

A Randomized, Controlled, Phase 2 Study of AMG 317, an IL-4R α Antagonist, in Patients with Asthma

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Rationale: IL-4 and IL-13 share many biological functions important in the development of allergic airway inflammation and are implicated in the pathogenesis of asthma. AMG 317 is a fully human monoclonal antibody to IL-4R α that blocks both IL-4 and IL-13 pathways.

Objectives: To evaluate efficacy and safety of AMG 317 in patients with moderate to severe asthma.

Methods: In this phase 2, randomized, double-blind, placebo-controlled study, patients received weekly subcutaneous injections of placebo or AMG 317 (75–300 mg) for 12 weeks, followed by a 4-week follow-up period. The primary endpoint was change from baseline at Week 12 in Asthma Control Questionnaire (ACQ) symptom score.

Measurements and Main Results: Mean ACQ change (SE) was -0.49 (0.09) in placebo ($n = 74$), and -0.43 (0.11), -0.58 (0.12), and -0.70 (0.09) in the AMG 317 75 mg ($n = 73$), 150 mg ($n = 73$), and 300 mg ($n = 74$) groups, respectively (treatment effect $P = 0.25$). No statistically significant differences were observed in the secondary endpoints. Numerical decreases in number of and time to exacerbations were noted in patients receiving AMG 317 150 mg and 300 mg. Preplanned analyses by tertile of baseline ACQ revealed that patients with higher baseline ACQ scores (≥ 2.86) were more likely to respond to AMG 317. Serious adverse events were reported in three patients, each noted as not related to study drug.

Conclusions: AMG 317 did not demonstrate clinical efficacy across the overall group of patients. Clinically significant improvements were observed in several outcome measures in patients with higher baseline ACQ scores. AMG 317 was safe and well tolerated in this study population.

Clinical trial registered with www.clinicaltrials.gov (NCT 00436670).

Keywords: IL-4; IL-13; Asthma Control Questionnaire

Among the chemokines and cytokines believed to contribute to asthma pathogenesis (1), IL-4 and IL-13 appear to be important to a number of the mechanisms relevant in this disease state (2). IL-4 and IL-13 mediate IgE production, mucus hypersecretion, airway hyperresponsiveness, and inflammatory cellular influx (3–5). Prior studies have evaluated the efficacy of medications that inhibited the activity of IL-4 alone in patients with asthma (6, 7). These studies yielded mixed results, and it has been speculated that concomitant inhibition of IL-4 and IL-13 may

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Inhibition of IL-4 and IL-13 via the common receptor chain IL-4R α has been proposed as promising in the treatment strategy for asthma.

What This Study Adds to the Field

This was the first clinical trial of a new therapeutic agent, AMG 317, for asthma that inhibits the IL-4 and IL-13 pathways. In the overall study, the primary and key secondary endpoints were not met, although decreases in number and time to exacerbations were noted in the higher AMG 317 dose groups. In addition, AMG 317 demonstrated clinically significant levels of activity in a subset of patients with the most uncontrolled or symptomatic asthma.

be required to adequately block the biologic effects of this pathway.

The IL-4 receptor α chain (IL-4R α) is used by both IL-4 and IL-13, providing a single target to affect the downstream signals for both cytokines (8). AMG 317 is a fully human monoclonal IgG2 antibody that binds with high affinity ($K_d = 1.8 \times 10^{-10}$ M) to IL-4R α . AMG 317 potentially blocks the biologic activities of both IL-4 and IL-13, and has been shown to have important effects on inflammation *in vitro*. Given the potential of this molecule to potentially suppress the effects of IL-4 and IL-13, we sought to examine the safety and efficacy of AMG 317 in patients with moderate to severe atopic asthma. Some of the results of this study have been previously reported at the American Academy of Allergy, Asthma and Immunology 2009 Annual Meeting (9).

METHODS

Patients

Patients aged 18 to 65 years, with moderate to severe asthma, and receiving stable doses of inhaled corticosteroids (ICS) (≥ 200 to $\leq 1,000$ μ g/d fluticasone or equivalent) were eligible for enrollment. Key inclusion criteria included Asthma Control Questionnaire (ACQ) score 1.5 or higher, percentage of predicted FEV₁ greater than or equal to 50% to less than or equal to 80% at screening, and greater than or equal to 12% reversibility over baseline FEV₁ with β -agonist inhalation. Key exclusion criteria included an acute asthma exacerbation within 3 months and history of any chronic pulmonary condition other than asthma.

Study Design

In this phase 2, randomized, double-blind, placebo-controlled study, patients with moderate to severe asthma received one of three doses of

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AMG 317 (75 mg, 150 mg, or 300 mg) or placebo subcutaneously once weekly for 12 weeks. After the screening visit, patients completed two weekly run-in visits and then were randomly assigned 1:1:1:1 to the four treatment groups, stratified by previous use of long-acting β -agonists. Assignment to treatment group was based on a stratified randomization schedule via an Interactive Voice Response System. A 4-week follow-up period followed the 12-week treatment period.

The primary endpoint was the change in ACQ symptom score from baseline to Week 12. Key secondary endpoints included changes in pre- and post-bronchodilator FEV₁, morning and evening peak expiratory flow rates (PEFR), diurnal and interday variation of PEFR, rescue β -agonist use, and Asthma Quality of Life Questionnaire score. Asthma exacerbations were also evaluated, and two definitions were used: (1) need for systemic steroids, or (2) need for systemic steroids or doubling of ICS dose. The hypothesis tested was that change from baseline ACQ score at Week 12 would be greater in patients receiving AMG 317 300 mg compared with placebo.

Exploratory endpoints included changes in serum IgE levels, sputum eosinophils, and fractional exhaled nitric oxide (FeNO). Safety evaluations included incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs).

Statistical Analyses

Planned enrollment was approximately 300 patients (75 per treatment group). This sample size assumed a mean difference between the highest-dose group and placebo of 0.5 in the change from baseline in ACQ and an SD of 1. This sample size was designed to have greater than 80% power to detect a statistically significant difference between the highest-dose group and placebo at an α level of 0.05 for the primary endpoint. The anticipated dropout rate was approximately 10%.

Categorical variables were summarized using the number and percentage of patients; ordinal variables were summarized using the median; continuous variables were summarized using mean, SE or SD, median, minimum, maximum, and number of patients. Patient stratification at randomization was based on previous use of long-acting β -agonists.

Efficacy analyses were performed using the intent-to-treat population. Safety analyses were conducted for all patients who received at least one dose of investigational product. Covariates included corticosteroid dose, baseline FEV₁, percentage of predicted FEV₁, body mass

index (BMI), and baseline ACQ. Missing data were imputed using the last-observation-carried-forward method. A preplanned analysis of efficacy by baseline tertiles of disease severity was performed.

