

Phase I, randomized, parallel-group, double-blind, placebo-controlled trial to evaluate the effects of erenumab (AMG 334) and concomitant sumatriptan on blood pressure in healthy volunteers

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Abstract

Objectives: The aim of this study was to assess the effects of concomitant administration of erenumab and sumatriptan on resting blood pressure, pharmacokinetics, safety, and tolerability in healthy subjects.

Methods: In this phase I, parallel-group, one-way crossover, double-blind, placebo-controlled study, healthy adult subjects were randomized (1:2) to receive either intravenous placebo and subcutaneous sumatriptan 12 mg (i.e. two 6-mg injections separated by 1 hour) or intravenous erenumab 140 mg and subcutaneous sumatriptan 12 mg. Blood pressure was measured pre-dose and at prespecified times post-dose. The primary endpoint was individual time-weighted averages of mean arterial pressure, measured from 0 hours to 2.5 hours after the first dose of sumatriptan. Pharmacokinetic parameters for sumatriptan were evaluated by calculating geometric mean ratios (erenumab and sumatriptan/placebo and sumatriptan). Adverse events and anti-erenumab antibodies were also evaluated.

Results: A total of 34 subjects were randomized and included in the analysis. Least squares mean (standard error) time-weighted averages of mean arterial pressure were 87.4 (1.0) mmHg for the placebo and sumatriptan group and 87.4 (1.2) mmHg for the erenumab and sumatriptan group. Mean difference in mean arterial pressure between groups was -0.04 mmHg (90% confidence interval: $-2.2, 2.1$). Geometric mean ratio estimates for maximum plasma concentration of sumatriptan was 0.95 (90% confidence interval: 0.82, 1.09), area under the plasma concentration–time curve (AUC) from time 0 to 6 hours was 0.98 (90% confidence interval: 0.93, 1.03), and AUC from time 0 to infinity was 1.00 (90% confidence interval: 0.96, 1.05). No clinically relevant safety findings for co-administration of sumatriptan and erenumab were identified.

Conclusion: Co-administration of erenumab and sumatriptan had no additional effect on resting blood pressure or on pharmacokinetics of sumatriptan. Trial registration: ClinicalTrials.gov, NCT02741310.

Keywords

Erenumab, blood pressure, migraine, sumatriptan, clinical trial, pharmacokinetics, safety

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Introduction

Migraine is a disabling neurological disease, the symptoms of which impact work productivity (1) and increase healthcare expenditures (2). Pharmacological therapy for migraine traditionally includes acute and preventive treatments. The goal of acute migraine treatment is to relieve the symptoms associated with migraine attacks, particularly headache pain, whereas the goal of preventive treatment is to reduce migraine frequency/severity (3). Nonsteroidal anti-inflammatory drugs and migraine-specific drugs, such as triptans, are frequently used as acute migraine medications (4,5). Triptans are selective serotonin 5-HT_{1B/1D} receptor agonists that have vasoconstrictive effects on human blood vessels, including cerebral and coronary arteries, mediated through activation of 5-HT_{1B} receptors situated on vascular smooth muscle cells (6–8). Triptans are active mainly at the cranial vasculature but can also cause peripheral vasoconstriction (9) and have been shown to slightly increase blood pressure (BP) (10); consequently, they are contraindicated in patients with uncontrolled hypertension. However, these medications are generally well tolerated among patients with migraine (11), including those with controlled hypertension (9,12).

In addition to the treatment of migraine attacks with acute medications, many patients may benefit from preventive therapy. Current standard preventive treatments include orally administered medications such as topiramate, propranolol, and amitriptyline, which are underused (13) mostly because of safety and tolerability issues (14). Calcitonin gene-related peptide (CGRP) is a neuropeptide that is involved in the pathophysiology of migraine through nociceptive modulation in the trigeminal vascular system (15–18) and has been shown to mediate vasodilation (19). Clinical trials of monoclonal antibodies that target the CGRP pathway suggest that CGRP inhibition is a promising approach in migraine prevention (20–26). Erenumab is a fully human monoclonal antibody that binds to and inhibits the CGRP receptor (27) and has shown efficacy in the prevention of migraine (24–26). Patients who suffer from frequent and moderate to severe migraine attacks require both acute and preventive therapies to manage their symptoms (28). Due to the well-known vasoconstrictive effects of triptans, and the theoretical risk of BP increase with CGRP inhibition, it is important to assess the effect of concomitant administration of erenumab and sumatriptan on BP. To date, clinical trials with erenumab have shown no evidence of increased BP following erenumab administration (24–26), including an analysis of BP using 24-hour ambulatory BP monitoring (29).

The objectives of this study were to assess the effects of combination treatment of erenumab and sumatriptan compared with sumatriptan and placebo on resting

BP, pharmacokinetics (PK), safety, and tolerability in healthy subjects. The clinical hypothesis for the study was that there would be no clinically meaningful difference between the effects of placebo and sumatriptan compared with erenumab and sumatriptan on resting BP in healthy subjects.

