



Randomized, Double-Blind, Placebo-controlled Study of Brodalumab, a Human Anti-IL-17 Receptor Monoclonal Antibody, in Moderate to Severe Asthma

William W. Busse¹, Stephen Holgate², Edward Kerwin³, Yun Chon⁴, JingYuan Feng⁴, Joseph Lin⁴, and Shao-Lee Lin⁴

¹University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; ²University of Southampton, Southampton, United Kingdom;

³Clinical Research Institute of Southern Oregon, PC, Medford, Oregon; and ⁴Amgen Inc., Thousand Oaks, California

Rationale: IL-17 signaling has been implicated in development and persistence of asthma. Cytokine-targeted strategies blocking IL-17 receptor signaling may be beneficial in asthma treatment.

Objectives: To determine efficacy and safety of brodalumab, a human anti-IL-17 receptor A monoclonal antibody, in subjects with inadequately controlled moderate to severe asthma taking regular inhaled corticosteroids.

Methods: Three hundred two subjects were randomized to brodalumab (140, 210, or 280 mg) or placebo. Primary endpoint was change in Asthma Control Questionnaire (ACQ) score from baseline to Week 12. Secondary endpoints included FEV₁, symptom scores, and symptom-free days. Prespecified subgroup analyses were conducted to identify potential responsive subpopulations. Analyses included randomized subjects receiving one or more doses of investigational product using last-observation-carried-forward imputation.

Measurements and Main Results: Demographics and baseline characteristics were generally balanced among groups (n = 302; n = 226 brodalumab). For the overall study population, no treatment differences were observed. Nine prespecified subgroups were examined without corrections for multiple testing. In only the high-reversibility subgroup (post-bronchodilator FEV₁ improvement ≥ 20%; n = 112) was an ACQ change with nominal significance noted; ACQ responses were nominally significant in the 210-mg group (estimated treatment difference, 0.53) but not significant in the higher 280-mg group (estimated treatment difference, 0.38). Adverse events, generally balanced among groups, were most commonly asthma, upper respiratory tract infection, and injection site reaction.

Conclusions: Inhibition of IL-17 receptor A did not produce a treatment effect in subjects with asthma. The results of the high-reversibility subgroup analysis are of uncertain significance, requiring further study of brodalumab in this asthma subpopulation.

Clinical trial registered with www.clinicaltrials.gov (NCT01199289).

Keywords: IL-17; Asthma Control Questionnaire; randomized controlled trial

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

IL-17 signaling has been implicated in development and persistence of asthma. Thus, cytokine-targeted strategies blocking IL-17 receptor signaling may be beneficial in asthma treatment.

What This Study Adds to the Field

There was no evidence of an effect of brodalumab in the overall study population of subjects with inadequately controlled moderate to severe asthma; however, a high bronchodilator reversibility subgroup was identified as a potential subpopulation that may respond to brodalumab treatment with clinically meaningful responses. These results support further study of brodalumab in this subpopulation with severe asthma.

(Received in original form December 26, 2012; accepted in final form October 23, 2013)

Funded by Amgen Inc.

Author Contributions: All authors participated in drafting and revising the manuscript and approving the final manuscript. W.W.B. and S.H. participated in data collection and interpretation; Y.C., J.Y.F., J.L., and E.K. participated in conception and design and data collection, analysis, and interpretation. S.-L.L. participated in study conception and design and data analysis and interpretation.

Correspondence and requests for reprints should be addressed to William W. Busse, M.D., Allergy, Pulmonary, and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, K4/910 CSC, MC 9988, 600 Highland Avenue, Madison, WI 53792. E-mail: wwb@medicine.wisc.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 188, Iss. 11, pp 1294–1302, Dec 1, 2013

Copyright © 2013 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201212-2318OC on November 7, 2013

Internet address: www.atsjournals.org

Despite guideline-directed care of asthma, including treatment with inhaled corticosteroids (ICS), short-acting β_2 -agonist (SABA), leukotriene receptor antagonists (LTRAs), and long-acting β_2 -agonist (LABA), there remains significant uncontrolled disease (1–3). This residual uncontrolled disease may be due to nonresponsive patient subpopulations whose disease activity is driven by inflammatory processes that are not targeted by currently available therapeutics. Although asthma has been thought of as an inflammatory disease largely driven by a Th2-mediated response, Th17 cells can contribute to airway hyperresponsiveness by recruiting both eosinophils and neutrophils (4, 5). Th17 cells predominantly act through the production of the IL-17 family of cytokines (IL-17A–17F) (6), of which IL-17A and IL-25 (IL-17E) are believed to play roles in the lung inflammatory process through distinct IL-17 receptor A (IL-17RA)-containing heteromeric receptor complexes expressed in airway smooth muscle cells (7). Studies in animal models of asthma have shown that antigen challenge increases IL-17 expression and neutrophil recruitment via IL-17RA (8–10). Moreover, increased IL-17A and IL-17F levels in the lungs of patients with active asthma (4, 11, 12) are positively correlated to neutrophilic inflammation (13) and disease severity (12, 14). This increased disease severity may be due to IL-17RA-mediated airway hyperresponsiveness via enhanced smooth muscle cell contraction (5) and migration (15). Although IL-17A may play a large role in the disease pathology of asthma, IL-25 signaling is also involved, mediating downstream Th2 events such as secretion of IL-4, IL-5, and IL-13 from Th2 cells (16). Thus, cytokine-targeted strategies aimed at blocking IL-17RA signaling may be beneficial in the treatment of asthma.

Brodalumab (AMG 827) is a human, anti-IL-17RA immunoglobulin G2 (IgG2) monoclonal antibody that binds with high affinity to human IL-17RA, blocking the biologic activity of IL-17A, -17F, -17A/F heterodimer, and -17E (IL-25). Blocking IL-25 activity, in addition to that of IL-17A and IL-17F, is a distinguishing feature of brodalumab, in contrast to blocking the IL-17 family ligands individually. Brodalumab has been studied in more than 800 subjects in phase 1 and phase 2 clinical trials and has been shown to have a safety profile supportive of continued clinical development (17–19). In early-phase studies, brodalumab has shown partially nonlinear kinetics, with a larger increase in exposure than the proportionate increase in dose, such that the blood levels and exposure are broader than what may appear to be nominal dose differences. Doses ranging from 140 to 280 mg every 2 weeks result in serum levels sufficient to inhibit more than 90% of IL-17 and IL-25 receptor activity (17). Brodalumab has been studied in other diseases involving increased IL-17 activation (rheumatoid arthritis, psoriasis, psoriatic arthritis, and Crohn disease). In contrast to the lack of observed effect in rheumatoid arthritis (19) and the negative response in active Crohn disease (20), brodalumab has demonstrated significant improvements in plaque psoriasis in a 12-week, phase 2 study (18) and is currently being tested in phase 3 studies of psoriasis.