In *post hoc* analyses to identify variables that predicted ACQ improvement, all baseline characteristics (sex, age, race, weight, height, BMI, previous use of a long-acting β -agonist, ICS dose, rescue medication use, atopic dermatitis status, allergic rhinitis status, prebronchodilator FEV₁, post-bronchodilator FEV₁, percentage of predicted FEV₁, reversibility, disease duration, ACQ, Asthma Quality of Life Questionnaire, morning and evening PEFR, total symptom score, nighttime symptoms, shortness of breath, chest tightness, cough, wheezing, and IgE levels) were analyzed using linear and logistic regression models and regression tree analysis. Efficacy data were analyzed using SAS v9.1.3 software (SAS Institute Inc., Cary, NC). Regression Tree analysis was performed using CART version 5.0 (Salford Systems, San Diego, CA).

RESULTS

Baseline demographics and disease characteristics are shown in Table 1. More than half of the patients were women (58%), most were white (71%), and the mean (SD) age was 41 (11) years (range, 18–64 yr). Baseline demographics were generally balanced across treatment groups. However, the mean (SD) BMI of 31 (8) kg/m² (range, 18–69 kg/m²) was significantly higher in the AMG 317 groups compared with placebo ($P = 0.003$). In pairwise comparisons, the mean (SD) BMI in the AMG 150 mg was significantly higher than placebo ($P = 0.005$).

Baseline disease characteristics were also generally balanced across treatment groups and were representative of patients with inadequately controlled moderate to severe asthma. The mean (SD) duration of asthma was 26 (14) years. The mean (SD) ACQ score at baseline was 2.5 (0.7). The total diary symptom score was significantly lower in the placebo group compared with the AMG 317 groups overall ($P = 0.033$) and in pairwise comparisons to the 150 mg group (mean score [SD] of 4.57 [2.69]; $P = 0.012$) and the 300 mg group (mean score [SD] of 4.60 [2.49]; $P = 0.012$). Overall, the baseline disease severity

TABLE 1. BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

	AMG 317			
	Placebo (N = 74)	75 mg QW (N = 73)	150 mg QW (N = 73)	300 mg QW (N = 74)
Sex, n female (%)	41 (55)	45 (62)	44 (60)	40 (54)
Race, n (%)				
White	46 (62)	57 (78)	54 (74)	53 (72)
Black/African American	18 (24)	11 (15)	9 (12)	14 (19)
Hispanic/Latino	10 (14)	3 (4)	9 (12)	5 (7)
Other	0 (0)	2 (3)	1 (1)	2 (3)
Age, yr, mean (minimum, maximum)	39.5 (19, 63)	43.2 (19, 63)	41.3 (22, 64)	41.4 (18, 59)
BMI, kg/m ² , mean (SD)	29.6 (7.3)	29.1 (7.0)	33.4 (8.4)	31.8 (8.7)
Duration of disease, yr, mean (minimum, maximum)	26.4 (3, 62)	26.0 (1, 54)	26.0 (4, 57)	25.1 (2, 54)
ACQ, mean score (SD)	2.50 (0.63)	2.46 (0.70)	2.58 (0.76)	2.62 (0.72)
AQLQ, mean score (SD)	4.75 (0.99)	4.59 (1.12)	4.43 (1.22)	4.43 (1.05)
All rescue β -agonist use, puffs/d, mean (SD)	4.2 (4.6)	3.4 (3.0)	3.7 (3.7)	3.4 (3.0)
ICS dose*, μ g/d, median (minimum, maximum)	440 (176, 1,000)	440 (176, 880)	440 (90, 1,100)	440 (100, 1,000)
A.M. peak flow, L/min, mean (SD)	351.4 (104.6)	361.4 (106.9)	390.3 (122.6)	373.4 (95.2)
Total diary symptom score, mean (SD)	3.46 (2.17)	3.98 (2.00)	4.57 (2.69)	4.60 (2.49)
Prebronchodilator FEV ₁ , L, mean (SD)	2.26 (0.65)	2.33 (0.68)	2.37 (0.62)	2.34 (0.68)
Predicted prebronchodilator FEV ₁ , %, mean (SE)	67.1 (1.3)	69.8 (1.5)	69.0 (1.3)	67.4 (1.6)
Reversibility,† %, mean (SD)	30.8 (15.9)	26.7 (12.7)	21.5 (9.3)	24.6 (12.6)
Total serum IgE, IU/ml, mean (SD)	404 (573)	340 (724)	497 (987)	566 (1,526)
Sputum eosinophils, cells $\times 10^9$, median/mean (SD)‡	1.8/3.8 (6.2)	2.7/3.0 (2.2)	0.6/0.7 (0.3)	0.7/5.4 (10.9)
FeNO, ppb, median/mean (SD)‡	29.5/35.6 (24.2)	26.0/36.2 (31.5)	17.5/19.0 (4.6)	10.6/17.8 (16.8)

Definition of abbreviations: ACQ = Asthma Control Questionnaire; A.M. = morning; AQLQ = Asthma Quality of Life Questionnaire; BMI = body mass index; FeNO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; QW = once weekly.

* ICS dose is fluticasone propionate equivalents.

† Mean reversibility of patients who demonstrated reversibility during screening (excluding those who reported historical reversibility).

‡ Exploratory outcome substudies with 22 patients in the sputum eosinophil substudy and 27 patients in the exhaled nitric oxide substudy with baseline values.

in the patients in this study was consistent with inadequately controlled moderate to severe asthma in terms of ACQ, FEV₁, and other clinical characteristics.

A total of 294 patients enrolled in the study from 52 U.S. sites and were randomly assigned to a treatment group (Figure 1). Two patients did not receive investigational product; one patient had an abnormal laboratory value and one patient withdrew consent. The remaining 292 patients received placebo (n = 74), AMG 317 75 mg (n = 73), AMG 317 150 mg (n = 73), or AMG 317 300 mg (n = 72). Two hundred forty-four (84%) patients completed Week 12 (treatment phase) of the study; 243 (83%) completed the study.

There were 294 patients in the intent-to-treat analysis subset (all randomized patients) and 292 patients in the safety analysis subset (all patients who received at least one dose of investigational product). A total of 243 (83%) patients completed the study.