Methods

Subjects

Healthy adults aged 18 to 55 years, with a body mass index between 18 and 32 kg/m², and in good general health at screening were eligible. The general health of subjects was confirmed by medical history evaluation, BP assessment, physical examination, 12-lead electrocardiogram, neurological examination, and clinical laboratory assessment (serum chemistry, hematology, or urinalysis). Women were eligible to participate if they were not pregnant or breastfeeding and if they were either using an acceptable method of contraception or were physiologically incapable of becoming pregnant. Subjects with elevated BP (systolic BP [SBP] \geq 140 mmHg or diastolic BP [DBP] \geq 90 mmHg), elevated heart rate ($>$ 100 beats/min), a prolonged corrected QT interval (obtained using Fridericia's formula; \geq 450 msec for men and \geq 470 msec for women), or history of prolonged QT syndrome were excluded. Subjects were also excluded if they had an unstable medical condition (resulting in hospitalization within 28 days of study day 1, major surgery within 6 months of study day 1, or in the judgement of the study investigator) or had suffered a major cardiovascular event or been treated with a percutaneous coronary intervention or coronary artery bypass graft within 6 months of study day 1. Subjects with a history of malignancy or impaired renal or hepatic function were also excluded. In addition, subjects who had previously received erenumab or any other large molecule that targets CGRP, had a history or evidence of substance or alcohol abuse, or those who had a contraindication to sumatriptan were excluded.

Subjects were asked to avoid strenuous exercise during screening and 48 hours before endpoint assessments (days 1, 2, 4, and 5) and any exercise or consumption of caffeinated food and beverages \geq 30 minutes before endpoint assessment (days 1, 2, 4, and 5). Smoking was prohibited 30 days prior to the beginning of the treatment period and during the study, as was the consumption of \geq 2 alcoholic drinks daily during the study or any alcohol within 24 hours of a clinic visit. Use of any over-the-counter or prescription medication within 14 days or 5 half-lives (whichever was longer), or any investigational product within 30 days or 5 half-lives (whichever was longer), of receiving the first dose of erenumab or placebo was prohibited.

Use of simple analgesics was permitted during the study, except within the 48 hours before receiving sumatriptan.

Study design and procedures

We performed a phase 1, parallel-group, one-way crossover, double-blind, placebo-controlled, concomitant therapy study in healthy subjects conducted at one center in Belgium from 22 February 2016 (first subject enrolled) to 11 August 2016 (last subject completed follow-up). The study comprised the following three phases: Screening (21 days), treatment (6 days), and safety follow-up (83 days). The trial protocol was approved by an independent ethics committee of the University Hospitals KU Leuven, all participants provided written informed consent, and the study was conducted in accordance with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

All subjects attended a screening visit within 21 days prior to receiving the first dose of the study drug. At day 1, after the screening phase, eligible subjects were randomly assigned in a 1:2 ratio to intravenous (IV) placebo and subcutaneous (SC) sumatriptan (group A) or IV erenumab and SC sumatriptan (group B) (Figure 1). The 6-day treatment period was composed of two parts. Part 1 included subjects in groups A and B that received IV placebo on day 1 and sumatriptan 12 mg (two 6-mg SC injections separated by 1 hour) on day 2. There was a 2-day washout period between parts 1 and 2. In part 2, subjects in group A received IV placebo on day 4 and sumatriptan 12 mg (two 6-mg SC injections separated by 1 hour) on day 5, while subjects

in group B received IV erenumab 140 mg on day 4 and sumatriptan 12 mg (on day 5 6-mg SC injections separated by 1 hour). Sumatriptan injections were administered and subsequent BP measurements were taken following the same schedule on days 2 and 5. The subjects returned for a follow-up visit at day 89.

The study utilized a simple fixed permuted block randomization without stratification. Treatment allocations were made sequentially based on the fixed randomization schedule as subjects were enrolled in the trial. Participants and all study site personnel, except for the pharmacist, were blinded to the assigned treatment groups during the study. Per Amgen standard procedure, unblinded subject enrollment logs were delivered directly to the unblinded site pharmacist in a sealed tamper-evident envelope. Erenumab and sumatriptan were administered at the center by a qualified person. Erenumab was supplied in 5-ml clear glass vials, and placebo was formulated and packaged to match the vials containing erenumab. Sumatriptan was supplied as 6-mg prefilled auto injectors containing 6 mg of sumatriptan succinate. The first 6-mg dose of sumatriptan was administered to the right thigh and the second dose (given 1 hour later) was administered to the left thigh. Individual subject treatment assignments were unblinded to personnel involved in assessing sumatriptan PK and anti-erenumab antibody laboratory values.

