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

Jan de Hoon[1], Anne Van Hecken[1], Corinne Vandermeulen[1], Lucy Yan[2], Brian Smith[2], Jiyun Sunny Chen[2], Edgar Bautista[2], Lisa Hamilton[3], Javier Waksman[4], Thuy Vu[2] and Gabriel Vargas[2]

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 I 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 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.

Study Highlights

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.

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 3–13% of patients remaining on therapy for ≥6 months.[7] Medicines approved for prevention of episodic and chronic migraines include β-blockers, antiepileptics, 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 trigeminovascular system.[10–12] The potent vasodilator neuropeptide calcitonin

[1]Center for Clinical Pharmacology, University Hospitals of Leuven, Leuven, Belgium; [2]Early Development, Amgen, Thousand Oaks, California, USA; [3]Global Biostatistical Science, Amgen Ltd., Uxbridge, UK; [4]Global Safety, Amgen, Thousand Oaks, California, USA. Correspondence: Jan de Hoon (jan.dehoon@uzleuven.be)

Received 17 October 2016; accepted 14 July 2017; advance online publication 00 Month 2017. doi:10.1002/cpt.799

Table 1 Baseline demographic characteristics

	Single-dose study				Multiple-dose study			
	Healthy subjects		Patients with migraine		Healthy subjects		Patients with migraine	
Variable	Placebo ($n = 12$)	Erenumab ($n = 36$)	Placebo ($n = 6$)	Erenumab ($n = 6$)	Placebo ($n = 8$)	Erenumab ($n = 24$)	Placebo ($n = 4$)	Erenumab ($n = 12$)
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 (21–43)	27.1 (19–42)	28.5 (20–50)	23.8 (18–33)	32.1 (20–50)	32.1 (18–55)	37.0 (21–49)	31.5 (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.

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 (i.v.) infusion of CGRP can induce migraine-like attacks in migraineurs.[17,18] CGRP blockade by small-molecule CGRP receptor antagonists (i.e., 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 I 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-h 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, one 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 adverse event (AE) (polyarthritis), but remained on study.

