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A phase 2, randomized, double-blind, placebo-controlled trial of AMG 301, a pituitary adenylate cyclase-activating polypeptide PAC1 receptor monoclonal antibody for migraine prevention

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Abstract

Objective: To assess the safety and efficacy of AMG 301, an inhibitor of the pituitary adenylate cyclase-activating polypeptide (PACAP)-1 (PAC1) receptor, for prevention of migraine.

Methods: In a double-blind trial, patients were randomized 4:3:3 to placebo, AMG 301 210 mg every 4 weeks, or AMG 301 420 mg every 2 weeks for 12 weeks. Effect on monthly migraine days and other secondary measures were assessed over weeks 9–12. Safety and tolerability were assessed.

Results: Of 343 randomized patients (mean age, 41.8–42.5 years), the majority were women (85.4–90.4%), white (94.1–96.2%), and had episodic migraine (62.5–67.9%). A total of 305 patients completed treatment (placebo, n = 124; AMG 301 210 mg, n = 94; AMG 301 420 mg, n = 87). Least squares mean reduction at week 12 in monthly migraine days from baseline was −2.5 (0.4) days for placebo and −2.2 (0.5) days for both AMG 301 treatment groups. No difference between AMG 301 and placebo on any measure of efficacy was observed; mean (95% confidence interval) treatment difference versus placebo for monthly migraine days for AMG 301 210 mg, 0.3 (−0.9 to 1.4); AMG 301 420 mg, 0.3 (−0.9 to 1.4). The incidence of adverse events was similar across groups.

Conclusion: AMG 301 offered no benefit over placebo for migraine prevention; further studies may be necessary to fully understand the role of PACAP isoforms and its receptors in migraine pathophysiology.

Study Registration: ClinicalTrials.gov: NCT03238781

Keywords

AMG 301, chronic migraine, episodic migraine, pituitary adenylate cyclase-activating polypeptide, preventive treatment

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Introduction

A majority of treatments currently available as the standard of care for migraine prevention were originally developed for other indications (1), and they are typically associated with tolerability issues, leading to poor patient adherence (2) and ultimately poor treatment outcomes. The historically high, unmet need in migraine prevention has led to much research effort directed to better understanding the pathophysiology of migraine. Subsequent research led initially to the development of small molecules, and more recently, monoclonal antibodies targeting the calcitonin gene–

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related peptide (CGRP) receptor and the CGRP ligand (3). Four of these monoclonal antibodies have been clinically developed for the prevention of migraine (4), but not all patients respond sufficiently to CGRP pathway inhibition (4,5).

Like CGRP, pituitary adenylate cyclase-activating polypeptide (PACAP), a neuropeptide expressed in the trigeminovascular system, is believed to play a role in migraine pathophysiology (6,7). PACAP is a member of the vasoactive intestinal polypeptide (VIP)/secretin/glucagon superfamily. PACAP occurs in two forms: A 38 amino acid peptide (PACAP-38) and a truncated 27 amino acid form (PACAP-27). Of these, PACAP-38 is the predominant form; $>90\%$ of PACAP in the CNS is PACAP-38 (6). While PACAP appears to play a major role in the parasympathetic pathway, and its receptors are also found in the trigeminal ganglion, the trigeminocervical complex, the hypothalamus, and the thalamus, PACAP does not appear to act via an increase in CGRP or tumor necrosis factor (8–10). Three G-protein-coupled receptors for PACAP have been identified (VPAC1, VPAC2, and PAC1 receptors); of these, the PAC1 receptor has a 1000-fold higher binding affinity for PACAP ($\approx$ 0.5 nM) than for VIP (>500 mM), whereas the VPAC1 and VPAC2 receptors both have a similar binding affinity for PACAP and VIP ($\approx$ 1 nM) (11). Activation of all three receptors stimulates adenylate cyclase activity, increasing intracellular cyclic adenosine monophosphate (cAMP) production (6,11). However, activation of the PAC1 receptor, in particular, by PACAP-38 stimulates adenylate cyclase to a substantially greater degree than does VIP (11). It has been speculated that the elevation of cAMP resulting from PACAP-38 activation of the PAC1 receptor in peripheral trigeminal nociceptors results in nociception (6,11).

Infusion of PACAP-38 (7) and PACAP-27 (12), and to a much lesser extent VIP (13,14), has been shown to cause migraine-like attacks in migraine patients. Because the PAC1 receptor has a higher affinity for PACAP-38 versus VIP and VIP does not induce migraine attacks in the majority of patients, it was considered possible that PACAP-38 may induce migraine-like attacks via its activity at the PAC1 receptor rather than at the VPAC1 or VPAC2 receptors (14). Furthermore, PAC1 receptor but not VPAC1 or VPAC2 receptor mRNA expression was increased in the trigeminal ganglion of rats in an animal model of migraine (15). Investigation of PAC1 receptor inhibition, therefore, may lead to a better understanding of the role of PACAP in migraine (6,14). Subsequently, AMG 301, a human monoclonal antibody selective for inhibition of the PAC1 receptor, was developed (16).

The objective of this phase 2 trial was to evaluate the efficacy and safety of AMG 301 for the prevention of migraine across the continuum of episodic migraine (EM) and chronic migraine (CM). The primary hypothesis was that AMG 301 would cause a greater reduction in monthly migraine days (MMD) from baseline over the last 4 weeks of the 12-week double-blind period compared with placebo.