Measures

Safety and tolerability: BP, adverse events (AEs), physical examinations, 12-lead electrocardiograms,

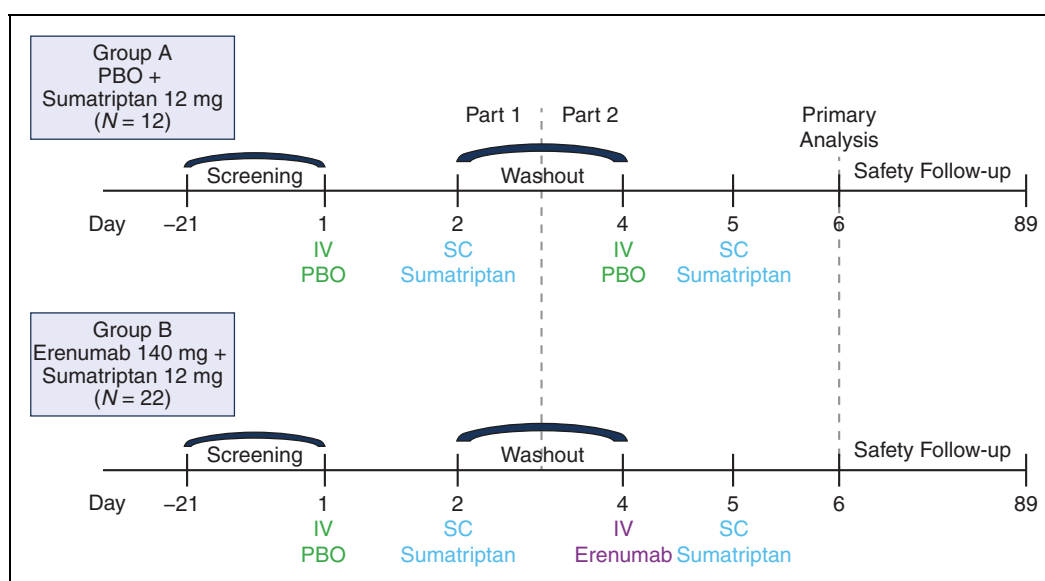


Figure 1. Study design.

IV: intravenous; PBO: placebo; SC: subcutaneous.

laboratory assessments, vital sign measurements, and anti-erenumab antibodies were evaluated.

Vital signs: Baseline measures of BP and heart rate were recorded prior to dosing and calculated as the average of the last recording during the screening phase and the recording immediately before the first dose on day 1. During the 6-day treatment period, BP and heart rate were measured 2 hours after administration of placebo on day 1 and after randomized treatment (placebo or erenumab) on day 4; after the first dose of sumatriptan on days 2 and 5, measurements were taken at hours 1 (immediately after the second dose of sumatriptan), 1.25, 1.5, 2, 2.5, 3, 3.5, 4.5, 7, 13, and 25. BP measurements were taken using an Omron 705IT (Omron Healthcare Inc., Kyoto, Japan) with the subject in the semi-recumbent position, in duplicate, and averaged.

Assessment of AEs: Subjects were monitored regularly during the study for AEs, which were coded using the Medical Dictionary for Regulatory Activities, version 18.0, and graded using the Common Terminology Criteria for Adverse Events, version 4.0.

Electrocardiograms, physical examinations, and laboratory safety assessments: 12-lead electrocardiograms were recorded in triplicate before dosing; at 1, 1.5, 2, 3, 7, and 25 hours post-sumatriptan dose (days 2 and 5); and 2 hours post-dose of randomized treatment (day 4). Physical examinations and laboratory safety assessments were performed at multiple time points during the study.

Cohorts of subjects were enrolled in a staggered fashion after review of blinded safety data from six subjects (four subjects in the erenumab and sumatriptan group and two subjects in the placebo and sumatriptan group), so that no more than four subjects received erenumab on day 4, followed by sumatriptan on day 5. The next six subjects were not dosed until the safety review had been conducted.

Antibody analysis: Blood samples were collected prior to dosing on day 1 and at the end of study (day 89) for anti-erenumab antibody testing. Blood samples were collected in 5-ml serum separation tubes and a validated, two-tiered, Meso Scale Discovery electrochemiluminescence bridging immunoassay (Meso Scale Diagnostics, Rockville, MD, USA) was used to detect anti-erenumab-binding antibodies in the serum. The sensitivity of the assay was 24.73 ng/ml and the lower limit of reliable detection (LLRD) was 100 ng/ml. Serum samples that were confirmed to be anti-erenumab antibody positive were analyzed for the presence of neutralizing antibodies using a validated cell-based bioassay. The assay sensitivity was 0.553 µg/ml and LLRD was 1.14 µg/ml.