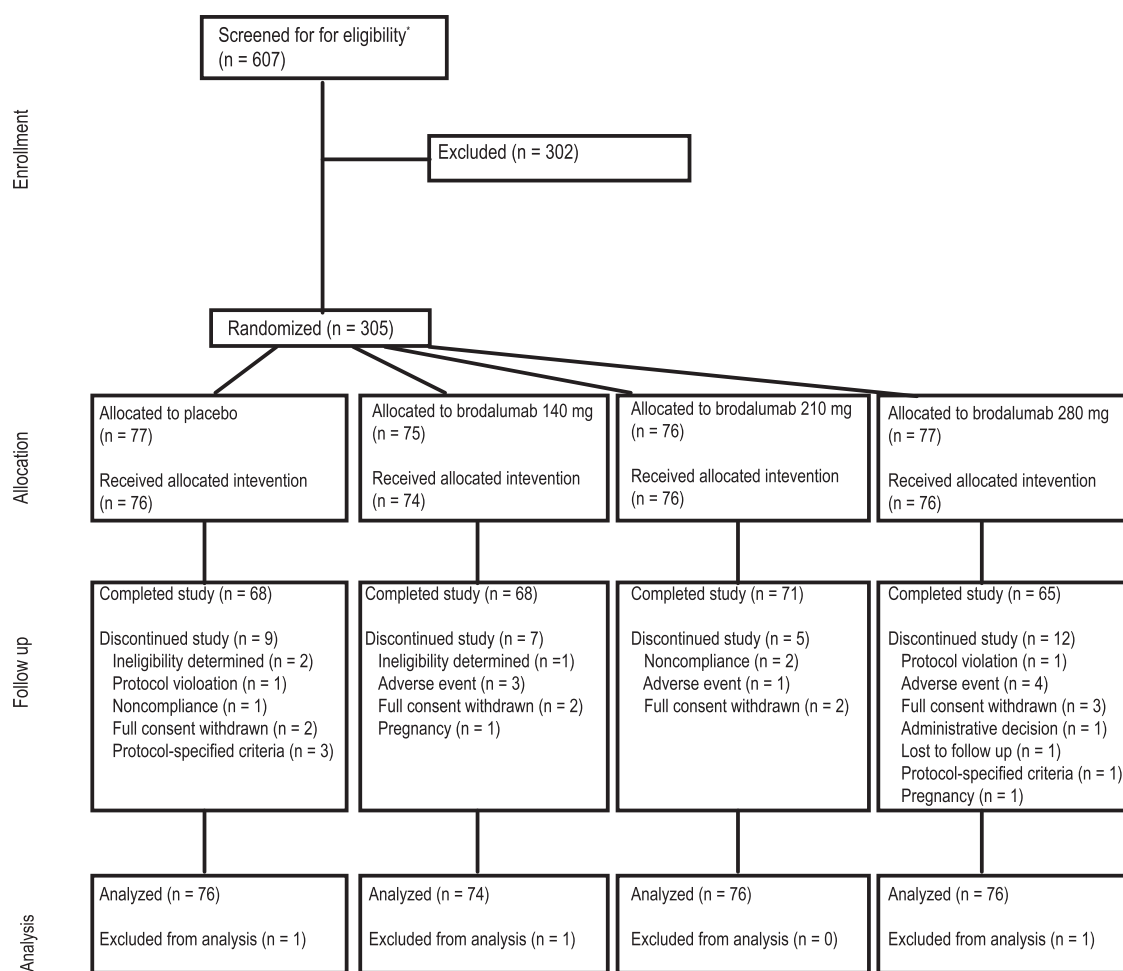
Here we report the first study of an anti-IL-17 in humans with asthma. The primary objective of this study was to evaluate

efficacy and safety of brodalumab in subjects with inadequately controlled moderate to severe asthma despite receiving regular ICS. Some of the results of this study have been previously reported in the form of an abstract (21).

METHODS

Subjects

Subjects aged 18 to 65 years with inadequately controlled physician-diagnosed moderate to severe asthma on stable ICS (≥ 200 and $\leq 1,000$ $\mu\text{g/d}$ of fluticasone powder or equivalent for ≥ 3 mo before screening, and had to be on a stable dose for ≥ 30 d) with or without additional LABAs were eligible (*see* Table E1 in the online supplement). Patients were recruited from each clinical site's existing patients or from referral based on inadequately controlled asthma determined by Asthma Control Questionnaire (ACQ) scores greater than or equal to 1.5, greater than or equal to 50% to less than or equal to 80% predicted FEV₁, and greater than or equal to 12% reversibility over baseline FEV₁ with SABA inhalation. Key exclusion criteria included evidence of active infection or hematologic or immune suppression (Table E1). Subjects could have previously received LABA, theophylline, inhaled anticholinergics, oral β_2 -agonists, leukotriene antagonists, or cromolyn therapeutics. Use of asthma medications, other than ICS and as-needed albuterol/salbutamol, was not permitted during the study after a 2-week washout for LTRAs and 1 week for LABA or theophylline. LABAs were not allowed during the study period to ensure the study population had the potential for lung function improvement and



*Excludes subjects from site 12002

Figure 1. Flow chart of the study.

