Phase 1, Randomized, Double-blind, Placebo-controlled, Single-dose and Multiple-dose Studies of Erenumab in Healthy Subjects and Patients With Migraine

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ABSTRACT

Monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) signaling are being explored as prophylactic treatments for migraine. Erenumab (AMG 334) is the first potent, selective, and competitive human mAb antagonist of the CGRP receptor. We report the data from two phase 1 studies assessing the safety, pharmacokinetics (PK), and pharmacodynamics of single and multiple administrations of erenumab in healthy subjects and patients with migraine. The results indicate that the PK profile of erenumab is nonlinear from 1 mg to 70 mg and the linear portion of the clearance from 70 mg to 210 mg is consistent with other human immunoglobulin (Ig)G2 antibodies. Single doses of erenumab resulted in >75% inhibition of capsaicin-induced dermal blood flow, with no apparent dose dependency for erenumab ≥21 mg. Erenumab was generally well tolerated with an acceptable safety profile, supporting further clinical development of erenumab for migraine prevention.

INTRODUCTION

Migraine is a pervasive neurological disorder with an estimated global prevalence of 14.7% and more than 1 billion people worldwide suffer from this condition.[1] Symptoms of migraine, including pain, sensitivity to light, sound, and odors, vision changes (auras), nausea, vomiting, tingling/numbness, and language disturbances, pose significant disabling effects on sufferers' physical, social, and occupational functioning.[2] A subset of people are bedridden during episodes of migraine headaches.[3] Moreover, >40% of patients with migraines have unmet needs, including disability, treatment dissatisfaction, and opioid/barbiturate overuse or dependence.[4] Thus, new treatments, both for prophylaxis and acute therapy, are eagerly awaited to help alleviate the burden of migraine-related disability.[5]

While triptans are effective during the early stages of a migraine, they are primarily used for acute migraine.[2, 6] Treatment persistence with triptans is low, with only 3% to 13% of patients remaining on therapy for ≥6 months.[7] Medicines approved for prevention of episodic and chronic migraines include β-blockers, anti-epileptics, and antidepressants.[8] However, due to significant adverse events and limited efficacy, adherence to prophylactic compounds is typically poor.[2] Therefore, new treatments that are more effective, better tolerated, and have fewer contraindications, are needed.[9]

Although migraine pathophysiology is not fully understood, migraine headache is associated with activation of the trigemino-vascular system.[10-12] The potent vasodilator neuropeptide calcitonin gene-related peptide (CGRP),[13] is thought to play a pivotal role in this process.[14] CGRP is released by trigeminal neurons,[15] and serum concentrations of CGRP are elevated during acute migraine or cluster headaches.[16] Also, triptan-mediated relief of migraine pain coincides with normalization of serum CGRP concentrations, while intravenous (IV) infusion of CGRP can induce migraine-like attacks in migraineurs.[17, 18] CGRP blockade by small-molecule CGRP receptor antagonists (ie, gepants) has

demonstrated efficacy in relieving acute migraine headache.[19-21] Unfortunately, hepatotoxicity or formulation issues with some of these agents led to discontinuation of their development, and small molecule CGRP receptor antagonists are not yet available for clinical use.[19, 22, 23]

Erenumab, or AMG 334, a human immunoglobulin (Ig) G2 monoclonal antibody (mAb), is a potent, selective, and full competitive antagonist of the CGRP receptor[24] that prevents native CGRP ligand binding. Here we report results from two phase 1 studies evaluating the safety and tolerability of single and multiple erenumab administrations in healthy subjects and in patients with migraine. We also examined the pharmacokinetics (PK) of erenumab and its effects on 24-hour ambulatory blood pressure (BP) and on capsaicin-induced increases in dermal blood flow (DBF) as an indicator of CGRP receptor antagonism.

RESULTS

Participant disposition and demographics

The single-dose study enrolled 49 healthy subjects and 12 patients with migraine (**Table 1**). Of these, 1 healthy subject in the placebo group did not receive study drug and was discontinued from the study for administrative reasons. In the multiple-dose study, 32 healthy subjects were enrolled in Part A, and 16 patients with migraine were enrolled in Part B; all enrolled patients completed the study.
One healthy subject who received erenumab at 70 mg discontinued treatment due to an AE (polyarthritis), but remained on study.

Pharmacokinetics

After a single subcutaneous (SC) administration, erenumab exposure increased more than dose proportionally at doses 1−70 mg, and approximately dose proportionally at doses 70−210 mg (**Table 2**).

With single erenumab SC doses of 1−70 mg, mean AUC_{last} increased 2,009-fold (from 0.0851 to 171 day•µg/mL) and and C_{max} increased 812-fold (from 0.0077 to 6.25 µg/mL); whereas following a 3-fold increase in erenumab dose from 70 to 210 mg SC, mean AUC_{last} increased 3.8-fold (from 171 to 652 µg•day/mL) and mean C_{max} increased 2.4-fold (from 6.25 to 15.2 µg/mL). Median t_{max} ranged from 4 to 11 days throughout the dose range. Based on PK modeling, the elimination half-life of erenumab for a typical 70-kg subject receiving 70 mg SC was estimated as approximately 21 days. Mean serum erenumab concentration–time profiles by cohort are shown in **Figure 1**. In the single-dose study, detectable serum levels of erenumab were observed 30 to 160 days postdose, with doses ≥70 mg resulting in detectable levels at ≥100 days postdose.

In the multiple-dose study, after 3 SC doses of erenumab, mean accumulation ratios ranged from 1.42 to 1.69 across all doses in healthy subjects and from 1.50 to 1.78 across all doses in patients with migraine (**Table 3**). Values for t_{max} ranged from approximately 3 to 13 days following the first SC dose and from approximately 6 to 14 days following the third SC dose across all cohorts (**Table 3**).

No apparent differences in PK properties between healthy subjects and patients with migraine were observed except median t_{max} in the single-dose study, which was longer in patients with migraine than in healthy subjects (erenumab 140 mg SC: 11.0 vs 5.5 days; **Table 2**). Although formal statistical testing was not performed, there was substantial overlap between the PK parameters of healthy subjects and patients with migraine in the multiple dose study.

Pharmacodynamics

Dermal blood flow inhibition

In the single-dose study, on day 4 (the first time point assessed), percent DBF inhibition versus placebo ranged from 74.6% to 94.6% across the dose range of 21 mg to 140 mg erenumab SC (**Table 4**). In the multiple-dose study, on day 8 (the first time point assessed, and around the point of t_{max}), erenumab treatment resulted in significant inhibition of DBF compared with placebo across all cohorts in both healthy subjects and patients with migraine, with no difference in drug effect between populations (**Table 4**). There was no apparent erenumab dose dependency in healthy subjects or patients with migraines. Results at days 57 and 85 in healthy subjects and at days 57, 85, and 169 in patients with migraine were consistent with results from day 8; at time points after day 169, the DBF inhibition associated with erenumab was not significant compared with placebo (data not shown).

24-Hour ambulatory blood pressure

In the multiple-dose study, no association was observed between serum erenumab concentrations and systolic or diastolic BP in healthy subjects or patients with migraine (**Figures 2A and 2B**). There were no statistically significant differences in least squares mean 24-hour or nocturnal BP between placebo and erenumab groups across all doses studied in healthy subjects (**Figure 2**). Among patients with migraine, there were no significant differences in least squares mean 24-hour or nocturnal diastolic BP measurements between placebo and erenumab across most of the erenumab dosages; however, a statistically significant increase in the least square mean 24-hour (difference from placebo 6.65 mmHg; *P*=0.033) and nocturnal systolic BP (difference from placebo 7.47 mmHg; *P*=0.037) was observed on day 36 in patients who received erenumab 21 mg, although this may not be a real effect because it was not seen at higher doses of erenumab.