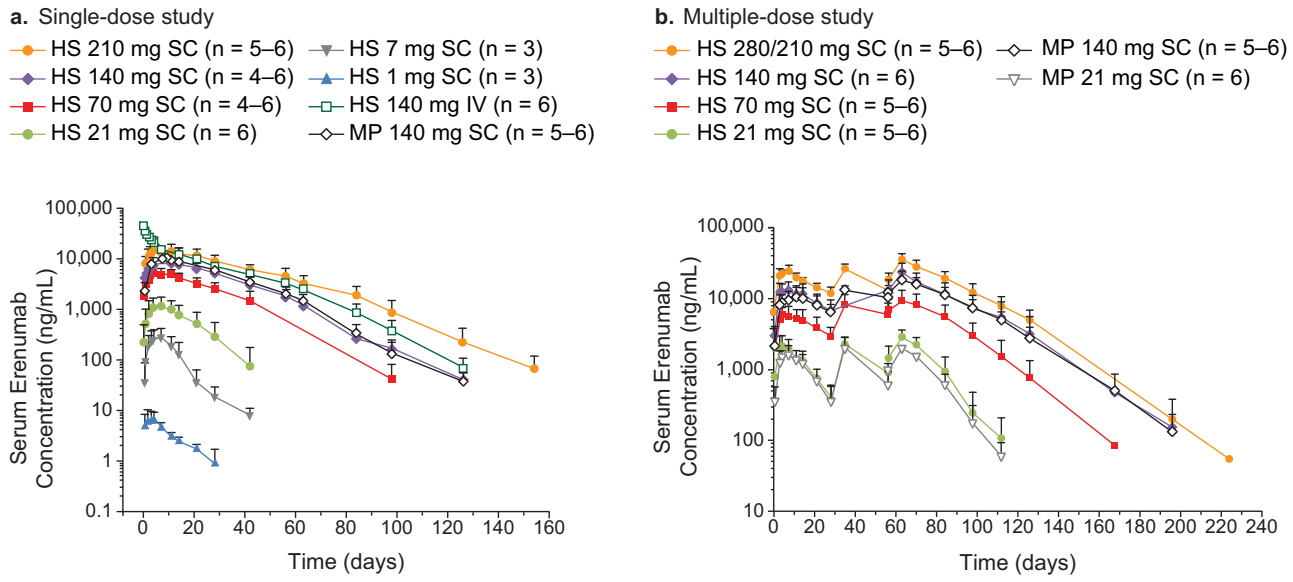
Pharmacokinetics

After a single subcutaneous (s.c.) 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 s.c. doses of 1–70 mg, mean AUC_{last} increased 2,009-fold (from 0.0851 to 171 day·μg/mL) and C_{max} increased 812-fold (from 0.0077 to 6.25 μg/mL), whereas following a 3-fold increase in erenumab dose from 70–210 mg s.c., mean AUC_{last} increased 3.8-fold (from 171–652 μg·day/mL) and mean C_{max} increased 2.4-fold (from 6.25–15.2 μg/mL). Median t_{max}

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.



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

Figure 1 Mean serum erenumab concentration–time profiles by cohort in the single-dose (a) and multiple-dose (b) studies.

ranged from 4–11 days throughout the dose range. Based on PK modeling, the elimination half-life of erenumab for a typical 70-kg subject receiving 70 mg s.c. was estimated as ~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 s.c. doses of erenumab, mean accumulation ratios ranged from 1.42–1.69 across all doses in healthy subjects and from 1.50–1.78 across all doses in patients with migraine (**Table 3**). Values for t_{max} ranged from ~3–13 days following the first s.c. dose and from ~6–14 days following the third s.c. 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 s.c.: 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 timepoint assessed), percent DBF inhibition vs. placebo ranged from 74.6–94.6% across the dose range of 21 mg to 140 mg erenumab s.c. (**Table 4**). In the multiple-dose study, on Day 8 (the

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

	After first dose		After last dose			
Erenumab dosage	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)[a]	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}.
[a]Erenumab was administered at 280 mg for the first dose, then 210 mg for the second and third doses.

first timepoint 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 timepoints after Day 169, the DBF inhibition associated with erenumab was not significant compared with placebo (data not shown).

24-H 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,b**). There were no statistically significant differences in least squares mean 24-h 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-h 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-h (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 six 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 timepoints. 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, 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 one subject in the placebo group (gastroenteritis), one subject in the erenumab 1-mg s.c. group (diarrhea), two subjects in the erenumab 70-mg s.c. group (abdominal pain and vomiting ($n = 1$), conjunctivitis and tendinitis ($n = 1$)), and two subjects in the erenumab 210-mg s.c. group (diarrhea ($n = 1$), gastroenteritis and headache ($n = 1$)). Among patients with migraine, AEs with a CTCAE grade ≥2 were seen in two patients in the placebo group (diarrhea ($n = 1$), influenza-like illness ($n = 1$)) and two patients in the erenumab 140-mg s.c. 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, 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%, respectively), headache (29.2% and 12.5%, respectively), and gastroenteritis (20.8% and 12.5%, respectively). Among the patients with migraine, the most commonly reported AEs were nasopharyngitis (erenumab, 50.0%; placebo, 0%), leukocyturia (41.7% and 0%, respectively), hematuria (25.0% and 50.0%, respectively), and oropharyngeal pain (25.0% and 0%, respectively).

No deaths occurred during the study. SAEs were reported in three 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, one 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 one 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 I studies, including PK and pharmacodynamics (PD: i.e., 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 1–280 mg. At doses of ≥21 mg s.c., erenumab potently inhibited the capsaicin-induced DBF increase, providing PD evidence for its mechanism of action as an 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

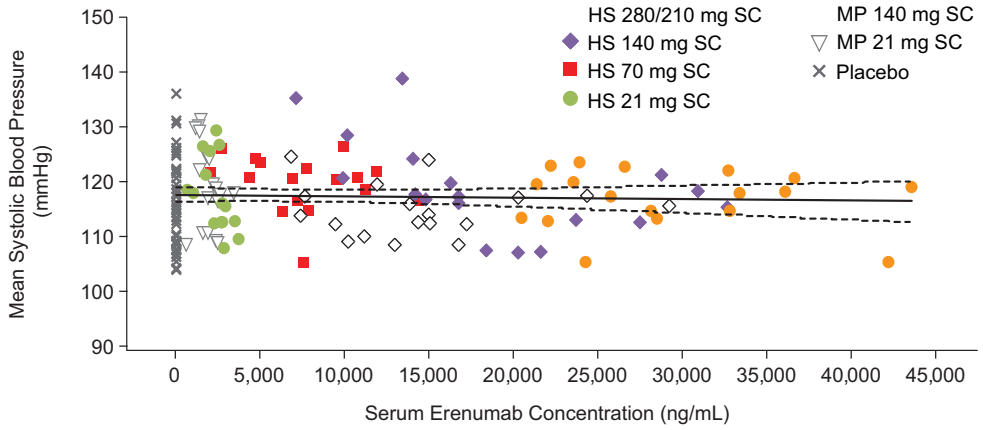
Table 4 Dermal blood flow inhibition postcapsaicin challenge by erenumab dose

