)	50.2 (12.8)	51.0 (13.7)	0758
Sex, % female (n)	87.7 (93)	86.0 (43)	89.3 (50)	0768
Onset age (years), mean (SD)	18.3 (9.9)	18.7 (10.5)	17.9 (9.4)	0.750
BMI (kg/m^2), mean (SD)	23.45 (4.13)	22.98 (3.89)	23.88 (4.32)	0.268
Weight (kg), mean (SD)	64.1 (12.4)	63.4 (11.5)	64.7 (13.2)	0.576
Clinically relevant comorbidities, % (n)	53.8% (57/99)	40.4 (20/44)	66.1 (37/55)	0.011
Vascular, % (n)	21.2 (21/99)	18.2 (8/44)	23.6 (13/55)	0.623
Psychiatric, % (n)	17.2 (17/99)	9.1 (4/44)	23.6 (13/55)	0.066
Gastroenterological, % (n)	14.1 (14/99)	11.4 (5/44)	16.4 (9/55)	0.569
Neurological, % (n)	3 (3/99)	4.5 (2/44)	1.8 (1/55)	0.583
Immunological, % (n)	9.1 (9/99)	4.5 (2/44)	12.7 (7/55)	0.291
Endocrinological, % (n)	12.1 (12/99)	9.1 (4/44)	14.5 (8/55)	0.540
MMDs, mean (SD)	17.6 (8.8)	13.5 (7.7)	21.3 (8.2)	<0.001
MHDs, mean (SD)	20.5 (8.5)	16.4 (8.3)	24.1 (6.9)	<0.001
MAMs, mean (SD)	17.8 (18.2)	8.9 (7.1)	27.1 (21.5)	<0.001
Medication overusers, % (n)	57.5 (61)	34.0 (17)	79.6 (44)	<0.001
MIDAS, mean (SD)	69.6 (52.6)	58.1 (45.2)	78.9 (57.2)	0.052
HIT-6, mean (SD); n	65.1 (8.3); 103	64.7 (9.4); 47	65.4 (7.2); 56	0.656
ASC-12, mean (SD)	6.2 (4.9)	5.4 (5.1)	6.9 (4.8)	0.108
MSQ restrictive mean, (SD), n	41.7 (21.6); 104	42.4 (19.1); 49	41.1 (23.8); 55	0.771
MIBS-4, mean (SD), n	1.3 (1.2); 104	1.4 (1.1): 49	1.3 (1.2):55	0.621
mTOQ-6, mean (SD), n	17.6 (4.7); 103	17.9 (4.7); 48	17.4 (4.6); 55	0.579
Previous ineffective treatments, median (IQR) [range]	4 (3) [0–10]	4 (3) [0–10]	5 (4) [0–9]	0.008
OnabotulinumtoxinA, % (n)	40.6 (43)	26.0 (13)	53.6 (30)	0.005
CGRP targeted therapies, % (n)	52.8 (56)	34.0 (17)	69.8 (39)	<0.001
Concomitant preventive therapy, % (n)	34.9 (37)	26.0 (13)	42.9 (24)	0.102

ASC-12, 12-item Allodynia Symptom Checklist; BMI, body mass index; HIT-6, Headache Impact Test; IQR, interquartile range; MAMs, monthly acute medications; MHDs, monthly headache days; MIBS-4, Migraine Interictal Burden Scale; MIDAS, Migraine Disability Assessment questionnaire; MMDs, monthly migraine days; MSQ, Migraine-Specific Quality-of-Life Questionnaire; mTOQ-6, Migraine Treatment Optimization Questionnaire-6.
In the case of missing data, the number of available data is reported.

(25.5%), decreased appetite (16.0%), nausea (15.0%) and fatigue (6.6%). In three patients, adverse events induced treatment discontinuation (two for nausea and one for somnolence/weakness).

Of note, patients reported a mean reduction of body weight of 1 kg ($p < 0.001$) since baseline.

Discussion

Pivotal and additional RCTs widely demonstrated atogepant efficacy, safety, and tolerability. Our study showed that atogepant is effective, safe and well-tolerated in preventing migraine both in EM and CM patients also in real-life 12-week treatment conditions.