Antidrug antibodies

A total of 6 erenumab-treated healthy subjects (n=1 in the single-dose study and n=5 in the multiple-dose study) tested positive for anti-erenumab-binding antibodies at postdose time points. One subject in the multiple-dose study tested positive for anti-erenumab-neutralizing antibodies. The presence of anti-erenumab-binding antibodies in these subjects had a minimal effect on serum erenumab concentrations and was not associated with AEs.

Safety and tolerability

Single-dose study

AEs were reported in 83.3% (40/48) of healthy subjects and 91.7% (11/12) of patients with migraine (Supplemental Tables 1 and 2). The only AE commonly reported (in ≥20% of subjects in the erenumab groups) in healthy subjects was headache (erenumab, 25.0%; placebo, 25.0%). In patients with migraine, nasopharyngitis (erenumab, 50.0%; placebo, 50.0%), arthralgia (33.3% and 0%, respectively), and influenza-like illness (33.3% and 16.7%, respectively) were most commonly reported.

No subjects/patients withdrew from the study due to AEs, and there were no deaths or serious AEs (SAEs). Most AEs were mild or moderate in severity, and there were no clinically meaningful changes in laboratory assessments or vital signs. In the healthy subjects group, AEs with a Common Terminology Criteria for AEs (CTCAE) grade ≥2 were seen in 1 subject in the placebo group (gastroenteritis), 1 subject in the erenumab 1-mg SC group (diarrhea), 2 subjects in the erenumab 70-mg SC group (abdominal pain and vomiting [n=1], conjunctivitis and tendinitis [n=1]), and 2 subjects in the erenumab 210-mg SC group (diarrhea [n=1], gastroenteritis and headache [n=1]). Among patients with migraine, AEs with a CTCAE grade ≥2 were seen in 2 patients in the placebo group (diarrhea [n=1], influenza-like illness [n=1]) and 2 patients in the erenumab 140-mg SC group (arthralgia [n=1], neutropenia [n=1]).

Multiple-dose study

AEs were reported in 84.4% (27/32) of healthy subjects and 100% (16/16) of patients with migraine (Supplemental Tables 3 and 4). The most commonly reported AEs among healthy subjects (≥20% of subjects in the erenumab groups) were nasopharyngitis (erenumab, 29.2%; placebo, 0%), upper respiratory tract infection (29.2% and 12.5%), headache (29.2% and 12.5%), and gastroenteritis (20.8% and 12.5%). Among the patients with migraine, the most commonly reported AEs were nasopharyngitis (erenumab, 50.0%; placebo, 0%), leukocyturia (41.7% and 0%), hematuria (25.0% and 50.0%), and oropharyngeal pain (25.0% and 0%).

No deaths occurred during the study. SAEs were reported in 3 subjects. One subject (healthy subject in the erenumab 70-mg group) was hospitalized for a biopsy as part of his clinical workup; this subject reported an AE (CTCAE grade 2) of polyarthritis, discontinued treatment after the second dose, and was withdrawn from the study. In the migraine group, 1 patient in the erenumab 140-mg group experienced an SAE (grade 3) of depressed mood and suicidal ideation which were considered to be not related to treatment by the investigator and 1 patient in the erenumab 21-mg group experienced neutropenia (grade 3). There were no clinically meaningful changes in laboratory assessments or vital signs.

DISCUSSION

Safety and tolerability data of two phase 1 studies, including PK and pharmacodynamics (PD: ie, effects on BP and inhibition of capsaicin-induced DBF) after single and multiple administrations of erenumab in healthy subjects and patients with migraine, are reported. Overall, erenumab was well tolerated and had an acceptable safety profile in both populations after single and multiple doses ranging from 1 to 280 mg. At doses of ≥21 mg SC, erenumab potently inhibited the capsaicin-induced DBF increase

providing PD evidence for its mechanism of action as a mAb targeting the CGRP receptor. Based on these findings erenumab is in further clinical development for the prevention of chronic and episodic migraine.

Erenumab is the first and only fully human IgG2 mAb currently in clinical development for migraine prevention which acts as a potent, selective and competitive antagonist of the CGRP receptor. In contrast, all other mAbs in development for the prevention of migraine are humanized mAbs directed against the CGRP ligand: ALD403, TEV-48125 (previously LBR-101) and LY2951742 (or galcanezumab).[22, 23, 25] Compared to currently available prophylactic treatments for migraine, mAbs share a number of characteristics making them particularly attractive tools.[8, 9, 26] These characteristics include lack of off-target toxicity and long effective half-life, which should translate into better tolerability and improved compliance. In addition, as mAb elimination is mainly the result of proteolysis and does not involve metabolism by liver enzymes, drug–drug interactions and hepatotoxicity are very unlikely, in contrast with some of the small molecule CGRP receptor antagonists such as telcagepant (MK-0974), where clinical development was stopped because of hepatotoxicity.[27] So far, there is no indication that erenumab, or any of the mAbs targeting CGRP, cause liver toxicity, supporting the notion that hepatotoxicity is not directly linked to inhibition of the CGRP pathway.

Single and multiple doses of erenumab were found to be generally well tolerated and had an acceptable overall safety profile. In the multiple-dose study, 1 healthy subject was discontinued from the trial because of the development of polyarthritis. Although it is unlikely that this was related to erenumab, it cannot be completely excluded. There was an imbalance of nasopharyngitis and upper respiratory infections in the multiple-dose study, but not the single dose study. In the phase 2 studies of erenumab the rates of nasopharyngitis and upper respiratory infections were low and similar among placebo and

treatment groups (8% vs 6-9% and 2% vs 1-3%).[28] Although there was a high incidence of headache in healthy subjects in the present study, these data are difficult to interpret as headaches are a commonly observed adverse event in phase 1 trials. Moreover, it should be noted that the rate was equivalent in erenumab- and placebo-treated subjects in the single-dose study. Despite the excellent short-term tolerability and safety profile of erenumab and other mAbs for migraine prevention, their long-term safety remains to be established. There is a theoretical cardiovascular risk with inhibition of the CGRP pathway, as CGRP is among a number of mediators (including eg, substance P, neurokinins, and nitric oxide) released during ischemia that have potent vasodilatory properties. As these mediators may act as safeguards during cerebral and cardiac ischemia, CGRP signaling blockade may, in theory, exacerbate ischemic events.[29, 30] Accordingly, preclinical and clinical safety erenumab studies are being conducted to better characterize putative cardiovascular impacts CGRP pathway antagonization. Importantly, in the phase 2 studies, no increased incidence was observed for cardiovascular events compared to placebo.[31, 32]

Based on the PK data, erenumab exhibits nonlinear characteristics of a target-mediated drug disposition that have been reported for mAb therapeutics targeting membrane-bound receptors.[33] At doses of ≥ 70 mg, erenumab behaves like a typical human IgG2 mAb showing a proportional increase in erenumab concentrations with increasing dose in healthy subjects and in patients with migraine, presumably due to saturation of the target-mediated clearance pathway and antibody clearance that approximates the usual protein catabolism rate; thus, the estimated half-life at higher doses is closer to that of a typical IgG2 (~23 days).[31] At doses of <70 mg, where target-mediated clearance predominates, total erenumab clearance decreases with increasing dose/concentrations, and therefore erenumab concentrations increase more than dose proportionally. After 3 single-dose administrations of erenumab, similar trends in PK parameters were observed across the dose range studied in both populations. The long elimination

half-life of >20 days for erenumab is illustrative of mAbs in general and turns this class of agents into valuable options for the prevention of migraine.