Methods

Trial design

A phase 2a, multicenter, randomized, double-blind, placebo-controlled trial of subcutaneous AMG 301 was undertaken in adults with CM or EM who were considered eligible for preventive treatment and fulfilled eligibility criteria (more detailed eligibility criteria are provided in the *Patients* section below; ClinicalTrials.gov: NCT03238781). After an initial screening period of $\leq$ 3 weeks followed by a baseline period of 4 weeks, during which patients were required to complete a daily electronic headache diary, investigators confirmed that patients met eligibility criteria and had provided informed consent, patients were enrolled in the trial and randomized 4:3:3 to placebo, AMG 301 210 mg every 4 weeks (Q4W), or AMG 301 420 mg every 2 weeks (Q2W) for 12 weeks (Figure 1); to maintain blinding, patients received a total of six subcutaneous injections Q2W. Full details are provided in the *Trial treatments* section. A safety follow-up visit was conducted 18 weeks after the last dose of investigational drug.

Before the start of the trial, an interactive voice response/interactive web response system was used to facilitate randomization and stratification, and the randomization treatment assignment was generated by the sponsor's Global Randomization and Blinding group independent of the study. Randomization was stratified by baseline migraine frequency (CM versus EM) and geographical region (North America vs. rest of world). CM and EM categories were defined based on frequency of migraine and non-migraine headache, determined during the 4-week baseline period (using the daily electronic diary) in line with the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria (17) for CM (CM: $\geq$15 headache days and $\geq$8 migraine-like days; EM: <15 headache days and $\geq$4 migraine-like days).

The trial protocol was approved by each site's institutional review board or independent ethics committee, and each patient was required to provide written informed consent before participation in the trial.

Pre-planned interim analyses were undertaken for administrative purposes for future study planning without additional *p*-value adjustments (this study was not modified based on the interim effect size results).

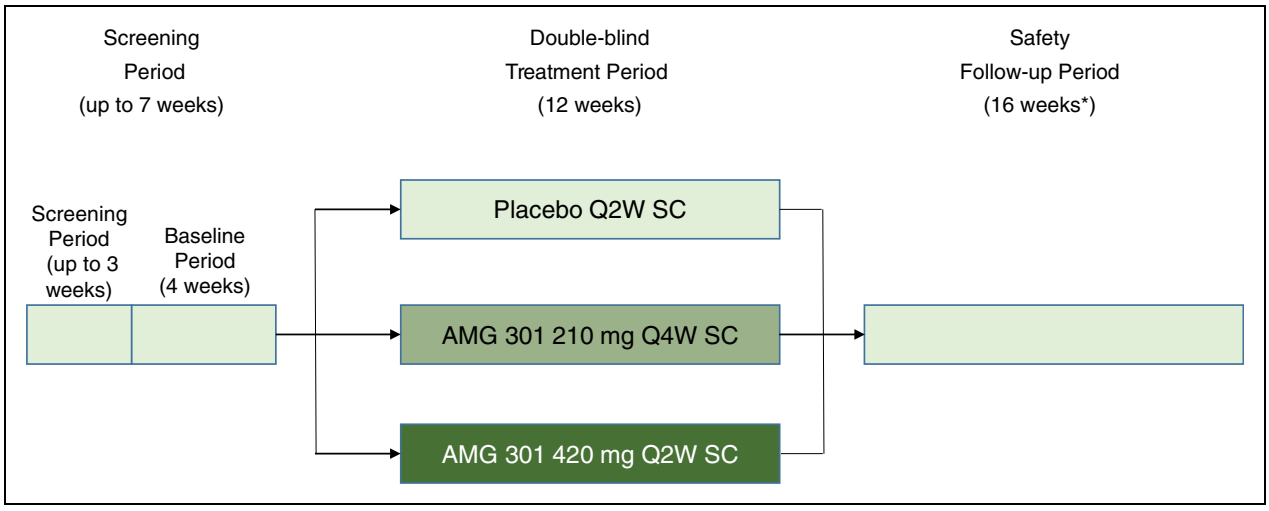

Figure 1. Trial design.
Q2W: every 2 weeks; Q4W: every 4 weeks; SC: subcutaneous.
*18 weeks after last dose of investigational product.

An independent data review team reviewed the results and made recommendations regarding the safety of patients, up to and including early stopping of the trial, if deemed necessary.

Assuming a treatment effect compared to placebo of −2.0 MMD for both AMG 301 mg treatment groups and a common SD of 4.7 MMD, the planned sample size of 135 patients for the placebo group, 100 patients for the AMG 301 420 mg Q2W, and 100 patients for the AMG 301 210 mg Q4W group were to provide ≥80% power using a two-sample t-test for each AMG 301 group versus placebo, with a two-sided significance level of 0.05, maintaining a family-wise alpha level of 0.10, assuming a 10% dropout.

Patients

To be eligible for enrolment, patients with EM or CM were required to be ≥18 to ≤ 60 years of age, with a ≥12-month history of migraine and a migraine frequency of ≥4 migraine days per month over the 3 months before screening. Patients were also required to have failed one or more previous migraine preventive treatment as a result of tolerability issues or lack of efficacy and to be taking (or have taken in the past) triptans or ergotamine as acute treatment (patients unable to take triptans or ergotamine due to contraindications were allowed in the trial if all other criteria were fulfilled). Patients with medication overuse headache were not excluded from the study. Finally, patients must have achieved a ≥80% compliance rate on the daily electronic diary during the 28-d baseline period (i.e. completed ≥23 daily diary entries). Patients who were aged > 50 years at onset of migraine; with a history of cluster headache, hemiplegic migraine headache, or continuous migraine pain; or unable to differentiate migraine from other headaches were excluded as were those taking preventive migraine treatments within 2 months of baseline (4 months for onabotulinumtoxinA or monoclonal antibodies targeting the CGRP pathway). In addition to standard baseline characteristics, the cranial autonomic parasympathetic symptom (CAPS) score was assessed. Lacrimation, conjunctival injection, eyelid edema, ear fullness, and nasal congestion were graded 0 (absent) to 2 (present and conspicuous), giving a total possible CAPS score of 10 (18).