The ADVANCE trial evaluated the safety and tolerability of atogepant 10, 30 and 60 mg once a day in patients with EM (13). The changes from baseline across 12 weeks of treatment were −4.2 days with atogepant 60 mg and −2.5 days with placebo. The 50% RR MMD was observed in 60.8% for 60 mg and 29.0% for placebo. The most common adverse events were constipation (6.9–7.7% across atogepant doses) and nausea (4.4–6.1% across atogepant doses).

A phase 3 open-label randomized trial (14) compared atogepant 60 mg with the standard of care (SOC) for EM prevention over one year. TEAEs occurred in 67.0% of participants treated with atogepant 60 mg. Constipation was the only TEAE more frequently reported in 7.2% of patients with atogepant (3.1% in the SOC group). At the same time, other AEs were more frequent in the SOC than in the atogepant group, particularly fatigue (6.1% vs. 2.6%), weight increase (5.6% vs. 1.3%) and dizziness (11.2% vs. 3.1%). Serious TEAEs were reported in 4.4% (24/543) for atogepant.

The PROGRESS study was a randomized, double-blind, placebo-controlled, phase 3 trial considering 778 participants with CM randomly assigned to atogepant 30 mg twice a day (n = 257), atogepant 60 mg once a day (n = 262) or placebo (n = 259) (15). Change from baseline in mean MMDs across 12 weeks was −6.9 with atogepant 60 mg once a day and −5.1 with placebo. The most common adverse events for atogepant were constipation (60 mg once a day 26 (10%) and placebo 8 (3%)) and nausea (60 mg once a day 25 (10%) and placebo 9 (4%)).

Finally, atogepant 60 mg once a day showed significant reductions in mean MMDs compared to placebo (−4.2 vs.

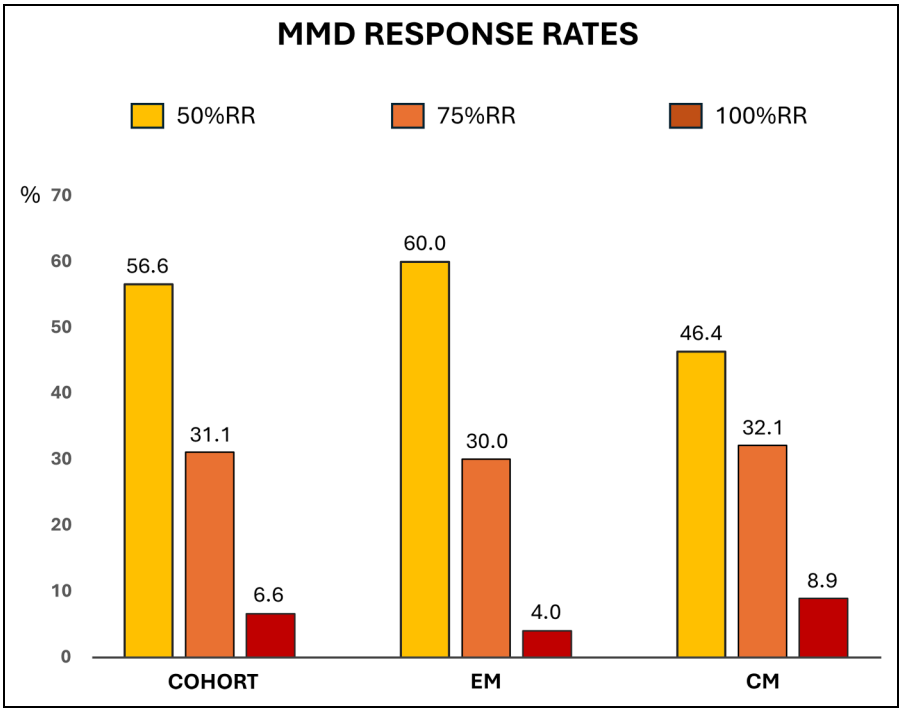

Figure 2. Monthly migraine day response rates (RR, 50%, 75% and 100%) in the whole cohort left, and in the episodic (EM) and chronic (CM) migraine groups.

−1.9, respectively, $p < 0.0001$) across 12 weeks in patients with EM who had previously been failed by two to four classes of conventional oral preventive treatments (ELEVATE study) (16). The most common TEAE with atogepant was constipation in 16 (10%) of 156 participants (vs. 4 (3%) of 157 for placebo).