Erenumab significantly inhibited capsaicin-induced increases in DBF, typical for interference with the CGRP pathway.[34,35] Notably, capsaicin challenge results were similar in healthy subjects and in migraineurs. Although inhibition of capsaicin-induced vasodilation is not evidence of antimigraine efficacy, it does provide confidence in the mechanism of action of erenumab, effectively competing with native CGRP for binding to the CGRP receptor. In view of the accepted role of CGRP in the pathophysiology of migraine, the "capsaicin model" is being used as a target engagement biomarker in the early clinical development of compounds interfering with the CGRP pathway.[36] Indeed, by applying capsaicin onto the skin, transient receptor potential cation channel subfamily V member 1 (TrpV1) channels are activated and a CGRP-dependent increase in dermal blood flow can be quantified. However, while the inhibition of capsaicin-induced vasodilation by erenumab was very useful as a target engagement biomarker, it did not fully predict the clinical response data. The erenumab phase 2 study demonstrated efficacy for a dosage of 70 mg SC given monthly; while, in terms of efficacy, doses of 7 and 21 mg did not differentiate from placebo. Based on the degree of inhibition of capsaicin-induced vasodilation we would have predicted that 21 mg erenumab would have shown clinical efficacy. That it did not, suggests that peripheral CGRP-receptor binding, as evaluated by this biomarker, is not a direct marker of efficacy of antibody treatment for migraine, perhaps due to difficulties for the antibody to gain access to the relevant target tissues including ganglia. Nevertheless, the biomarker assay did provide a useful target engagement assessment which guided phase 2 dose selection. It delineated the minimum dose of erenumab which might be expected to have efficacy and enabled us to choose 3 doses, one of which demonstrated clinical efficacy.

Lack of dose dependency at doses ≥21 mg SC is in contrast to LY2951742 for which the degree of inhibition on capsaicin-induced DBF is related to drug serum concentration.[37] These differences likely reflect the differences in the targets of the 2 antibodies: erenumab targets the CGRP receptor preventing CGRP ligand binding and lack of dose dependency at higher doses of erenumab indicates saturation of CGRP receptors; whereas LY2951742 inhibits CGRP signaling by binding to the ligand CGRP itself and dose dependency at high LY2951742 doses indicates that E_{max} has not been reached.
The value of the capsaicin model has been convincingly shown in previous exploratory trials with small molecule CGRP receptor antagonists, including MK-0974 (telcagepant) and MK-3207.[34, 37] Both molecules potently inhibited the DBF response to capsaicin, which was used for dose selection for subsequent migraine efficacy studies. PK/PD modeling based on pooled data from this study demonstrated that erenumab inhibits capsaicin-induced increases in DBF with an estimated IC50 of 255 ng/mL (1.7 nM).[31] This is much more potent than that reported for telcagepant (IC50 of 101 nM) and similar in potentency to MK-3207 (IC50 of 1.59 nM).[34, 37] Experience with these small molecules, having an E_{max} value around 92%, also shows that the efficacious dose needed to treat acute migraine headache was usually higher than the dose inhibiting the dermal response to capsaicin. These data suggest that next to a peripheral blockade of CGRP receptors, as evaluated in the capsaicin model, central blockade might be an additional factor in determining clinical efficacy for which higher doses seem to be needed. Although erenumab is being developed for migraine prevention and not for acute migraine, higher doses than expected based on peripheral target engagement seem to be required for clinical efficacy.[31]

The influence of erenumab on BP was carefully evaluated in light of a potential role of CGRP as a vasodilator in maintaining cardiovascular homeostasis.[38] At concentrations effectively inhibiting the capsaicin response, erenumab was not associated with meaningful changes in vital signs. Based on 24-hour BP monitoring, no apparent relationship could be established between erenumab serum

concentrations and systolic or diastolic BP in healthy subjects or patients with migraine. Although a small, temporary increase in nocturnal systolic BP was observed with erenumab 21-mg SC in patients with migraine, it was not confirmed with the 140-mg dose. The small sample size of the current study makes it statistically underpowered to determine whether the numerical increase in BP observed in this study with erenumab 21-mg SC in patients with migraine, is a real effect of CGRP-inhibition on BP. A lack of BP-increasing effects after CGRP-inhibition is supported by studies with small-molecule CGRP receptor antagonists where there is no evidence of vasoconstriction after CGRP receptor blockade.[39,40] Further, there was no additional increase in BP observed with erenumab in a recent study with primary objective to evaluate the safety of concomitant use of sumatriptan and erenumab.[41]

Given the substantial unmet medical need for better tolerated and more effective treatments for migraine, especially in the prevention of chronic migraine,[2, 5, 42] the development of novel therapies is warranted. Findings from the current studies suggest that erenumab is a safe and potent selective inhibitor of the CGRP receptor and support the ongoing clinical development of erenumab as a preventative treatment in patients with migraines.

METHODS

Study populations

Both studies enrolled healthy men and women of nonchildbearing potential (single-dose: 18‑45 years of age; multiple dose: 18–55 years of age) and men and women with migraine (18‑55 years of age). Participants from both studies had a body mass index of ≥18.0 to ≤32.0 kg/m^2. Patients with migraine were required to have had migraines for ≥6 months prior to enrollment, with ≥3 migraine days (single-dose study)/attacks (multiple-dose study) per month in the 3 months prior to enrollment and during screening. In the multiple-dose study, onset of migraine was required to be before the age of 50 years.

Key exclusion criteria included: <2-fold increase in DBF after capsaicin challenge; elevated BP (defined as systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg in the single-dose study or systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg in the multiple-dose study) at screening or on the day prior to drug administration; basilar or hemiplegic migraine headache; use of ≥3 types of prophylactic antimigraine drugs in the past 10 years; and chronic tension-type headache or other headaches for ≥15 days/month (single-dose study).

Study protocols and amendments, informed consent forms, and other written subject information were reviewed and approved by the Independent Ethics Committee of the University Hospitals of Leuven. Studies were conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations. All participants provided written informed consent prior to inclusion. Study protocols from both studies were registered with ClinicalTrials.gov (NCT01688739 and NCT01723514).

Study designs

Sequential-dose-escalation, single-dose study

This was a single-center, double-blind, placebo-controlled, sequential-dose-escalation, single-dose study (**Figure 3A**). Healthy subjects who were randomized 3:1 to receive erenumab or placebo were divided into 6 cohorts (n=8 per cohort). In Cohorts 1–5, subjects received study drug or placebo as a SC injection, whereas in Cohort 6, subjects received IV infusions. Sentinel dosing was performed in Cohorts 1, 2, 3, 5, and 6: ie, the first 2 subjects were dosed (1 received erenumab and 1 received matching placebo) and observed for at least 72 hours (24 hours for Cohort 6) for safety monitoring before the remaining 6 subjects were dosed. Cohort 4 was a lower-dose cohort that was added by amendment for determination of the PD threshold, as evidenced by inhibition of capsaicin-induced increase in DBF. All

cohorts were dosed sequentially, with dose escalation performed after available safety data (ie, AEs, electrocardiograms, vital signs [BP, heart rate, and temperature], and laboratory parameters) were evaluated through day 15 for the current cohort and for previous lower dose cohorts. A seventh cohort consisted of 12 migraineurs randomized 1:1 to receive erenumab or placebo. Enrollment and dosing in Cohort 7 was initiated after the Cohort 2 dose regimen was found to be safe and well tolerated. The length of follow-up for each cohort was determined based on the PK prediction of time required to reach a serum level below the lower limit of quantification.