Efficacy

Change in ACQ scores by treatment groups during the study are shown in Figure 2A. All groups improved from baseline. At Week 12, the change in ACQ score in the AMG 317 dose groups (mean [SE] change of, -0.43 [0.11], -0.58 [0.12], and -0.70 [0.09] in patients receiving AMG 317 75 mg, 150 mg, and 300 mg, respectively) was not significantly greater compared with placebo (mean [SE] change of -0.49 [0.09]; $P = 0.25$) (Table 2). Pairwise comparisons of change in ACQ scores at Week 12 from individual AMG 317 dose groups showed no significant difference over placebo. Similarly, there were no significant differences in the secondary endpoints (Table 2). The changes from baseline to Week 12 in prebronchodilator FEV₁ showed a trend toward significance in the overall AMG 317 group (least square means = -0.02 L for placebo; -0.06 L for AMG 317 75 mg; 0.01

L for 150 mg; 0.09 L for 300 mg; $P = 0.098$) and in the AMG 317 300 mg group (difference between least square means [95% confidence interval] = 0.112 [-0.012, 0.235]; $P = 0.076$) compared with placebo (Figure 2B). Although BMI was found to be significantly lower in the placebo group compared with the AMG 317 150 mg group at baseline, in this data set, BMI did not appear to correlate with efficacy in the covariate analyses. Stratification of patients by previous use of long-acting β -agonists had no apparent effect on the study outcomes.

Asthma exacerbations requiring systemic steroids were more common and time to onset of exacerbation was shorter in the placebo (14%) and AMG 317 75 mg (15%) groups than in patients in the AMG 317 150 mg (7%) and 300 mg groups (7%) (Figure 3). Similarly, the incidence of asthma exacerbations requiring systemic steroids or a doubling of ICS were higher in the placebo (15%) and AMG 317 75 mg (18%) groups than in the AMG 317 150 mg (8%) and 300 mg (8%) groups. This apparent treatment effect on reduction in exacerbations was limited by the small number of events, with not enough power to detect a difference.

The mean (median) decrease in levels of total serum IgE in an exploratory analysis was 28 (0) IU/ml at 12 weeks for patients receiving placebo. In patients receiving AMG 317, mean (median) decreases were 24 (6.0), 46 (12.5), and 282 (39.0) IU/ml in the 75 mg, 150 mg, and 300 mg groups, respectively, after 12 weeks of treatment. Changes in IgE did not correlate with changes in efficacy outcomes, such as ACQ and FEV₁. In a small sputum substudy (n = 18), patients receiving AMG 317 75 mg (n = 6), 150 mg (n = 3), and 300 mg (n = 5) had a median (mean) decrease in sputum eosinophil counts of 0.6% (0.8%), 0.4% (0.4%), and 0.0% (4.7%), respectively. In the placebo group (n = 4), sputum eosinophil counts worsened (increased)

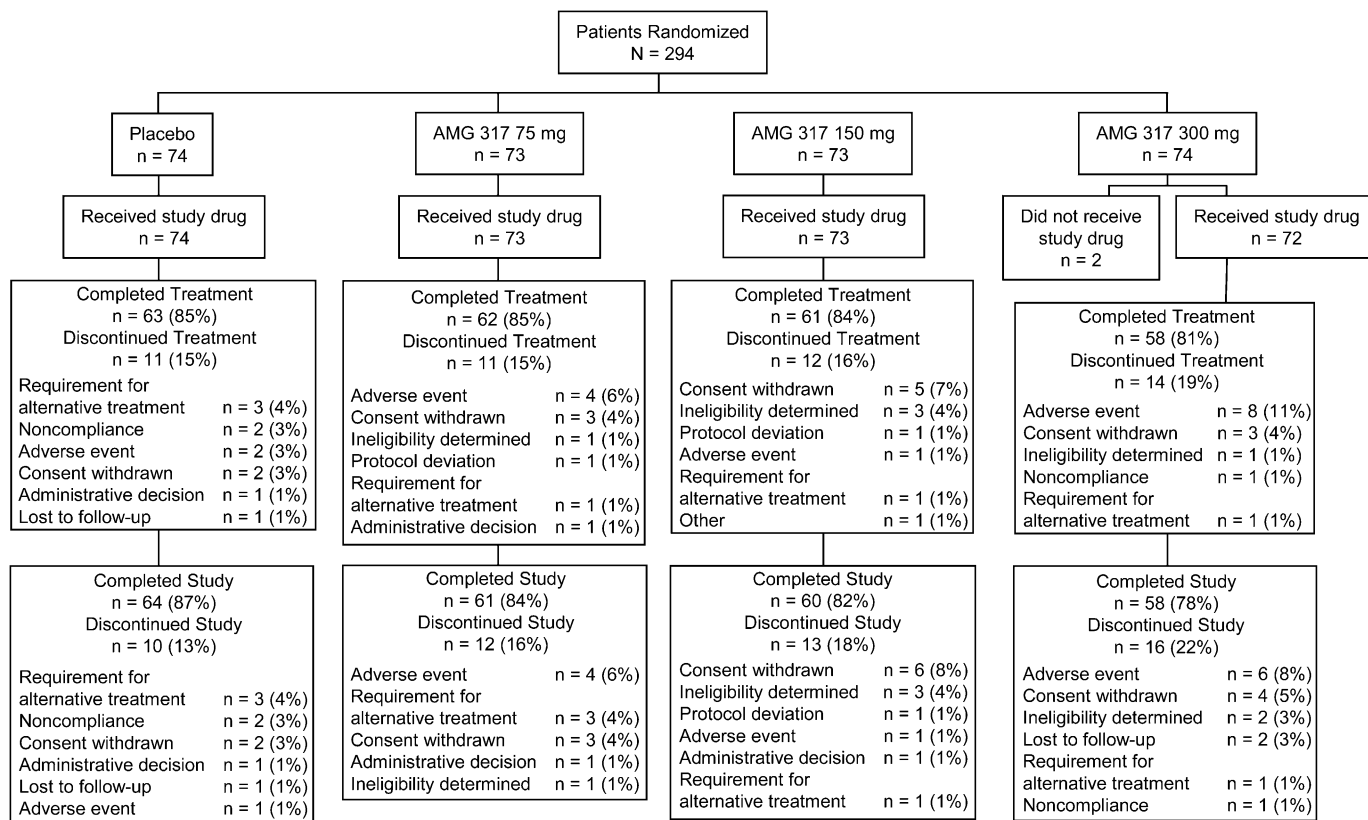


Figure 1. Patient flow.