In the present study, we found that the MMD reductions from baseline to week 12 were slightly larger than those observed in the atogepant RCTs: MMDs variation was −4.9 in the STAR EM group vs. −4.2 in EM subjects change recorded both in ADVANCE and ELEVATE studies (for atogepant 60 mg), whereas, in CM patients, MMD reduction was 8.6 in our study, which is larger than that of the PROGRESS study (i.e. 6.9 with atogepant 60 mg once a day). These findings should be evaluated in light of the previous failure of anti-CGRP mAbs beyond a mean of four SOC treatment failures in 52.8% of patients.

The proportion of patients with a 50% reduction in MMDs compared to baseline is probably considered worldwide as the most adequate cut-off point to define the efficacy of prophylactic treatments. In our cohort, the MMD 50% RR at T3 was 60.0% for the EM group and 46.4% for CM patients. In atogepant EM patients RCTs, the MMD 50% RR in the same interval was 60.8% in the ADVANCE study and 51% in patients from the ELEVATE study, with the latter being the most appropriate comparison for our study, given the previous two to four SOC preventive failures in its population. Also, in the STAR CM group, the MMD 50% RR (46.4%), was slightly larger than that reported in the PROGRESS study (43% with atogepant 30 mg twice a day and 41% with 60 mg once a day). Notably, in the PROGRESS study, approximately 80% of participants had previous preventive medication use; still, no specification was reported about the number of SOC preventive failures. Conversely, in our study, the median number of failed preventives at baseline was 4 (3), and more importantly, 53% of the whole cohort previously failed at least one anti-CGRP mAb. Given the failure of both SOC and anti-CGRP mAbs, our study population has unique features compared to RCTs. This resistant (in some cases, refractory) population nevertheless benefitted from atogepant treatment, at least in the short term.

Similarly, disability improved substantially with atogepant treatment: our patients (whole cohort) reported a MIDAS reduction of more than 40 points after 12 weeks of therapy (from 69 at baseline to approximately 28 after 12 weeks), which is a considerable reduction within such a short time period and in such hard-to-treat patients.

The impact of atogepant on migraine burden was confirmed by the results of several questionnaires. Allodynia severity decreased consistently (the ASC-12 score reduced from 6.2 at baseline to 3.8 at T3, $p < 0.001$), suggesting that a reduction in the migraine frequency was rapidly associated with improved central sensitization.

The significant increase in the MSQ scale score found in our analysis, both globally and when considering the role function restrictive only, confirms how positively atogepant

Table 2. Comparison of baseline characteristics between Responders and Non-Responders.