Parameters	Healthy subjects							Patients with migraine	
		Erenumab							Erenumab
Single-dose study, Day 4	Placebo *n* = 12	1 mg SC *n* = 3	7 mg SC *n* = 3	21 mg SC *n* = 6	70 mg SC *n* = 6	140 mg SC *n* = 6	140 mg IV *n* = 6	210 mg SC *n* = 6	Placebo *n* = 6	140 mg SC *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 vs. placebo[a]	—	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[b]	—	−16.5%	39.0%	74.6%	90.3%	94.6%	94.5%	88.5%	—	90.5%

		Erenumab				Erenumab	
Multiple-dose study, Day 8	Placebo *n* = 6	21 mg SC *n* = 6	70 mg SC *n* = 6	140 mg SC *n* = 6	Placebo *n* = 4	21 mg SC *n* = 6	140 mg SC *n* = 6
LS geometric mean	8.5	1.8	2.5	1.8	13.2	2.6	1.6
Lsgmr vs. placebo[a]	—	−79.3	−71.2	−79.52	—	−80.0	−87.6
95% CI	—	−87.5, −65.7	−82.7, −52.0	−88.3, −64.2	—	−91.5, −52.9	−94.5, −71.9
P-value	—	<0.001	<0.001	<0.001	—	<0.001	<0.001
Percent inhibition of dermal blood flow[b]	—	89.9%	80.6%	90.1%	—	86.6%	94.8%

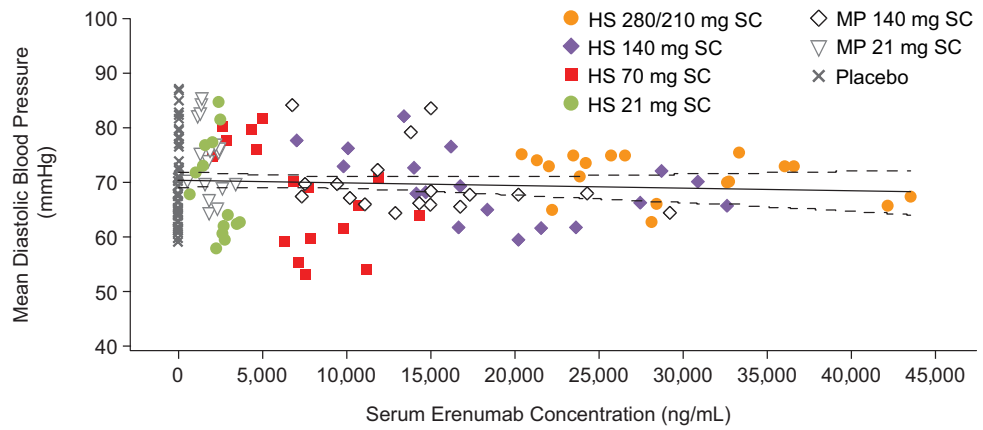
CI, confidence interval; LS, least squares; lsgmr, least squares geometric mean ratio; SC, subcutaneous.
[a]Lsgmr of the 30-min postcapsaicin measure to the precapsaicin measure vs. placebo. [b]Percent inhibition of capsaicin-induced increase of dermal blood flow = ((lsgmr for placebo − lsgmr for dose)/(lsgmr for placebo − 1)) * 100.

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 2 Mean 24-h ambulatory blood pressure (systolic [a] and diastolic [b]) vs. erenumab concentration by dose (multiple-dose study, Day 8).

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, one 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 II 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 AE in phase I 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, e.g., 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 on CGRP pathway antagonization. Importantly, in the phase II 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 $\geq$70 mg, erenumab behaves like a typical human IgG2 mAb, showing a proportional increase in erenumab concentrations with increasing dose in healthy subjects and in patients with migraine, presumably due to saturation of the target-mediated clearance pathway and antibody clearance that approximates the usual protein catabolism rate; thus, the estimated half-life at higher doses is closer to that of a typical IgG2 ($\sim$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 three 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 II study demonstrated efficacy for a dosage of 70 mg s.c. given monthly; while, in terms of efficacy, doses of 7 and 21 mg did not differ 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 that guided phase II dose selection. It delineated the minimum dose of erenumab that might be expected to have efficacy and enabled us to choose three doses, one of which demonstrated clinical efficacy.

