

Pharmacokinetics, Safety, and Tolerability of Tezepelumab (AMG 157) in Healthy and Atopic Dermatitis Adult Subjects

Jane R. Parnes^{1,*}, John T. Sullivan¹ , Li Chen¹ and Clapton Dias²

Tezepelumab (AMG 157) is a monoclonal antibody that targets thymic stromal lymphopoietin and has shown benefits in treating asthma. We assessed the safety, tolerability, and pharmacokinetics of single-ascending and multiple-ascending doses in two randomized, double-blind, placebo-controlled phase I studies. Healthy and atopic dermatitis subjects were enrolled in the single-dose study, and healthy subjects in the multiple-dose study. Tezepelumab showed linear pharmacokinetics in both healthy and atopic dermatitis subjects. The half-life after a subcutaneous or intravenous administration ranged from 19.9 to 25.7 days. After multiple doses, the mean area under the curve accumulation ratio was 1.82, 1.64, and 1.59 for the 35 mg, 105 mg, and 210 mg monthly subcutaneous doses, respectively. The mean maximum serum concentration (C_{max}) accumulation ratio was 1.59, 2.84, and 6.74 for the 210 mg dose given every 28, 14, and 7 days, respectively. Tezepelumab was well tolerated in both studies with no evidence of immunogenicity.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ The pharmacokinetic profiles of tezepelumab, a monoclonal antibody with evidence of efficacy in treating asthma and potential benefit in atopic dermatitis, have not been well characterized in the literature. The safety of first-in-human experience with tezepelumab in healthy adults has not been described.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ The study evaluated the initial safety of tezepelumab in humans, its pharmacokinetic profiles, and its preliminary clinical activity in atopic dermatitis.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ The results demonstrate that tezepelumab exhibits linear pharmacokinetic patterns. These results enabled dose and regimen selections in subsequent studies.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ The data provide the foundational safety and pharmacokinetics for potentially the most important advance in asthma treatment in the past 40 years. This biologic agent has received breakthrough therapy designation from the US Food and Drug Administration in non-eosinophilic severe asthma patients.

Tezepelumab (also known as AMG 157 or MEDI9929/AMG 157) is a fully human monoclonal antibody (immunoglobulin G2 λ) that targets thymic stromal lymphopoietin (TSLP), an epithelial-cell-derived cytokine that promotes inflammatory responses to environmental stimuli through its activities on multiple pathways, including (but not limited to) activities on dendritic cells¹⁻³ and mast cells.⁴ Increased TSLP expression has been associated with asthma,^{5,6} and increased levels of TSLP protein are found in the skin lesions of patients with atopic dermatitis (AD).^{2,7,8} By binding to TSLP, tezepelumab prevents its interaction with the TSLP receptor complex and inhibits multiple downstream inflammatory pathways. Preclinical data support the role of TSLP in both asthma^{5,9,10} and AD,¹¹ indicating that tezepelumab may be effective as a treatment in both diseases.

Data from two double-blind, placebo-controlled clinical studies have shown tezepelumab to be a promising new treatment for asthma. In a proof-of-concept study, three monthly doses of intravenous (IV) tezepelumab 700 mg attenuated asthmatic responses to allergen challenge in patients with mild asthma.¹² In a phase II study, subcutaneous (SC) tezepelumab at doses of 70 mg every 4 weeks up to 280 mg every 2 weeks for 52 weeks reduced the rates of clinically significant asthma exacerbations in patients whose asthma had not been controlled by the use of long-acting beta-agonists and medium-to-high doses of inhaled glucocorticoids.¹³ Importantly, tezepelumab diminished exacerbations independent of baseline eosinophil counts. Accordingly, this therapeutic agent is the first new treatment in several decades that has shown promise in all patients

¹Amgen Inc., Thousand Oaks, California, USA; ²BioMarin Pharmaceutical Inc., Novato, California, USA. *Correspondence: Jane R. Parnes (jparnes@amgen.com)