	Cohort (n = 106)	Non-Responders(n = 46)	Responders (n = 60)	*p*
Age (years), mean (SD)	50.6 (13.2)	53.3 (13.4)	49.6 (12.9)	0.068
Sex, % female (n)	87.7 (93)	87.0 (40)	88.3 (53)	0.529
Onset age (years), mean (SD)	18.3 (9.9)	18.9 (9.7)	17,8 (10.1)	0.594
BMI (kg/m^2), mean (SD)	23.45 (4.13)	23.53 (3.84)	23.40 (4.36)	0.792
Weight (kg), mean (SD)	64.1 (12.4)	64.5 (12.2)	63.8 (12.7)	0.876
Clinically relevant comorbidities, % (n)	53.8% (57)	60.9 (28)	48.3 (29)	0.240
Vascular, % (n)	21.2 (21/99)	22.7 (10/44)	20.0 (11/55)	0.807
Psychiatric, % (n)	17.2 (17/99)	15.9 (7/44)	18.2 (10/55)	0.796
Gastroenterological, % (n)	14.1 (14/99)	18.2 (8/44)	10.9 (6/55)	0.387
Neurological, % (n)	3 (3/99)	4.5 (2/44)	1.8 (1/55)	0.582
Immunological, % (n)	9.1 (9/99)	9.1 (4/44)	9.1 (5/55)	1.000
Endocrinological, % (n)	12.1 (12/99)	6.8 (3/44)	16.4 (9/55)	0.217
CM, % (n)	52.8 (56)	56.5 (26)	50.0 (30)	0.559
MMDs, mean (SD)	17.6 (8.8)	18.2 (9.3)	17.2 (8.6)	0.593
MHDs, mean (SD)	20.5 (8.5)	21.5 (8.2)	19.8 (8.7)	0.313
MAMs, mean (SD)	17.8 (18.2)	15,8 (11.2)	19.1 (21.8)	0.541
Medication overusers, % (n)	57.5 (61)	55.7 (34)	44.3 (27)	0.003
MIDAS, mean (SD)	69.6 (52.6)	63.1 (51.8)	74.6 (53.1)	0.268
HIT-6, mean (SD); n	65.1 (8.3); 103	63.9 (10.5); 44	65.9 (6.06); 59	0.206
ASC-12, mean (SD)	6.2 (4.9)	5.91 (4.6)	6.48 (5.2)	0.558
MSQ restrictive, mean (SD); n	41.7 (21.6); 104	42.9 (21.1); 45	40.8 (22.2); 59	0.609
MIBS-4, mean (SD); n	1.3 (1.2); 104	1.3 (1.2); 45	1.4 (1.2); 59	0.775
mTOQ-6, mean (SD); n	17.6 (4.7); 103	17.1 (4.9); 45	18.1 (4.4); 58	0.289
Previous ineffective treatments, median (IQR) [range]	4 (3) [0–10]	5 (3) [0–10]	3 (4) [1–9]	0.007
OnabotulinumtoxinA, % (n)	40.6 (43)	56.5 (26)	28.3 (17)	0.005
CGRP targeted therapies, % (n)	52.8 (56)	65.2 (30)	43.3 (26)	0.031
Erenumab, % (n)	34.9 (37)	41.3 (19)	30.0 (18)	0.304
Concomitant preventive therapy, % (n)	34.9 (37)	39.1 (18)	31.7 (19)	0.538
Triptan responders, % (n)	61.3 (65)	52.2 (24)	68.3 (41)	0.109

ASC-12, 12-item Allodynia Symptom Checklist; BMI, body mass index; HIT-6, Headache Impact Test; IQR, interquartile range; MAMs, monthly acute medications; MHDs, monthly headache days; MIBS-4, Migraine Interictal Burden Scale; MIDAS, Migraine Disability Assessment questionnaire; MMDs, monthly migraine days; MSQ, Migraine-Specific Quality-of-Life Questionnaire; mTOQ-6, Migraine Treatment Optimization Questionnaire-6.
All variables are intended at baseline. In the case of missing data, the number of available data is reported.

treatment may impact the essential aspects of patients' health-related quality of life over the 12 weeks.

Similarly, the significant increase (i.e. 3 points) in the mTOQ-6 score confirms that atogepant treatment has also optimized the response to acute treatment of migraine attacks, restoring function or planning daily activities (27). Accordingly, we observed a reduction in MAMs and, consequently, a reversion from medication overuse in approximately half of patients.

Finally, PGIC is a clinical assessment tool used to evaluate the patient's perception of improvement or deterioration in health status over time. This scale probably resembles all the measures above and expresses patients' perceptions about the effectiveness of a treatment. In our study, more than half of the participants stated that they felt better and had a definite improvement that made a real and worthwhile difference from baseline, and two-thirds of them affirmed that they presented at least a slight but noticeable health status change.

Atogepant was well tolerated in our study and no serious AEs emerged. Even if 47 patients (44.3%) reported adverse events related to atogepant, only three patients discontinued treatment for scarce tolerability. The most common events were constipation (25.5%), decreased appetite (16.0%), nausea (15.0%) and fatigue (6.6%). The very low discontinuation rate (6.6%) was equally high for those patients who stopped the therapy due to a lack of effectiveness. This point is of pivotal importance because the low discontinuation rate makes a substantial difference from oral SOC preventive therapies (28).