Trial treatments

AMG 301 was provided as 70 mg/mL in 1-mL vials; placebo was provided in a matching formulation and identical container. All patients received a total of six subcutaneous, 1 mL injections Q2W. Patients randomized to placebo received six placebo injections Q2W on day 1 and weeks 2, 4, 6, 8, and 10. Those randomized to AMG 301 210 mg Q4W received three AMG 301 70-mg injections on day 1 and weeks 4 and 8 with three matching placebo injections and six placebo injections on weeks 2, 6, and 10. Those randomized to AMG 301 420 mg Q2W received six AMG 301 70-mg injections Q2W on day 1 and weeks 2, 4, 6, 8, and 10. All treatments were administered into the upper arm, upper thigh, or abdomen.

Dose adjustment was not permitted. Investigators could, however, discontinue treatment for any patient experiencing a severe or life-threatening adverse event considered to be treatment related.

Endpoints

Patient electronic daily diaries were the primary tool used to collect data on efficacy outcomes. Patients entered headache data (e.g. start and stop times, worst severity assessment, pain features, and headache-associated symptoms) and acute medication use (e.g. medication name, date, dose, and frequency) each day. The patient also used the electronic diary to complete the Migraine Physical Function Impact Diary (MPFID; daily at home), a 13-item patient reported outcome tool designed to measure the impact of migraines in daily life based on a 24-h recall. The MPFID measures across two major domains, "Impact on everyday activities" (seven items) and "Physical impairment" (five items) (19). Each item is assessed using a five-point scale (1, activity completed without difficulty through 5, unable to complete activity) (19). Scores across each MPFID domain were calculated as a sum of responses and rescaled on a 0–100 scale (the higher the score, the greater the burden of migraine).

The primary endpoint was the change in MMD from baseline to the last 4 weeks of the 12-week treatment period. The secondary efficacy outcomes were also evaluated over the last 4 weeks of the 12-week treatment period and included the proportion of patients achieving $\geq$50% reduction in MMD from baseline, change from baseline in monthly acute migraine-specific medication days (MSMD), mean MPFID–physical impairment (MPFID-PI) scores, and mean MPFID–everyday activities (MPFID-EA) scores. A pre-specified subgroup analysis was undertaken to assess the change in MMD from baseline to the last 4 weeks of the 12-week treatment period in patients with CM and in those with EM. Safety and tolerability of AMG 301 were also evaluated.

Statistical analysis

The primary analysis dataset included all patients who received at least one treatment dose and completed at least one post-baseline monthly electronic diary measurement and was used for all efficacy analyses. The effect of a number of covariates on treatment outcomes was assessed, including region (North America vs. rest of world), baseline migraine frequency (CM vs. EM), and corresponding baseline value for the endpoint being analysed. In general, MMD, acute migraine-specific medication use, and MPFID data were prorated based on the number of days with available information if $\geq$50% of data were available. A linear mixed effects model including treatment group, baseline value, stratification factors, scheduled visit, and the interaction of treatment group with scheduled visit was used for the primary endpoint and other continuous endpoints, with 95% confidence intervals and unadjusted two-sided *p*-values of the means. The Cochran-Mantel-Haenszel test was used for categorical endpoints, such as the proportion of patients achieving a $\geq$50% reduction in MMD from baseline, without imputation for missing data (observed data). For all endpoints, nominal *p*-values without multiplicity adjustment are presented. To maintain a type I error at 0.10, each of the pairwise comparisons (i.e. AMG 310 210 mg vs. placebo and AMG 310 420 mg vs. placebo) were tested for the primary endpoint at an alpha level of 0.05. Statistical analyses were undertaken using SAS system version 7.1 or later (SAS Institute, Cary, NC, USA).

Results

Patients

The trial was completed as planned. In total, 343 patients from 46 sites were randomized to treatment. The majority of the investigators were headache specialists. Patients were randomized at a 4:3:3 ratio; 137 patients to placebo, 104 patients to AMG 301 210 mg Q4W, and 102 patients to AMG 301 420 mg Q2W were included in the analysis dataset (Figure 2). All randomized patients received $\geq$1 dose of the investigational product. A total of 305 patients (88.9%) completed the double-blind treatment phase; 124 patients (90.5%) receiving placebo, 94 patients (90.4%) receiving AMG 301 210 mg Q4W, and 87 patients (85.3%) receiving AMG 301 420 mg Q2W. The investigational product was discontinued by 38 patients (11.1%), primarily due to patient request (n = 25, 7.3%) and adverse event (n = 10, 2.9%); the numbers of patients discontinuing were similar across treatment groups.

Baseline demographics and clinical characteristics were generally balanced among the treatment groups (Table 1). Patients had a mean age of 41.8 to 42.5 years, 85.4% to 90.4% of treatment subgroups were women, and 94.1% to 96.2% were white. Baseline migraine classification was EM for 62.5% to 67.9% of patients. At baseline, mean MMD ranged from 12.1 to 12.5 days, mean monthly headache days ranged from 13.1 to 13.9 days, and mean monthly acute MSMD ranged from 7.2 to 8.1 days.

