ORIGINAL ARTICLE

A Monoclonal Antibody to PACAP for Migraine Prevention

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ABSTRACT

BACKGROUND

Targeting pituitary adenylate cyclase–activating polypeptide (PACAP) is a new avenue for treating migraine. The efficacy and safety of intravenous Lu AG09222, a humanized monoclonal antibody directed against the PACAP ligand, for migraine prevention are unclear.

METHODS

In a phase 2, double-blind, randomized, placebo-controlled trial, we enrolled adult participants (18 to 65 years of age) with migraine for whom two to four previous preventive treatments had failed to provide a benefit. The trial included a 4-week treatment period and an 8-week follow-up period. Participants were randomly assigned in a 2:1:2 ratio to receive a single-dose baseline infusion of 750 mg of Lu AG09222, 100 mg of Lu AG09222, or placebo. The primary end point was the mean change from baseline in the number of migraine days per month, during weeks 1 through 4, in the Lu AG09222 750-mg group as compared with the placebo group.

RESULTS

Of 237 participants enrolled, 97 received 750 mg of Lu AG09222, 46 received 100 mg of Lu AG09222, and 94 received placebo. The mean number of baseline migraine days per month was 16.7 in the overall population, and the mean change from baseline over weeks 1 through 4 was −6.2 days in the Lu AG09222 750-mg group, as compared with −4.2 days in the placebo group (difference, −2.0 days; 95% confidence interval, −3.8 to −0.3; P=0.02). Adverse events with a higher incidence in the Lu AG09222 750-mg group than in the placebo group during the 12-week observation period included coronavirus disease 2019 (7% vs. 3%), nasopharyngitis (7% vs. 4%), and fatigue (5% vs. 1%).

CONCLUSIONS

In a phase 2 trial, a single intravenous infusion of 750 mg of Lu AG09222 showed superiority over placebo in reducing migraine frequency over the subsequent 4 weeks. (Funded by H. Lundbeck; HOPE ClinicalTrials.gov number, NCT05133323.)

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CME

Migraine affects approximately 1 billion persons worldwide and accounts for more years lived with disability than all other neurologic disorders combined.[1] Some affected persons receive preventive treatment to reduce the frequency, duration, and intensity of their migraine attacks.[2] Established preventive medications, such as propranolol and topiramate, are often discontinued owing to an inadequate response or unacceptable side effects.[3] More recently developed therapeutics include monoclonal antibodies and small-molecule receptor antagonists that target the signaling molecule calcitonin gene–related peptide (CGRP).[4] However, 40 to 70% of persons with migraine do not have a sufficient benefit (as defined by a ≥50% reduction in the number of migraine days per month) from the CGRP-targeted medications,[1] which underscores the pressing need for new mechanism-based therapeutic agents.

A potential mediator of migraine pathogenesis is the signaling molecule pituitary adenylate cyclase–activating polypeptide (PACAP).[5] Experimental studies have shown that intravenous infusion of PACAP induces migraine attacks in persons with migraine.[6,7] Blocking PACAP signaling may therefore constitute a promising drug target for migraine prevention. Lu AG09222 is a humanized monoclonal antibody that binds to both isoforms of PACAP and inhibits their receptor-mediated signaling.[8] Experiments in animals have shown that Lu AG09222 prevents neurogenic inflammation, vasodilation, and parasympathetic lacrimation, which are considered to be surrogate markers of migraine in rodent models.[8] Furthermore, a recent phase 1 trial involving healthy volunteers showed that pretreatment with Lu AG09222 can inhibit PACAP-induced dilation of cranial arteries and reduce concomitant headache.[9]

On the basis of the accumulating evidence regarding PACAP signaling and its importance in migraine pathogenesis, we conducted a phase 2a, proof-of-concept trial (HOPE) to evaluate the efficacy, safety, and side-effect profile of Lu AG09222 for migraine prevention among persons who had received a diagnosis of episodic or chronic migraine. The primary objective was to evaluate the efficacy of Lu AG09222 by assessing the change from baseline in the number of migraine days per month over weeks 1 through 4 in the Lu AG09222 750-mg group as compared with the placebo group.