In our study, patients reported a significant mean body weight reduction of 1 kg since baseline. This observation confirms the results of a recent study using data from five clinical trials and evaluating weight change with atogepant used as a preventive migraine treatment (29). More participants treated with atogepant 60 mg once-daily compared to placebo experienced ≥7% weight loss at any time in the pooled episodic migraine placebo-controlled trials (4.9%

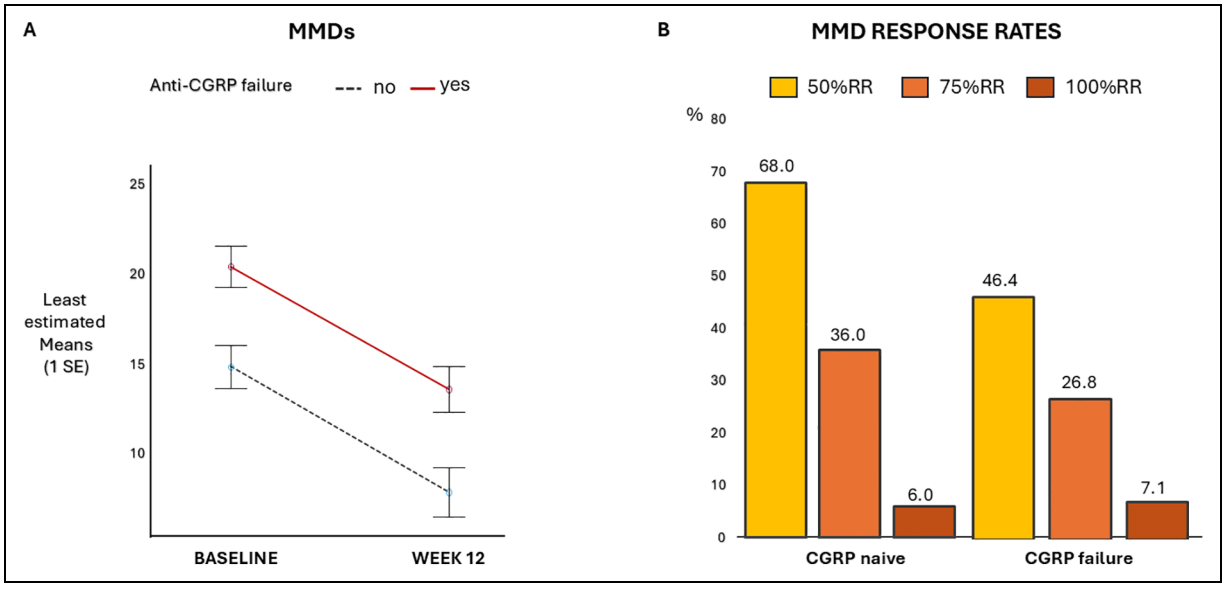

Figure 3. (a) Showing monthly migraine days (MMDs) variation from baseline to 12 weeks of atogepant therapy in patients with previous experience of ineffective anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) (red line) and those naïve to that treatment (black dotted line). (b) Monthly migraine day response rates (RR, 50%, 75% and 100%) in patients with anti-CGRP mAbs failure (right) and those anti-CGRP naïve (left).

Table 3. Patient reported outcomes at baseline and after 12-week therapy with atogepant.

	T0	T3	*p*
MIDAS, mean (SD); n = 104	69.1 (51.8)	28,4 (31.9)	<0.001
HIT-6, mean (SD); n = 100	64.8 (8.3)	54.9 (11.3)	0.242
ASC-12, mean (SD); n = 106	6.2 (4.9)	3.8 (4.5)	0.001
MSQ role-function restrictive, mean (SD), n = 101	41.8 (21.4)	66.6 (25.6)	0.026
MIBS-4, mean (SD), n = 102	1.3 (1.2)	4.4 (4.2)	0.237
mTOQ-6, mean (SD), n = 101	17.6 (4.6)	20.5 (4.2)	<0.001

ASC-12, 12-item Allodynia Symptom Checklist; HIT-6, Headache Impact Test; MIBS-4, Migraine Interictal Burden Scale; MIDAS, Migraine Disability Assessment questionnaire; MSQ, Migraine-Specific Quality-of-Life Questionnaire; mTOQ-6, Migraine Treatment Optimization Questionnaire-6.

vs. 2.8%), chronic migraine placebo-controlled trial (5.8% vs. 2.0%) and pooled open-label extension and long-term safety trials (24.0% vs.14.7% in standard care (long-term safety only)).

Real-world evidence has gained more and more relevance in recent years, also in the field of migraine treatment (30,31). RCTs remain undoubtedly the gold standard for demonstrating the efficacy of treatments. They test a therapeutic hypothesis in a prespecified setting, reaching high internal validity but leading to low generalizability because they are performed in conditions that sometimes differ substantially from clinical practice settings. Conversely, real-life studies evaluate the effectiveness of a treatment (i.e. the measurable benefit from a treatment when administered in a clinical routine). Accordingly, real-world trials have higher generalizability and may provide reliable and further information (e.g. the effect after long-term use and the persistence of a treatment benefit, the predictors of response) and should be used to share clinical experience among experts and to improve everyday clinical practice (32.33).