Received December 17, 2018; accepted January 28, 2019. doi:10.1002/cpt.1401

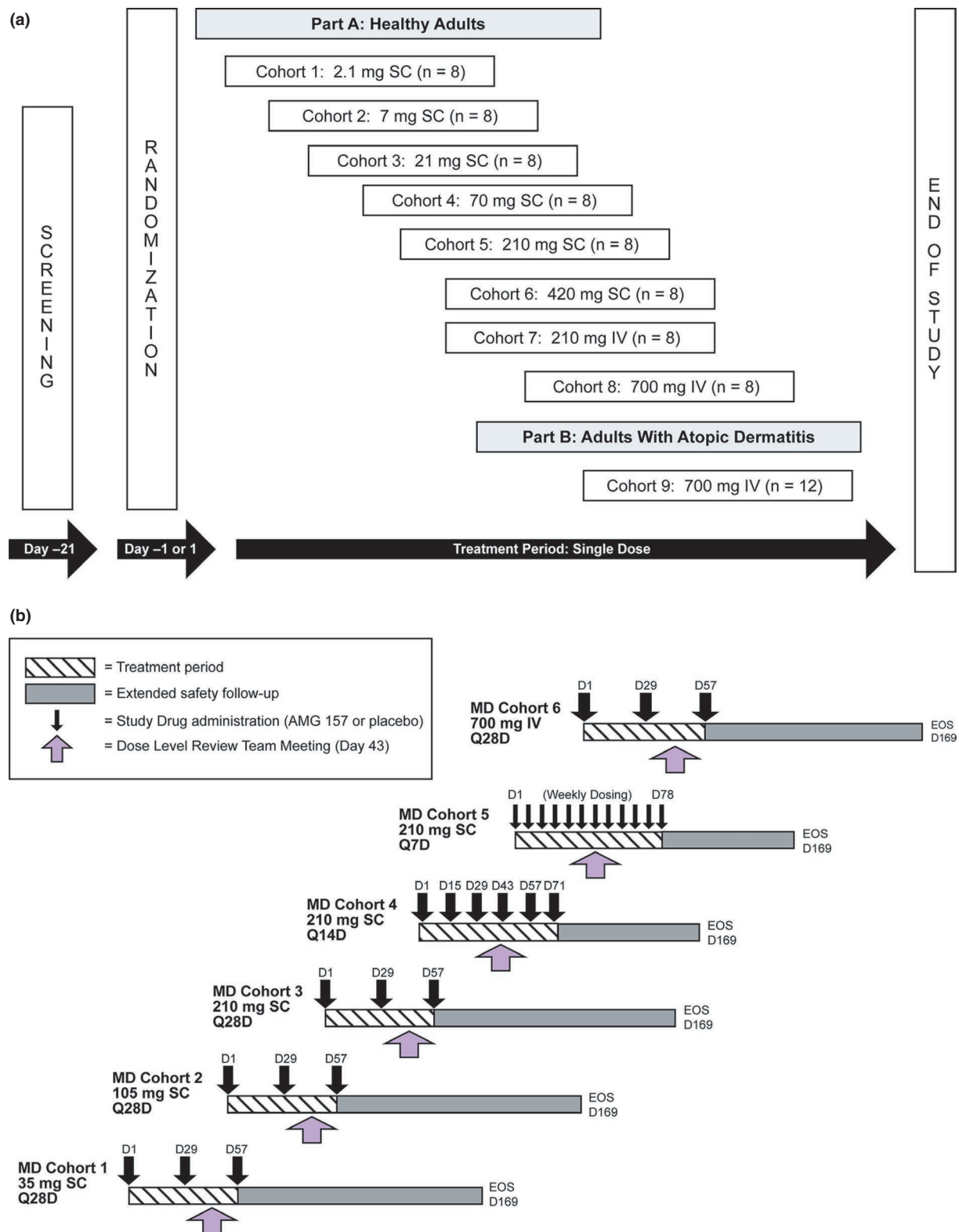


Figure 1 Design and treatment schema of the single-ascending dose (SAD) and multiple-ascending dose (MAD) studies of tezepelumab. (a) SAD study. Subjects in cohorts 1–8 were randomized 6:2 and subjects in cohort 9 were randomized 9:3 to either tezepelumab or placebo, administered intravenously (IV) or subcutaneously (SC). The end of study was day 113. (b) MAD Study. In each multi dose (MD) cohort, eight healthy subjects were randomized 6:2 to either tezepelumab or placebo IV or SC once every 7, 14, or 28 days (Q7D, Q14D, Q28D, respectively) from study day 1 (D1) through the end of study (EOS) on day 169 (D169). [Colour figure can be viewed at wileyonlinelibrary.com]

who suffer from asthma. In addition to the clinical improvements, tezepelumab treatment was also associated with decreases in blood eosinophil counts, fraction of exhaled nitric oxide levels, and total serum IgE levels in asthma patients.

Here we report the results from two phase I, dose-escalating studies that evaluated the pharmacokinetic and safety profiles of tezepelumab in healthy and AD subjects, which had been conducted before the above-cited allergen challenge and asthma studies and provided the basis for the dosing regimen selected in those and other clinical studies. One was a first-in-human, randomized, double-blind, placebo-controlled, single-ascending dose (SAD) study of tezepelumab in healthy and AD subjects; AD subjects participated in only one dose cohort. The second study was a randomized, double-blind, placebo-controlled, multiple-ascending dose (MAD) study of tezepelumab in healthy subjects. In both studies, SC and IV administrations were tested. In addition to pharmacokinetic and safety endpoints, the activity of a single dose of tezepelumab was evaluated on signs and symptoms of AD.

RESULTS

Study population

A total of 78 subjects enrolled in the SAD study, including 64 healthy subjects in cohorts 1 through 8 and 14 AD subjects in cohort 9 (see **Figure 1a** for study design). Two AD subjects dropped out of the study before receiving the study drug and were replaced to ensure that 12 were randomized and treated with either tezepelumab or placebo. The SC doses ranged from 2.1 mg to 420 mg and the IV doses were 210 mg and 700 mg. As required by the randomization ratio of 3:1, 48 healthy and 9 AD subjects received a single dose of tezepelumab, and 16 healthy and 3 AD subjects received a single dose of placebo.

In the MAD study, 48 healthy subjects were planned for enrollment in 6 cohorts (**Figure 1b**). Because one subject in cohort 5 discontinued the study treatment prematurely, a replacement was enrolled, resulting in a total of 49 for the entire study. Of the 49 subjects, 37 received at least one dose of tezepelumab, and 12 received at least one dose of placebo. Fifteen subjects discontinued from the study before completion, including 11 (30%) who received tezepelumab and 4 (33%) who received placebo. At least half of the subjects in each dose cohort completed the study, and the frequency of discontinuation did not appear to be associated with tezepelumab dose. In the highest SC dose cohort (210 mg every 7 days), five of the seven (71%) subjects completed all 12 scheduled doses. In the IV dose cohort (700 mg every 28 days), five of the six (83%) subjects completed all three scheduled doses.

The demographics and baseline characteristics of the subjects in both studies are summarized in **Table 1**. In both studies, the distribution of demographics was similar between those who were randomized to tezepelumab and those to placebo. Most subjects were men, and the majority were Hispanic or Latino.