METHODS

TRIAL DESIGN AND OVERSIGHT

HOPE was a phase 2a, multicenter, double-blind, randomized, placebo-controlled trial involving adults with migraine. The aim was to establish whether the inhibition of PACAP signaling by Lu AG09222 represents an effective mechanism for migraine prevention. The protocol (available with the full text of this article at NEJM.org) was approved by the relevant ethics committee at each trial site. The trial was conducted in adherence with the International Council for Harmonisation guidelines and all applicable regulatory requirements. A total of 25 sites across Europe and North America enrolled at least one participant. The trial included a 4-week screening period (28 to 30 days), a 4-week treatment period, and an 8-week follow-up period (Fig. 1). Participants provided written informed consent before they underwent any trial-related procedures.

This trial was industry-sponsored, with H. Lundbeck as the sole sponsor and data owner. The sponsor developed the trial protocol, took responsibility for the initiation and management of the trial, and, in collaboration with the aca-

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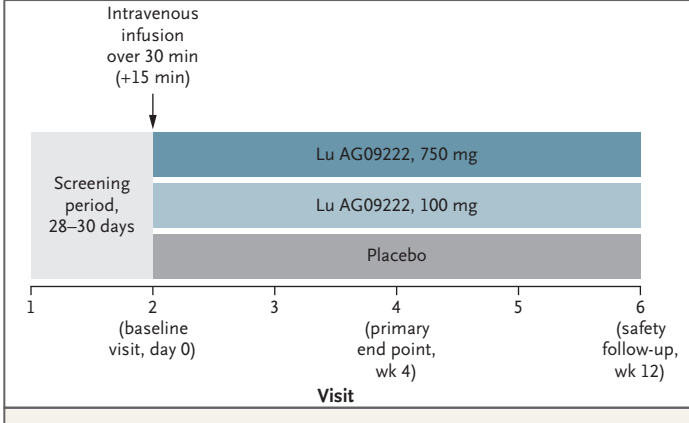

Figure 1. Trial Design.

Participants were randomly assigned in a 2:1:2 ratio to receive a single-dose baseline infusion of 750 mg of Lu AG09222, 100 mg of Lu AG09222, or placebo. Infusions were to be administered over a period of 30 minutes (or 45 minutes if needed).

demic author (the first author), participated in the collection, management, analysis, and interpretation of the data, as well as in the manuscript development and the decision to submit the manuscript for publication (see the Supplementary Methods section of the Supplementary Appendix, available at NEJM). The first draft of the manuscript was written by a medical writer, in accordance with Good Publication Practice guidelines, who was funded by the sponsor and whose contribution was under the direct supervision and collaborative guidance of the first author and the other authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

TRIAL PARTICIPANTS

Eligible participants, who were recruited from outpatient academic or private clinics and clinical research sites, were 18 to 65 years of age and had received a diagnosis of migraine without aura, migraine with aura, or chronic migraine according to the *International Classification of Headache Disorders, 3rd Edition*.[10] Participants were required to have had an onset of migraine disease at 50 years of age or younger, have at least 8 migraine days during the 4-week screening period, and provide documented evidence of failure of two to four preventive migraine medications within the past 10 years. Treatment failure could have been due to inadequate efficacy (no clinically meaningful improvement at the locally recommended dose for ≥3 months), safety reasons (discontinuation due to adverse events), or contraindications (ineligibility due to medical reasons). Eligible participants had not had a response to preventive migraine medications, which included CGRP-directed therapies (monoclonal antibodies or gepants), propranolol, metoprolol, topiramate, amitriptyline, flunarizine, candesartan, valproate, divalproex, and botulinum toxin.

Persons were excluded if they had a personal history of any headache disorder other than migraine or had previously received a monoclonal antibody targeting the PACAP ligand. Also excluded were persons with a history of any confounding or clinically significant pain disorder (e.g., fibromyalgia, chronic low back pain, or complex regional pain syndrome). The complete inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix.