Multiple-dose study

This was a single-center, randomized, double-blind, placebo-controlled, ascending-multiple-dose study conducted in 2 parts (A and B; **Figure 3B**). In Part A, 32 healthy subjects were randomized to 4 cohorts (n=8 per cohort) at dose levels of 70, 21, 140, or 280 (first dose)/210 (second dose)/210 (third dose) mg SC. In Part B, 16 patients with migraine were randomized to 2 cohorts at dose levels of 21 or up to 140 mg SC (protocol allowed for lower dosing [between 21 and 140 mg SC] based on emerging PK and PD data). In each cohort, participants were randomized 3:1 to receive erenumab or placebo and received a total of 3 SC injections of erenumab or placebo on Days 1, 29, and 57, respectively. Cohorts A1, A2, and B1 were run in parallel, with enrollment into Cohorts A3 (140 mg) and B2 (up to 140 mg) based on safety data through to at least Day 43 from Cohort A1 and any available safety data from Cohorts A2 and B1. Enrollment into Cohort A4 (280 mg x 1 dose SC. then 210 mg x 2 doses SC) was based on safety data through to at least Day 43 from Cohort A3, and any available safety data from Cohorts A1, A2, B1, and B2.

In both studies, participants were admitted to the research facility on day −1 and remained there until all scheduled assessments were completed on the day of dosing. Thereafter, participants returned to the research center on an outpatient basis for scheduled study procedures.

Study assessments

Pharmacokinetics

In the single-dose study, blood samples erenumab serum concentration determinations were taken on Day 1 (pre-dose and 8 hours post-dose), and on days 2, 3, 4, 5, 8, 12, 15, 22, 29, and 43 in all healthy cohorts; for the migraine cohort, samples were taken on day 1, and on days 4, 8, 12, 15, 29, and 43. Blood sampling continued until the end of the study on days 57, 64, 85, 99, 127, and 155, if applicable. In the multiple-dose study, blood samples for erenumab serum concentration determinations were taken on days 1, 4, 5, 8, 12, 15, 22, 29, 36, 57, and on multiple days during the follow-up period through the end of the study (days 64, 71, 85, 99, 113, 127, 169, and 197). Samples were taken predose and 8 hours postdose on days 1 and 57, and pre-dose on day 29.

Pharmacodynamics

Inhibition of capsaicin-induced DBF was used as a target engagement biomarker to evaluate CGRP receptor antagonism.[34, 35] Because these procedures were potentially unblinding, personnel who performed these assessments were not involved in tolerability evaluation. A topical dose of capsaicin 1000 µg per 20 µL of ethanol 100%/Tween-20/distilled water mixture (3/3/4) was applied to 2 sites on the volar surface of the left or right forearm, with vehicle applied to 1 site only on the same arm as a control. DBF was assessed by laser Doppler perfusion imaging immediately before and 0.5 hours after capsaicin or vehicle application.

In both studies, vital signs and electrocardiograms were regularly recorded at prespecified time points. In addition, 24-hour continuous ambulatory BP monitoring was conducted for 2 consecutive days in all cohorts of the multiple-dose study during screening and starting on days –2, 8, 36, and 64.

Safety and tolerability

Tolerability was evaluated by AE reporting and AEs were evaluated for each dose cohort, across cohorts, and by relationship to study drug.

Statistical analysis

Sample-size determination

Samples sizes, based on practical considerations, were consistent with sample sizes used in phase 1 studies. In the single-dose study, approximately 48 healthy subjects and 20 migraineurs were to be enrolled. In the multiple-dose study, approximately 32 healthy subjects and 16 migraineurs were to be enrolled.

Pharmacokinetic analyses

Noncompartmental analysis of erenumab was performed (Phoenix WinNonlin v.6.3 software) on individual serum erenumab concentrations to estimate maximum observed drug concentration (C_{max}), time at which C_{max} occurred (t_{max}), terminal elimination half-life, area under the serum concentration-time curve (AUC_{last} and AUC_{inf}), accumulation ratio (AR) calculated as ($AUC_{tau,Dose3}$)/($AUC_{tau,Dose1}$); systemic clearance (CL), and volume of distribution (V) where data permits. Analysis of variance (ANOVA) was used to compare the logged PK parameters between healthy subjects and migraineurs.

Pharmacodynamic analyses

Repeated measures analysis of covariance (ANCOVA) was performed to determine the ratio of DBF measures at 30 minutes postcapsaicin challenge versus prechallenge. Data were log transformed and adjusted for prechallenge measurements. Independent variables were treatment, day, and treatment-by-day interaction. Percentage inhibition at each dose was calculated as:

$$\frac{lsgmr\ for\ placebo - lsgmr\ for\ dose}{lsgmr\ for\ placebo - 1} X100$$

where lsgmr = least square geometric mean of ratio.

Complementary, more detailed, PK/PD modeling—analyzing the relationship between erenumab serum exposure and inhibition of capsaicin-induced increase in DBF—has also been performed.[34]

In the multiple-dose study, outpatient 24-hour continuous BP monitoring data were averaged across all number of observations per hour; hourly data were summarized and analyzed using a repeated measure ANCOVA.

STUDY HIGLIGHTS

- **What is the current knowledge on the topic?** Monoclonal antibodies targeting the CGRP pathway are under investigation for the prevention of chronic and episodic migraine. Erenumab (AMG 334) is unique in that it is the first human mAb in clinical development that targets the CGRP *receptor*, in contrast to humanized mAbs that target the CGRP *ligand*.

- **What question did this study address?** What is the safety and tolerability of erenumab? What are the PK characteristics of erenumab? What are the effects of erenumab on blood pressure and capsaicin-induced vasodilation?
- **What this study adds to our knowledge?** Erenumab is a safe, well tolerated, and potent selective inhibitor of the CGRP receptor. From doses of 70 mg and above, it behaves as a typical human IgG2 mAb showing linear PK and a long elimination half-life.
- **How this might change clinical pharmacology or translational science?** These results support the ongoing clinical development of erenumab in the prevention of migraine, and may eventually add to the preventative armamentarium for this common and burdensome disorder.

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CONFLICTS OF INTERESTS/DISCLOSURES

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AUTHOR CONTRIBUTIONS

All authors participated in writing the manuscript and approved submission of the manuscript.

Jan de Hoon, Lucy Yan, Edgar Bautista, Javier Waksman, and Gabriel Vargas designed the research. Jan de Hoon, Anne Van Hecken, and Corinne Vandermeulen performed the research. Brian Smith, Jiyun Sunny Chen, Lisa Hamilton, and Thuy Vu analyzed the data.

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TABLES

FIGURE LEGENDS

Figure 3. Study design All cohorts were dosed sequentially with dose escalation occurring after review of 15 days of safety and laboratory data, except for the cohorts of patients with migraine who were started in parallel following a higher dose in healthy subjects. Follow-up duration was based on PK prediction of time to reach serum level below the lower limit of quantification. Participants in the multiple-dose study received a total of 3 SC doses of erenumab or placebo on days 1, 29, and 57. [1]Cohort 4 was added in the single-dose study to allow for determination of PD threshold, as evidenced by inhibition of capsaicin-induced increase in dermal blood flow.

Supplementary Files

Table 1. Baseline demographic characteristics

Variable	Single-dose study				Multiple-dose study			
	Healthy subjects		Patients with migraine		Healthy subjects		Patients with migraine	
	Placebo	Erenumab	Placebo	Erenumab	Placebo	Erenumab	Placebo	Erenumab
	(n = 12)	(n = 36)	(n = 6)	(n = 6)	(n = 8)	(n = 24)	(n = 4)	(n = 12)
Men, n (%)	12 (100)	36 (100)	2 (33.3)	1 (16.7)	8 (100)	21 (87.5)	1 (25.0)	3 (25.0)
Mean age (range), years	28.6	27.1	28.5	23.8	32.1	32.1	37.0	31.5
	(21–43)	(19–42)	(20–50)	(18–33)	(20–50)	(18–55)	(21–49)	(19–49)
Mean BMI (SD), kg/m^2	25.5 (1.3)	24.2 (2.6)	22.3 (2.3)	22.4 (3.8)	24.2 (3.8)	23.5 (3.7)	25.8 (2.3)	23.0 (3.1)

BMI, body mass index; SD, standard deviation.