Pharmacokinetic profiles

In the SAD study, the serum concentrations of tezepelumab after single-dose IV and SC administrations were obtained from all 48 healthy subjects who received the active drug. The serum concentration-vs.-time profiles of healthy subjects who received

tezepelumab exhibited linear pharmacokinetics, as indicated by the near dose-proportionality between the dose and exposure (**Figure 2a,b**). The time to maximum concentration (t_{max}) after a single SC dose ranged from 81 to 237 hours (approximately 3–10 days). The bioavailability of the SC 210 mg dose, relative to the IV 210 mg dose, was estimated to be 81% (**Table 2**). Mean estimates of terminal half-life ($t_{1/2,z}$) after single SC and IV doses ranged from 19.9 to 25.7 days.

Tezepelumab serum concentrations were obtained from the nine AD subjects who received a single dose of 700 mg IV tezepelumab (**Figure 2b**). The pharmacokinetic profile of tezepelumab in AD subjects was similar to that in healthy subjects (**Table 2**). The mean SD maximum observed serum concentration (C_{max}) was 219 (38.3) $\mu\text{g/mL}$ in healthy subjects and 253 (57.2) $\mu\text{g/mL}$ in AD subjects, and the mean (SD) areas under the concentration-vs.-time curve from time zero to the time of the last quantifiable concentration (AUC_{0-t}) were 3,440 (253) and 3,660 (990) $\text{day}\cdot\mu\text{g/mL}$, respectively.

In the MAD study, tezepelumab serum concentrations were obtained in 37 healthy subjects who received multiple-dose IV and SC administrations. The results showed linear pharmacokinetics of tezepelumab with increasing dose and were in good agreement with the single-dose results (**Figure 2c** and **Table 3**). No apparent time-dependent changes in the clearance of tezepelumab were observed after multiple doses. The mean (SD) areas under the concentration-vs.-time curve over the dosing interval (AUC_{τ}) accumulation ratio were 1.82 (0.262), 1.64 (0.0883), and 1.59 (0.242) for the 35 mg, 105 mg, and 210 mg monthly (every 28 days) dose cohorts, respectively. The mean (SD) C_{max} accumulation ratios were 1.59 (0.288), 2.84 (0.965), and 6.74 (1.69) for the 210 mg SC dose given every 28, 14, and 7 days, respectively. Taken together, these accumulation ratios were consistent with the dosing regimen and an IgG monoclonal antibody exhibiting linear pharmacokinetics and a 21-day half-life.

Safety and tolerability

The numbers and percentages of subjects who experienced adverse events are summarized in **Table 4**.

In the SAD study, single injections of tezepelumab at doses up to 420 mg SC and 700 mg IV were well tolerated in both healthy and AD subjects. No subjects died or discontinued the study because of adverse events. One AD subject who received placebo had two serious adverse events reported (right knee infection and postoperative pain) after a knee injury and subsequent surgical debridement. No other serious adverse events were reported. Among the 48 healthy subjects who received either SC or IV tezepelumab, 29 (60%) reported at least one adverse event, regardless of whether it was considered related to the study treatment by the investigators. Among the 16 healthy subjects in the placebo group, 11 (69%) reported at least one adverse event. The most common adverse events in healthy subjects were upper respiratory tract infection (7 (15%) tezepelumab, 5 (31%) placebo), headache (7 (15%) tezepelumab, 1 (6%) placebo), and myalgia (4 (8%) tezepelumab, 0 placebo). Among the AD subjects, seven of nine (78%) subjects who received IV tezepelumab and three of three (100%) who received placebo had at least one adverse event. The most common adverse events were worsening atopic dermatitis (2 (22%) tezepelumab, 1

Table 1 Demographic and baseline characteristics of subjects in the single-dose and multiple-dose studies

	Single-dose				Multiple-dose	
	Healthy volunteers		AD patients		Healthy volunteers	
	Tezepelumab (N = 48)	Placebo (N = 16)	Tezepelumab (N = 9)	Placebo (N = 3)	Tezepelumab (N = 37)	Placebo (N = 12)
Sex, n (%)						
Female	11 (23)	3 (19)	2 (22)	0 (0)	5 (14)	2 (17)
Male	37 (77)	13 (81)	7 (78)	3 (100)	32 (86)	10 (83)
Race, n (%)						
White or Caucasian	13 (27)	4 (25)	1 (11)	0 (0)	13 (35)	4 (33)
Black or African American	5 (10)	1 (6)	0	1 (33)	2 (5)	1 (8)
Hispanic or Latino	26 (54)	11 (69)	8 (89)	2 (67)	22 (59)	7 (58)
Asian	2 (4)	0	0	0	0	0
Other	2 (4)	0	0	0	0	0
Age (years), median	33.0	32.0	51.0	45.0	33.0	34.0
Weight (kg), median	75.75	79.55	76.50	101.50	76.90	83.30
Height (cm), median	171.0	166.1	172.0	180.0	172.0	172.0
BMI (kg/m ²), median	25.80	27.75	27.93	30.14	26.53	27.76

AD, atopic dermatitis; BMI, body mass index.

(33%) placebo), upper respiratory tract infection (2 (22%) tezepelumab, 1 (33%) placebo), pyrexia (2 (22%) tezepelumab, 0 placebo), and insomnia (1 (11%) tezepelumab, 2 (67%) placebo). In both subjects with pyrexia, the severity was Grade 1 on the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 scale, and the events were considered not related to the study drug by the investigator. All the adverse events reported in this study were mild or moderate in severity. There was no apparent trend of dose relationship in the incidence of adverse events.

Notable clinical laboratory abnormalities were observed in one healthy subject who had increased hepatic enzyme levels, including a 24-fold, 5-fold, and 4-fold increase for aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase, respectively, after receiving 700 mg IV tezepelumab. The elevations in aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase values were not accompanied by an increase in total bilirubin. The investigator considered these liver enzyme elevations to be not related to the study drug but rather to the subject's intermittent alcohol abuse. This subject chose not to return to the study site for further follow-up assessments. No other apparent trends of abnormalities or changes related to tezepelumab were observed in clinical laboratory tests, electrocardiograms (ECGs), and physical examinations during the study.