In the full analysis set, cranial autonomic parasympathetic symptom (CAPS) scores were available for 99.7% (n = 342) of patients at baseline and ranged from 0–10. CAPS scores were skewed toward the lower end of the scale at baseline (0, n = 210; 1, n = 54; 2, n = 48; 3, n = 15; $\geq$4, n = 15), and tended to remain low and unchanged throughout the course of

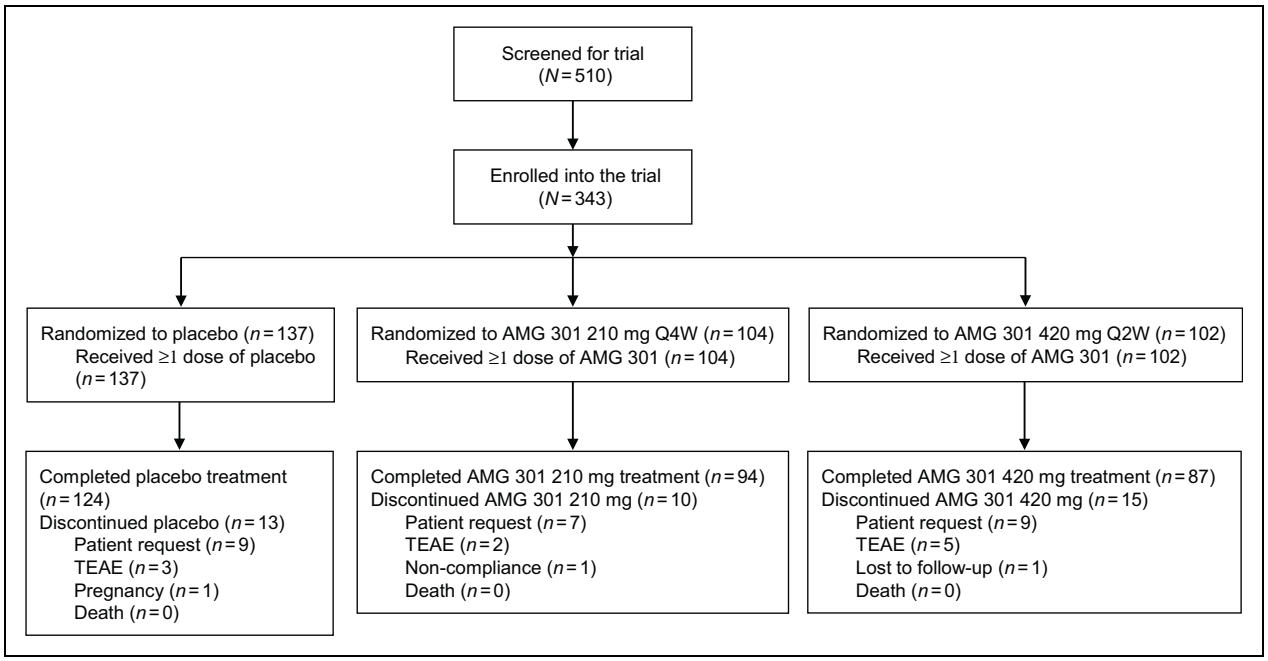

Figure 2. Patient disposition.
Q2W: every 2 weeks; Q4W: every 4 weeks; TEAE: treatment-emergent adverse event.

Table 1. Patient demographics and baseline clinical characteristics.

		AMG 301		
	Placebo (N = 137)	210 mg Q4W (N = 104)	420 mg Q2W (N = 102)	Total (N = 343)
Age, mean (SD), years	41.8 (9.9)	42.3 (9.7)	42.5 (9.4)	42.2 (9.7)
Women, n (%)	117 (85.4)	94 (90.4)	90 (88.2)	301 (87.8)
White, n (%)	129 (94.2)	100 (96.2)	96 (94.1)	325 (94.8)
Disease duration, mean (SD), years	21.5 (11.5)	23.4 (11.1)	22.9 (11.6)	22.5 (11.4)
Number of previous migraine prophylactic treatment failures by category, n (%)*				
1	69 (50.4)	42 (40.4)	45 (44.1)	156 (45.5)
2	30 (21.9)	32 (30.8)	29 (28.4)	91 (26.5)
3	26 (19.0)	19 (18.3)	19 (18.6)	64 (18.7)
≥4	12 (8.7)	11 (10.6)	9 (8.8)	32 (9.3)
Migraine frequency, n (%)				
CM	44 (32.1)	39 (37.5)	36 (35.3)	119 (34.7)
EM	93 (67.9)	65 (62.5)	66 (64.7)	224 (65.3)
MMD, mean (SD)	12.2 (5.1)	12.5 (4.8)	12.1 (5.3)	12.3 (5.1)
Monthly headache days, mean (SD)	13.5 (5.3)	13.9 (4.9)	13.1 (5.2)	13.5 (5.2)
Monthly acute MSMD, mean (SD)	7.2 (5.7)	8.1 (5.3)	7.5 (4.9)	7.5 (5.3)
Acute headache medication use, n (%)	135 (98.5)	101 (97.1)	100 (98.0)	336 (98.0)
Migraine specific	115 (83.9)	95 (91.3)	89 (87.3)	299 (87.2)
Non-migraine specific	78 (56.9)	51 (49.0)	54 (52.9)	183 (53.4)

CM: chronic migraine; EM: episodic migraine; MMD: monthly migraine days; MSMD: migraine-specific medication days; n: number of patients with the specific characteristic; N: number of patients in the respective treatment group; Q2W: every 2 weeks; Q4W: every 4 weeks.
*Failures were defined by tolerability issues or insufficient efficacy.

the study (CAPS scores at week 12: 0, n = 214; 1, n = 42; 2, n = 21; 3, n = 11; ≥4, n = 13).