TRIAL PROCEDURES

A total of 230 participants were planned for randomization, with the use of interactive-response technology, to one of three groups (in a 2:1:2 ratio): 750 mg of Lu AG09222, 100 mg of Lu AG09222, or placebo. Randomization was to be stratified according to geographic region (North America or Europe) and the presence or absence of cranial autonomic parasympathetic symptoms (CAPS) at baseline (score of >0 or score of 0); enrollment levels in North America precluded stratification according to region. The CAPS total score ranges from 0 to 10, reflecting the sum of five item scores (each rated 0 for absent, 1 for present but mild, or 2 for present and conspicuous), with higher scores indicating worse symptoms.[11] Fewer participants were assigned to the Lu AG09222 100-mg group because this dose was evaluated in an exploratory manner to help understand the required dose range for future dose-finding exploration. We expected that approximately 30% of the randomly assigned participants would have episodic migraine (headache occurring on ≤14 days per month).

Participants received Lu AG09222 or placebo at the baseline visit by means of a one-time intravenous infusion. Participants assigned to the Lu AG09222 groups received the drug added to 0.9% normal saline for a total volume of 100 ml over a period of approximately 30 minutes; those assigned to the placebo group received 100 ml of 0.9% normal saline over the same time period. The trial-site personnel responsible for preparation of the infusions of Lu AG09222 or placebo were aware of the trial-group assignments, whereas personnel responsible for administration of the infusions were not.

Electronic case-report forms used third-party software (Rave) to capture trial-related information during site visits. Participants completed a daily headache electronic diary (eDiary) from the screening visit until the safety follow-up visit or the efficacy follow-up or withdrawal visit. The eDiary included the occurrence of headache events and symptoms for the derivation of migraine and headache end points. The eDiary also included information regarding headache characteristics, headache severity (rated as mild, moderate, or severe; a migraine was defined as having moderate or severe pain), headache start and stop times, and intake of medications for the treatment

of headache or migraine (allowed and disallowed medications are listed in the Supplementary Methods section). The eDiary was distributed to each participant at the screening visit after training by site staff, and data from the 28 days after the screening visit were used to determine eligibility criteria, baseline migraine and headache values, and eDiary adherence. Ongoing evaluation of eDiary adherence was performed by the trial site on the basis of eDiary reports. The electronic data were transferred by the vendor and kept in a secure designated storage area outside the electronic case-report forms. An independent data and safety monitoring committee reviewed safety data on an ongoing basis during the trial.

END POINTS

Table S2 shows the alignment of the trial end points reported here with the trial objectives. The primary end point was the mean change from baseline in the number of migraine days per month, during weeks 1 through 4, in the Lu AG09222 750-mg group as compared with the placebo group. Secondary end points were a reduction from baseline of at least 50% in the number of migraine days per month (weeks 1 through 4) and the mean change from baseline in the number of headache days per month over weeks 1 through 4 in the Lu AG09222 750-mg group as compared with the placebo group. Exploratory end points included the mean change from baseline in the number of migraine attacks (which can last 4 to 72 hours) per month, the mean change from baseline in the number of headache episodes per month, and the mean change from baseline in the number of days per month in which medications for the treatment of headache or migraine were used over weeks 1 through 4 in the Lu AG09222 750-mg group as compared with the placebo group. All end-point assessments in the Lu AG09222 100-mg group were performed for exploratory purposes only.

The safety of Lu AG09222 was also evaluated. Safety end points included adverse events, absolute values, and changes from baseline in clinical safety laboratory test values and vital signs, potentially clinically significant safety laboratory test values, the development of specific antidrug antibodies (including neutralizing antibodies), and the score on the Columbia–Suicide Severity Rating Scale.

STATISTICAL ANALYSIS

We calculated that 86 participants per trial group for the 750-mg dose of Lu AG09222 and placebo (assuming 30% with episodic migraine and 70% with chronic migraine) would provide the trial with at least 80% power at a one-sided 5% significance level to detect a treatment effect of at least 2.1 days for the primary end point. Full details are provided in the statistical analysis plan (available with the protocol). No formal power calculation was performed for the 100-mg dose of Lu AG09222 because this group was included for exploratory purposes only; therefore, 43 participants were considered to be sufficient, which resulted in a randomization ratio of 2:1:2.