During the MAD study, 24 (65%) of the 37 subjects in the tezepelumab group and 10 (83%) of the 12 subjects in the placebo group reported at least one adverse event. The most common adverse events were headache (22% tezepelumab, 17% placebo), creatine phosphokinase increased (8% tezepelumab, 17% placebo), viral infection (8% tezepelumab, 17% placebo), injection site pain (8% tezepelumab, 0 placebo), and pruritus (8% tezepelumab, 0 placebo). Injection site reactions, such as injection site pain, hematoma, and swelling, appeared to be more frequent with

tezepelumab administration than placebo, but the intensity did not increase with dose. No other dose-related trends were observed.

No subjects died or withdrew from the study because of adverse events. One subject in the group of 35 mg SC every 28 days had a serious adverse event of acute hepatitis C, with seroconversion occurring more than 30 days after the last dose of tezepelumab. The investigator considered this event to be unrelated to the study drug. No proximal cause of the subject's hepatitis C infection was identified, but his history included abuse of alcohol and other drugs, and incarceration.

Clinically significant laboratory values that met CTCAE Grade 3 or higher were observed in nine subjects (six tezepelumab, three placebo). The most common Grade 3 or 4 laboratory abnormality was creatine phosphokinase increased in five (14%) subjects in the tezepelumab group and three (25%) in the placebo group. Most of these significant laboratory values occurred in two subjects: one subject with acute hepatitis C, as noted above, and another subject who reported having begun a vigorous exercise program during the study. The latter subject was removed from the study due to noncompliance with the protocol. No other trends related to tezepelumab were observed in laboratory tests, vital signs, or physical examinations.

In the MAD study, no notable changes in tezepelumab-treated subjects were apparent in clinical laboratory tests, vital signs, or physical examinations.

Antitezepelumab antibodies

No subjects in either study tested positive for treatment-emergent antitezepelumab antibodies after receiving tezepelumab. Two subjects in the SAD study, both of whom received placebo during the study, and one subject in the MAD study, who received 210 mg tezepelumab SC every 14 days, tested positive for anti-AMG 157