Efficacy

Placebo was associated with a least squares (LS) mean (SE) change from baseline in MMD in the last 4 weeks of the 12-week double-blind treatment period of −2.5 (0.4) days versus −2.2 (0.5) days for each of the AMG 301 dose groups (Figure 3(a)). The change from baseline in MMD for each of the AMG 301 dose groups was not different from placebo. The treatment difference from placebo was 0.3 (95% CI, −0.9 to 1.4; $p = 0.66$) for AMG 301 210 mg Q4W and 0.3 (95% CI, −0.9 to 1.4; $p = 0.65$) for AMG 301 420 mg Q2W (Table 2).

Based on observed data, of 119 patients receiving placebo in the analysis dataset, 27 patients (22.7%) achieved ≥50% reduction from baseline in MMD (≥50% responders); 18 of 93 patients (19.4%) receiving AMG 301 210 mg Q4W were ≥50% responders, as were 16 of 85 patients (18.8%) receiving AMG 301 420 mg Q2W (Figure 3(b)).

Similarly, there was no treatment difference in change from baseline for monthly acute MSMD between placebo and either of the two AMG 301 dose groups (Figure 3(c) and Table 2).

There was no treatment difference in change from baseline in either of the major domains of the MPFID (impact on everyday activities or physical impairment sub-domains) between the two AMG 301 dose groups and placebo (Figure 4).

In the sub-group of patients with EM, the treatment difference in change in MMD from baseline between placebo and AMG 301 210 mg Q4W was 0.2 (95% CI, −1.1, 1.5; $p = 0.75$) and between placebo and AMG 301 420 mg Q2W was 0.7 (95% CI, −0.6, 2.0; $p = 0.28$; Supplementary Table 1). In the sub-group of patients with CM, the treatment difference in change in MMD from baseline between placebo and AMG 301 210 mg Q4W was 0.6 (95% CI, −1.7, 2.8; $p = 0.62$) and between placebo and AMG 301 420 mg Q2W −0.5 (95% CI, −2.9, 1.8; $p = 0.65$).

Safety

Overall, the incidence of treatment-emergent adverse events (TEAEs) was similar in patients receiving placebo (65.7%) and in those receiving AMG 301 (66.0%; Table 3). The majority of TEAEs were grade 1 or 2, with 6.6% of placebo recipients and 6.3% of AMG 301 recipients having a grade ≥3 TEAE. Serious adverse events occurred in 2.2% of the placebo group and in 1.5% of the overall AMG 301 group. TEAEs rarely led to discontinuation of the investigational product (placebo, 2.2%; AMG 301, 3.4%), and there were no fatal TEAEs.

The most common TEAEs for placebo and AMG 301, respectively, were nasopharyngitis (9.5% and 8.3%), fatigue (5.8% and 6.8%), influenza (3.6% and 5.3%), constipation (0.0% and 4.9%), upper respiratory tract infection (2.9% and 4.9%) and gastroenteritis (3.6% and 4.4%). AMG 301 420 mg Q2W appeared to be as well tolerated as AMG 301 210 Q4W (Table 3). TEAEs leading to discontinuation of investigational product occurred in three patients (2.2%) in the placebo group and seven patients (3.4%) in the AMG 301 treatment groups; > 1 TEAE may have led to discontinuation in a patient. TEAEs leading to discontinuation included fatigue, pyrexia, contusion, migraine, depression, and cough (n = 1 for each) in the placebo group and migraine (n = 4), tinnitus, oral hypoesthesia, chest discomfort, injection site erythema, injection site pruritus, hypersensitivity, muscle spasms, paresthesia, anxiety, throat irritation, and swelling face (n = 1 for each) in the AMG 301 treatment groups. Serious adverse events included cholelithiasis, gastroenteritis, and migraine with aura (n = 1 for each) in the placebo group, and erythema nodosum, hypersensitivity and polycystic ovaries (n = 1 for each) in the AMG 301 treatment groups. Overall, 16 (7.8%) patients receiving AMG 301 developed anti-AMG 301 binding antibodies over the duration of the trial; anti-AMG 301 binding antibodies were transient in one patient.

Discussion

Inhibition of PACAP or associated receptors as potential therapeutic targets for the treatment of migraine, particularly in migraine non-responsive to CGRP pathway inhibition, is a current area of active research (20). PACAP and PAC1 receptors are widely distributed centrally, being present in structures such as the trigeminal nucleus caudalis and the trigeminal ganglion, typically associated with nociception and migraine pathophysiology (20). Similarly, PACAP and PAC1 receptors have a wide distribution in the periphery and are involved in a range of physiological processes, including maintenance of neurogenic vasodilation (16).

Provocation studies have found PACAP-38 infusion causes sustained dilation of the middle meningeal artery, which co-occurs with the induced headache and is reversed by the administration of subcutaneous sumatriptan; PACAP-38 does not appear to have any dilatory effect on the middle cerebral artery (21). PACAP-38 has also been found to induce premonitory symptoms in a subgroup of patients, a possible marker of involvement of the CNS (22).

Since the PAC1 receptor has a high affinity for PACAP (11), and PACAP, but not VIP, appears to