With adjustment for an expected 5% dropout rate, a total sample of 230 participants was planned. The type I error was controlled only for the main analysis of the primary end point comparing the Lu AG09222 750-mg group with the placebo group, because the analyses including the Lu AG09222 100-mg group were for exploratory purposes only. No further testing strategy was applied, and no correction for multiplicity was performed. Other analyses were considered to be exploratory and therefore are reported as point estimates with 95% confidence intervals from which causal inferences should not be made (see the Supplementary Appendix).

Missing data for the primary end point were imputed with the use of a sequential regression–based multiple-imputation method, on the basis of the imputation models established from the corresponding randomization group.[12] The change from baseline in the number of migraine days per month over weeks 1 through 4 was analyzed with the use of an analysis of covariance model. The model included baseline migraine days per month as a continuous covariate and trial group, type of migraine (episodic or chronic), and CAPS score (>0 or 0) as fixed factors. For the primary end point, prorating was used to calculate migraine days per month if the eDiary was completed on at least 14 of the 28 days of each 4-week period, with migraine days per month classified as "missing" if the eDiary was completed on fewer than 14 of the 28 days. The estimated mean differences between the Lu AG09222 750-mg group and the placebo group for the primary end point are presented with two-sided P values and 95% confidence intervals. In accordance with the prespecified analyses

in the statistical analysis plan, a 90% confidence interval with a one-sided P value is reported for the primary end point in the Supplementary Appendix.

The secondary end point of a reduction from baseline of at least 50% in the number of migraine days per month over weeks 1 through 4 was analyzed with the use of logistic regression, with missing data imputed with the use of multiple imputation as described above. The model included baseline migraine days per month as a continuous covariate and trial group, type of migraine, and CAPS score as fixed factors. The model was fitted with the use of the maximum-likelihood method and the logit link function. A post hoc analysis was conducted to estimate the relative risk in the Lu AG0922 750-mg group as compared with the placebo group; the result of the prespecified analysis of the odds ratio based on the profile likelihood is reported in the Supplementary Appendix. The secondary end point of change from baseline in the number of headache days per month over weeks 1 through 4 was analyzed similarly to the primary end point with the use of an analysis of covariance model but with baseline headache days per month as a covariate. Exploratory end points, including for the 100-mg dose of Lu AG09222, were analyzed in a manner similar to that used for secondary end points.

The analysis populations are defined in the Supplementary Methods section. Analyses of the change from baseline in the number of migraine days per month over weeks 1 through 4, a reduction from baseline of at least 50% in the number of migraine days per month over weeks 1 through 4, and safety end points were conducted in the all-participants-treated population (participants who had received an infusion of Lu AG09222 or placebo). The change from baseline in the number of headache days per month (weeks 1 through 4) and all exploratory efficacy end points were conducted in the full analysis population (participants in the all-participants-treated population who had a valid baseline assessment of the number of migraine days per month and a valid assessment of the number of migraine days per month over weeks 1 through 4). All statistical analyses were conducted with the use of SAS software, version 9.4 or later (SAS Institute).

RESULTS

PARTICIPANTS

A total of 337 persons were screened, of whom 237 underwent randomization and 233 were included in the full analysis population (Fig. 2). The baseline demographic and clinical characteristics of the participants were generally similar in the three trial groups (Table 1). The mean age of the participants was 42.5 years (range, 19 to 65), 100% were White, and most were women (88%). This trial is generally representative of the sex and age of the broader population of persons with migraine but is limited with respect to race and ethnic group and geographic representation (Table S3). At baseline, the mean number of headache days per month was 17.4, the mean number of migraine days per month was 16.7, and the mean number of days per month in which medications for the treatment of headache or migraine were used was 13.1 (Table 1). All the participants took concomitant medications during the trial, with no clinically relevant differences among the trial groups in their use (Table S4).

PRIMARY AND SECONDARY EFFICACY END POINTS

Table 2 summarizes the results for the primary, secondary, and exploratory efficacy end points. For the primary end point, the mean change from baseline in the number of migraine days per month over weeks 1 through 4 was −6.2 days in the Lu AG09222 750-mg group, as compared with −4.2 days in the placebo group (difference, −2.0 days; 95% confidence interval [CI], −3.8 to −0.3; P=0.02) (Fig. S1).