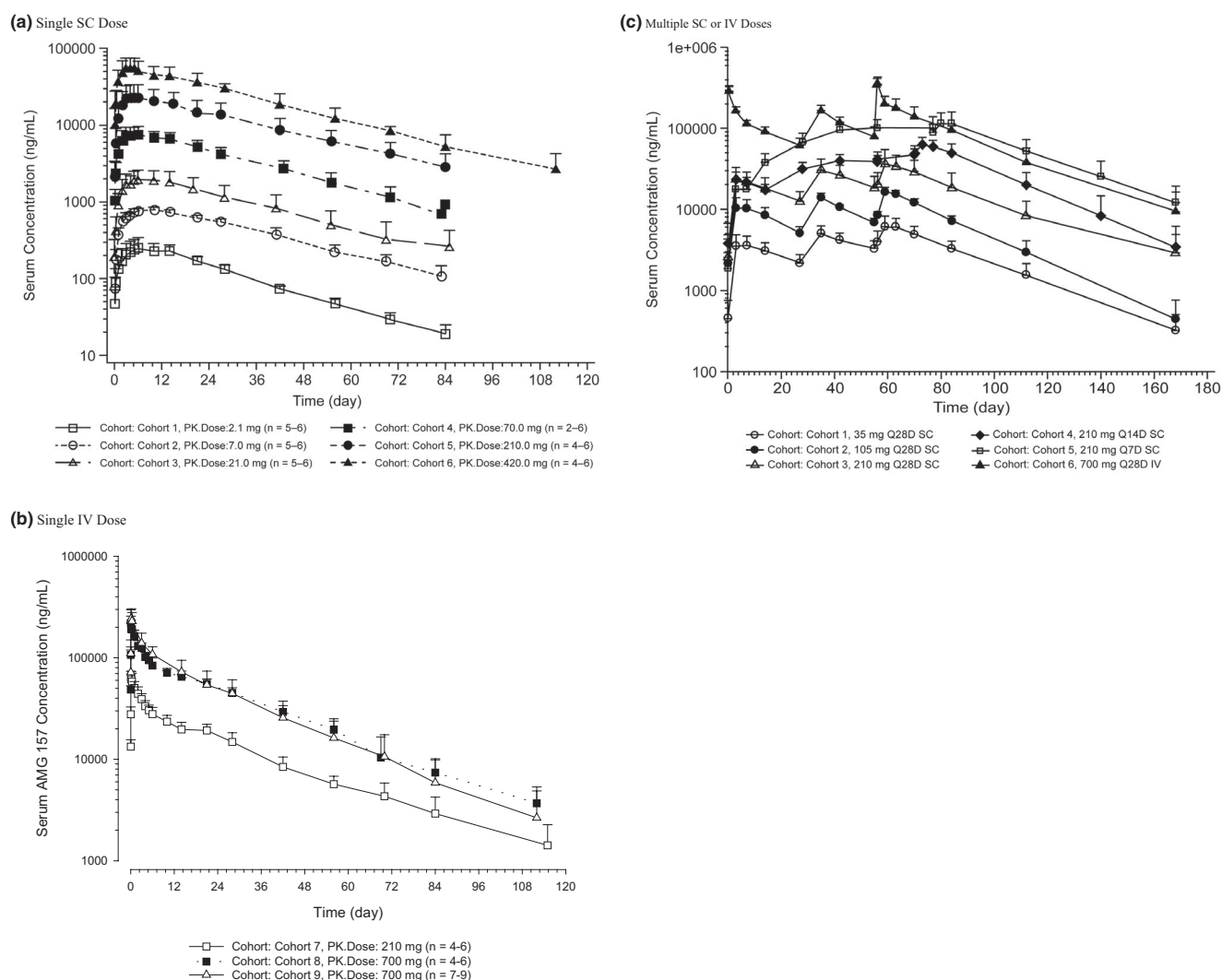


Figure 2 Mean (standard deviation) serum concentration-time profiles (Semilog) following tezepelumab administration in healthy subjects and subjects with atopic dermatitis. **(a)** Single SC dose (all healthy subjects). **(b)** Single IV dose (cohorts 7 and 8: healthy subjects; cohort 9: subjects with atopic dermatitis). **(c)** Multiple SC or IV doses (all healthy subjects). IV, intravenous; PK, pharmacokinetic; SC, subcutaneous.

antibodies, most likely resulting from pre-existing serum molecules capable of binding to tezepelumab. None of these tested positive for neutralizing antibodies. No other subjects, including those on placebo, were tested positive for anti-tezepelumab antibodies.

Efficacy of single-dose tezepelumab in atopic dermatitis

In the SAD study, 12 subjects with AD were randomly assigned to receive a single IV dose of either tezepelumab 700 mg ($n = 9$) or placebo ($n = 3$). After the treatment, five (56%) of the nine subjects on tezepelumab achieved 50% reduction from baseline (day -1, before study treatment) in Eczema Area and Severity Index (EASI) score (i.e., EASI 50 response) at one or more of the postdose time points from day 15 to day 113 (end of study), compared with one (33%) of three subjects on placebo. In addition, two (22%) subjects on tezepelumab achieved 75% reduction from baseline (EASI 75), and one (11%) achieved 90% (EASI 90) at one or more of the postdose time points, compared with none for both response rates among those on placebo.

The mean (SD) changes in EASI score from baseline to the follow-up visits are summarized by treatment group in **Table 5**. Because of the small sample size and large intersubject variations, no formal statistical comparison was made between the tezepelumab and placebo groups.

DISCUSSION

These two studies present the initial safety experience in humans and the first complete characterization of the single-dose and multiple-dose pharmacokinetics of tezepelumab, an anti-TSLP human monoclonal antibody with evidence of efficacy in asthma and potential therapeutic benefit in atopic dermatitis and other inflammatory disorders.

At single doses ranging from 2.1 to 420 mg SC and 210 to 700 mg IV, tezepelumab demonstrated linear pharmacokinetics, which was similar between healthy subjects and those with AD. At multiple doses of 35 to 210 mg SC and 700 mg IV with dosing intervals ranging from 7 to 28 days, tezepelumab exhibited

Table 2 Single-ascending-dose study: mean (standard deviation) pharmacokinetic parameter estimates of tezepelumab after IV or SC administration

Route	Dose (mg)	N	$t_{1/2,z}$ (day)	t_{max}^a (hour)	C_{max} ($\mu\text{g/mL}$)	AUC_{0-t} (day· $\mu\text{g/mL}$)	AUC_{inf} (day· $\mu\text{g/mL}$)
Healthy volunteers							
IV	210	6	24.5 (6.28)	1.13 (1.08–8.00)	64.4 (10.2)	1,150 (176)	1,200 (208)
	700	6	20.7 (6.44)	1.04 (1.02–1.17)	219 (38.3)	3,440 (253)	3,530 (322)
SC	2.1	6	19.9 (4.81)	190.94 (117.87–332.15)	0.257 (0.0824)	8.12 (1.96)	8.69 (1.97)
	7	6	23.4 (4.30)	237.09 (140.50–335.07)	0.792 (0.0593)	32.9 (2.75)	36.6 (4.60)
	21	6	22.7 (4.81)	142.10 (117.43–336.10)	2.01 (0.620)	76.7 (31.6)	84.6 (37.9)
	70	6	22.5 (1.35)	130.87 (69.27–237.90)	7.82 (2.25)	278 (64.3)	303 (70.3)
	210	6	25.7 (5.52)	93.65 (70.22–359.17)	23.6 (10.3)	867 (349)	976 (409)
	420	6	23.3 (2.89)	80.89 (68.27–116.58)	58.0 (19.3)	2,050 (627)	2,140 (677)
Patients with AD							
IV	700	9	22.2 (4.72)	4.08 (1.00–8.12)	253 (57.2)	3,660 (990)	3,830 (1,230)

AD, atopic dermatitis; AUC_{0-t} , area under the concentration-time curve from time zero to the time of the last quantifiable concentration; AUC_{inf} , area under the concentration-time curve from time zero extrapolated to infinity; C_{max} , maximum observed concentration in serum; IV, intravenous; SC, subcutaneous; $t_{1/2,z}$, half-life associated with terminal phase of the concentration-time profile; t_{max} , time C_{max} was observed.

^aMedian (minimum–maximum).