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	Placebo (N = 76)	Brodalumab (N = 226)	Total (N = 302)
Sex, female, n (%)	53 (70)	126 (56)	179 (59)
Race, n (%)			
White	69 (91)	185 (82)	254 (84)
Black	5 (7)	26 (12)	31 (10)
Asian	2 (3)	8 (4)	10 (3)
American Indian or Alaskan Native	0 (0)	2 (1)	2 (1)
Hispanic or Latino	3 (4)	17 (8)	20 (7)
Multiple	0 (0)	4 (2)	4 (1)
Other	0 (0)	1 (0)	1 (0)
Age, yr	46.8 (11.2)	45.4 (11.5)	45.7 (11.4)
Weight, kg	84.1 (19.0)	86.9 (22.0)	86.2 (21.3)
Height, cm	167.6 (8.6)	169.2 (9.9)	168.8 (9.6)
ACQ score	2.48 (0.65)	2.52 (0.66)	2.51 (0.66)
AQLQ score	4.44 (0.99)	4.56 (1.04)	4.53 (1.03)
Atopic,* n (%)	60 (79)	190 (84)	250 (83)
FEV ₁ , prebronchodilator, L	2.06 (0.50)	2.20 (0.60)	2.16 (0.58)
% Predicted FEV ₁ , prebronchodilator	64.7 (8.7)	65.4 (8.5)	65.2 (8.5)
FEV ₁ , post-bronchodilator, L	2.49 (0.62)	2.60 (0.72)	2.57 (0.69)
% Predicted FEV ₁ , post-bronchodilator	78.2 (12.9)	77.3 (10.9)	77.6 (11.4)
% Reversibility	21.1 (12.7)	18.9 (13.5)	19.4 (13.3)
Duration of asthma, yr	24.8 (16.1)	24.3 (13.5)	24.4 (14.2)
Baseline ICS dose, µg/d fluticasone equivalent	541 (270)	497 (251)	508 (256)
Daily rescue β-agonist use, puffs/d	4.34 (7.34)	3.86 (5.06)	3.98 (5.71)
Previous LABA use, yes, n (%)	58 (76)	153 (68)	211 (70)
AM PEF, L/min	318.7 (97.2)	358.7 (114.8)	348.6 (111.9)
Daily asthma symptom scores	5.52 (3.86)	5.82 (3.41)	5.74 (3.52)
Nighttime asthma symptom scores	1.00 (1.01)	1.10 (1.10)	1.07 (1.08)
eNO, median (IQR), parts/billion	22.0 (13.0, 29.5)	24.0 (16.0, 38.3)	23.5 (14.8, 35.8)
Peripheral eosinophils, median (IQR), %	2.9 (1.7, 4.5)	2.9 (1.9, 4.3)	2.9 (1.8, 4.3)
Total serum IgE, median (IQR), IU/ml	141 (44, 311)	122 (60, 320)	132 (52, 320)

Definition of abbreviations: ACQ = Asthma Control Questionnaire; AM PEF = morning peak expiratory flow; AQLQ = Asthma Quality of Life Questionnaire; eNO = exhaled nitric oxide; IQR = interquartile range; LABA = long-acting β₂-agonist.

Data represent mean (SD) unless otherwise indicated.

*Atopy status was defined as a positive skin prick test response (>3-mm wheal) or a positive RAST result.

thereby to increase the chance of identifying any signal of a brodalumab effect. After a 4-week run-in period, in which controller medications doses were stabilized, no changes to the types or dosages of asthma medications or allergen immunotherapy were allowed during the study except for the use of systemic corticosteroids during an asthma exacerbation.

Study Design

This was a phase 2a, randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy and safety of brodalumab in subjects with asthma. Randomization (1:1:1:1) to receive brodalumab (140, 210, 280 mg) or placebo subcutaneously at Day 1 and Weeks 1, 2, 4, 6, 8, and 10 was assigned by an interactive voice response system based on a permuted block design within each strata (baseline atopy status and ICS dose [<500 µg and ≥ 500 µg fluticasone powder or equivalent]). Institutional review board or ethics committee at each site approved the protocol. This study was conducted in accordance with principles of the Food and Drug Administration and International Conference on Harmonization Good Clinical Practice regulations/guidelines. All subjects provided written informed consent, and the study was approved by the institutional review board of each participating site. The first subject enrolled October 4, 2010, and the last subject completed the study December 21, 2011. Representatives of Amgen designed the study in collaboration with the authors, collected data, and conducted the data analyses. All the authors interpreted the data and participated in the preparation of the manuscript with support from a professional medical writer employed by Amgen. All the authors made the decision to submit the manuscript for publication and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol.

Efficacy and Safety Evaluations

The primary endpoint was ACQ total score (long-form ACQ-7) change from baseline to Week 12; reductions greater than or equal to 0.5 were considered clinically meaningful changes (22). Secondary endpoints

included changes from baseline in pre- and post-bronchodilator FEV₁, morning peak expiratory flow (AM PEF), rescue SABA use, daily asthma symptom score, and symptom-free days. Safety was assessed by adverse events (AEs) and routine hematologic and laboratory values. An independent data review team reviewed unblinded safety data throughout the study. A low rate of neutropenia (~1%) has been reported across different candidate therapies targeting IL-17 signaling. Thus, in addition to risk of infection, injection site reactions, and immunogenicity (antibrodalumab antibodies), safety events of special interest included any potential for decreased neutrophil counts.

The ACQ was administered at every scheduled study visit at Day 1 and Weeks 1, 2, 4, 6, 8, 10, 12, and 16 for the 7-day recall in prior week. For FEV₁ evaluations, prebronchodilator spirometric evaluations were performed in the morning before any use of bronchodilators. Post-bronchodilator measurements were recorded 15 to 45 minutes after bronchodilator use. Exhaled nitric oxide values were assessed on site by using the Niox Mino (Niox, Morrisville, NC). Subjects received an electronic diary (e-diary, AM3 device; ERT, Philadelphia, PA) to record their rescue SABA use and asthma symptoms twice a day. A peak flow meter was dispensed, and patients were instructed to measure PEF twice daily at least 6 hours after the last use of an SABA; reminders were included in the daily electronic diary. Symptoms were assessed on a 21-point scale (each of seven items on a 0- to 3-point Likert scale) and included nighttime awakenings/symptoms, wheezing, shortness of breath, cough, chest tightness, and activity limitation. Atopy status was assessed for all patients by using either skin prick tests or RAST. All screening and on-study laboratory samples (with the exception of urine pregnancy) were processed and sent to central laboratories (Covance, Indianapolis, IN; Covance, Geneva Switzerland; Covance, Republic of Singapore). Analysis of samples for antibrodalumab antibody testing was done by PPD Development (Richmond, VA).

Prespecified Subgroup Analyses

Prespecified subgroup analyses were designed to identify the phenotype of patients who may preferentially respond to brodalumab treatment.

Prespecified subgroup analyses were based on a high bronchodilator reversibility subpopulation (FEV₁ improvement ≥ 20% after bronchodilator treatment), baseline FEV₁% predicted (tertiles), ACQ (tertiles), ICS dose (≥500 µg or <500 µg), fractional exhaled nitric oxide (≥23.5 or <23.5), peripheral eosinophils (≥6% or <6%), sex, race (white or nonwhite), and weight (≥100 kg or <100 kg). The 20% cutoff for reversibility was based on the historical recommendation that significant reversibility be defined as greater than or equal to 20% improvement in post-bronchodilator FEV₁ (e.g., Global Initiative for Asthma Guidelines 2006) and the mean improvement in FEV₁ at screening.