PK analysis: Blood samples for measuring sumatriptan concentrations were collected before and at 1 hour after the first dose, and at 0, 10, 15, and 30 minutes, and

1, 2, 3.5, and 6 hours after the second dose of sumatriptan on days 2 and 5. Blood samples were collected in 4-ml K3 EDTA collection tubes. Sumatriptan was isolated from human plasma through solid-phase extraction before injection on a Zorbax SB-C18 column (50 × 4.6 mm, 5 mm) (Agilent, Santa Clara, CA, USA) and analysis by liquid chromatography–tandem mass spectrometry using an AB Sciex API 4000 system (SCIEX, Framingham, MA, USA). The lower limit of quantification was 0.100 ng/ml and the nominal assay range was 0.100 ng/ml to 150 ng/ml.

Trial outcomes: The primary endpoint was individual time-weighted averages of mean arterial pressure (MAP), measured from 0 hours pre-dose to 2.5 hours post-dose of the first dose of sumatriptan. To determine if time-weighted average of MAP was similar between subjects who received placebo and sumatriptan and those who received erenumab and sumatriptan, a two-sided 90% confidence interval (CI) for the between-group treatment difference, selected *a priori* to study initiation, was calculated. If the upper bound of the 90% CI was < 5 mmHg, the hypothesis that the effect on time-weighted MAP of placebo and sumatriptan was similar to that of erenumab and sumatriptan was deemed to have been supported. The rationale for this decision was based on the previous publication by Depré et al. (30). Time-weighted SBP and DBP were analyzed in a similar fashion as time-weighted MAP.

Secondary endpoints included PK parameters for sumatriptan. Geometric mean ratios were calculated for sumatriptan when administered with placebo or with erenumab: The time to the maximum observed plasma concentration (t_{max}), maximum observed plasma concentration (C_{max}), the area under the plasma concentration–time curve (AUC) from time 0 to 6 hours (AUC_{6hr}) after the second dose of sumatriptan, and AUC from time 0 to infinity (AUC_{∞}). Other secondary endpoints evaluated were vital signs, electrocardiograms, physical examinations, laboratory safety tests, AEs, and anti-erenumab antibodies.

A *post-hoc* analysis evaluated the change in MAP in all subjects after receiving sumatriptan alone, after receiving placebo alone, and after receiving erenumab alone (calculated using measurements from 0 hours pre-dose [baseline] to 2 hours post-dose on day 5 for sumatriptan and placebo, and day 4 for erenumab).

Statistical analyses

At least 20 subjects needed to be enrolled and randomized in the study to achieve a > 99% probability that the upper limit of the 90% CI for the treatment difference would lie below 5 mmHg, if the true difference was 0. The power calculations were based on an assumed within-subject standard deviation (SD) of 3.2 mmHg

and using an alpha of 0.05 and one-sided tests. These assumptions were based on results from an earlier phase 1 trial of erenumab in healthy volunteers (29). The true differences could be as high as 2.5 mmHg and would still have had 76.9% power to support the hypothesis. To assess safety, a total sample size of approximately 30 adult subjects was planned to be recruited, for an allocation of 20 subjects to the erenumab group and 10 subjects to placebo.

MAP was calculated using the following formula: $MAP = DBP + 0.33 * (SBP - DBP)$. Individual time weighted averages in MAP were calculated as the measurement–time curve from pre-dose (0 hours) to 2.5 hours of MAP divided by the time period over which the measurements were made. An average of duplicate BP measurements at each time point were used to calculate the time-weighted averages. A two-sided 90% CI (equivalent to a one-sided upper 95% CI) for the mean treatment difference between treatment groups was calculated using a linear mixed-effects model with fixed effects for treatment group, study period, and random effects for subjects. Statistical analyses were conducted using SAS[®] (version 9.4; SAS Institute, Inc., Cary, NC, USA).

The plasma PK parameters for sumatriptan were determined using non-compartmental analysis of the plasma concentration–time data using Phoenix WinNonlin, version 6.4. AUC_{6hr} was estimated using the linear trapezoidal method and AUC_{∞} was estimated as the sum of AUC_{last} and $C_{last}/\lambda z$ (C_{last} is the last observed concentration, AUC_{last} is the AUC from time 0 up to the last observed concentration, and λz is the first-order terminal rate constant). C_{max} was determined by inspection of the data. Log-transformed PK parameters for sumatriptan were analyzed using a linear mixed-effects model with treatment group as a fixed effect and subjects as a random effect. The 90% CIs for the mean differences (test/reference) between erenumab and sumatriptan (test) and placebo and sumatriptan (reference) for log-transformed C_{max} , AUC_{6hr} , and AUC_{∞} were calculated. Summary statistics were provided for t_{max} . The safety analysis set was used for the primary and secondary endpoint and included all subjects who received at least one injection, and the PK analysis set included all subjects for whom at least one PK parameter or endpoint could be adequately estimated.