Table 3 Multiple-ascending dose study: mean (standard deviation) PK parameter estimates of tezepelumab after first and last IV and SC dose in healthy volunteers

Treatment	Period	N	t_{max}^a (hour)	C_{max}^b ($\mu\text{g/mL}$)	AUC_{τ}^b (day· $\mu\text{g/mL}$)	AR_AUC	AR_ C_{max}
35 mg Q28D SC	1st dose	6	160 (69.7–167)	3.70 (1.16)	78.9 (23.4)	NA	NA
	Last dose	5	166 (68.6–176)	6.29 (2.02)	136 (35.9)	1.82 (0.262)	1.79 (0.392)
105 mg Q28D SC	1st dose	5/6 ^c	71.5 (70.4–167)	10.7 (3.13)	237 (50.5)	NA	NA
	Last dose	3	71.8 (70.7–167)	16.6 (2.02)	333 (28.8)	1.64 (0.0883)	1.66 (0.0901)
210 mg Q28D SC	1st dose	6	118 (68.7–166)	23.6 (9.50)	481 (171)	NA	NA
	Last dose	5	167 (69.3–168)	37.4 (17.5)	799 (338)	1.59 (0.242)	1.59 (0.288)
210 mg Q14D SC	1st dose	6	70.7(69.9–168)	23.8 (5.40)	263 (49.2)	NA	NA
	Last dose	6	66.5 (65.1–162)	63.8 (13.5)	787 (180)	2.89 (0.892)	2.84 (0.965)
210 mg Q7D SC	1st dose	7	164 (66.9–165)	18.0 (4.58)	84.3 (34.9)	NA ^d	NA
	Last dose	5	74.4 (65.9–164)	117 (45.6)	732 (224)	8.23 (1.93)	6.74 (1.69)
700 mg Q28D IV	1st dose	6	4.00 (1.13–4.17)	294 (48.2)	2,980 (395)	NA	NA
	Last dose	5	3.97 (1.17–4.03)	370 (74.9)	4,050 (1,270)	1.34 (0.314)	1.30 (0.176)

AR, accumulation ratio based on AUC_{τ} or C_{max} (calculated as $AUC_{\text{period } 2}/AUC_{\text{period } 1}$ or $C_{\text{max,period } 2}/C_{\text{max,period } 1}$, respectively); AUC_{τ} , area under the concentration-time curve over the dosing interval; C_{max} , maximum observed concentration in serum; IV, intravenous; N, number of subjects summarized; NA, not applicable; Q14D, biweekly; Q28D, once a month; Q7D, weekly; SC, subcutaneous; SD, standard deviation; t_{max} , time of maximum observed concentration.

^a t_{max} is reported as median (minimum–maximum). ^b C_{max} and AUC_{τ} are reported as mean (SD). ^cN = 6 for t_{max} and C_{max} ; N = 5 for AUC_{τ} . ^dAR_AUC was calculated as $AUC_{\tau, \text{period } 2}/AUC_{0-t, \text{period } 1}$ for cohort 5 only.

linear pharmacokinetics in good agreement with single-dose pharmacokinetics. While there were minor apparent differences between various cohorts in the pharmacokinetics parameters, given the sample sizes and individual variances, there was no convincing evidence that the pharmacokinetics profile was different between healthy subjects and those with atopic dermatitis. The accumulation ratios of AUC and C_{max} were as expected for an IgG with a half-life of approximately 21 days. The highly consistent and reliable pharmacokinetic profiles of tezepelumab observed in these studies provided the basis for designing the dosing regimens in subsequent phase II clinical trials,

in which tezepelumab was given either IV at 700 mg monthly or SC at 70 mg monthly, 210 mg monthly, and 280 mg every 2 weeks.^{12,13}

These two studies also established the safety and tolerability of multiple doses of tezepelumab up to 700 mg IV every 28 days and up to 210 mg SC weekly for 3 months in healthy subjects. The proportion of subjects who experienced adverse events was similar between the tezepelumab and placebo groups. No deaths or serious adverse events related to tezepelumab were reported in any study subjects. Repeated tezepelumab SC injections appeared to be associated with increased occurrence of injection site reactions. The

Table 4 Summary of adverse events in the single-dose and multiple-dose studies

	Single-dose				Multiple-dose	
	Healthy volunteers		Atopic dermatitis patients		Healthy volunteers	
	Tezepelumab (N = 48)	Placebo (N = 16)	Tezepelumab (N = 9)	Placebo (N = 3)	Tezepelumab (N = 37)	Placebo (N = 12)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All adverse events	29 (60)	11 (69)	7 (78)	3 (100)	24 (65)	10 (83)
Treatment-related events	6 (13)	5 (31)	3 (33)	3 (100)	7 (19)	2 (17)
Serious adverse events	0	0	0	1 (33)	1 (3)	0
Adverse events leading to discontinuation	0	0	0	0	0	0
Most common adverse events						
Upper respiratory tract infection	7 (15)	5 (31)	2 (22)	1 (33)	2 (5)	2 (17)
Headache	7 (15)	1 (6)	0	0	8 (22)	2 (17)
Myalgia/musculoskeletal pain	4 (8)	0	1 (11)	0	2 (5)	1 (8)
Pyrexia	1 (2)	1	2 (22)	0	0	1 (8)
Creatine phosphokinase increased	0	0	0	0	3 (8)	2 (17)
Viral infection	0	0	0	0	3 (8)	2 (17)
Injection site pain	0	0	0	0	3 (8)	0
Pruritus	0	0	0	0	3 (8)	0
Atopic/contact dermatitis	3 (6)	0	2 (22)	1 (33)	2 (5)	0
Insomnia	1 (2)	0	1 (11)	2 (67)	1 (3)	0

proportions of subjects with infection and other types of adverse events were similar between the tezepelumab and placebo groups in both studies. There was no evidence of immunogenicity in these studies. These results are consistent with the safety findings in the clinical trials of tezepelumab in asthma patients, which did not find increased incidence of infection in tezepelumab-treated patients compared with placebo.^{12,13}

Both studies were phase I studies intended to evaluate the initial safety, pharmacokinetics, and a preliminary assessment of the drug's potential efficacy in AD. The sample sizes were small, and most of the study subjects were healthy adult subjects, thus limiting the insight into the drug's effects in those with asthma or AD. Nevertheless, the small group of subjects with AD in the SAD study provided evidence that the pharmacokinetics remains unaltered by AD. The single-dose regimen and small sample size precluded any definitive conclusions on the efficacy of tezepelumab in the treatment of AD, but the results were consistent with a larger phase IIa study of tezepelumab in AD with longer treatment.¹⁴

In conclusion, tezepelumab was well tolerated and exhibited a predictable linear pharmacokinetic profile and acceptable safety and tolerability in healthy and AD adult subjects.