Statistical Methods

The sample size of 300 subjects was calculated to provide greater than or equal to 80% power to detect a linear trend of ACQ composite score change from baseline (contrast coefficients: -3, -1, 1, 3; α = 0.05) assuming changes of 0.3 (140 mg), 0.4 (210 mg), and 0.5 (280 mg) as compared with placebo, a variance of ACQ composite score change of 1 (22), and a 15% dropout rate.

Analyses used data from all randomized subjects receiving one or more doses of study drug (intent to treat). The primary endpoint was tested for linear trend of treatment effect using linear contrast (contrast coefficients: -3, -1, 1, 3) in an analysis of covariance adjusting for baseline ACQ, atopy status, and ICS dose category. For the subgroup analyses, a linear trend test in an analysis of covariance model was used for the comparison of the overall treatment group versus placebo, and estimated treatment differences for individual treatment groups were compared versus placebo. All *P* values are nominal and not adjusted for multiplicity. Last observation carried forward was used to impute missing data.

RESULTS

Subject Characteristics

Of 607 patients who were screened, 315 subjects enrolled in the study at 47 sites in 10 countries (Austria, Belgium, Canada, Finland, Hungary, Netherlands, Poland, Russia, South Korea, and the United States); 297 patients did not meet inclusion/exclusion

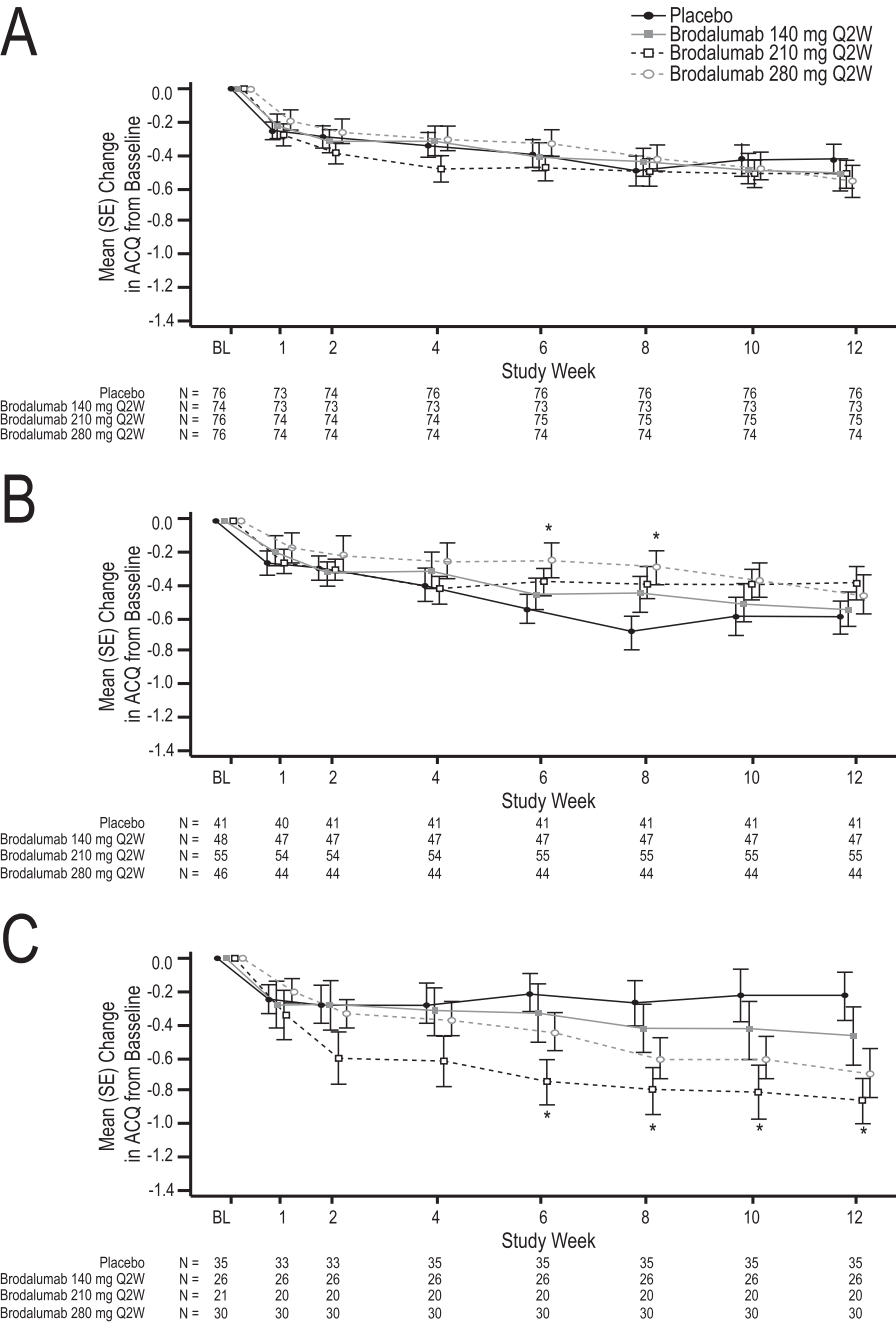


Figure 2. Change in Asthma Control Questionnaire (ACQ) score from baseline by treatment group in (A) the overall study population, (B) the low-reversibility subgroup, and (C) the high-reversibility subgroup. Data represent mean (SE). Q2W = every 2 weeks. *Nominal *P* < 0.05, uncorrected.