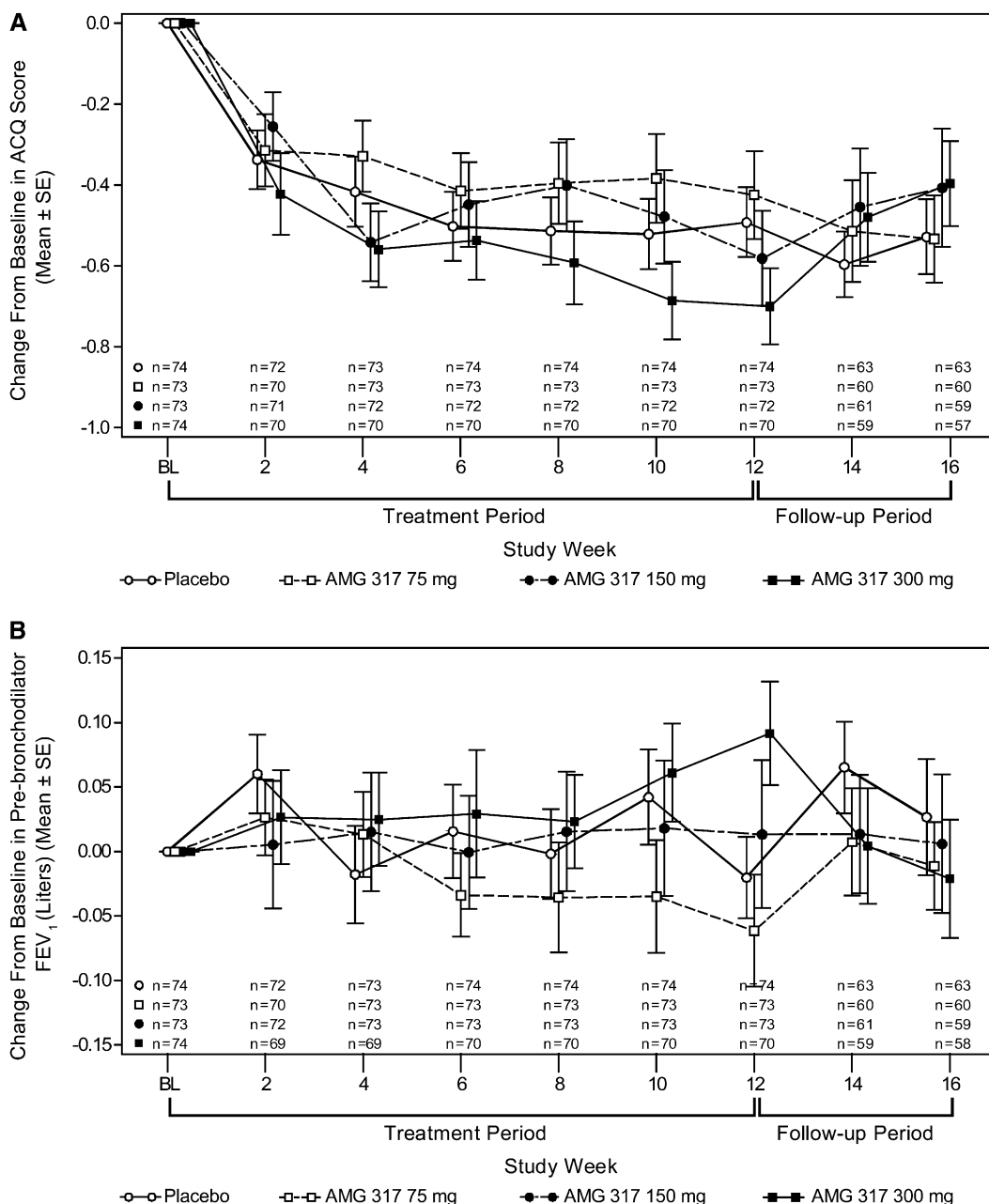


Figure 2. Changes in efficacy outcomes in all patients. Changes in (A) ACQ score and (B) prebronchodilator FEV₁ from baseline through 12 weeks of treatment and 4 weeks of follow-up are shown for patients receiving placebo, AMG 317 75 mg, 150 mg, and 300 mg.

from baseline, with a median (mean) change of -2.7% (-11.3%). In a small substudy of FeNO ($n = 23$), patients receiving AMG 317 75 mg ($n = 9$), 150 mg ($n = 4$), and 300 mg ($n = 5$) had a median (mean) increase of 1.1 (9.5), 4.3 (3.7), and 5.0 (12.7) ppb, respectively. In the placebo group, ($n = 5$), FeNO increased by a median (mean) of 13.1 (31.4) ppb.

In the preplanned analysis of efficacy by baseline tertiles of ACQ, patients with the top tertile of baseline ACQ scores (ACQ score ≥ 2.86) demonstrated the greatest response to treatment. Mean changes in ACQ scores from baseline to Week 12 were greater in patients receiving AMG 317 (mean change [SE] of -1.09 [0.27], -1.03 [0.20], and -1.28 [0.14] for 75 mg, 150 mg, and 300 mg groups, respectively) than in patients receiving placebo (mean [SE] improvement of -0.76 [0.23]) (Table 3). Improvements occurred within the first 2 weeks of treatment and were maintained until the end of the treatment period at Week 12. ACQ improvement at Week 12 in the AMG 317 300 mg group approached a minimally important difference

(MID) of 0.5 relative to placebo (10) (Figure 4A). The mean change from baseline in prebronchodilator FEV₁ values indicated a dose response (Figure 4B). In the AMG 317 300 mg group, the mean FEV₁ values were clearly improved over placebo, whereas in the other AMG 317 groups, slight improvements were observed. The difference in improvement between the placebo and AMG 317 300 mg group at Week 12 (0.34 L) was greater than the MID (0.23 L) (11). Patients receiving AMG 317 300 mg had the greatest change from baseline in weekly morning PEFR at Week 12. The change from baseline in the top tertile of patients receiving AMG 317 300 mg (22 L/min) achieved the minimum clinically significant change in peak flow of approximately 20 L/min (11) (Figure 4C). In an analysis of patients in the top ACQ tertile, the decrease in rescue β -agonist use was greater in the placebo group (2.4 puffs/d) than in the AMG 317 groups (0.5, 0.8, and 1.5 puffs/d in the 75 mg, 150 mg, and 300 mg groups, respectively). However, one outlier patient who went from 29 puffs/d at baseline to 3 puffs/d at Week 12