Lack of dose-dependency at doses $\geq$21 mg s.c. 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 two 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 IC_{50} of 255 ng/mL (1.7 nM).[31] This is much more potent than that reported for telcagepant (IC_{50} of 101 nM) and similar in potency to MK-3207 (IC_{50} 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

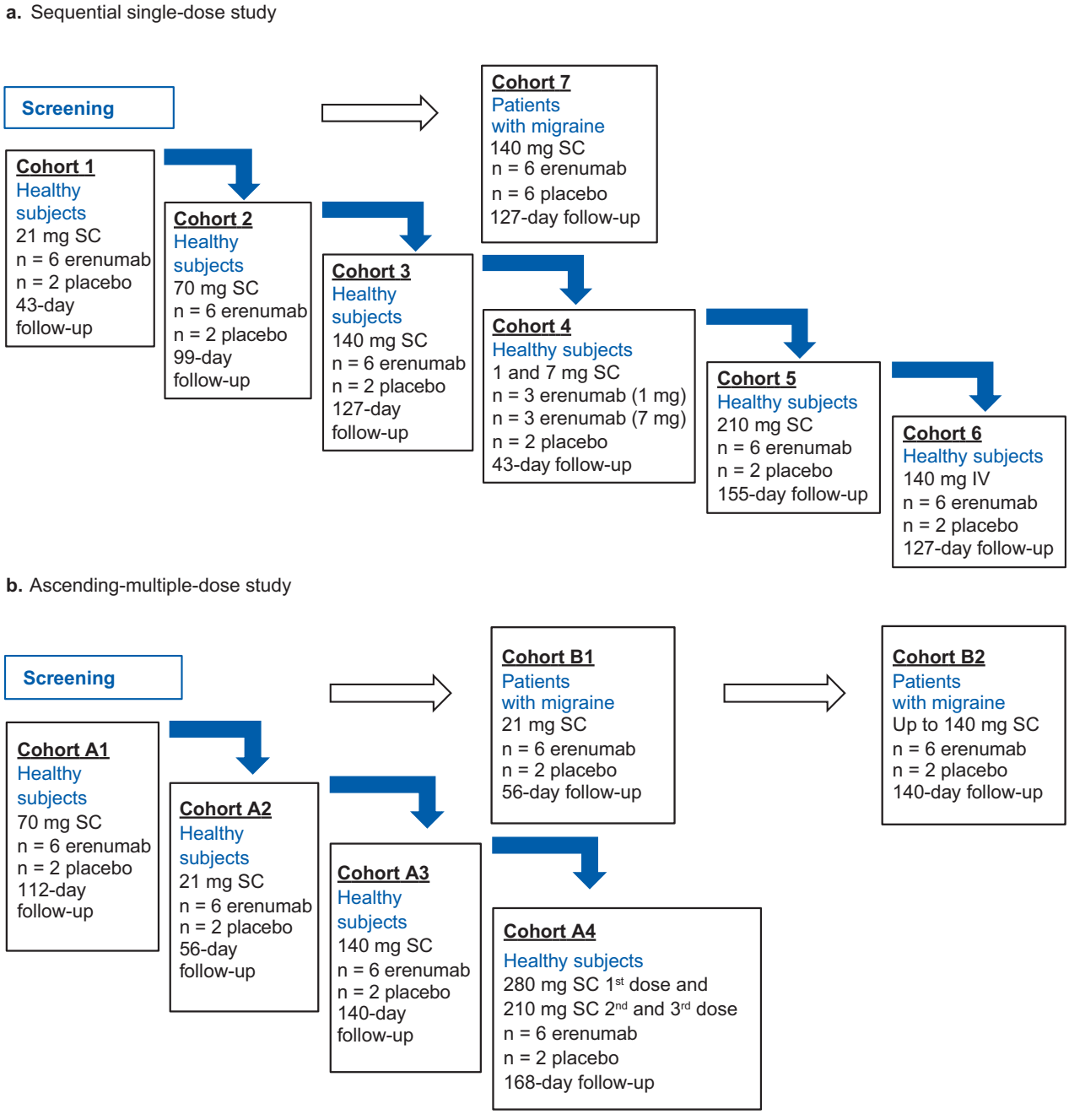


Figure 3 Study design of the single-dose (a) and multiple-dose (b) studies. All cohorts were dosed sequentially with dose escalation occurring after review of 15 days of safety and laboratory data, except for the cohorts of patients with migraine who were started in parallel following a higher dose in 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 three s.c. doses of erenumab or placebo on Days 1, 29, and 57. 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. [Color figure can be viewed at wileyonlinelibrary.com]