Table 2. PK parameter estimates following single-dose administration of erenumab by cohort

Treatment	C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (day•µg/mL)	AUC_{inf} (day•µg/mL)	CL (L/day)	V_z (L)
Healthy subjects						
1 mg SC (n = 3)	0.008 (0.004)	4.0 (2 - 7)	0.085 (0.017)	NR	NR	NR
7 mg SC (n = 3)	0.302 (0.145)	7.0 (4 - 7)	4.01 (2.07)	4.13 (2.04)	NR	NR
21 mg SC (n = 6)	1.17 (0.646)	7.0 (3 - 10)	23.5 (15.5)	24.5 (17.0)	NR	NR
70 mg SC (n = 4–6)	6.25 (2.03)	6.0 (3 - 11)	171 (60.9)	174 (78.6)	NR	NR
140 mg SC (n = 6)	9.18 (1.97)	5.5 (4 - 21)	332 (57.9)	333 (57.9)	NR	NR
210 mg SC (n = 6)	15.2 (4.78)	8.5 (4 - 11)	652 (221)	653 (222)	NR	NR
140 mg IV (n = 6)	47.8 (4.09)	0.069 (0.069 - 0.38)	614 (112)	615 (112)	0.234 (0.042)	3.86 (0.768)
Patients with migraine						
140 mg SC (n = 6)	9.93 (3.42)	11 (7.0 - 14)	367 (102)	367 (103)	NR	NR

All PK parameters are expressed as mean (SD), except for t_{max}, which is presented as median (range).

AUC_{inf}, area under the concentration–time curve from time zero to infinity; AUC_{last}, area under the concentration–time curve from time zero to time of last quantifiable concentration; CL, systemic clearance; C_{max}, maximum concentration; IV, intravenous; NR, not reported; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation; t_{max}, time to achieve C_{max}; V_z, volume of distribution at terminal phase.

Table 3. PK parameter estimates following multiple-dose administration of erenumab, by cohort

Erenumab Dosage	After first dose		After last dose			
	C_{max} (µg/mL)	t_{max} (day)	C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (day•µg/mL)	Mean AR
Healthy subjects						
21 mg SC (n = 6)	2.15 (0.91)	4.0 (3.0–6.9)	2.6 (0.95)	6.9 (5.9–7.9)	59.3 (27.8)	1.42 (0.23)
70 mg SC (n = 5–6)	6.26 (2.55)	4.0 (3.0–11.0)	9.63 (3.60)	7.9 (6.9–14.0)	342 (144)	1.56 (0.28)
140 mg SC (n = 6)	13.8 (4.00)	5.9 (3.1–13.0)	23.7 (7.89)	6.9 (6.9–8.0)	848 (376)	1.69 (0.12)
280/210 mg SC (n = 6)[1]	24.9 (4.90)	6.9 (3.0–6.9)	36.3 (6.18)	6.9 (6.9–8.0)	1410 (332)	NR
Patients with migraine						
21 mg SC (n = 6)	1.76 (0.74)	6.9 (4.0–7.0)	2.00 (0.55)	6.9 (6.9–7.9)	45.0 (15.7)	1.50 (0.74)
140 mg SC (n = 5–6)	11.0 (3.85)	11 (4.0–13.0)	18.4 (5.98)	6.9 (6.9–7.0)	773 (214)	1.78 (0.14)

All PK parameters are expressed as mean (SD), except for t_{max}, which is presented as median (range).

AR, accumulation ratio calculated as $(AUC_{tau,Dose3})/(AUC_{tau,Dose1})$; AUC_{last}, area under the concentration–time curve from time zero to time of last quantifiable concentration; C_{max}, maximum concentration; NR, not reported; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation; t_{max}, time to achieve C_{max}.

[1]Erenumab was administered at 280 mg for the first dose, then 210 mg for the second and third doses.

Table 4. Dermal blood flow inhibition post-capsaicin challenge by erenumab dose

Parameters	**Healthy subjects**								**Patients with migraine**	
Single-dose Study,					**Erenumab**					**Erenumab**
Day 4	**Placebo**	**1 mg SC**	**7 mg SC**	**21 mg SC**	**70 mg SC**	**140 mg SC**	**140 mg IV**	**210 mg SC**	**Placebo**	**140 mg SC**
	n = 12	**n = 3**	**n = 3**	**n = 6**	**n = 6**	**n = 6**	**n = 6**	**n = 6**	**n = 6**	**n = 6**
LS geometric mean	8.6	9.9	5.6	2.9	1.7	1.4	1.4	1.9	11.9	2.0
Lsgmr versus placebo[*]	—	1.1	0.7	0.3	0.2	0.2	0.2	0.2	—	0.2
95% CI	—	0.6, 2.1	0.4, 1.2	0.2, 0.6	0.1, 0.3	0.1, 0.3	0.1, 0.3	0.1, 0.4	—	0.1, 0.3
P-value	—	0.66	0.17	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	—	< 0.0001
Percent inhibition of dermal blood flow[**]	—	−16.5%	39.0%	74.6%	90.3%	94.6%	94.5%	88.5%	—	90.5%
Multiple-dose Study,					**Erenumab**					**Erenumab**
Day 8	**Placebo**			**21 mg SC**	**70 mg SC**	**140 mg SC**			**Placebo**	**21 mg SC**	**140 mg SC**
	n = 6			**n = 6**	**n = 6**	**n = 6**			**n = 4**	**n = 6**	**n = 6**
LS geometric mean	8.5			1.8	2.5	1.8			13.2	2.6	1.6
Lsgmr versus placebo[*]	—			−79.3	−71.2	−79.52			—	−80.0	−87.6
95% CI	—			−87.5,	−82.7,	−88.3,			—	−91.5,	−94.5,

		−65.7	−52.0	−64.2		−52.9	−71.9
P-value	—	< 0.001	< 0.001	< 0.001	—	< 0.001	< 0.001
Percent inhibition of dermal blood flow[**]	—	89.9%	80.6%	90.1%	—	86.6%	94.8%

[*]Lsgmr of the 30-minute post-capsaicin measure to the pre-capsaicin measure versus placebo.

[**]Percent inhibition of capsaicin-induced increase of dermal blood flow = ((lsgmr for placebo − lsgmr for dose)/(lsgmr for placebo − 1))* 100.

CI, confidence interval; LS, least squares; lsgmr, least squares geometric mean ratio; SC, subcutaneous.