TABLE 2. CLINICAL RESPONSES AT WEEK 12 BY TREATMENT GROUP IN FULL STUDY POPULATION

		Brodalumab Q2W			
Response (Change from Baseline)	Placebo (N = 76)	140 mg (N = 74)	210 mg (N = 76)	280 mg (N = 76)	P Value*
ACQ	n = 76	n = 73	n = 75	n = 74	
LS mean	−0.431	−0.498	−0.506	−0.544	0.3731
FEV ₁ , prebronchodilator	n = 76	n = 73	n = 75	n = 74	
LS mean	0.056	0.009	0.034	0.037	0.8521
AM PEF	n = 76	n = 74	n = 76	n = 75	
LS mean	1.490	−15.357	−5.234	−3.999	0.7834
SABA use	n = 76	n = 74	n = 76	n = 75	
LS mean	−0.561	−0.230	−0.795	−0.759	0.469
Daily symptom score, % change	n = 76	n = 74	n = 76	n = 75	
LS mean	−10.59	−29.37	−24.47	−23.33	0.5603
Nighttime symptom score, % change	n = 76	n = 74	n = 76	n = 75	
LS mean	−39.01	−16.83	−26.67	−24.52	0.4528
Symptom-free days	n = 76	n = 74	n = 76	n = 76	
LS mean	0.243	0.181	0.226	0.201	0.5147

Definition of abbreviations: ACQ = asthma control questionnaire; AM PEF = morning peak expiratory flow; LS mean = least-squares mean; Q2W = every 2 weeks; SABA = short-acting β_2 -agonist.

*P value from a linear trends test using linear contrast in analysis of covariance model adjusted for stratification factors and baseline ACQ.

criteria (Figure 1, Table E1). Due to major issues of Good Clinical Practice compliance, 10 subjects from one site (site 12002) were excluded from all analyses. Of the 305 subjects randomized (228 to brodalumab and 77 to placebo), 302 subjects received at least one dose of investigational product (IP) (226 brodalumab and 76 placebo); 3 subjects were randomized in error and did not receive investigational product IP (Figure 1); 272 (89.2%) subjects completed the study.

There were higher percentages of women in the placebo group than in the brodalumab groups. There was a higher

percentage of Black subjects in the 140-mg brodalumab group than in the other groups. Prebronchodilator FEV₁ and AM PEF were lower at baseline in the placebo than in the brodalumab groups (Tables 1 and E2). For the total study population, mean (SD) duration of asthma was 24.4 (14.2) years and mean (SD) baseline ACQ score was 2.51 (0.66); the majority of subjects were atopic (83%) and had previously used LABAs (70%). The mean (SD) baseline ICS dose was 508.2 (255.9) $\mu\text{g}/\text{d}$ of fluticasone equivalent. Mean (SD) prebronchodilator FEV₁ was 2.16 (0.58) L, and mean (SD) AM PEF was 348.6 (111.9) L/min.

TABLE 3. DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF HIGH- AND LOW-REVERSIBILITY SUBGROUPS

	High Reversibility (N = 112)	Low Reversibility (N = 190)	Overall (N = 302)
Sex, female, n (%)	74 (66)	105 (55)	179 (59)
Race, n (%)			
White	96 (86)	158 (83)	254 (84)
Black	14 (13)	17 (9)	31 (10)
Asian	1 (1)	9 (5)	10 (3)
American Indian or Alaskan Native	1 (1)	1 (1)	2 (1)
Hispanic or Latino	6 (5)	14 (7)	20 (7)
Multiple	0 (0)	4 (2)	4 (1)
Other	0 (0)	1 (1)	1 (0)
Age, yr	45.4 (11.1)	45.9 (11.6)	45.7 (11.4)
Weight, kg	83.0 (19.7)	88.1 (22.0)	86.2 (21.3)
Height, cm	168.5 (9.4)	169.0 (9.7)	168.8 (9.6)
ACQ	2.58 (0.61)	2.47 (0.68)	2.51 (0.66)
AQLQ	4.42 (1.00)	4.60 (1.04)	4.53 (1.03)
Atopic,* n (%)	97 (87)	153 (80)	250 (83)
FEV ₁ , prebronchodilator, L	2.06 (0.53)	2.23 (0.59)	2.16 (0.58)
% Predicted FEV ₁ , prebronchodilator	62.9 (8.0)	66.6 (8.6)	65.2 (8.5)
FEV ₁ , post-bronchodilator, L	2.72 (0.71)	2.48 (0.67)	2.57 (0.69)
% Predicted FEV ₁ , post-bronchodilator	83.3 (11.6)	74.2 (9.9)	77.6 (11.4)
% Reversibility	32.8 (11.8)	11.6 (5.6)	19.4 (13.3)
Duration of asthma, yr	22.0 (12.7)	25.8 (14.8)	24.4 (14.2)
Baseline ICS dose, $\mu\text{g}/\text{d}$ fluticasone equivalent	499 (227)	514 (272)	508 (256)
Daily rescue β -agonist use, puffs/d	4.17 (6.17)	3.87 (5.43)	3.98 (5.71)
Previous LABA use, yes, n (%)	76 (68)	135 (71)	211 (70)
AM PEF, L/min	341.0 (102.2)	353.1 (117.2)	348.6 (111.9)
Daily asthma symptom scores	6.02 (3.56)	5.58 (3.50)	5.74 (3.52)
Nighttime asthma symptom scores	1.15 (1.04)	1.02 (1.10)	1.07 (1.08)
eNO, median (IQR), parts/billion	25.5 (16.5, 39.0)	21.8 (14.0, 31.0)	23.5 (14.8, 35.8)
Peripheral eosinophils, median (IQR), %	3.0 (2.0, 4.7)	2.9 (1.8, 4.1)	2.9 (1.8, 4.3)
Total serum IgE, median (IQR), IU/ml	144 (59, 303)	126 (50, 367)	132 (52, 320)

Definition of abbreviations: ACQ = Asthma Control Questionnaire; AM PEF = morning peak expiratory flow; AQLQ = Asthma Quality of Life Questionnaire; eNO = exhaled nitric oxide; IQR = interquartile range; LABA = long-acting β_2 -agonist.

Data represent mean (SD) unless otherwise indicated.

*Atopy status was defined as a positive skin prick test response (>3-mm wheal) or a positive RAST result.