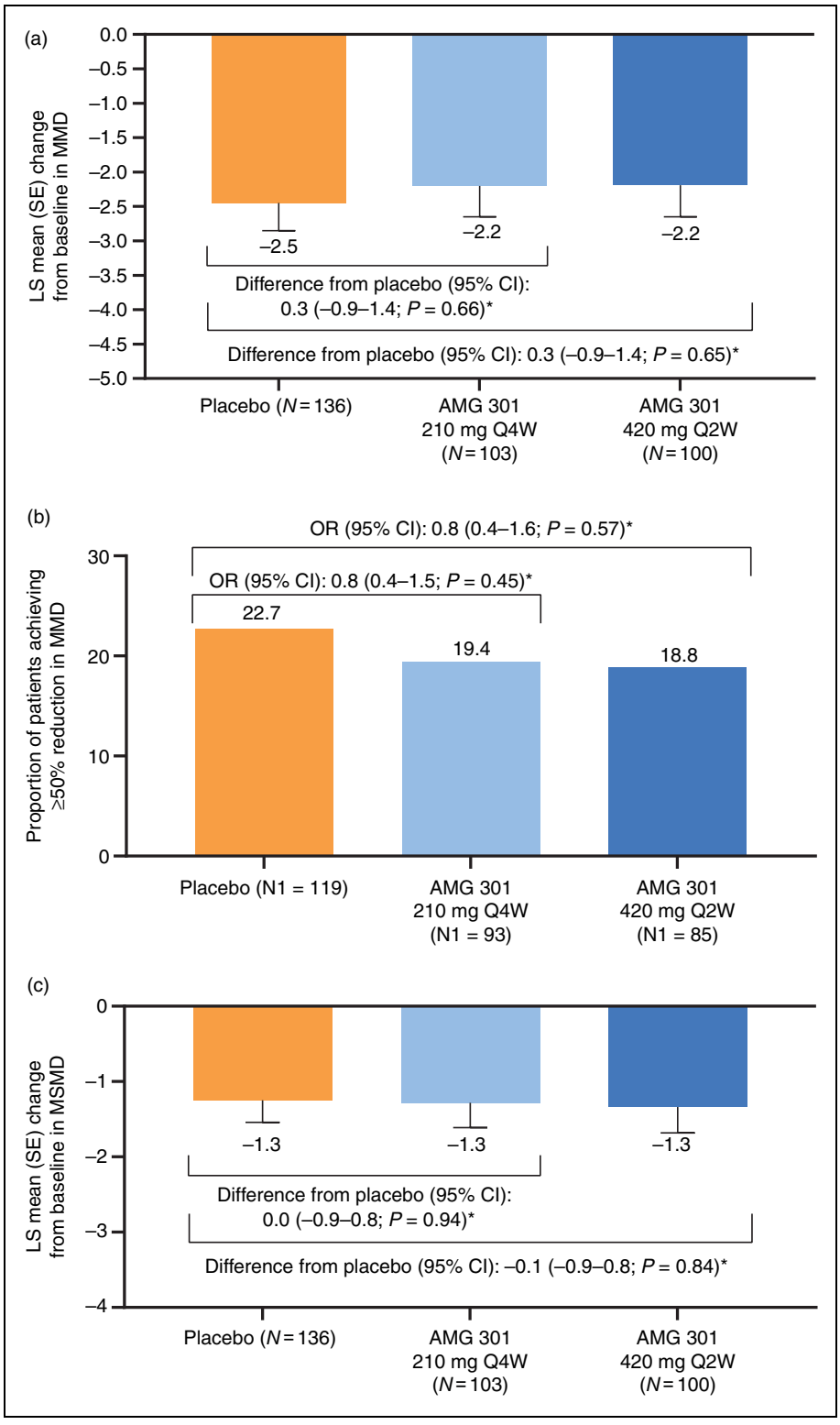

Figure 3. Effect of AMG 301 and placebo on (a) change from baseline of MMD, (b) proportion of patients achieving a ≥ 50% reduction in MMD, and (c) change from baseline of monthly acute migraine-specific medication use as assessed in the last 4 weeks of a 12-week double-blind treatment period.
LS: least squares; MMD: monthly migraine days; MSMD: migraine-specific medication days; N: number of patients in the primary analysis dataset (i.e. received ≥ 1 dose of investigational product and completed ≥ 1 post-baseline monthly electronic diary measurement); N1: number of patients with observed data; OR: odds ratio; Q2W: every 2 weeks; Q4W: every 4 weeks.
*Odds ratio versus placebo.

Table 2. Summary of primary and secondary efficacy outcomes assessed at week 12*.

		AMG 301	
	Placebo (N = 136)	210 mg Q4W (N = 103)	420 mg Q2W (N = 100)
Primary outcome			
Baseline MMD, mean (SD)	12.2 (5.2)	12.5 (4.8)	12.1 (5.4)
Change from baseline in MMD, LS mean (SE)	−2.5 (0.4)	−2.2 (0.5)	−2.2 (0.5)
Difference from placebo (95% CI)		0.3 (−0.9, 1.4)	0.3 (−0.9, 1.4)
p-value		0.66†	0.65†
Secondary outcomes			
≥ 50% reduction from baseline in mean MMD, n/N1 (%)	27/119 (22.7)	18/93 (19.4)	16/85 (18.8)
Odds ratio (95% CI)		0.8 (0.4, 1.6)	0.8 (0.4, 1.5)
p-value		0.57‡	0.45‡
Baseline MSMD, mean (SD)	7.1 (5.8)	8.1 (5.3)	7.5 (4.9)
Change from baseline in MSMD, LS mean (SE)	−1.3 (0.3)	−1.3 (0.3)	−1.3 (0.3)
Difference from placebo (95% CI)		−0.0 (−0.9, 0.8)	−0.1 (−0.9, 0.8)
p-value		0.94†	0.84†

LS: least squares; MMD: monthly migraine days; MSMD: migraine-specific medication days; n: number of responders; N: number of patients in the primary analysis dataset (i.e. received ≥ 1 dose of investigational product and completed ≥ 1 post-baseline monthly electronic diary measurement); N1: number of patients with observed data; Q2W: every 2 weeks; Q4W: every 4 weeks.

*Assessed over the last 4 weeks of the 12-week trial period.

†Adjusted analysis used a generalized linear mixed model that included treatment, visit, treatment-by-visit interaction, stratification factors of region and baseline migraine frequency (CM versus EM), and baseline value as covariates and assumed a first-order autoregressive covariance structure. The *p*-values for pairwise comparisons were nominal without multiplicity adjustment.