The percentage of participants who had a reduction from baseline of at least 50% in the number of migraine days per month was 32% in the Lu AG09222 750-mg group and 27% in the placebo group (Fig. S2). The mean change from baseline in the number of headache days per month over weeks 1 through 4 was −5.8 days in the Lu AG09222 750-mg group and −4.1 days in the placebo group (difference, −1.7 days; 95% CI, −3.5 to 0.0) (Fig. S3).

EXPLORATORY EFFICACY END POINTS

With regard to the number of migraine attacks per month, the mean change from baseline was

–4.7 attacks in the Lu AG09222 750-mg group and –3.1 attacks in the placebo group (difference, –1.7 attacks; 95% CI, –2.9 to –0.4) (Table 2). The mean change from baseline in the number of headache episodes per month was –4.4 episodes in the Lu AG09222 750-mg group and –3.0 episodes in the placebo group (difference, –1.4 episodes; 95% CI, –2.7 to –0.1). With regard to the number of days per month in which medications for the treatment of headache or migraine were used, the mean change from baseline was –5.1 days in the Lu AG09222 750-mg group and –3.4 days in the placebo group (difference, –1.7 days; 95% CI, –3.0 to –0.3).

SAFETY

Overall, most adverse events were classified by the investigator as being mild. Common adverse events (incidence of ≥5% in any group) that started or increased in intensity on or after the date of the infusion were coronavirus disease 2019, nasopharyngitis, and fatigue (Table 3). There was one serious adverse event in the Lu AG09222 750-mg group, which was identified as sympathetic posterior cervical syndrome and reported 1 month after the infusion. This event was deemed by the investigator to be unrelated to Lu AG09222; the participant had a preexisting medical history of vertebrogenic pain syndrome. No adverse events resulted in withdrawal from participation or interruption of Lu AG09222 infusion. In the two Lu AG09222 groups, the overall incidence of the development of antidrug antibodies was 11% (16 of 142 participants). The dose-specific incidence was 12% (12 of 96 participants) with the 750-mg dose of Lu AG09222 and 9% (4 of 46 participants) with the 100-mg dose of Lu AG09222.

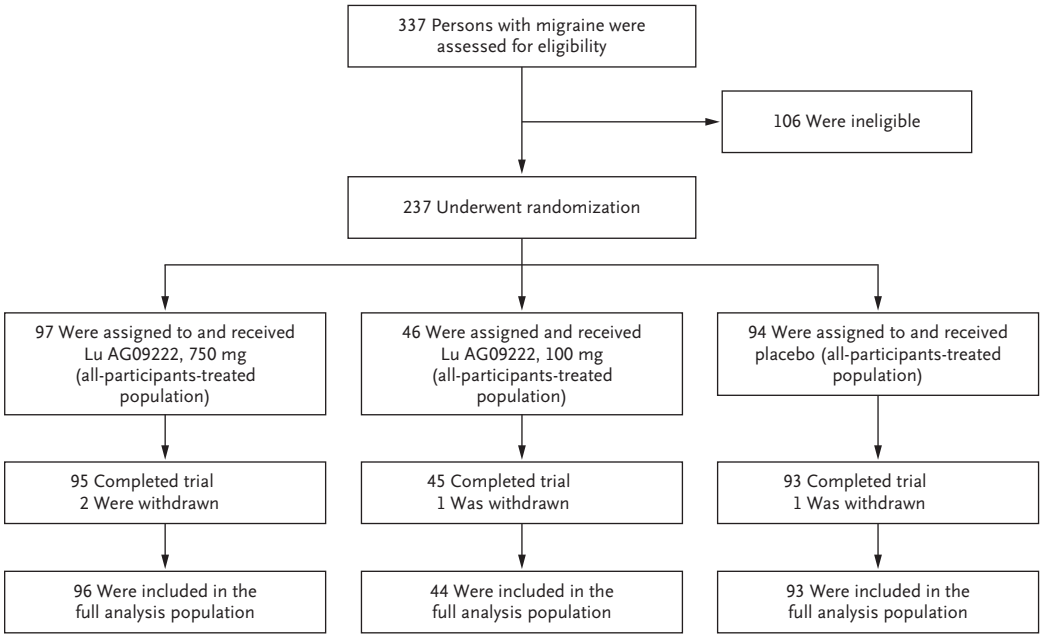

Figure 2. Enrollment and Trial Flow.