TABLE 2. EFFICACY OUTCOMES AT WEEK 12 IN ALL PATIENTS

	AMG 317			
	Placebo (N = 74)	75 mg QW (N = 73)	150 mg QW (N = 73)	300 mg QW (N = 74)
Mean change in ACQ, score (SE)	−0.49 (0.09)	−0.43 (0.11)	−0.58 (0.12)	−0.70 (0.09)
95% CI	−0.32, −0.66	−0.21, −0.64	−0.35, −0.82	−0.52, −0.89
Mean change in AQLQ, score (SE)	0.64 (0.09)	0.52 (0.15)	0.71 (0.16)	0.74 (0.17)
Mean change in frequency of rescue β -agonist use, puffs/d (SE)	−1.1 (0.6)	−0.5 (0.3)	−0.8 (0.4)	−0.8 (0.4)
Mean change in A.M. PEFR, L/min (SE)	−7.9 (5.1)	−9.4 (6.3)	−10.3 (6.4)	6.9 (6.0)
Mean change in P.M. PEFR, L/min (SE)	−8.8 (5.7)	−6.5 (6.6)	−3.9 (4.9)	2.3 (6.0)
Mean change in prebronchodilator treatment FEV ₁ , L (SE)	−0.02 (0.03)	−0.06 (0.04)	0.01 (0.06)	0.09 (0.04)
95% CI	−0.08, 0.04	−0.15, 0.03	−0.10, 0.13	0.01, 0.17
Mean change in predicted prebronchodilator treatment FEV ₁ , % (SE)	−1.0 (1.0)	−1.4 (1.3)	1.0 (1.7)	2.6 (1.1)
Median % asthma symptom-free d (minimum, maximum)	17 (1, 99)	27 (1, 92)	16 (1, 95)	25 (1, 97)
Mean total change in daily asthma symptoms score (SE)	−1.0 (0.2)	−1.2 (0.3)	−1.8 (0.3)	−1.7 (0.3)
Median/mean change in IgE, IU/ml (SE)	0.0/−28 (28)	−6.0/−24 (21)	−12.5/−46 (26)	−39.0/−282 (146)

Definition of abbreviations: ACQ = Asthma Control Questionnaire; A.M. = morning; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; PEFR = peak expiratory flow rate; P.M. = evening; QW = once weekly.

accounted for 50% improvement in the placebo group (no other patients had ≥ 20 puffs/d at baseline). Excluding this patient, the frequency of β -agonist use decreased by a mean of 0.1, 0.4, and 1.2 puffs/d in patients with severe disease receiving AMG 317 75 mg, 150 mg, and 300 mg, respectively, compared with placebo. The minimum patient perceivable difference is a change of 0.8 puffs/d (11).

In the subgroup analysis of patients in the top tertile of baseline ACQ, the number of patients with at least one asthma exacerbation (requiring systemic steroids or a doubling of ICS) was 5, 4, 2, and 1 in the placebo, AMG 317 75 mg, AMG 317 150 mg, and AMG 317 300 mg groups, respectively. Although the sample size in the subgroup analysis was small, similar trends in the incidence of asthma exacerbations were observed in both the overall and the subgroup analyses.

Post hoc regression analyses were performed using baseline demographics and disease characteristics to identify factors that predicted change in ACQ score at Week 12. Results indicated that a higher ACQ score at baseline consistently predicted the best ACQ response by logistic regression analysis ($c = 0.752$), linear regression analysis ($R^2 = 0.1599$), and regression tree analysis. Analyses of change in ACQ by baseline reversibility demonstrated that patients with higher baseline reversibility ($\geq 20\%$) had greater improvements in ACQ scores when compared with placebo.

Safety

Overall, AEs were reported for more patients in the AMG 317 dose groups (83%) than in the placebo group (73%) (Table 4). The incidence of AEs was numerically higher in patients receiving AMG 317 compared with placebo. This increase was largely driven by injection site reactions in the AMG 317 dose groups. Only three patients had SAEs (cholelithiasis in two patients in the AMG 317 75 mg group and irregular heart rate and panic attack in one patient in the placebo group). These SAEs were judged to be unrelated to treatment with AMG 317 and no dose-related trend was observed. No deaths occurred during the study period.

Twelve patients withdrew from the study because of an AE, including one patient in the placebo group (1%) and 11 patients (5%) receiving AMG 317. Across treatment groups, AEs most commonly causing study withdrawal included asthma (one patient receiving placebo, one each in the AMG 317 75 mg and 150 mg groups, and two patients receiving AMG 317 300 mg) and injection site pain (two patients in the AMG 317 300 mg group). The remaining AEs leading to study withdrawal included upper respiratory infection ($n = 1$); nausea, vomiting, and headache ($n = 1$); urticaria ($n = 1$); fatigue and cognitive disturbance ($n = 1$); and injection site edema and erythema ($n = 1$). Investigational product was withdrawn because of an AE in 15 patients,

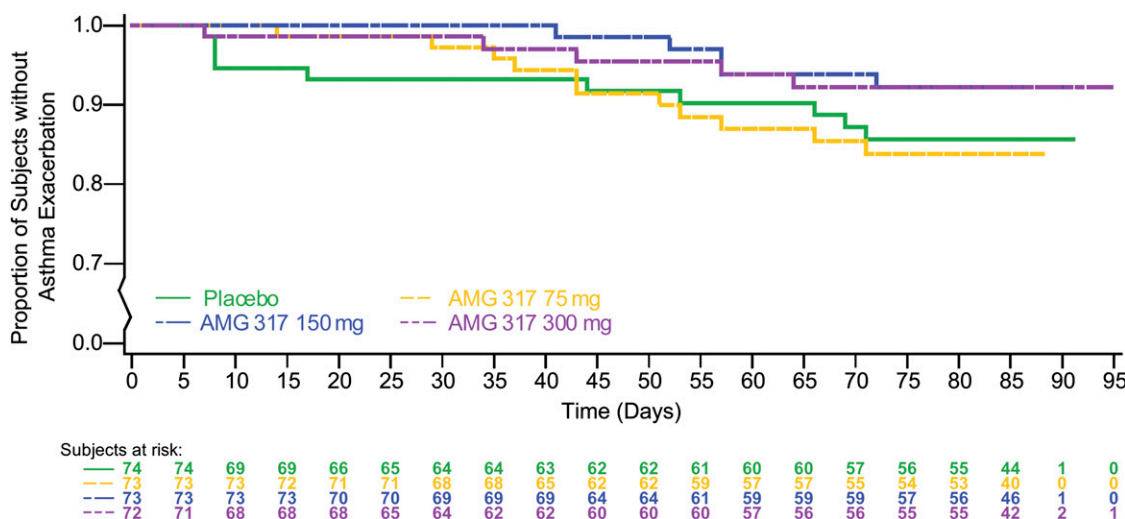


Figure 3. Time to asthma exacerbation. Kaplan-Meier plots depicting time to exacerbation, defined as need for systemic steroids or doubling of inhaled corticosteroids (ICS) dose, are shown for patients receiving placebo, AMG 317 75 mg, 150 mg, or 300 mg.