‡The common odds ratios and *p*-values were obtained from a Cochran-Mantel-Haenszel (CMH) test stratified by region and baseline migraine frequency (CM vs. EM). The same analysis was repeated for each visit. *p*-values for pairwise comparisons versus placebo were nominal *p*-values obtained from the CMH test using data including placebo and corresponding AMG 301 dose group only.

be implicated in the pathogenesis of migraine based on provocation experiments (14), therapeutic blockade of the PAC1 receptor is one area of interest.

Preclinical data found AMG 301, a selective human monoclonal antibody inhibitor of the PAC1 receptor, to be as effective as sumatriptan in inhibiting evoked nociceptive activity in the trigeminocervical complex in rats, supporting further investigation of AMG 301 in the treatment of migraine (23). However, in the current trial, when administered in doses as high as 420 mg Q2W, AMG 301 was found to be no more effective than placebo in reducing MMD after 12 weeks of treatment, overall and in the EM and CM subgroups. Similarly, AMG 301 did not have any additional effect compared with that seen with placebo on other measures of migraine efficacy, such as a reduction in the use of monthly acute migraine-specific medication. This outcome is similar to that observed with the orexin receptor antagonists, agents that showed preclinical effect (24) but no prophylactic effect in clinical trials (25). Based on the results of this trial alone, subcutaneous AMG 301 does not appear to be effective in the prevention of migraine.

It is unclear whether the lack of efficacy might be due to pharmacologic properties of AMG 301 *per se* (e.g. differences in the affinity of anti-PAC1 receptor antibodies), whether the concentrations of AMG 301 achieved at the target were insufficient to produce effective inhibition of the PAC1 receptor; whether selective inhibition of the PAC1 receptor alone is insufficient to reduce migraine frequency in the trial population; or whether targeting the PAC1 receptor will be effective in certain subpopulations of migraine only (26–28).

In the study population, a minority of patients had evidence of parasympathetic autonomic symptoms at baseline (based on CAPS), which mirrors the findings of others in patients with migraine (18,29). It remains to be determined whether PAC1 receptor inhibition might be of more benefit in headache conditions associated with more prominent autonomic/parasympathetic components, such as those with cluster headache (30); evaluation of PAC1 receptor inhibition in these populations may be warranted.

It is also possible that PACAP exerts its migraine-inducing activity via VPAC1 or VPAC2 receptors or via all three receptors. Indeed, VPAC1 and VPAC2 receptors appear to have a role in vasodilation (31,32), while PAC1 receptors are implicated in pronociceptive transmission (33). Monoclonal antibodies targeting PACAP directly are also currently being actively investigated for prevention of migraine (20).

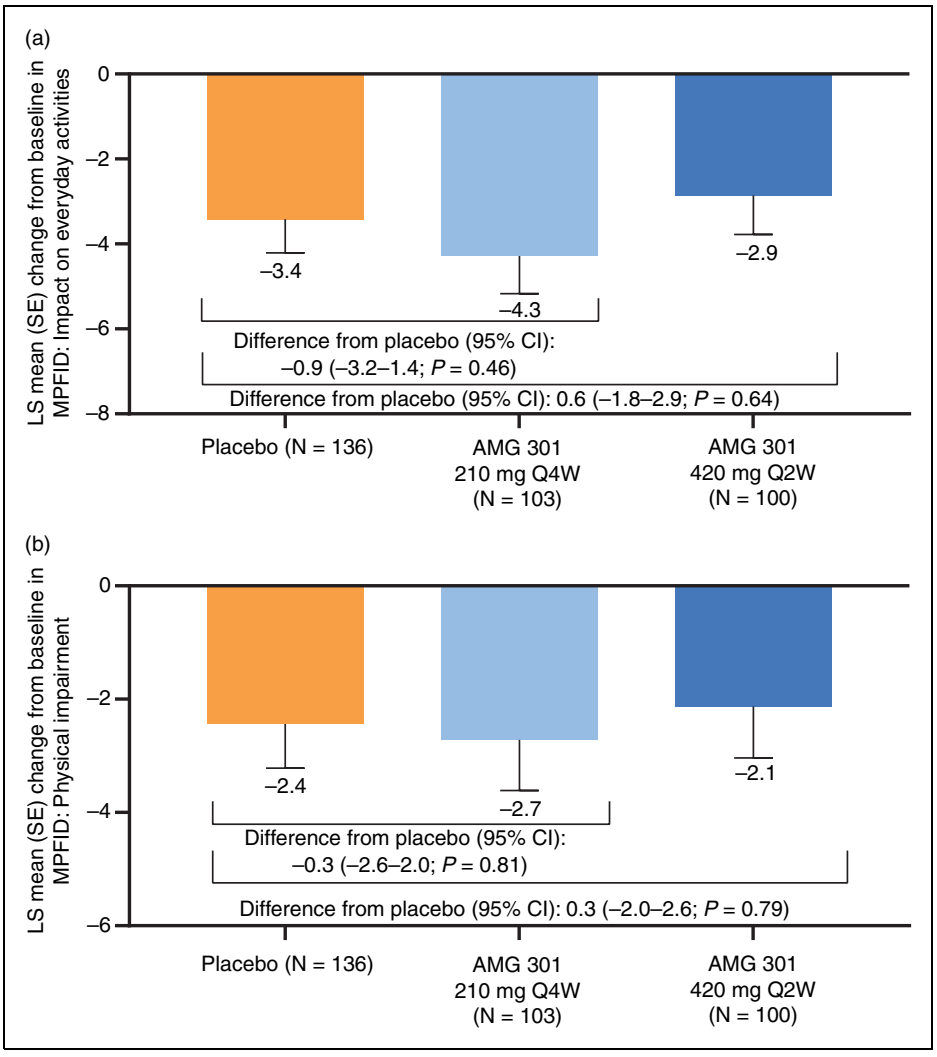

Figure 4. Effect of AMG 301 and placebo on change from baseline for (a) MPFID impact on everyday activities sub-score, and (b) MPFID on physical impairment sub-score as assessed in the last 4 weeks of a 12-week double-blind treatment period.
LS: least squares; MPFID: Migraine Physical Function Impact Diary; N: number of patients in the primary analysis dataset (i.e. received ≥ 1 dose of investigational product and completed ≥ 1 post-baseline monthly electronic diary measurement); Q2W: every 2 weeks; Q4W: every 4 weeks.