This is the first study reporting atogepant effectiveness and tolerability in the short term in a real-life setting. Our results confirm the positive impact of atogepant on the treatment of EM and CM patients. Even if, in the present study, the ≥50% responder rate at week 12 is lower than those reported with mAbs anti-CGRP for CM patients in RWE (34), the main novelty is that patients resistant to previous anti-CGRP mAbs may benefit from atogepant after only 12 weeks of treatment. More specifically, 43.3% of patients achieving a 50% MMD RR had a previous unsatisfactory response to anti-CGRP mAbs.

Pharmacological differences can explain why the switch among anti-CGRP mAbs was reported to produce an improved migraine outcome in real life, despite the similar mechanism of action (35,36). These differences are even more substantial when comparing mAbs to

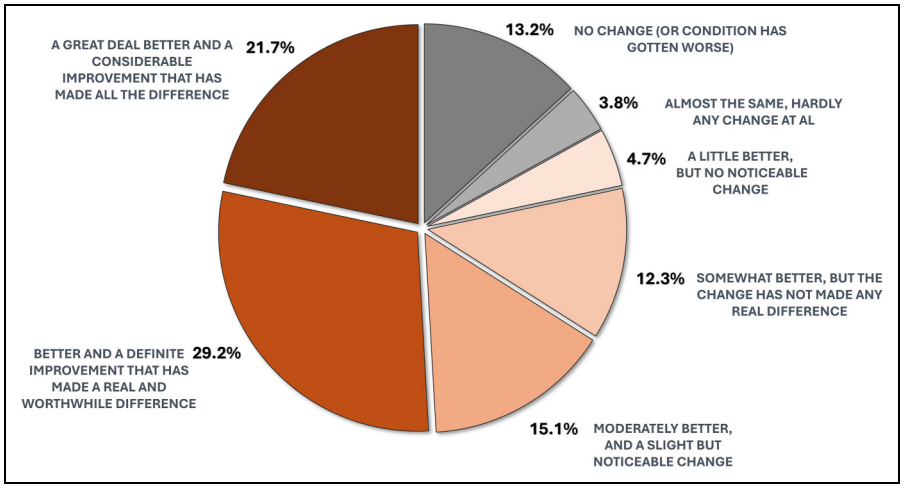

Figure 4. Percentual response to the Patient Global Impression of Change (PGIC) questionnaire at the end of the 12-week therapy with atogepant Please replace the figure with the one attached .

gepants (37). Regardless of the mechanism of action, the main differences between anti-CGRP mAbs and gepants lie in their pharmacokinetic features, with very different molecular structures, size (small 50 Da molecules vs. big 150 kDa mAbs), administration routes (oral vs. subcutaneous/intravenous), half-life (11 hours vs. at least one month) and potential interaction with other drugs. These unique characteristics require different clinical management (e.g. drug–drug interactions and adherence) but expand the treatment choice in patients that failed anti-CGRP mAbs (38,39). Indeed, the present study demonstrates a sustained effectiveness of atogepant in patients who failed one or more mAbs. Other mechanisms can also play a role, such as different affinities with amylin and adrenomedullin receptors (40). Finally, a recent additional relevant action has been proposed. Atogepant, different from mAbs, also antagonizes α-CGRP-mediated recruitment of the regulatory protein β-arrestin and internalization of the CGRP receptor, suggesting that, beyond cAMP production, it can inhibit other receptor signaling intracellular pathways (41). Accordingly, in our cohort, although anti-CGRP mAb naïve patients were significantly more frequent Responders (65.2%), the multivariate analysis did not confirm previous unsatisfactory anti-CGRP mAb use (including erenumab) as a main unfavorable prognostic factor.