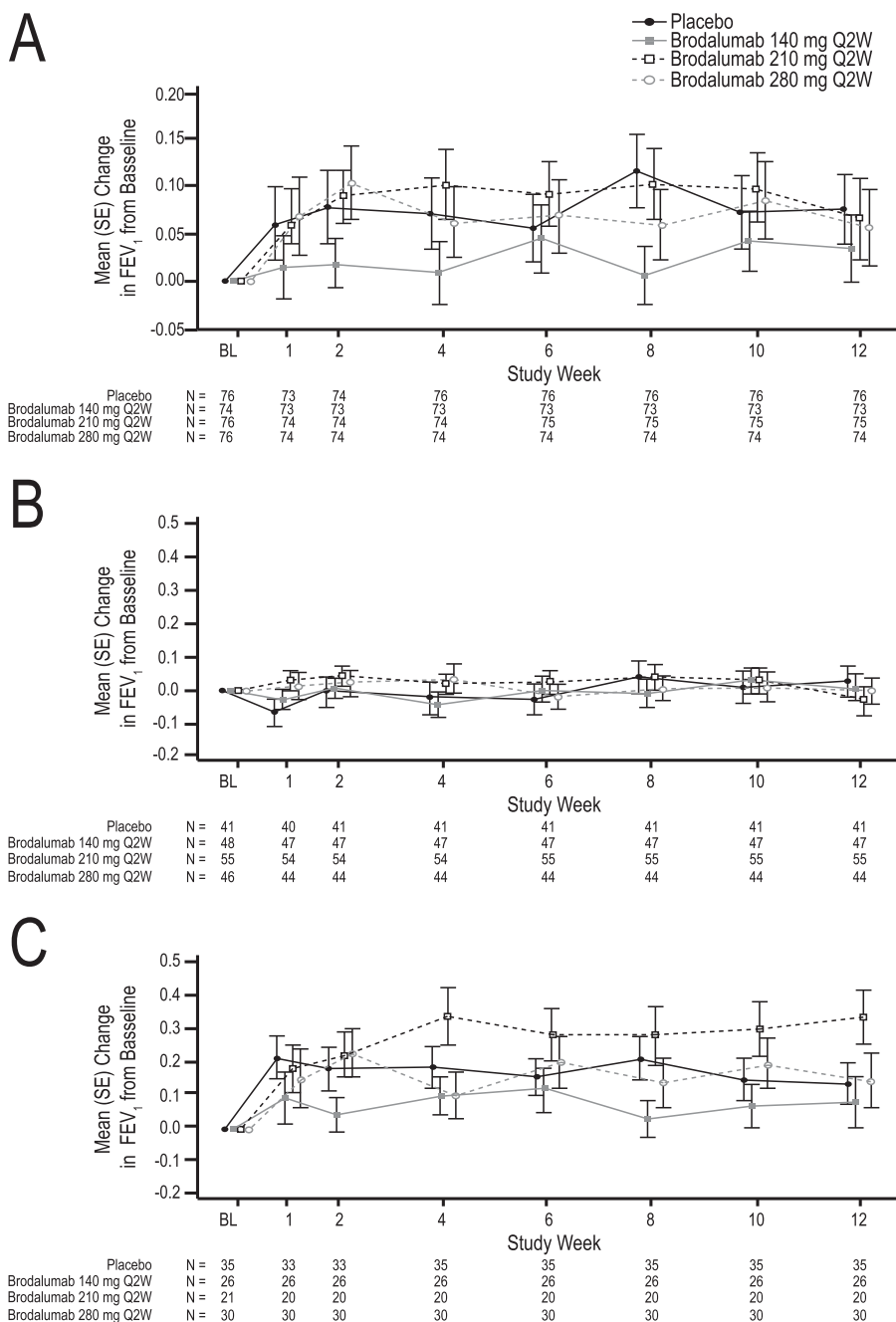


Figure 3. Change in prebronchodilator FEV₁ from baseline by treatment group in (A) the overall study population, (B) the low-reversibility subgroup, and (C) the high-reversibility subgroup. Data represent mean (SE). Q2W = every 2 weeks.

Efficacy

Overall treatment effect on change from baseline in ACQ scores at Week 12 for the full study population was not statistically significant ($P = 0.37$, linear trend test), and none of the pairwise comparisons of each brodalumab treatment group with placebo were statistically significant (Figure 2A, Table 2). There was no evidence of clinically meaningful efficacy on ACQ scores at any time point (Figure 2A). Overall treatment effects for all of the secondary endpoints for the full study population were not statistically significant ($P > 0.05$, linear trend test and pairwise comparisons). There was no evidence of clinically meaningful differences in lung function (Figure 3, Table 2) or asthma symptoms (Figure 4, Table 2). Least-squares mean changes from baseline in FEV₁ ($P = 0.85$), AM PEF ($P = 0.78$), and SABA use ($P = 0.47$; Table 2) were all nonsignificant. There were no significant differences in percent changes from baseline

daily symptoms ($P = 0.56$) and nighttime symptoms ($P = 0.45$) or changes in proportion of symptom-free days ($P = 0.51$) among any of the treatment groups (Figure 4, Table 2).

Prespecified Subgroup Analyses

Among the nine prespecified subgroup analyses, the high-reversibility subgroup was the only one demonstrating clinically meaningful treatment effects. The baseline demographics for the high-bronchodilator reversibility ($n = 112$; placebo, $n = 35$; 140 mg, $n = 26$; 210 mg, $n = 21$; 280 mg, $n = 30$) and the low-reversibility ($n = 190$; placebo, $n = 41$; 140 mg, $n = 48$; 210 mg, $n = 55$; 280 mg, $n = 46$) subgroups were generally similar to the overall study population (Table 3). The subgroup with a high degree of FEV₁ reversibility was composed of more women (66 vs. 55%) and more atopic subjects (87 vs. 80%) than the lower-reversibility