Table 3. Overview of adverse events.

		AMG 301		
	Placebo (N = 137)	210 mg Q4W (N = 104)	420 mg Q2W (N = 102)	All (N = 206)
All TEAEs, n (%)	90 (65.7)	71 (68.3)	65 (63.7)	136 (66.0)
Grade ≥3	9 (6.6)	5 (4.8)	8 (7.8)	13 (6.3)
Serious	3 (2.2)	1 (1.0)	2 (2.0)	3 (1.5)
Leading to discontinuation of IP	3 (2.2)	2 (1.9)	5 (4.9)	7 (3.4)
Fatal	0	0	0	0
Most frequent TEAEs (≥3% in either AMG 301 dose group), n (%)				
Nasopharyngitis	13 (9.5)	10 (9.6)	7 (6.9)	17 (8.3)
Fatigue	8 (5.8)	5 (4.8)	9 (8.8)	14 (6.8)
Influenza	5 (3.6)	5 (4.8)	6 (5.9)	11 (5.3)

(continued)

Table 3. Continued.

		AMG 301		
	Placebo (N = 137)	210 mg Q4W (N = 104)	420 mg Q2W (N = 102)	All (N = 206)
Constipation	0 (0.0)	4 (3.8)	6 (5.9)	10 (4.9)
Upper respiratory tract infection	4 (2.9)	5 (4.8)	5 (4.9)	10 (4.9)
Gastroenteritis	5 (3.6)	4 (3.8)	5 (4.9)	9 (4.4)
Migraine	3 (2.2)	2 (1.9)	6 (5.9)	8 (3.9)
Injection site erythema	2 (1.5)	2 (1.9)	5 (4.9)	7 (3.4)
Hypertension	1 (0.7)	2 (1.9)	5 (4.9)	7 (3.4)
Influenza-like illness	1 (0.7)	3 (2.9)	4 (3.9)	7 (3.4)
Sinusitis	6 (4.4)	4 (3.8)	3 (2.9)	7 (3.4)
Dizziness	3 (2.2)	4 (3.8)	1 (1.0)	5 (2.4)
Developed binding anti-AMG 301 antibodies, n/N1 (%)*	N/A	4/104 (3.8)	12/100 (12.0)	16/204 (7.8)
Transient†	N/A	0	1 (8.3)	1 (6.3)

IP: investigational product; N/A: not applicable; n: number of patients with the given adverse event; N: number of patients in the safety analysis dataset (i.e. received ≥ 1 dose of IP); N1: number of patients with no evidence of anti-AMG 301 antibodies at baseline and a postbaseline result; Q2W: every 2 weeks; Q4W: every 4 weeks; TEAE: treatment-emergent adverse event.

*Percentage calculated based on the number of patients with no evidence of anti-AMG 301 antibodies at baseline and a postbaseline result.

†Indicates a negative result at the last time point tested; percentage based on the number of patients who developed anti-AMG 301 antibodies postbaseline.

Note: Neutralizing activity of binding antibodies was not assessed.

While the target remains of interest (28), further studies with other inhibitors of PAC1 will be required to fully understand a possible role of PACAP/PAC1 receptor in migraine pathophysiology.

Conclusions

AMG 301, a human monoclonal antibody against the PAC1 receptor, was no more effective than placebo in reducing MMD or monthly acute MSMD or achieving ≥50% reduction in MMD when administered subcutaneously for the prevention of CM or EM. AMG 301 had a favorable tolerability profile, with no new safety risks identified. While these results do not show efficacy of PAC1 receptor inhibition with AMG 301, further studies may be necessary to fully understand the potential role of PACAP and its receptors in the pathophysiology of migraine.

Clinical implications

- The role of PAC1 receptor inhibition in the treatment of migraine is currently under investigation.
- Subcutaneous AMG 301, a human monoclonal antibody selective for inhibition of the PAC1 receptor, does not appear to offer any benefit compared with placebo in the prevention of CM and EM.
- Further research may be required to understand the potential role of PACAP and its receptors in the pathophysiology of migraine.

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Data sharing

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MA is a consultant, speaker or scientific advisor for Alder, Allergan, Amgen, Eli Lilly, Lundbeck, Novartis and Teva; and a primary investigator for Alder, Allergan, Amgen, Eli Lilly, Novartis and Teva. He has no ownership interest and does not own stocks in any pharmaceutical company. He serves as associate editor of *Cephalalgia*, associate editor of *Headache*, and associate

editor of the *Journal of Headache and Pain*; and is the President of the International Headache Society.
DD is a speaker, consultant or scientific advisor for Allergan, Amgen, Eli Lilly, Novartis, and Teva, as well as a primary investigator for Alder, Allergan, Amgen, Eli Lilly, Novartis, and Teva.
JHB reports no conflicts. JK is an employee of Novartis and owns Novartis stock. LZ, HP and DDM are employees of Amgen Inc., and own Amgen stock/stock options.

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