Results

Demographics

Thirty-four subjects were enrolled and randomized in this study and 30 subjects completed the study. Mean (SD) MAP was 87.5 (5.0) mmHg and age was 28.5 (9.6) years at baseline. A total of 24/34 subjects were male and 33/34 subjects were Caucasian (Table 1).

Table 1. Baseline demographics and characteristics.

	Group A (placebo and sumatriptan) n = 12	Group B (erenumab and sumatriptan) n = 22
Age, years	27.3 (8.6)	29.1 (10.3)
Sex, n (%)		
Female	4 (33.3)	6 (27.3)
Male	8 (66.7)	16 (72.7)
Race, n (%)		
Caucasian	12 (100)	21 (95.5)
Black or African American	0 (0.0)	1 (4.5)
BMI, kg/m ²	23.7 (2.8)	23.7 (2.7)
Blood pressure, mmHg		
Mean arterial pressure	88.3 (5.3)	87.0 (4.8)
Systolic blood pressure	122.6 (6.3)	122.8 (6.8)
Diastolic blood pressure	71.4 (6.3)	69.4 (5.1)

BMI: body mass index.

Figures in brackets in Age, BMI and Blood pressure rows unless otherwise stated, data are mean (standard deviation).

Table 2. Time-weighted average mean arterial pressure, systolic blood pressure, and diastolic blood pressure.

	Placebo and sumatriptan ^a n = 34	Erenumab and sumatriptan n = 20
Mean arterial pressure, mmHg		
LS mean (SE)	87.4 (1.0)	87.4 (1.2)
Difference in LS mean (90% CI)	−0.04 (−2.2, 2.1)	
Systolic blood pressure, mmHg		
LS mean (SE)	120.9 (1.3)	119.0 (1.6)
Difference in LS mean (90% CI)	−1.9 (−4.8, 0.9)	
Diastolic blood pressure, mmHg		
LS mean (SE)	70.8 (1.0)	71.9 (1.2)
Difference in LS mean (90% CI)	1.01 (−1.0, 3.0)	

CI: confidence interval; LS: least squares; SE: standard error.

Analysis adjusted for treatment and time as covariates and subject as random effect in a linear mixed-effects model.

^aSubjects receiving sumatriptan are from group A and group B; subjects in group B received erenumab on day 5 in part 2.

Primary endpoint

Least squares mean (standard error) time-weighted averages of MAP were 87.4 (1.0) mmHg for the placebo and sumatriptan group and 87.4 (1.2) mmHg for the concomitant erenumab and sumatriptan group (Table 2). The mean difference in MAP between the

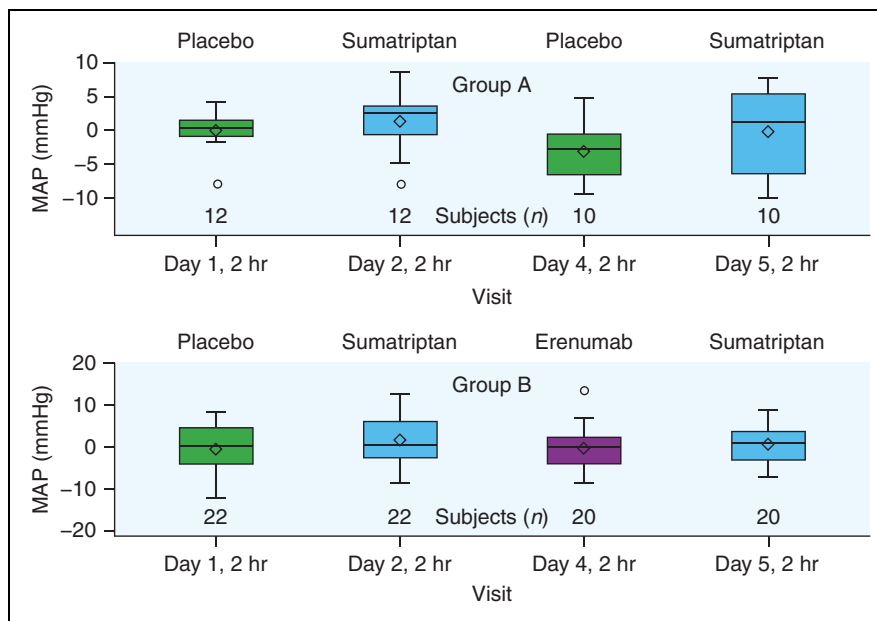


Figure 2. Change in MAP from pre-dose (0 hours) to 2 hours post-dose. Horizontal inner line represents the median, diamond symbol represents the mean, width of the box represents the interquartile range, and whiskers represent 1.5 times above or below the interquartile range.

MAP: mean arterial pressure.

groups was -0.04 mmHg (90% CI: $-2.2, 2.1$). Given that the upper bound of the 90% CI was below the predefined upper bound of 5 mmHg, the difference in time-weighted averages of MAP between treatment groups was not considered clinically significant.