TABLE 3. EFFICACY OUTCOMES AT WEEK 12 IN PATIENTS WITH BASELINE ACQ SCORE GREATER THAN OR EQUAL TO 2.86

	AMG 317			
	Placebo (N = 18)	75 mg QW (N = 17)	150 mg QW (N = 24)	300 mg QW (N = 24)
Mean change in ACQ, score (SE)	−0.76 (0.23)	−1.09 (0.27)	−1.03 (0.20)	−1.28 (0.14)
Mean change in AQLQ, score (SE)	0.89 (0.25)	1.38 (0.38)	0.95 (0.26)	1.29 (0.36)
Mean change in A.M. PEFR, L/min (SE)	−8.4 (14.9)	−5.0 (12.6)	−5.5 (11.7)	13.8 (11.8)
Mean change in P.M. PEFR, L/min (SE)	−8.3 (17.8)	5.9 (19.3)	−0.1 (7.5)	21.0 (10.2)
Mean change in prebronchodilator treatment FEV ₁ , L (SE)	−0.07 (0.07)	0.10 (0.06)	0.09 (0.10)	0.26 (0.08)*
Mean change in predicted prebronchodilator treatment FEV ₁ , % (SE)	−2.8 (2.5)	2.8 (1.7)	3.5 (2.8)	7.4 (2.2)
Mean change in frequency of use of rescue β -agonists, puffs/d [†] (SE)	−2.40 (2.33)	−0.48 (0.96)	−0.82 (1.10)	−1.52 (0.60)
Median % asthma symptom-free d (minimum, maximum)	17 (1, 51)	38 (2, 78)	18 (1, 55)	31 (1, 79)
Mean total change in daily asthma symptoms score (SE)	−1.5 (0.8)	−2.1 (0.7)	−2.6 (0.7)	−2.5 (0.5)
Median / Mean change in IgE, IU/ml (SE)	1.5/−23.5 (55.9)	−6.5/−9.4 (7.9)	−14.5/−25.5 (63.0)	−56.0/−113.3 (32.5)

Definition of abbreviations: ACQ = Asthma Control Questionnaire; A.M. = morning; AQLQ = Asthma Quality of Life Questionnaire; PEFR = peak expiratory flow rate; P.M. = evening; QW = once weekly.

* $P < 0.01$ by pairwise comparison.

[†] One outlier patient (placebo group) was excluded from the analysis. The patient had 29 puffs/d at baseline and 3 puffs/d at Week 12. All other patients had ≤ 20 puffs/d at baseline.

including 2 placebo patients (3%) and 13 patients in the AMG 317 groups (6%).

Of 292 patients who had received investigational product, 1 (1%) patient receiving placebo, and 6 (8%), 9 (12%), and 2 (3%) patients receiving AMG 317 75 mg, 150 mg, and 300 mg, respectively, tested positive for neutralizing antibodies against AMG 317. No SAEs were reported in patients with neutralizing antibodies.

DISCUSSION

The primary endpoint of the study, change in ACQ from baseline to Week 12, was not met; however, evidence of biologic effect with dose-responsive reduction in IgE and clinical activity was noted, especially in the AMG 317 300-mg dose group. All groups, including patients receiving placebo, demonstrated improvements in ACQ from baseline. Patients receiving the highest doses of AMG 317 experienced fewer exacerbations than patients receiving placebo or the lowest dose of AMG 317. Patients in the ACQ baseline top tertile (ACQ ≥ 2.86) who received AMG 317 300 mg demonstrated a consistent trend of more clinically meaningful effects in change in ACQ, FEV₁, and morning peak flow. AMG 317 was generally safe and well tolerated at all doses administered during the study.

Post hoc regression analyses were performed to evaluate relationships, if any, with response across all baseline and demographic characteristics. Results demonstrated that a higher baseline ACQ score correlated with the best response, suggesting that AMG 317 was more effective in the most symptomatic patients. Because of the *post hoc* nature of the regression analyses, these results should be interpreted with caution. Although the reasons for lack of significant differences in outcome measures between AMG 317 and placebo are unclear, a number of possibilities can be speculated: dosages lower than 300 mg were inadequate, the mechanism of action of AMG 317 (dual inhibition of IL-4 and IL-13) was not optimal to alleviate asthma symptoms, the duration of treatment was insufficient, or the patient phenotypes were not appropriate to realize a significant benefit.

The doses of AMG 317 selected for this study were based on the pharmacokinetic and pharmacodynamic data as well as safety data from the phase 1 studies. In these studies, the pharmacokinetics supported weekly dosing. The lowest dose (75 mg) was selected such that the steady-state minimum observed concentration values remained below the concentration required for 90% maximum inhibition of chemokine release as modeled from the phase 1 study. The targeted clinical

dose (150 mg) was selected such that the steady-state minimum observed concentration values were above the concentration required for 90% maximum inhibition. Based on the doses tested in the phase 1 studies, AMG 317 300 mg represented the highest subcutaneous dose that allowed maintenance of a significant safety margin. The 300 mg dosage tested in this study may have been suboptimal to realize maximum clinical benefit. In general, results of pharmacodynamic assessments from peripheral blood are not necessarily applicable to the ultimate tissues of interest and may not predict clinical efficacy.

Pitrakinra, an anti-IL-4 variant that targets allergic Th2 inflammation by inhibiting the IL-4 and IL-13 pathways, was tested in patients with mild asthma in an allergen challenge model (2–5, 12). Patients receiving pitrakinra had a statistically significant smaller decrease in FEV₁ over 4- to 10-hour post-allergen challenge. In contrast with the results of our study, a significant decrease in FeNO was reported in patients receiving pitrakinra; however, the results from our substudy may be limited because of the small sample size. The allergen challenge data in humans, along with preclinical data in mice, and the *ex vivo* whole blood assays taken together suggest that blocking the IL-4/IL-13 pathways may offer clinical benefit in asthma (3, 5). However, the ability to predict clinical response based on pharmacodynamic measures and experimental models alone is limited.

Immunomodulation of chronic inflammatory pathways may require treatments of longer duration to maximize effects. Whether treatments of longer duration than were tested in this study may have demonstrated greater clinical efficacy is speculative.

Asthma is known to be a highly heterogeneous disease (13–15) and selection of the appropriate patient population for specific interventions presents a challenge. The preplanned tertile analysis of baseline characteristics in this study identified a subset of patients with more symptomatic disease at baseline who were more likely to respond to treatment with AMG 317. Patients with higher reversibility appeared to have a better response to AMG 317. Similar observations were made in a study of golimumab, an antibody against tumor necrosis factor- α . Greater efficacy was noted in a subset of patients with higher reversibility, but no significant improvements in FEV₁ or incidence of severe exacerbations were observed in the overall population of patients with severe persistent asthma (16). These data suggest that heterogeneity of the study population contributes to the overall clinical response and that certain patient phenotypes may be responsive to IL-4/IL-13 inhibition.