METHODS

Study designs

The schematics of the study design, including the dose escalation process, are displayed in **Figure 1a** (SAD) and **Figure 1b** (MAD).

The SAD study of tezepelumab, was a randomized, double-blind, placebo-controlled study that tested six SC doses (2.1, 7, 21, 70, 210, and 420 mg) and two IV doses (210 and 700 mg) in comparison with placebo, in healthy subjects. Once the safety of 700 mg tezepelumab was established in healthy subjects, a cohort of adult subjects with AD were randomized to receive a single dose of either 700 mg IV tezepelumab or placebo.

As this was the first human study of tezepelumab, a sentinel pair was used for cohort 1 (2.1 mg SC, healthy subjects). Specifically, the first two subjects in this cohort were randomized at a 1:1 ratio to receive either tezepelumab or placebo and were monitored for safety and tolerability. Once the safety in the sentinel pairs was confirmed, the subsequent six subjects were randomized at a 5:1 ratio for tezepelumab or placebo treatment. In cohorts 2 through 8 (escalating SC doses, healthy subjects), all eight subjects

Table 5 Summary of percent change in EASI score from baseline in patients with atopic dermatitis

	Tezepelumab 700 mg IV (N = 9)	Placebo IV (N = 3)
Day 15		
<i>n</i>	9	3
Mean (SD) %	-12.47 (43.32)	15.10 (55.84)
Day 29		
<i>n</i>	9	3
Mean (SD) %	-23.61 (32.82)	-25.03 (20.38)
Day 43		
<i>n</i>	9	3
Mean (SD) %	-17.04 (44.28)	-32.41 (31.81)
Day 57		
<i>n</i>	9	2
Mean (SD) %	-22.83 (41.23)	-1.89 (37.24)
Day 85		
<i>n</i>	8	3
Mean (SD) %	-31.70 (42.14)	-23.01 (21.16)
End of study		
<i>n</i>	9	3
Mean (SD) %	-25.25 (49.40)	-11.28 (54.63)

EASI, Eczema Area and Severity Index; IV, intravenous; SD, standard deviation.

in each cohort were randomized to receive tezepelumab or placebo at a 6:2 ratio. In cohort 9 (700 mg IV, AD subjects), a sentinel pair was again used to first establish safety and tolerability, and the subsequent 10 subjects were randomized to receive tezepelumab at a ratio of 8:2, for a total of 12 evaluable subjects in this cohort. Each dose escalation decision was based on a blinded review of safety data up to day 15 of the previous dose cohort with consideration of predefined stopping rules. Subjects were to be followed for safety up to day 113 after the study drug administration on day 1.

The MAD study was a randomized, double-blind, placebo-controlled study in healthy subjects. In five cohorts, the following dose regimens of tezepelumab were compared with placebo: 35, 105, and 210 mg SC every 28 days for three doses; 210 mg SC every 14 days for six doses; and 210 mg SC every 7 days for 12 doses. In cohort 6, a regimen of tezepelumab 700 mg IV every 28 days for three doses was compared with placebo. In each cohort, eight healthy subjects were randomized at a 6:2 ratio to receive either tezepelumab or placebo. The cohorts enrolled sequentially. The initial dose was given on day 1. Each dose escalation proceeded only when the dose in the previous cohort was determined to be safe and well tolerated by a blinded review of available safety data through day 43. All subjects were followed for safety up to day 169.

Pharmacokinetic assays and analysis were conducted by unblinded scientists, who ensured that the results did not unblind individual treatment assignments.

The SAD study was conducted at seven centers in the United States, including one center that conducted the testing in all healthy subjects and six centers that performed the study in AD subjects. The MAD study was conducted at one center in the United States. Both studies were approved by the institutional review boards of the study centers.

Study populations

In the SAD study, subjects in cohorts 1–8 were healthy adults between 18 and 45 years with a body mass index between 18 and 32 kg/m².

Women were enrolled if they were of nonreproductive potential, defined as postmenopausal or had had hysterectomy, bilateral tubal ligation, or bilateral oophorectomy. Men were required to use highly effective methods of birth control during the study. Potential subjects were excluded if they had had a recent infection within 30 days before randomization; were at risk for tuberculosis; had a history of malignancy within 5 years; had a history of significant dermatological conditions; had Type 1 or Type 2 diabetes; had used cytotoxic or immunosuppressive medications or any investigational drug within 30 days or 5 half-lives (whichever was longer) before randomization; had used any other therapeutic monoclonal antibody; tested positive for drug or alcohol use at screening or before randomization; tested positive for HIV antibodies, hepatitis B surface antigen, or hepatitis C antibodies; or had used nicotine or tobacco-containing products within 6 months before randomization. Cohort 9 consisted of adult subjects between the age of 18 and 60 years with active moderate-to-severe AD at screening, as verified by the Hanifin and Rajka diagnostic criteria.¹⁵ The severity of dermatitis was confirmed by a Rajka and Langeland score of at least 4.5.¹⁶ The subjects had to have an Eczema Area and Severity Index (EASI) score of at least 15 and their AD-affected area had to be at least 10% of body surface area at screening and before receiving the study treatment. Subjects who had received phototherapy with possible effects on AD within 6 weeks before randomization or had used corticosteroids (not including topical, inhaled, or intranasal) within 4 weeks before randomization were also excluded.