Among the 106 persons who were ineligible, 9 were rescreened, of whom 6 subsequently underwent randomization. The most common reasons for ineligibility were that the person did not adhere to the electronic headache diary for at least 24 of the 28 days after the screening visit, the person did not have 8 to 26 days with migraine during the 28 days after the screening visit, the person did not provide written informed consent, and the person had more than one laboratory value out of the reference range that was a potential risk to the person.

Table 1. Baseline Demographic and Clinical Characteristics (All-Participants-Treated Population).*

Characteristic	Lu AG09222, 750 mg (N=97)	Lu AG09222, 100 mg (N=46)	Placebo (N=94)	Total (N=237)
Sex — no. (%)				
Male	8 (8)	8 (17)	13 (14)	29 (12)
Female	89 (92)	38 (83)	81 (86)	208 (88)
Age — yr				
Mean	42.5±9.9	42.5±9.4	42.5±9.5	42.5±9.6
Range	21–65	20–64	19–62	19–65
White race — no. (%)†	97 (100)	46 (100)	94 (100)	237 (100)
Geographic region — no. (%)				
Europe	95 (98)	45 (98)	92 (98)	232 (98)
North America	2 (2)	1 (2)	2 (2)	5 (2)
Type of migraine — no. (%)				
Chronic	68 (70)	32 (70)	62 (66)	162 (68)
Episodic	29 (30)	14 (30)	32 (34)	75 (32)
No. of migraine days per month	16.7±4.1	16.2±4.5	16.9±4.6	16.7±4.3
No. of headache days per month	17.5±4.1	17.0±4.6	17.5±4.7	17.4±4.4
No. of days per month in which medications for the treatment of headache or migraine were used	13.1±4.7	11.9±4.5	13.6±4.8	13.1±4.8
No. of migraine attacks per month	12.5±5.0	12.1±5.5	13.3±6.8	12.7±5.8
No. of headache episodes per month	13.3±5.7	12.9±5.9	13.8±7.1	13.5±6.3
CAPS score‡				
No. of participants evaluated	96	43	93	232
Mean	1.0±1.4	1.0±1.3	0.9±1.4	0.9±1.4
No. of previous failures of preventive treatment — no. (%)§				
2	56 (58)	22 (48)	55 (59)	133 (56)
3	31 (32)	21 (46)	34 (36)	86 (36)
4	10 (10)	2 (4)	5 (5)	17 (7)

* Plus–minus values are means ±SD. The all-participants-treated population included participants who had received an infusion of Lu AG09222 or placebo.
† Race was reported by the participant.
‡ The cranial autonomic parasympathetic symptoms (CAPS) score ranges from 0 to 10, with higher scores indicating worse symptoms. Scores were analyzed in the full analysis population, which included participants in the all-participants-treated population who had a valid baseline assessment of the number of migraine days per month and a valid assessment of the number of migraine days per month over weeks 1 through 4.
§ One participant who received 100 mg of Lu AG09222 had fewer than two previous failures of preventive treatment (one previous failure) and represents a protocol deviation.

Table 2. Summary of Efficacy End Points over Weeks 1 through 4.*

Population and End Point	Lu AG09222, 750 mg	Placebo	Mean Difference (95% CI)†
All-participants-treated population			
No. of participants evaluated	97	94	
Primary end point: change from baseline in no. of migraine days per month	–6.2±0.7	–4.2±0.7	–2.0 (–3.8 to –0.3)‡
≥50% Reduction from baseline in no. of migraine days per month — no. (%)§	31.2 (32)	25.2 (27)	1.2 (0.8 to 1.8)¶
Full analysis population			
No. of participants evaluated	96	93	
Change from baseline in no. of headache days per month	–5.8±0.6	–4.1±0.7	–1.7 (–3.5 to 0.0)
Change from baseline in no. of migraine attacks per month	–4.7±0.5	–3.1±0.5	–1.7 (–2.9 to –0.4)
Change from baseline in no. of headache episodes per month	–4.4±0.5	–3.0±0.5	–1.4 (–2.7 to –0.1)
Change from baseline in no. of days per month in which medications for the treatment of headache or migraine were used	–5.1±0.5	–3.4±0.5	–1.7 (–3.0 to –0.3)