Additionally, changes in SBP and DBP were similar between treatment groups. The mean difference in SBP was -1.93 mmHg (90% CI: $-4.8, 0.9$) and in DBP was 1.0 mmHg (90% CI: $-1.0, 3.0$) between groups (Table 2). In *post-hoc* analyses, mean (SD) change in MAP from pre-dose to 2 hours post-dose was -0.3 (5.2) mmHg for erenumab alone, 0.7 (4.8) mmHg for sumatriptan alone, and -0.5 (5.7) mmHg for placebo (Figure 2).

PK

The PK analysis set comprised samples from all 34 subjects. The statistical summary of sumatriptan PK parameters is provided in Table 3. Geometric mean ratio estimate for C_{max} was 0.95 (90% CI: 0.82, 1.09), for AUC_{6hr} was 0.98 (90% CI: 0.93, 1.03), and for AUC_{∞} was 1.00 (90% CI: 0.96, 1.05). Additionally, similar mean sumatriptan plasma concentration–time profiles and median t_{max} values for sumatriptan were observed for both treatment groups (Figure 3, Supplementary Table 1).

Table 3. Pharmacokinetic measures of sumatriptan.

	Placebo and sumatriptan ^a (reference) n = 34	Erenumab and sumatriptan (test) n = 20
C_{max} (ng/ml)		
LS mean ^b	83.50	79.00
Ratio ^{c,d} , (90% CI)	0.95 (0.82, 1.09)	
AUC_{6hr} (hr*ng/ml)		
LS mean ^b	133.33	130.59
Ratio ^{c,d} , (90% CI)	0.98 (0.93, 1.03)	
AUC_{∞} (hr*ng/ml)		
LS mean ^b	144.32	144.81
Ratio ^{c,d} , (90% CI)	1.00 (0.96, 1.05)	

AUC: area under the plasma concentration–time curve; AUC_{6hr} : AUC from time 0 to 6 hours; AUC_{∞} : AUC from time 0 to infinity; C_{max} : maximum observed plasma concentration; CI: confidence interval; LS: least squares.

Table is based on the safety analysis set.

^aSubjects receiving sumatriptan are from group A and group B; subjects in group B received erenumab on day 5 in part 2.

^bLS geometric mean using the SAS PROC MIXED procedure, version 9.3 (SAS Institute Inc., Cary, NC, USA).

^cRatios are test/reference.

^dThe ratio and CI are based on natural log scale data converted back to the original scale.

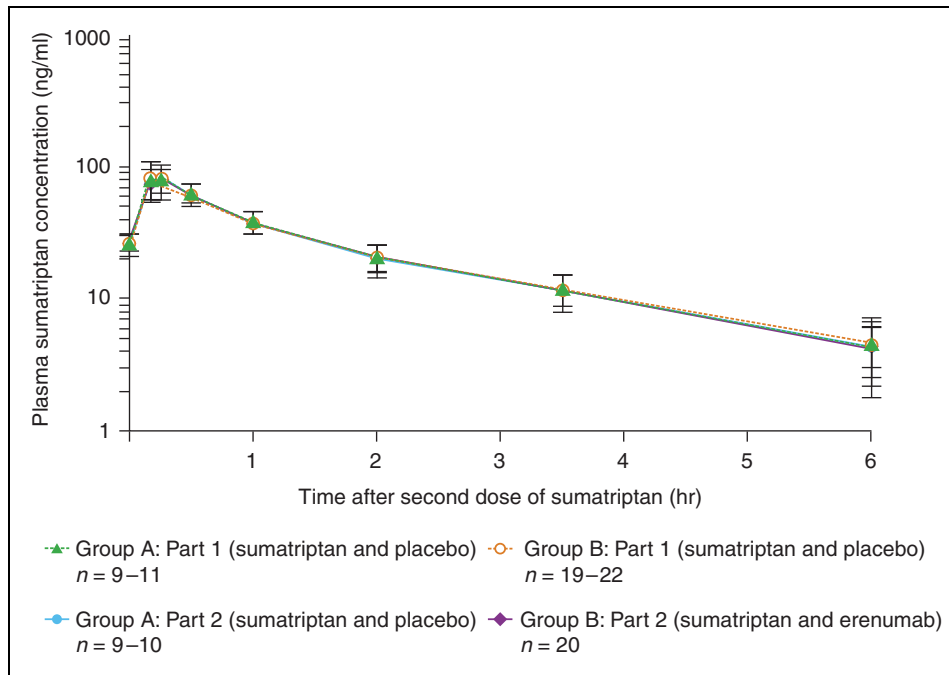


Figure 3. Plasma sumatriptan concentration over time. Data are mean \pm standard deviation.