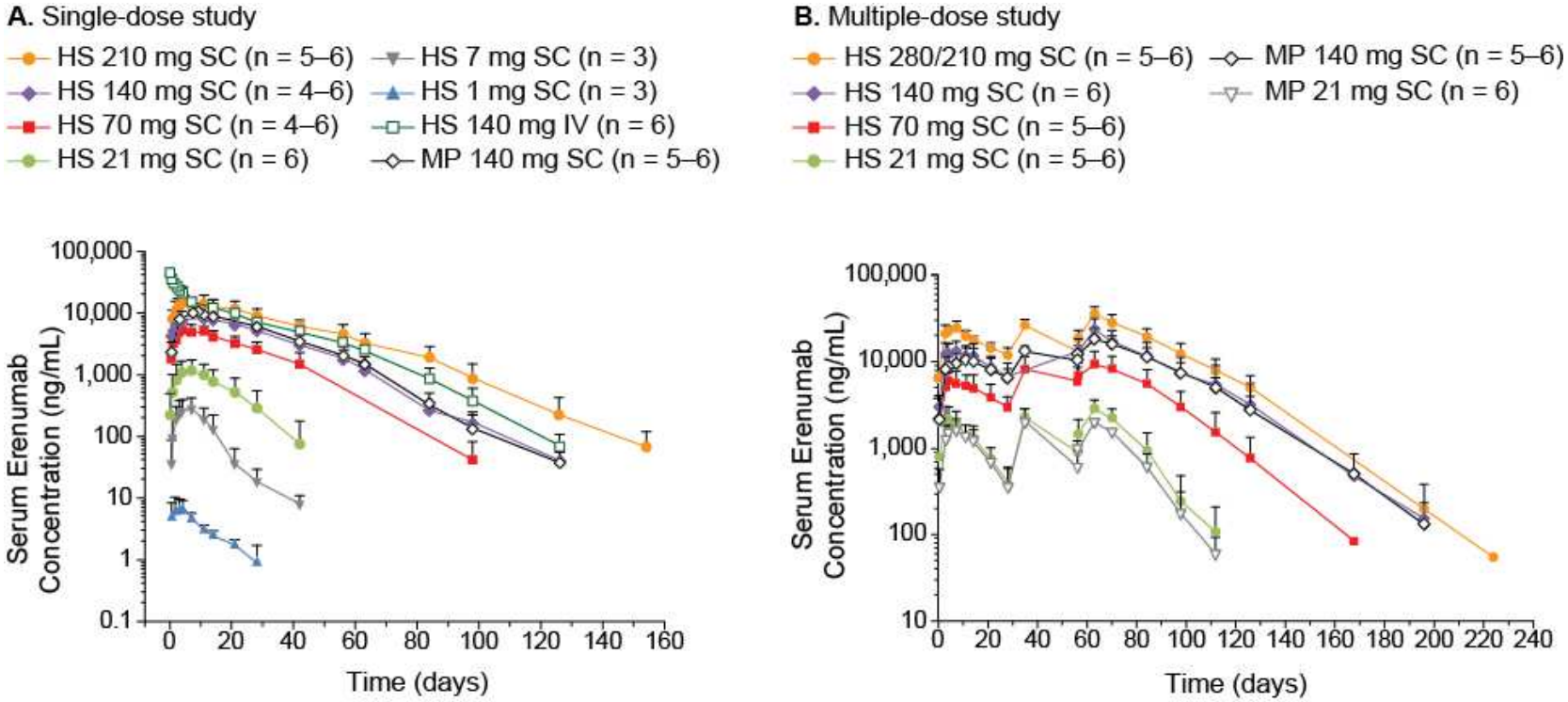
Supplemental Table 1. Adverse Events in Single-dose Study, Healthy Subjects

		Erenumab							
	Placebo (N = 12)	1mg SC (N = 3)	7mg SC (N = 3)	21mg SC (N = 6)	70mg SC (N = 6)	140mg SC (N = 6)	140mg IV (N = 6)	210mg SC (N = 6)	Total (N = 48)
Any adverse events	10 (83)	2 (67)	1 (33)	6 (100)	5 (83)	5 (83)	5 (83)	6 (100)	40 (83)
Headache	3 (25)	0 (0)	0 (0)	1 (17)	1 (17)	1 (17)	2 (33)	4 (66)	12 (25)
Nasopharyngitis	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (33)	2 (33)	1 (17)	6 (13)
Diarrhea	1 (8)	1 (33)	0 (0)	0 (0)	1 (17)	1 (17)	0 (0)	1 (17)	5 (10)
Oropharyngel pain	2 (17)	1 (33)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	4 (8)
Conjunctivitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	2 (33)	0 (0)	0 (0)	3 (6)
Dizziness	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (17)	1 (17)	3 (6)
Hematuria	0 (0)	0 (0)	0 (0)	2 (33)	0 (0)	1 (17)	0 (0)	0 (0)	3 (6)
Abdominal pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (170	0 (0)	0 (0)	1 (17)	2 (4)
Dizziness postural	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (17)	0 (0)	2 (4)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (17)	0 (0)	2 (4)
Gastroenteritis	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	2 (4)
Hypoesthesia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (33)	2 (4)

Injection-site hemorrhage	2 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)
Leukocyturia	0 (0)	0 (0)	0 (0)	1 (17)	1 (17)	0 (0)	0 (0)	0 (0)	2 (4)
Nausea	1 (8)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	2 (4)
Paresthesia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (17)	2 (4)
Tendonitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (17)	2 (4)
Upper respiratory tract infection	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	2 (4)
Dysaesthesia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Genital infection fungal	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Oral herpes	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Rhinitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (2)
Viral infection	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Abdominal pain upper	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Aphthous stomatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Gastrooesophageal reflux disease	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Toothache	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Arthralgia	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Back pain	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)

Joint stiffness	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Joint swelling	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Muscular weakness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (2)
Cough	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Rhinitis allergic	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Rhinorrhea	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Influenza-like illness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Injection-site erythema	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Malaise	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Pruritis generalized	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Rash popular	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Contusion	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Fall	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Thermal burn	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Eosinophilia	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Ear hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Ear pain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Electrocardiogram PR prolongation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (2)

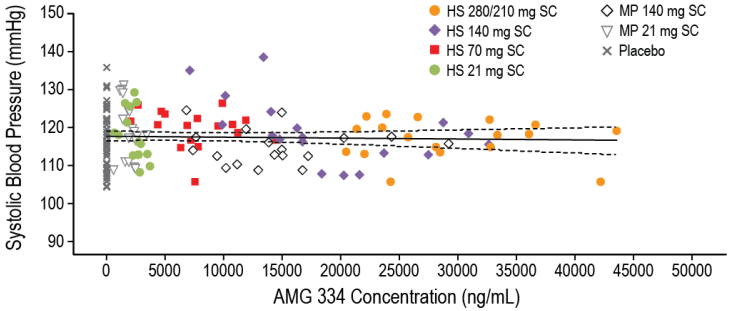
Figure 1.



HS, healthy subject; IV, intravenous; MP, patients with migraine; PK, pharmacokinetic; SC, subcutanous.

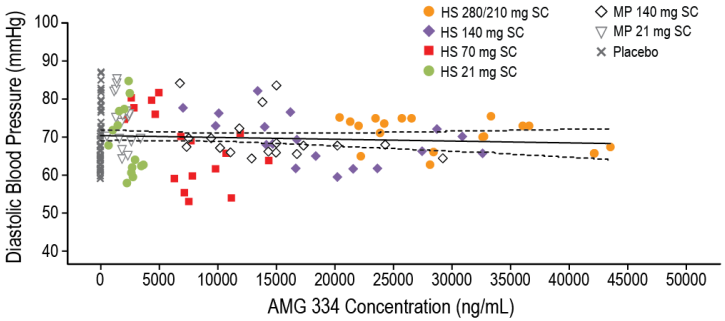
Figure 2.