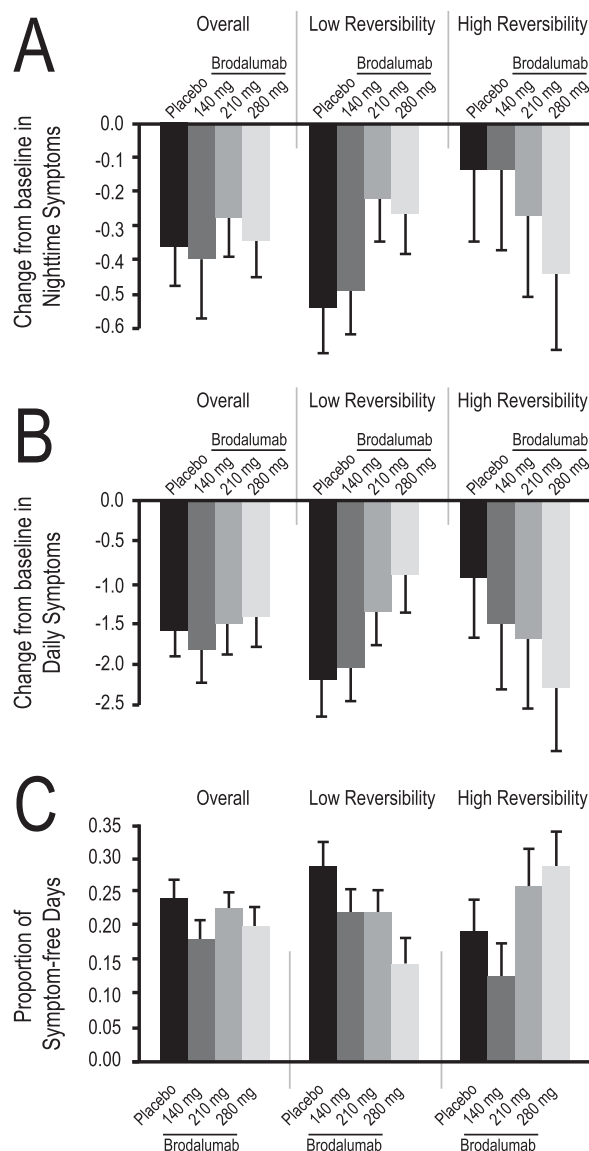


Figure 4. Change in asthma symptoms from baseline to Week 12 by treatment group for (A) absolute change in nighttime symptoms, (B) absolute change in daily symptoms, and (C) proportion of symptom-free days. Data represent least-squares mean.

subgroup. Consistent with their clinical phenotypes, ACQ scores, rescue SABA use, and fractional exhaled nitric oxide were higher, and prebronchodilator FEV₁ and AM PEF were lower in the high-reversibility group than in the lower-reversibility population (Table 3).

In the high-reversibility subgroup at Week 12, the least-squares mean changes in ACQ from baseline were -0.287 (placebo), -0.448 (140 mg), -0.820 (210 mg), and -0.670 (280 mg) ($P = 0.02$, linear trend test) (Figure 2C, Table E3). An assessment of an interaction between treatment and reversibility for ACQ change from baseline at Week 12 (observed) was performed, and the linear contrast test for the high-reversibility group, 210 mg versus placebo, had a nominal P value of 0.04 after adjusting the difference between high and low reversibility. The nominal P value for the overall interaction between reversibility and treatment was 0.11, suggestive of a trend for the different treatment effect in each stratum. The minimal important difference for change in ACQ (0.5) was surpassed in the

210-mg group, with a treatment difference of -0.53 at Week 12 (nominal $P = 0.02$) (Figure 2C). For mean change in ACQ, differences were observed in the 210-mg group by Week 2 and increased to a plateau at Week 10 (change from baseline of -0.802 , nominal $P = 0.03$) (Figure 2C). In contrast, there were no significant differences among groups for change in ACQ in the low-reversibility subgroup at Week 12; however, at Week 6 and Week 8 the change from baseline in ACQ in the 280-mg group was significantly lower than placebo (nominal $P < 0.05$) (Figure 2B, Table E4). The results of the subgroup analysis should be interpreted with caution, because the P values were not adjusted for multiplicity.

In the high-reversibility subgroup at Week 12, there were no significant treatment effects in FEV₁ (prebronchodilator), AM PEF, and SABA use (overall treatment effect, $P > 0.05$ for all treatment groups vs. placebo; Figure 3C, Table E3). There was a numerical trend for reduced daily symptom scores (overall $P = 0.08$ for brodalumab vs. placebo for percent change from baseline) and an increase in symptom-free days (overall $P = 0.03$ for brodalumab vs. placebo) (Figure 4C, Table E3).

Treatment effects on the primary and secondary endpoints at Week 12 for the low-reversibility subgroup population were not statistically significant ($P > 0.05$, linear trend test; Table E4), except for a small reduction in improvement in nighttime symptoms and symptom-free days. No differences were observed in any of the other eight prespecified subgroup analyses (data not shown).

Safety

Incidences of all AEs, including serious AEs (SAEs), were similar across treatment groups, and there appeared to be no relationship to brodalumab dose (Table 4). The most frequent AEs (occurring in $\geq 5\%$ of subjects in any treatment group) reported in the study were: asthma, injection site erythema, upper respiratory tract infection, erythema, nasopharyngitis, oral candidiasis, and sinusitis. There was a numerically greater incidence of AEs for brodalumab groups versus placebo for oral candidiasis (3.5% vs. 0%), worsening asthma (20.8% vs. 14.5%), injection site erythema (8.4% vs. 2.6%), and erythema (3.1% vs. 1.3%). AEs that led to discontinuation of the study or investigational product were more frequent with brodalumab than placebo (4% vs. 1.3%). The most common AE leading to withdrawal of investigational product was asthma (worsening) (six [2.7%] brodalumab subjects, zero [0%] placebo subjects). During the study, a total of seven subjects reported eight SAEs (Table 4). Two subjects (one brodalumab and one placebo) experienced asymptomatic and transient decreased neutrophil counts detected on routine complete blood count monitoring. An absolute neutrophil count of $1.75 \times 10^3/\mu\text{l}$ was noted on Day 15 in the subject on brodalumab, and there was no interruption in dosing. An absolute neutrophil count of $1.00 \times 10^3/\mu\text{l}$ was noted on Day 8 in the subject on placebo. Both cases were resolved with no additional treatment. Overall rates of infectious AEs and hypersensitivity reactions were balanced among treatment groups.

DISCUSSION

The efficacy and safety of brodalumab, a human anti-IL-17 receptor A monoclonal antibody, was evaluated in subjects with inadequately controlled moderate to severe asthma. Baseline mean ACQ scores, percent predicted FEV₁, and rescue medication use were consistent with a population of patients with moderate to severe asthma whose symptoms were not well controlled despite receiving standard of care, including ICS with and without LABA. There was no evidence of a treatment

TABLE 4. ADVERSE EVENTS

	Placebo (N = 76)	Brodalumab Q2W		
		140 mg (N = 74)	210 mg (N = 76)	280 mg (N = 76)
Adverse events				
Any	43 (56.6)	47 (63.5)	45 (59.2)	48 (63.2)
Serious*	1 (1.3)	3 (4.1)	1 (1.3)	2 (2.6)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to study discontinuation	0 (0.0)	3 (4.1)	1 (1.3)	4 (5.3)
Leading to IP discontinuation	1 (1.3)	3 (4.1)	1 (1.3)	5 (6.6)
CTCAE Grade 3, 4, or 5 [†]	30 (39.5)	32 (43.2)	30 (39.5)	33 (43.4)
Common adverse events [‡]				
Upper respiratory tract infection	6 (7.9)	8 (10.8)	4 (5.3)	8 (10.5)
Nasopharyngitis	5 (6.6)	5 (6.9)	3 (3.9)	3 (3.9)
Oral candidiasis	0 (0.0)	1 (1.4)	4 (5.3)	3 (3.9)
Sinusitis	4 (5.3)	2 (2.7)	4 (5.3)	0 (0.0)
Asthma [§]	11 (14.5)	18 (24.3)	15 (19.7)	14 (18.4)
Injection site erythema	2 (2.6)	5 (6.8)	7 (9.2)	7 (9.2)
Erythema	1 (1.3)	2 (2.7)	1 (1.3)	4 (5.3)

Definition of abbreviations: CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; IP = investigational product.