AEs

All 34 subjects were included in the safety analysis set. No serious AEs were reported. During part 1 of the study (when all subjects received placebo and sumatriptan), two subjects in each randomized treatment group experienced sumatriptan-related injection site reactions that led to treatment withdrawal. The events that led to subject withdrawal were injection site erythema, injection site swelling, and injection site urticaria (one AE each) in group A and injection site erythema and injection site swelling (two AEs each) in group B. No subject experienced AEs that led to treatment withdrawal during part 2 of the study (Table 4). All AEs were mild to moderate in severity.

In part 2, nine subjects (75.0%) in the placebo and sumatriptan group and 17 subjects (77.3%) in the erenumab and sumatriptan group reported AEs, and all were mild to moderate in severity. The most frequent AEs (occurring in $\geq 10\%$ of subjects in either group) were head discomfort (three subjects [25.0%] in the placebo and sumatriptan group and eight subjects [36.4%] in the erenumab and sumatriptan group), paresthesia (four subjects [33.3%] in the placebo and sumatriptan group and four subjects [18.2%] in the erenumab and sumatriptan group), musculoskeletal discomfort (no subjects in the placebo and sumatriptan group and four subjects [18.2%] in the erenumab and sumatriptan group), and headache (no subjects in the placebo and sumatriptan group and four subjects [18.2%] in the erenumab and sumatriptan group) (Table 4).

No clinically significant changes in serum chemistry, hematology laboratory values, vital signs, or 12-lead electrocardiograms were observed in either treatment group.

Anti-erenumab antibodies

One subject in the erenumab and sumatriptan group developed anti-erenumab-binding antibodies during part 2 of the study, which were shown to be neutralizing at the end of the study. The subject was tested at a 3-month follow-up visit and was negative for anti-erenumab-neutralizing antibodies.

Discussion

This study demonstrated that co-administration of erenumab and sumatriptan had no additional effect on resting BP beyond the effects of sumatriptan monotherapy and did not affect the PK of sumatriptan in healthy subjects. Additionally, a *post-hoc* analysis showed that administration of erenumab alone did not affect resting BP. As migraine treatment involves acute and preventive therapy, and patients with frequent attacks may need both to manage their symptoms (29), the results of this study suggest that combining erenumab and sumatriptan is unlikely to alter BP in a real-world setting.

Therapies like erenumab that target the CGRP pathway represent a promising new class of preventive treatment for patients with migraine (20–26,31). Monoclonal

Table 4. Subject incidence of adverse events.

n (%)	Part 1		Part 2	
	Group A	Group B	Group A	Group B
	Placebo and sumatriptan n = 12	Placebo and sumatriptan n = 22	Placebo and sumatriptan n = 12	Erenumab and sumatriptan n = 22
Adverse events	11 (91.7)	19 (86.4)	9 (75.0)	17 (77.3)
Adverse events leading to treatment discontinuation ^a	2 (16.7)	2 (9.1)	0 (0.0)	0 (0.0)
Adverse events reported by $\geq 10\%$ of subjects in any treatment arm				
Head discomfort	4 (33.3)	8 (36.4)	3 (25.0)	8 (36.4)
Paresthesia	4 (33.3)	3 (13.6)	4 (33.3)	4 (18.2)
Injection site erythema	2 (16.7)	4 (18.2)	1 (8.3)	2 (9.1)
Injection site swelling	2 (16.7)	4 (18.2)	1 (8.3)	2 (9.1)
Discomfort	4 (33.3)	0 (0.0)	1 (8.3)	0 (0.0)
Headache	1 (8.3)	3 (13.6)	0 (0.0)	4 (18.2)
Throat tightness	2 (16.7)	1 (4.5)	2 (16.7)	1 (4.5)
Musculoskeletal discomfort	0 (0.0)	1 (4.5)	0 (0.0)	4 (18.2)
Hematuria	–	–	1 (8.3)	3 (13.6)

Table based on safety analysis set.

^aFrom group A, the following events led to withdrawal: Injection site erythema, injection site swelling, and injection site urticaria (one adverse event each). From group B, the following events led to withdrawal: Injection site erythema and injection site swelling (two adverse events each).

antibodies that target the CGRP pathway have been shown to be efficacious in migraine prevention (20–26,32). Although CGRP is a potent vasodilator, small molecule or biologic CGRP antagonists appear to prevent CGRP-dependent vasodilation without eliciting vasoconstriction (33,34). The absence of vasoconstriction with CGRP antagonism was confirmed in an experimental study with a peptide CGRP receptor antagonist (CGRP₈₋₃₇). Intra-arterial infusion of CGRP₈₋₃₇ did not affect resting blood flow, suggesting that CGRP does not play a role in the regulation of peripheral vascular tone under normal, resting conditions (35,36).