A. Systolic Blood Pressure



Systolic Blood Pressure	Healthy Subjects					Patients With Migraine		
		Erenumab					Erenumab	
	Placebo n = 8	21 mg n = 6	70 mg n = 6	140 mg n = 6	280/210 mg n = 6	Placebo n = 4	21 mg n = 6	140 mg n = 6
Least square mean (mmHg)	117.9	117.7	118.5	120.9	117.3	114.1	116.7	115.5
Difference from placebo	–	–0.3	0.6	3.0	–0.6	–	2.6	1.4
90% CI	–	–4.3, 3.8	–3.4, 4.7	–1.0, 7.0	–4.8, 3.7	–	–2.5, 7.6	–3.5, 6.2
P-value vs placebo	–	0.92	0.80	0.22	0.82	–	0.39	0.64

B. Diastolic Blood Pressure

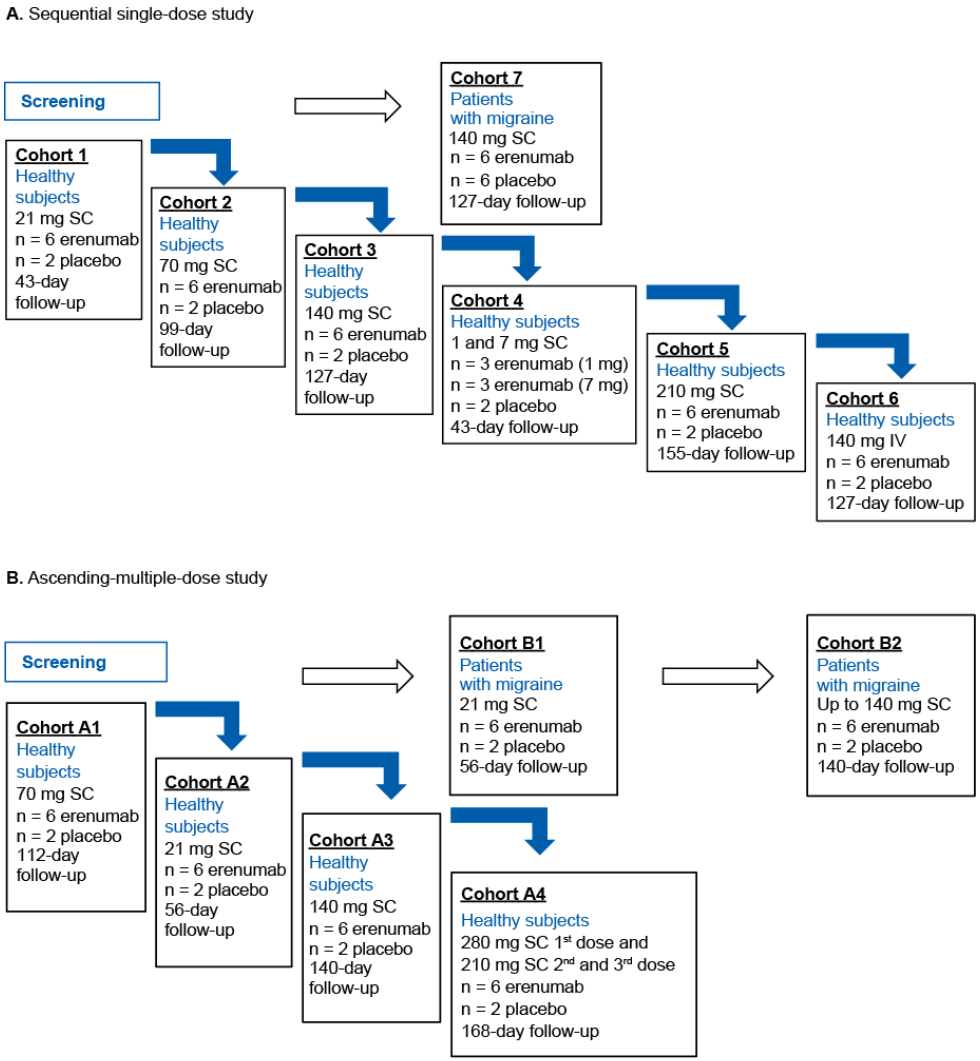


Diastolic Blood Pressure	Healthy Subjects					Patients With Migraine		
		Erenumab					Erenumab	
	Placebo n = 8	21 mg n = 6	70 mg n = 6	140 mg n = 6	280/210 mg n = 6	Placebo n = 4	21 mg n = 6	140 mg n = 6
Least square mean (mmHg)	68.5	68.7	69.3	71.2	68.6	70.3	71.6	70.7
Difference from placebo	–	0.2	0.9	2.8	0.1	–	1.3	0.4
90% CI	–	–2.6, 3.1	–2.0, 3.7	–0.1, 5.6	–2.9, 3.1	–	–2.2, 4.9	–3.1, 3.9
P-value vs placebo	–	0.89	0.61	0.11	0.94	–	0.53	0.84

CI, confidence interval; SC, subcutaneous.

In the graphs (A and B), solid lines represent regression lines; dashed lines represent upper and lower 95% CIs.

Figure 3.



IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetic; SC, subcutaneous.

Supplemental Table 1. Adverse Events in Single-dose Study, Healthy Subjects

		Erenumab							
	Placebo (N = 12)	1mg SC (N = 3)	7mg SC (N = 3)	21mg SC (N = 6)	70mg SC (N = 6)	140mg SC (N = 6)	140mg IV (N = 6)	210mg SC (N = 6)	Total (N = 48)
Any adverse events	10 (83)	2 (67)	1 (33)	6 (100)	5 (83)	5 (83)	5 (83)	6 (100)	40 (83)
Headache	3 (25)	0 (0)	0 (0)	1 (17)	1 (17)	1 (17)	2 (33)	4 (66)	12 (25)
Nasopharyngitis	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (33)	2 (33)	1 (17)	6 (13)
Diarrhea	1 (8)	1 (33)	0 (0)	0 (0)	1 (17)	1 (17)	0 (0)	1 (17)	5 (10)
Oropharyngel pain	2 (17)	1 (33)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	4 (8)
Conjunctivitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	2 (33)	0 (0)	0 (0)	3 (6)
Dizziness	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (17)	1 (17)	3 (6)
Hematuria	0 (0)	0 (0)	0 (0)	2 (33)	0 (0)	1 (17)	0 (0)	0 (0)	3 (6)
Abdominal pain	0 (0)	0 (0)	0 (0)	0 (0)	1 (170	0 (0)	0 (0)	1 (17)	2 (4)
Dizziness postural	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (17)	0 (0)	2 (4)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (17)	0 (0)	2 (4)
Gastroenteritis	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	2 (4)
Hypoesthesia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (33)	2 (4)

Injection-site hemorrhage	2 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)
Leukocyturia	0 (0)	0 (0)	0 (0)	1 (17)	1 (17)	0 (0)	0 (0)	0 (0)	2 (4)
Nausea	1 (8)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	2 (4)
Paresthesia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (17)	2 (4)
Tendonitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (17)	2 (4)
Upper respiratory tract infection	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	2 (4)
Dysaesthesia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Genital infection fungal	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Oral herpes	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Rhinitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (2)
Viral infection	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Abdominal pain upper	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Aphthous stomatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Gastrooesophageal reflux disease	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Toothache	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Arthralgia	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Back pain	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)

Joint stiffness	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Joint swelling	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Muscular weakness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (2)
Cough	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Rhinitis allergic	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Rhinorrhea	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Influenza-like illness	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Injection-site erythema	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (2)
Malaise	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Pruritis generalized	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Rash popular	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Contusion	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Fall	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Thermal burn	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Eosinophilia	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
Ear hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Ear pain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (2)
Electrocardiogram PR prolongation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (2)

Supplemental Table 2. Adverse Events in Single-dose Study, Migraine Subjects

	Placebo (N = 6)	Erenumab 140 mg (N = 6)	Total (N = 12)
Any adverse event	5 (83)	6 (100)	11 (92)
Nasopharyngitis	3 (50)	3 (50)	6 (50)
Influenza-like illness	1 (17)	2 (33)	3 (25)
Arthralgia	0 (0)	2 (33)	2 (17)
Diarrhea	2 (33)	0 (0)	2 (17)
Epistaxis	2 (33)	0 (0)	2 (17)
Leukocyturia	1 (17)	1 (17)	2 (17)
Pyuria	2 (33)	0 (0)	2 (17)
Gastroenteritis	1 (17)	0 (0)	1 (8)
Upper respiratory tract infection	1 (17)	0 (0)	1 (8)
Abdominal pain	0 (0)	1 (17)	1 (8)
Aphthous stomatitis	1 (17)	0 (0)	1 (8)
Dry mouth	0 (0)	1 (17)	1 (8)
Dyspepsia	0 (0)	1 (17)	1 (8)