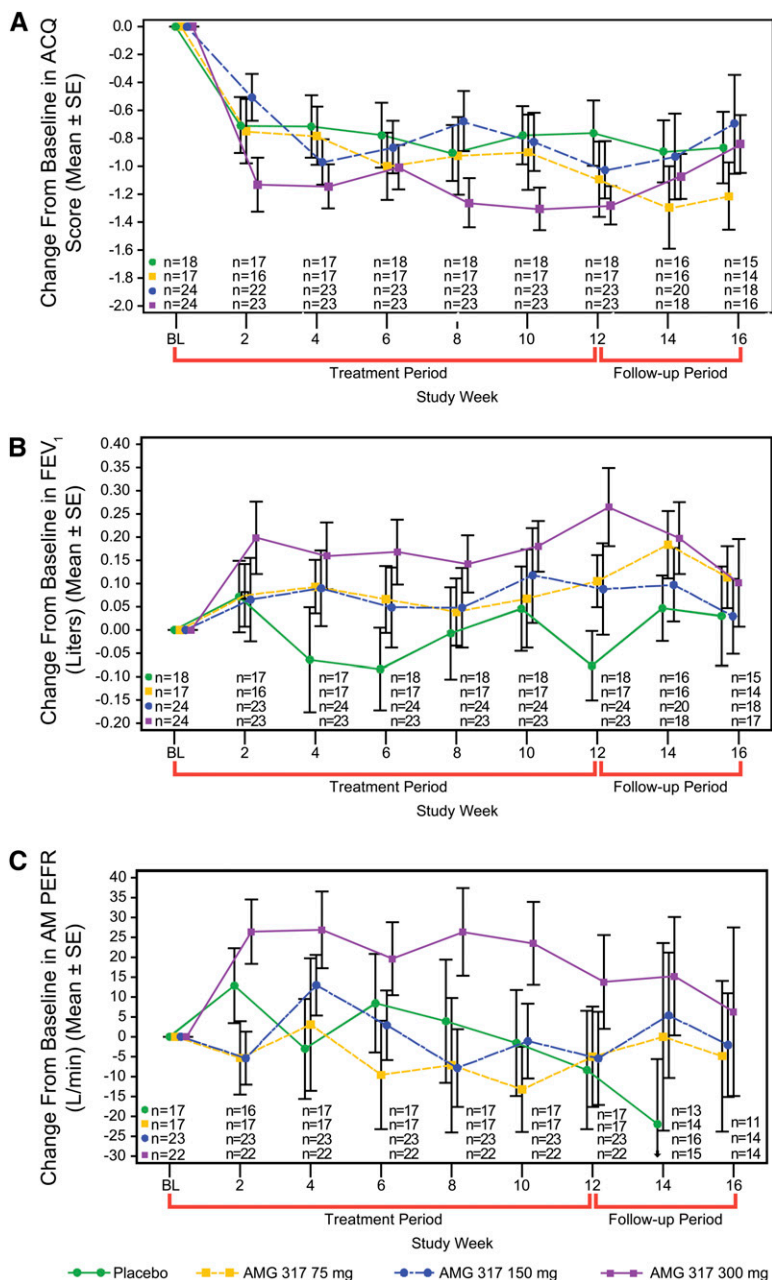


Figure 4. Changes in efficacy outcomes in the most symptomatic patients. Changes in (A) ACQ score (B) FEV₁, and (C) morning peak expiratory flow rate (PEFR) in patients with a baseline ACQ score ≥ 2.86 are shown for patients receiving placebo, AMG 317 75 mg, 150 mg, and 300 mg.

This study was the first trial of this magnitude of a new agent to treat asthma in the clinical efficacy setting that used change in ACQ as the primary endpoint. The ACQ is a validated, robust instrument that can distinguish between patients with controlled or uncontrolled asthma (17–19) and is therefore useful to understand clinical benefit. Importantly, the ACQ is a composite endpoint that assesses several domains of a patient's asthma control, including asthma symptoms, rescue β -agonist use, and lung function. ACQ has been used as a secondary endpoint in recent clinical trials (12, 20, 21), and the American Thoracic Society and the European Respiratory Society have recently recommended consideration of composite scores such as the ACQ as the primary endpoint in asthma clinical trials (22).

The patient population enrolled in the trial had sufficient range for improvement across the endpoints that were evaluated, demonstrating the strength of the study. The range of disease severity and reversibility allowed the identification of a subset of patients who showed the best response to treatment.

However, the sample size in the exploratory analyses limited the ability to demonstrate statistical significance.

There were stronger indications of clinical and biological activity with AMG 317 in a subset of patients with the most symptomatic disease at baseline. ACQ scores, FEV₁, and peak flow either achieved or approximated the MID for these measures. Improvements in efficacy that occurred in the 12-week treatment period declined in Weeks 13 through 16 after withdrawal of treatment. In addition, the dose-responsive decreases observed in serum IgE levels were consistent with AMG 317 activity across dose groups during study treatment.

In conclusion, AMG 317 was safe and well tolerated in this phase 2, randomized, controlled study in patients with moderate to severe asthma. Although the efficacy outcomes were not met for the study population at large, evidence of clinical and biologic effect with a dose response was observed. This study was not powered to evaluate asthma exacerbations; however, trends favoring lower number of asthma exacerbations in the

TABLE 4. SUMMARY OF ADVERSE EVENTS AND INCIDENCE OF ADVERSE EVENTS OCCURRING IN 5% OR MORE PATIENTS

	AMG 317			
	Placebo (N = 74)	75 mg QW (N = 72)	150 mg QW (N = 73)	300 mg QW (N = 72)
Patients reporting an adverse event*, no. (%)				
All adverse events	54 (73)	61 (85)	58 (78)	62 (86)
Serious adverse events	1 (1)	2 (3)	0 (0)	0 (0)
Patients reporting a treatment-related adverse event*, no. (%)				
All adverse events	18 (24)	29 (40)	32 (43)	31 (43)
Serious adverse events	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events occurring in ≥5% of patients receiving AMG 317, no. (%)				
Injection site reactions†	11 (15)	18 (25)	28 (38)	27 (38)
Headache	6 (8)	6 (8)	3 (4)	12 (17)
Asthma	13 (18)	14 (19)	14 (19)	10 (14)
Upper respiratory tract infection	7 (9)	10 (14)	10 (14)	10 (14)
Viral gastroenteritis	2 (3)	2 (3)	0 (0)	4 (6)
Nasal congestion	1 (1)	0 (0)	4 (5)	4 (6)
Nasopharyngitis	8 (11)	7 (10)	4 (5)	4 (6)
Viral upper respiratory tract infection	2 (3)	2 (3)	5 (7)	2 (3)
Muscle spasms	1 (1)	4 (6)	0 (0)	1 (1)
Sinusitis	5 (7)	4 (6)	6 (8)	1 (1)
Dizziness	2 (3)	4 (6)	1 (1)	0 (0)

Definition of abbreviations: QW = once weekly.