Along the same lines, different from the evidence from previous mAbs anti-CGRP experience (32,42), the body mass index (BMI) does not appear to influence the effect of the treatment. Indeed, the efficacy of atogepant also in overweight patients was demonstrated by pivotal RCT involving patients with a mean BMI above 25 kg/m^2 (13,15). One possibility is that the treatment efficacy overcomes the negative impact of obesity on migraine (43). Alternatively, an intriguing hypothesis is that atogepant has a specific action in the adipose tissue (44). It may also explain the minor weight loss observed with daily atogepant use in our cohort and RCTs, which is still not completely explained. Weight loss appears to be dose-dependent and independent of adverse events such as nausea (29). These observations point toward a pharmacologic mechanism. Indeed, Hay et al. (45) observed that atogepant can antagonize CGRP receptors in human adipocytes. The adipose tissue has a pathophysiological role in migraine progression through chronic inflammation, metabolic regulation and the dysregulation of adipocytokines such as leptin and adiponectin (46). The CGRP, with its ubiquitous expression, has also been involved in regulating lipolysis and energy expenditure, as well as in the inflammation of adipose tissue (47,48). In this light, one may speculate that the modulation of these CGRP properties represent an indirect extra-cerebral site of action of atogepant in migraine prevention.

The main limitation of the present study is the absence of a control group. Without a direct comparison, the interpretation of results must be cautiously approached because uncontrolled factors may have influenced the observed outcomes.

We did not find other predictors of response after a relatively short period of observation in a population of over 100 patients. Although previous preventive failures (including OBT-A and anti-CGRP therapies) were more frequent in the Non-Responder group, as well as medication overuse (Table 2), the multivariate analysis did not confirm the strength of this relationship. Again, this confirms the results of the PROGRESS study, which showed a similar reduction in MMDs in patients with and without MO and interestingly described a reduction approximately by half of acute medication overusers as in our cohort.

Conclusions

The STAR study demonstrates atogepant effectiveness in real life, observing migraine frequency reduction and

patients' reported outcome measures improvement. Even if 44% of subjects reported adverse events related to atogepant, only three of them discontinued the treatment for scarce tolerability. Moreover, we point out that 43% of hard-to-treat patients resistant to previous anti-CGRP mAbs treatment benefitted from atogepant after only 12 weeks.

These observations and the other results of our study suggest that atogepant can be considered as a new therapeutical approach, probably different from others targeting the CGRP pathway, which is now at the disposal of clinical practice for the effective treatment of our migraine patients.

Clinical implications

- Our study demonstrated the effectiveness of atogepant in preventing migraine after a 12-week treatment in real life conditions.
- Only three out of 106 patients discontinued treatment for adverse events.
- Moreover, 43% of patients previously resistant to anti-CGRP mAbs benefitted from atogepant after 12 weeks.
- Atogepant can be considered as a new therapeutic approach for effectively treating migraine patients in clinical practice.

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Declaration of conflicting interests

FV has received financial support from Allergan-AbbVie, Angelini and Lundbeck for investigator-initiated trials; consulting fees for the participation in advisory boards from AbbVie, Angelini, Eli Lilly, Lundbeck, Organon, Novartis, Pfizer and Teva; honoraria for scientific lectures and presentations from AbbVie, Eli Lilly, Lundbeck, Novartis, Organon, Pfizer and Teva; support for attending meetings from Abbvie, Amgen, Eli Lilly, Lundbeck, Pfizer and Teva; he has been Principal Investigator in clinical trials sponsored by AbbVie, Eli Lilly, Lundbeck, Pfizer and Teva; he is Co-Specialty Editor for *Frontiers in Neurology* Headache and Neurogenic Pain section.

LFI received fees and Honoraria for advisory boards, speaker panels from Teva, Eli Lilly, Lundbeck, Pfizer and AbbVie.

GS received honoraria from AbbVie

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Author contributions

FV, CA, SG and LFI had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; designed the study; and drafted the manuscript. CA performed statistical analysis. LFI and FV performed administrative and technical support. All authors recruited patients and critically reviewed the manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work, and have read and approved the final version of the manuscript submitted for publication.

Data availability

Data supporting the findings in the present study are reported within the article and also in the supplemental materials. The data collected and analyzed for the present study are available from the corresponding author upon reasonable request.

Ethical statement

The local Ethics committee approved the study as part of the Registro Italiano Cefalee (RICe) study (Studio RICe, 14591_oss CEAVC Studio RICe, 14591_oss and subsequent amendments).

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Supplemental material

Supplemental material for this article is available online.

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