Nausea	0 (0)	1 (17)	1 (8)
Vomiting	0 (0)	1 (17)	1 (8)
Asthenia	0 (0)	1 (17)	1 (8)
Injection site hemorrhage	0 (0)	1 (17)	1 (8)
Pyrexia	0 (0)	1 (17)	1 (8)
Cough	0 (0)	1 (17)	1 (8)
Pharyngeal erythema	0 (0)	1 (17)	1 (8)
Pharyngeal edema	0 (0)	1 (17)	1 (8)
Dysuria	1 (17)	0 (0)	1 (8)
Hematuria	1 (17)	0 (0)	1 (8)
Contusion	0 (0)	1 (17)	1 (8)
Fall	0 (0)	1 (17)	1 (8)
Limb injury	1 (17)	0 (0)	1 (8)
Ecchymosis	0 (0)	1 (17)	1 (8)
Swelling face	0 (0)	1 (17)	1 (8)
Neutropenia	0 (0)	1 (17)	1 (8)
Alanine aminotransferase increased	0 (0)	1 (17)	1 (8)
Aspartate aminotransferase increased	0 (0)	1 (17)	1 (8)

Breast cyst	0 (0)	1 (17)	1 (8)
Dysmenorrhea	0 (0)	1 (17)	1 (8)

Supplemental Table 3. Adverse Events in Multiple-dose Study, Healthy Subjects

		Erenumab				
	Placebo	21 mg SC	70 mg SC	140 mg SC	280/210 mg SC	Total
	(N = 8)	(N = 6)	(N = 6)	(N = 6)	(N = 6)	(N =24)
Any adverse events	5 (63)	6 (100)	6 (100)	6 (100)	4 (67)	22 (92)
Nasopharyngitis	0 (0)	2 (50)	3 (50)	3 (50)	2 (33)	7 (29)
Upper respiratory tract infection	1 (13)	2 (33)	2 (33)	3 (50)	0 (0)	7 (29)
Headache	1 (13)	0 (0)	2 (33)	3 (50)	2 (33)	7 (29)
Gastroenteritis	1 (13)	1 (17)	3 (50)	0 (0)	2 (33)	5 (20)
Hematuria	0 (0)	1 (17)	0 (0)	0 (0)	3 (5)	4 (17)
Leukocyturia	0 (0)	0 (0)	0 (0)	1 (17)	2 (33)	3 (13)
Diarrhea	0 (0)	1 (17)	1 (17)	1 (17)	0 (0)	3 (13)
Neck pain	0 (0)	2 (33)	0 (0)	0 (0)	0 (0)	2 (8)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	2 (33)	2 (8)
Influenza like illness	2 (25)	1 (17)	0 (0)	1 (17)	0 (0)	2 (8)
Fatigue	0 (0)	1 (17)	0 (0)	0 (0)	1 (17)	2 (8)
Oropharyngeal pain	1 (13)	1 (17)	0 (0)	1 (17)	0 (0)	2 (8)

Gingivitis	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (4)
Influenza	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (4)
Dizziness postural	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (4)
Hypoaesthesia	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (4)
Flank pain	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (4)
Myalgia	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (4)
Osteochondrosis	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	1 (4)
Arthralgia	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)
Back pain	1 (13)	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)
Polyarthritis	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)
Abdominal discomfort	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)
Abdominal pain	1 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain upper	1 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dyspepsia	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)
Mouth ulceration	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)
Paraesthensia oral	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)
Tongue discoloration	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)
Injection site haemorrhage	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (4)

Malaise	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (4)
Cough	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)
Eosinophilia	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (4)
Tooth fracture	1 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Blood glucose increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)
Blood immunoglobulin E increased	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	1 (4)
Neutrophil count decreased	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)
Depressed mood	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)
Rash	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (4)

Supplemental Table 4. Adverse Events in Multiple-dose Study, Migraine Subjects

		Erenumab		
	Placebo	21 mg SC	140 mg SC	Total
	(N = 4)	(N = 6)	(N = 6)	(N = 12)
Any adverse events	4 (100)	6 (100)	6 (100)	12 (100)
Nasopharyngitis	0 (0)	3 (50)	3 (50)	6 (50)
Leukocyturia	0 (0)	3 (50)	2 (33)	5 (42)
Oropharyngeal pain	0 (0)	3 (50)	0 (0)	3 (25)
Hematuria	2 (50)	2 (33)	1 (17)	3 (25)
Upper respiratory tract infection	0 (0)	1 (17)	1 (17)	2 (17)
Diarrhea	0 (0)	1 (17)	1 (17)	2 (17)
Dysmenorrhea	0 (0)	1 (17)	1 (17)	2 (17)
Fatigue	0 (0)	0 (0)	2 (33)	2 (17)
Nausea	0 (0)	1 (17)	0 (0)	1 (8)
Gastroenteritis	1 (25)	0 (0)	1 (17)	1 (8)
Gingivitis	0 (0)	1 (17)	0 (0)	1 (8)
Laryngitis	0 (0)	0 (0)	1 (17)	1 (8)

Sinusitis	0 (0)	1 (17)	0 (0)	1 (8)
Bronchitis	1 (25)	0 (0)	0 (0)	0 (0)
Arthralgia	0 (0)	0 (0)	1 (17)	1 (8)
Back pain	1 (25)	0 (0)	0 (0)	0 (0)
Musculoskeletal stiffness	0 (0)	0 (0)	1 (17)	1 (8)
Myalgia	1 (25)	0 (0)	0 (0)	0 (0)
Neck Pain	0 (0)	0 (0)	1 (17)	1 (8)
Musculoskeletal pain	1 (25)	0 (0)	0 (0)	0 (0)
Abdominal distention	1 (25)	0 (0)	0 (0)	0 (0)
Abdominal pain upper	0 (0)	1 (17)	0 (0)	1 (8)
Dental caries	0 (0)	0 (0)	1 (17)	1 (8)
Dyspepsia	0 (0)	0 (0)	1 (17)	1 (8)
Epistaxis	0 (0)	1 (17)	0 (0)	1 (8)
Injection site haemorrhage	0 (0)	1 (17)	0 (0)	1 (8)
Injection site pain	0 (0)	1 (17)	0 (0)	1 (8)
Local swelling	0 (0)	1 (17)	0 (0)	1 (8)
Malaise	1 (25)	0 (0)	0 (0)	0 (0)
Pyrexia	1 (25)	0 (0)	0 (0)	0 (0)

Leukopenia	0 (0)	0 (0)	1 (17)	1 (8)
Neutropenia	0 (0)	1 (17)	0 (0)	1 (8)
Dizziness postural	0 (0)	1 (17)	0 (0)	1 (8)
Paraesthesia	1 (25)	0 (0)	0 (0)	0 (0)
Joint dislocation	0 (0)	1 (17)	0 (0)	1 (8)
Concussion	1 (25)	0 (0)	0 (0)	0 (0)
Tooth fracture	1 (25)	0 (0)	0 (0)	0 (0)
Depressed mood	0 (0)	0 (0)	1 (17)	1 (8)
Depression	0 (0)	0 (0)	1 (17)	1 (8)
Insomnia	0 (0)	0 (0)	1 (17)	1 (8)
Suicidal ideation	0 (0)	0 (0)	1 (17)	1 (8)
Rash	0 (0)	0 (0)	1 (17)	1 (8)
Blister	1 (25)	0 (0)	0 (0)	0 (0)
Hyperhidrosis	1 (25)	0 (0)	0 (0)	0 (0)
Pruritis	1 (25)	0 (0)	0 (0)	0 (0)
Seasonal allergy	1 (25)	0 (0)	0 (0)	0 (0)