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.[30] At concentrations effectively inhibiting the capsaicin response, erenumab was not associated with meaningful changes in vital signs. Based on 24-h 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 s.c. 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 s.c. 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.[38,39] Further, there was no additional increase in BP observed with erenumab in a recent study with the primary objective to evaluate the safety of concomitant use of sumatriptan and erenumab.[40]

Given the substantial unmet medical need for better tolerated and more effective treatments for migraine, especially in the prevention of chronic migraine,[2,5,41] 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 and were divided into six cohorts (n = 8 per cohort). In Cohorts 1–5, subjects received study drug or placebo as an s.c. injection, whereas in Cohort 6 subjects received i.v. infusions. Sentinel dosing was performed in Cohorts 1, 2, 3, 5, and 6: i.e., the first two subjects were dosed (one received erenumab and one received matching placebo) and observed for at least 72 h (24 h for Cohort 6) for safety monitoring before the remaining six 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 a capsaicin-induced increase in DBF. All cohorts were dosed sequentially, with dose escalation performed after available safety data (i.e., 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 two parts (A and B; **Figure 3b**). In Part A, 32 healthy subjects were randomized to four cohorts (n = 8 per cohort) at dose levels of 70, 21, 140, or 280 (first dose)/210 (second dose)/210 (third dose) mg s.c. In Part B, 16 patients with migraine were randomized to two cohorts at dose levels of 21 or up to 140 mg s.c. (protocol allowed for lower dosing (between 21 and 140 mg s.c.) 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 three s.c. 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 × 1 dose s.c.. then 210 mg × 2 doses s.c.) 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 (predose and 8 h postdose), 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 h postdose on Days 1 and 57, and predose 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 1,000 μg per 20 μL of ethanol 100%/Tween-20/distilled water mixture (3/3/4) was applied to two sites on the volar surface of the left or right forearm, with vehicle applied to one site only on the same arm as a control. DBF was assessed by laser Doppler perfusion imaging immediately before and 0.5 h after capsaicin or vehicle application.

In both studies, vital signs and electrocardiograms were regularly recorded at prespecified timepoints. In addition, 24-h 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 I studies. In the single-dose study, ~48 healthy subjects and 20 migraineurs were to be enrolled. In the multiple-dose study, ~32 healthy subjects and 16 migraineurs were to be enrolled.

Pharmacokinetic analyses. Noncompartmental analysis of erenumab was performed (Phoenix WinNonlin v. 6.3 software, Certara, Princeton, NJ) 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 permit. 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 min postcapsaicin challenge vs. 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:

$$\frac{lsgmr\ for\ placebo - lsgmr\ for\ dose}{lsgmr\ for\ placebo - 1} \times 100$$

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—was also performed.[34]

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

Additional Supporting Information may be found in the online version of this article.

ACKNOWLEDGMENTS

Medical writing support was provided by Jennifer Villa of Oxford PharmaGenesis Inc., Newtown, PA, on behalf of Amgen Inc., and by Mandy Suggitt and Jon Nilsen of Amgen Inc. This work was funded by Amgen Inc.

CONFLICTS OF INTERESTS/DISCLOSURES

J. de Hoon reports research grants from Abide, 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, and UCB. A. Van Hecken has no disclosures. C. Vandermeulen has acted as Principal Investigator, for which the university received research grants, from AdImmune, GlaxoSmithKline, and Sanofi Pasteur. L. Yan, B. Smith, J.S. Chen, E. Bautista, L. Hamilton, J. Waksman, T. Vu, and G. Vargas are employees of Amgen, and own Amgen stock/stock options.

AUTHOR CONTRIBUTIONS

All authors participated in writing the article and approved submission of the article. J. de Hoon, L. Yan, E. Bautista, J. Waksman, and G. Vargas designed the research. J. de Hoon, A. Van Hecken, and C. Vandermeulen performed the research. B. Smith, J.S. Chen, L. Hamilton, and T. Vu analyzed the data.

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