In the MAD study, all subjects were healthy adults between the age of 18 and 45 years with body mass index of 18–32 kg/m². Women were of non-reproductive potential. Men were required to use highly effective methods of birth control during the study and for 5 months after the last dose of the study drug. The exclusion criteria were the same as those of the SAD study.

All subjects signed informed consent before entering the studies.

Pharmacokinetic analysis of tezepelumab

In the SAD study, blood samples were collected to measure the tezepelumab serum concentrations. Blood samples were collected at predose (within 30 minutes before dosing) and at prespecified time points from 15 minutes through 72 hours postdose on day 1 and from day 5 through day 113.

Serum pharmacokinetic parameters, including C_{max} , time at which t_{max} , AUC_{0-p} , and elimination half-life ($t_{1/2}$), after single dose SC or IV administration in healthy subjects and subjects with moderate- to- severe AD were estimated using noncompartmental methods.

In the MAD study, the blood samples were collected predose and at prespecified time points from day 1 through day 169 for pharmacokinetic analyses. Serum pharmacokinetic parameters of multiple-dose SC or IV tezepelumab were estimated using noncompartmental methods, including C_{max} , t_{max} , AUC_{τ} (area under the time-concentration curve over the dosing period), $t_{1/2}$ (terminal half-life), C_{max} accumulation ratio (first dose C_{max} /last dose C_{max}), and AUC accumulation ratio (first dose AUC_{τ} /last dose AUC_{τ}).

In both studies, the concentration of tezepelumab in human serum was measured using a validated enzyme-linked immunosorbent assay. Tezepelumab was captured by mouse anti-tezepelumab antibody and detected by horseradish peroxidase-labeled mouse antitezepelumab antibody. The lower limit of quantification/sensitivity of the assay was 10 ng/ml. In the SAD analysis, the accuracy was 2–7%, and the precision was 6–19%. In the MAD analysis, the accuracy was 2–7%, and the precision was 5–10%.

Safety and tolerability evaluations

In the SAD study, safety and tolerability were evaluated through treatment-emergent adverse events, clinically significant changes in vital signs, physical examinations, laboratory safety tests, and ECGs.

Blood samples were collected and analyzed for antitezepelumab antibodies, using an electrochemiluminescence-based immunoassay, before dosing and on days 29, 57, 85, and 113.

In the MAD study, treatment-emergent adverse events, clinical laboratory tests, ECGs, and vital signs were evaluated. Antitezepelumab antibodies were analyzed in blood samples collected before the first dose and at prespecified time points from days 28 through 169.

The immunoassay was the same for both the SAD and MAD studies and consisted of two steps: a screening assay to first detect the presence of antibodies to tezepelumab and a specificity assay, in which samples with a signal-to-noise value greater than the cut point (1.21) were then tested for specificity. The assay sensitivity is 20 ng/mL. The lower limit of reliable detection is 40 ng/mL. At the lower limit of reliable detection, the assay is able to tolerate 50 µg/mL of tezepelumab. At 500 ng/mL, the assay is able to tolerate at least 300 µg/mL of tezepelumab.

A validated non-cell-based receptor binding electrochemiluminescence bioassay was used to detect neutralizing anti-AMG 157 antibodies, in which the binding of human TSLP to the recombinant human TSLP receptor chimera was measured. All immunoassay positive post-dose samples were tested in the screening bioassay along with their corresponding predose samples, even if the latter did not test positive in the immunoassay. The assay sensitivity is 2 µg/mL. In the presence of 24.4 ng/mL of excess tezepelumab, this assay could detect 2 µg/mL of antitezepelumab neutralizing antibody.

Efficacy evaluation for single-dose tezepelumab in atopic dermatitis

In the SAD study, subjects with AD (cohort 9) were assessed for EASI score at screening and on days -1, 15, 29, 43, 57, 85, and 113. The EASI score is a composite index to measure the severity of AD and combines an assessment of the average intensity of four clinical signs (erythema, infiltration/papulation, excoriations, and lichenification) at four body areas (head/neck, upper extremities, trunk, and lower extremities) and the percentage of affected area for each of the four body areas.¹⁷ The percentages of subjects who achieved 50% and 75% improvement in EASI score from baseline and the change in EASI score from baseline were calculated for the tezepelumab and the placebo groups.

ACKNOWLEDGMENTS

Contributions of the following principal investigators for both studies are acknowledged as follows: Eric Simpson, MD (Oregon Health & Science University, School of Medicine, Portland, OR); Shawn Searle, MD (Dedicated Phase 1, Phoenix, AZ); Serena Mraz, MD (Solano Clinical Research, Dow Pharmaceutical Sciences, Inc, Vallejo, CA); David Fiorentino, MD (Stanford University, Redwood City, CA); Mark Christiansen, MD (Diablo Clinical Research, Walnut Creek, CA); Sunil Dhawan, MD (Center for Dermatology, Fremont, CA); Cindy Lamerson, MD (Nevada Center for Dermatology, Reno, NV). Jun Yan, PharmD (supported by Amgen Inc.) provided medical writing support. Amgen Clinical Pharmacology, Modeling & Simulation provided support in data analysis and graphic presentation.

FUNDING

The described studies were funded by Amgen Inc.

CONFLICT OF INTEREST STATEMENT

J.R.P., J.T.S., L.C., and C.D. were employees of Amgen at the time the studies were conducted.

AUTHOR CONTRIBUTIONS

J.R.P., J.T.S., L.C., and C.D. wrote the manuscript; J.R.P., L.C., and C.D. designed the research; J.R.P. and C.D. performed the research; J.R.P., J.T.S., L.C., and C.D. analyzed the data.

DATA SHARING STATEMENT

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

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