Although the findings of this study were observed in healthy subjects, they are consistent with observations from a study of the co-administration of sumatriptan and telcagepant, an orally administered small molecule CGRP receptor inhibitor, in patients with migraine (30). Depré et al. found that administration of telcagepant alone did not elevate BP and elevations in BP following co-administration of sumatriptan and telcagepant were similar to those observed following administration of sumatriptan alone (30). The use of triptan-based medications was permitted in trials of erenumab for the treatment of chronic and episodic migraine (24–26). In a phase 3 trial of erenumab in patients with episodic migraine, 59% of patients used triptans (24), and in a phase 2 trial of erenumab in

patients with chronic migraine, 78% of patients used triptans (26). In support of the combinatorial use of erenumab and triptans, no cardiovascular safety signal has been identified in any trials of erenumab (24–26). Additionally, an association between serum erenumab concentration and BP was not observed using 24-hour ambulatory BP monitoring in a phase 1 study of erenumab in healthy subjects and patients with migraine (29).

Both CGRP and serotonin are thought to be involved in the pathophysiological mechanisms underlying migraine through nociceptive mechanisms in the trigeminovascular system. Activation of the trigeminovascular system in migraine has been shown to cause the diminution of serotonin and release of CGRP (37). It has been observed that agonists of serotonin selectively normalize elevated levels of CGRP and that triptans reduce release of CGRP (38). The interplay of these neurotransmitters, and others, are thought to be key in providing nociceptive information to higher brain centers (38). The use of triptans in combination with CGRP pathway inhibitors, such as erenumab, may result in enhanced management of migraine.

The 12-mg dose of SC sumatriptan used in this study was selected because it is the maximum dose recommended for use within a 24-hour period and the 140-mg dose of erenumab is the highest dose planned for clinical use. Erenumab is intended to be

administered SC in clinic. However, in this study, erenumab was administered IV and sumatriptan SC, as the highest plasma concentrations for both these medications have been observed following single-dose administration through these routes (29,39). Exposures (C_{max}) following IV administration of erenumab 140 mg have been shown to be two-fold greater than those obtained during repeat administration of monthly erenumab 140 mg SC (29). Plasma PK samples were collected through to 6 hours after the administration of the second dose of sumatriptan to establish subject exposure to sumatriptan. The bounds of the 90% CI for the geometric mean ratios for all sumatriptan PK parameters in the presence and absence of erenumab were completely within 0.80 to 1.25, indicating there were no clinically relevant PK drug–drug interactions between sumatriptan and erenumab.

Erenumab, administered in combination with sumatriptan or with placebo, was well tolerated. The safety profile in both parts of the study and in both treatment groups was similar. All AEs were mild to moderate in severity and there were no serious AEs reported. Many of the reported AEs were consistent with the use of SC sumatriptan (40) and were considered to be related to sumatriptan and not to erenumab. Additionally, the AEs that led to treatment withdrawal were all sumatriptan-related injection site reactions that were reported in part 1 of the study when subjects had not yet received erenumab. In accordance with the favorable safety and

tolerability profile of erenumab observed in larger clinical trials (24–26), there were no clinically relevant safety concerns relating to erenumab identified in our study. Overall, no safety concerns were identified when erenumab was co-administered with sumatriptan.

Limitations of this study were that the majority of the subjects were male (while migraine is a disease that primarily affects females (41)), and the effects on BP were assessed in healthy subjects who did not suffer from migraine headaches. As changes in arterial function have previously been reported in patients with migraine (42,43), caution should be exercised when extrapolating these results to patients with migraine in a clinical setting. In addition, CGRP inhibition may in theory increase BP or aggravate ischemia (44,45). However, the results presented here, and in a phase 1 study of erenumab (29), showed no increase in BP with erenumab. Furthermore, in an exercise treadmill test, patients with stable angina treated with erenumab did not experience a reduction in exercise capacity versus placebo (46).

In conclusion, this study did not show evidence of pharmacodynamic (no increase in BP with erenumab with or without sumatriptan above that caused by sumatriptan alone) or PK interaction between erenumab and sumatriptan, and therefore, the results support the concomitant use of erenumab and triptans. Additionally, this study provides evidence that inhibition of the CGRP receptor with erenumab does not increase resting BP.

Clinical implications

- Patients who suffer from frequent and moderate to severe migraines require both acute and preventative therapies.
- Co-administration of erenumab and sumatriptan was well tolerated, with no additional effects on resting blood pressure or on the pharmacokinetics of sumatriptan.
- Furthermore, administration of erenumab alone did not affect resting blood pressure.
- The results from this study support the concomitant use of erenumab and triptans.

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Amgen, Galderma, Genentech, GlaxoSmithKline, Janssen Research & Development, Lilly Chorus, MSD, Novartis, Sanofi Pasteur, UCB, and Vertex; and acted as a consultant for Ablynx, Amgen, Eli Lilly, Genentech, Novartis, and UCB; AVH, MH have nothing to disclose; CV acted as sub-investigator for this study, for which the university received a research grant (Amgen); EL, OE, and GV are employees and stockholders of Amgen; YK and KG were employed by Amgen at the time of the study.

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