* Includes all patients who received one or more doses of AMG 317 or placebo.

† Includes injection site reactions of erythema, pain, induration, pruritus, urticaria, swelling, inflammation, discoloration, irritation, mass, rash, edema, and scab.

higher AMG 317 treatment groups were noted. Patients who were the most symptomatic appeared to have achieved the greatest clinical effect. This study provides additional evidence that IL-4 and IL-13 may be important in the pathophysiology of inflammatory lung disease and can be considered as part of a potential treatment strategy for asthma.

Conflict of Interest Statement: J.C. received \$5,001–\$10,000 from Merck, \$5,001–\$10,000 from Schering, and \$5,001–\$10,000 from GlaxoSmithKline in lecture fees; \$5,001–\$10,000 from multiple legal firms for nonpharmaceutical-related litigation; and \$50,001–\$100,000 from Amgen, \$10,001–\$50,000 from Novartis, \$50,001–\$100,000 from MedImmune, \$50,001–\$100,000 from Genentech, and \$10,001–\$50,000 from Alcon in industry-sponsored grants. W.B. received up to \$1,000 from Alexion, \$1,001–\$5,000 from AstraZeneca, \$1,001–\$5,000 from Boehringer Ingelheim, up to \$1,000 from Dainippon-Sumitomo, up to \$1,000 from Funxional Therapeutics, Ltd., \$1,001–\$5,000 from Novartis, and \$1,001–\$5,000 from TEVA in consultancy fees; \$1,001–\$5,000 from Altair, \$1,001–\$5,000 from Amgen, \$1,001–\$5,000 from Abbott Laboratories, \$1,001–\$5,000 from Astmatx, Inc., \$1,001–\$5,000 from Bristol-Meyers Squibb, \$1,001–\$5,000 from Centocor, up to \$1,000 from Genentech, up to \$1,000 from GlaxoSmithKline, \$1,001–\$5,000 from Merck, \$1,001–\$5,000 from Schering Plough, \$1,001–\$5,000 from Pfizer, and \$1,001–\$5,000 from Wyeth in advisory board fees; \$1,001–\$5,000 from Merck in lecture fees; and \$10,001–\$50,000 from Novartis, \$5,001–\$10,000 from Centocor, more than \$100,001 from GlaxoSmithKline, more than \$100,001 from MedImmune, and \$50,001–\$100,000 from Ception in industry-sponsored grants. E.O.M. received more than \$10,000 in grant/research support from Alcon, Alexza, Amgen, Antigen Labs, Apotex, Astellas, AstraZeneca, Boehringer Ingelheim, Capnia, Critical Therapeutics, GlaxoSmithKline, MAP, MEDA, Merck, Novartis, Schering-Plough, and Teva; less than \$10,000 for serving as a consultant or on an advisory board from Abbott, Alcon, Alexza Pharmaceuticals, Amgen, Boehringer Ingelheim, Capnia, Dainippon Sumitomo Pharma, Dey, Greer, ISTA, Johnson & Johnson, Kalypsys, MAP Pharmaceuticals, Meda, National Jewish Health, Sandoz, SRx, Teva, VentriRx, Wockhardt, and Wyeth, and more than \$10,000 for serving as a consultant or on an advisory board from Schering Plough; less than \$10,000 in speaker fees from AstraZeneca, GlaxoSmithKline, MEDA, Merck, and Sanofi-Aventis, and more than \$10,000 in speaker fees from Sepracor; less than \$10,000 as an expert witness from Kirkland & Ellis, LLP and Kaye Scholer, LLP, and more than \$10,000 for serving as an expert witness from Weil, Gotshal & Manges, LLP and Patterson, Belknap, Webb & Tyler, LLP. L.M. received \$3,000–\$5,000 from Novartis and \$3,000–\$5,000 from Abbott in consultancy fees; \$3,000 from Sepracor and \$2,000 from MEDA in advisory board fees; \$10,000–\$15,000 from AstraZeneca, \$10,000–\$15,000 from MEDA, and \$2,000 from Alcon in lecture fees; \$90,000 from GlaxoSmithKline in individual research grants; \$70,000 from GlaxoSmithKline in individual research grants; \$250,000 from GlaxoSmithKline in institutional research grants for multiple regulatory research studies; \$250,000

from Novartis in institutional research grants for multiple regulatory research studies; \$100,000 from Boehringer Ingelheim in institutional research grants for multiple regulatory research studies; and \$100,000 from Forrest in institutional research grants for multiple regulatory research studies. G.B. received \$2,500 from Sepracor in advisory board fees and \$60,000 from AstraZeneca, \$7,500 from Alcon, and \$7,500 from Schering Plough in lecture fees. J.F. received \$1,001–\$5,000 in promotional lecture fees from GlaxoSmithKline; more than \$100,001 from Amgen, \$50,001–\$100,000 from Greer Laboratories, more than \$100,001 from Stallergenes, \$50,001–\$100,000 from Ception, and \$50,001–\$100,000 from Sepracor in institutional grants. S.E.W. received \$1,001–\$5,000 from Amgen, \$10,001–\$50,000 from GlaxoSmithKline, \$1,001–\$5,000 from Wyeth, and \$1,001–\$5,000 from Genentech in consultancy fees; \$1,001–\$5,000 from GlaxoSmithKline, \$10,001–\$50,000 from Amria, \$10,001–\$50,000 from Epigenesis, and \$5,001–\$10,000 from Novartis in advisory board fees; \$1,001–\$5,000 from Critical Therapeutics and \$1,001–\$5,000 from Genentech in lecture fees; and \$50,001–\$10,000 from GlaxoSmithKline, \$5,001–\$10,000 from Amgen, \$10,001–\$50,000 from MedImmune, \$50,001–\$100,000 from Ception, and \$10,001–\$50,000 from Aerovance in industry-sponsored grants. She holds stock ownership or options in Almira and Epigenesis, and received more than \$100,001 from the NHLBI and more than \$100,001 from NIAID in sponsored grants. Y.C. is a full-time employee of Amgen and holds \$10,001–\$50,000 in stock ownership or options in the company. M.D. is an employee of Amgen and holds \$10,001–\$50,000 in stock ownership or options in the company. H.H.W. is a full-time employee of Amgen and holds \$50,001–\$100,000 in stock ownership or options in the company. S-L.L. is a salaried full-time employee of Amgen and holds more than \$100,001 in stock ownership or options in the company.

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