* Plus–minus values are means ±SE.
† The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
‡ P=0.02.
§ Missing values were imputed with the use of multiple imputation from own trial group, with 200 imputations used. Shown is the mean number of participants with a reduction from baseline of at least 50% in the number of migraine days per month from the 200 simulated data sets.
¶ Shown is the relative risk as compared with placebo.

DISCUSSION

In this phase 2 trial involving adults with migraine for whom two to four previous preventive treatments had failed to provide a benefit, the change from baseline in the number of migraine days per month over weeks 1 through 4 was greater with the 750-mg dose of Lu AG09222 than with placebo. These findings affirm the proof of concept, showing that inhibition of PACAP signaling by Lu AG09222 represents a new and potentially effective mechanism for migraine prevention.

An important aspect to consider is the previous failure of a monoclonal antibody directed against a specific PACAP-responsive receptor for migraine prevention.[13] PACAP binds to four receptor subtypes[14,15]; the specific receptor or receptors crucial for migraine remain uncertain. In this context, Lu AG09222 offers a different mechanism, targeting the PACAP ligand itself.[8] Targeting PACAP circumvents the challenges of identifying and targeting the specific PACAP-responsive receptor or receptors involved in migraine pathogenesis.[16-24] Of note, a phase 2 trial of another monoclonal antibody targeting the PACAP ligand for migraine prevention was terminated for unreported reasons after the inclusion of 19 patients in each of the two trial groups (ClinicalTrials.gov number, NCT04498910). Although that trial had a limited number of participants and investigated only a single dose of Lu AG09222, most of the adverse events in the trial were rated by the investigator as mild.

Our trial has several limitations. As a proof-of-concept trial, the sample size was small, the trial was short in duration and follow-up, and participants received only one dose of Lu AG09222. Although representative in terms of sex and age, the findings of our trial may not be fully generalizable to the broader population of persons with migraine given that the trial population was predominantly White and from European countries. Finally, persons with clinically significant cardiovascular disease or other confounding health issues were excluded from this trial; there-

Table 3. Safety End Points (All-Participants-Treated Population).*

Variable	Lu AG09222, 750 mg (N=97)	Lu AG09222, 100 mg (N=46)	Placebo (N=94)
≥1 Adverse event — no. of participants (%)	41 (42)	15 (33)	30 (32)
Total no. of adverse events	78	28	45
≥1 Serious adverse event — no. of participants (%)	1 (1)	0	0
Total no. of serious adverse events	1	0	0
Sympathetic posterior cervical syndrome	1	0	0
Adverse event leading to withdrawal from the trial — no. of participants	0	0	0
Adverse event leading to interruption of the infusion — no. of participants	0	0	0
Death — no. of participants	0	0	0
Adverse events with incidence of ≥5% in any group — no. of participants (%)			
Covid-19	7 (7)	2 (4)	3 (3)
Nasopharyngitis	7 (7)	0	4 (4)
Fatigue	5 (5)	2 (4)	1 (1)
Development of antidrug antibodies — no. of participants/total no. (%)	12/96 (12)	4/46 (9)	—

* Shown are adverse events that started or increased in intensity on or after the date of the infusion. Covid-19 denotes coronavirus disease 2019.

fore, the findings may not be indicative of efficacy or safety in all persons with migraine.

In this trial involving persons with migraine, a one-time 750-mg infusion of Lu AG09222 showed superiority over placebo in reducing the number of migraine days per month over the subsequent 4 weeks. This finding establishes proof of concept, supporting the notion that inhibition of PACAP signaling by Lu AG09222 represents a potentially effective mechanism for migraine prevention. Longer trials are warranted to ascertain the efficacy and safety of Lu AG09222 in persons with migraine.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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