* A serious adverse event was defined as an event that was fatal or life threatening, required or prolonged hospitalization, or caused persistent or substantial disability or incapacity or congenital anomaly or birth defect or an event that was considered by the investigator to be a medically important event.

[†] The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

[‡] Common adverse events were those that were reported in at least 5% of subjects in any treatment group.

[§] No asthma exacerbations required emergency department visits or hospitalizations.

effect of brodalumab in the full study population of subjects with asthma. Because asthma is a heterogeneous disease with clinical subphenotypes that respond to specific biologic therapy within a larger population, these findings are not necessarily unexpected (23). Due to their selective mechanism of action, monoclonal antibody therapies can require some level of stratification or patient selection to target only those patients likely to respond to a specific biologic to demonstrate efficacy (23).

The application of nonhierarchical and cluster statistical approaches to subphenotyping asthma has identified at least five clusters (24). Thus, in the current study, we performed prespecified subgroup analyses to identify patient phenotypes that may respond to IL-17 antagonism. Among the nine subgroups assessed, a clinical response to brodalumab was observed in only the high-reversibility population, with an estimated treatment difference for the 210-mg brodalumab dose group, the second highest dose (-0.53 , nominal $P = 0.02$) that exceeded the minimal important difference for ACQ (0.5) (22). This subgroup was present in 37% of the full study population and best fits, but does not completely overlap, as a cross between Clusters 2 and 4 identified by Moore and colleagues (24). Thus, this subpopulation of high reversibility may represent a distinct clinical phenotype and serve as a potential marker of both disease severity and inadequacy of control, wherein exacerbations may be a more appropriate endpoint to assess efficacy. However, results of the subgroup analyses need to be interpreted with caution due to the lack of correction for multiplicity. A prospective study would be needed to determine if there is a clinical response in this patient population and to clarify any questions raised by the lack of a clear dose-response in the current study's subgroup analysis.

Doses of brodalumab used in this study were based on the whole blood stimulation concentration required for 90% of maximum inhibition level (17). Based on pharmacokinetic modeling showing correlations with clinical activity in subjects with psoriasis (17), the 140-mg dose was expected to be submaximally efficacious, and the 210- and 280-mg doses were expected to be near or at maximal efficacy. In the current study, no treatment response was observed with the 140-mg dose and, in the high-

reversibility subgroup, maximal response was observed with the 210-mg dose but not the 280-mg dose.

Eighty-nine percent of subjects received all scheduled doses. Brodalumab demonstrated an acceptable safety profile. The incidence of AEs, including SAEs, were similar across treatment groups, including one case of asymptomatic and transient decreased neutrophil counts in both the placebo group and the brodalumab group. However, there were more local injection site erythema reactions noted in the brodalumab group. There was also an imbalance in oral candidiasis; however, all study subjects were on a background of ICS, which have reported similar incidence rates (between 2 and 6%) in all patients with asthma taking ICS (25–28). Herpes zoster and viral meningitis were reported as an SAE as one case from one subject in the 140-mg brodalumab group. The clinical course of these events was complicated by concurrent use of prednisone for sinusitis prescribed by a nonstudy physician and a medical history of chronic sinusitis; the case resolved after treatment with ceftriaxone and valacyclovir. Other subjects treated with brodalumab used concurrent prednisone on study for asthma exacerbations ($n = 24$), but no additional cases of viral meningitis or zoster associated with asthma exacerbations were reported. Although exacerbations can be triggered by upper respiratory infections, the number of exacerbations observed in this study was too low to draw any conclusions about the interactions among exacerbations, oral glucocorticoids, brodalumab, and rates of infections.

Conclusions

In the overall study population, there were no clinically or statistically significant improvements in primary and secondary endpoints. The response noted only in the high bronchodilator group is of unclear significance, because the statistical tests were applied without correction for the nine subgroups evaluated, and estimated treatment differences for ACQ changes were nominally significant in the middle dose tested and not in the higher dose. If further studies with this approach were to be undertaken

in asthma, the high bronchodilator subgroup may merit particular investigation.

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: Medical writing and editorial assistance were provided by Jon Nilsen, Ph.D. (Amgen, Inc.).

References

- Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE, Group GI; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836–844.
- Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006;6:13.
- Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real-world evaluation of asthma control and treatment (REACT): findings from a national web-based survey. *J Allergy Clin Immunol* 2007;119:1454–1461.
- Barczyk A, Pierzchala W, Sozańska E. Interleukin-17 in sputum correlates with airway hyperresponsiveness to methacholine. *Respir Med* 2003;97:726–733.
- Kudo M, Melton AC, Chen C, Engler MB, Huang KE, Ren X, Wang Y, Bernstein X, Li JT, Atabai K, et al. IL-17A produced by $\alpha\beta$ T cells drives airway hyper-responsiveness in mice and enhances mouse and human airway smooth muscle contraction. *Nat Med* 2012;18:547–554.
- Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol* 2009;9:556–567.
- Wang HB, Ghiran I, Matthaek K, Weller PF. Airway eosinophils: allergic inflammation recruited professional antigen-presenting cells. *J Immunol* 2007;179:7585–7592.
- Hoshino H, Lötvall J, Skoogh BE, Lindén A. Neutrophil recruitment by interleukin-17 into rat airways in vivo. Role of tachykinins. *Am J Respir Crit Care Med* 1999;159:1423–1428.
- Schnyder-Candrian S, Togbe D, Couillin I, Mercier I, Brombacher F, Quesniaux V, Fossiez F, Ryffel B, Schnyder B. Interleukin-17 is a negative regulator of established allergic asthma. *J Exp Med* 2006;203:2715–2725.
- Park SJ, Lee KS, Kim KH, Min KH, Moon H, Lee MH, Chung CR, Han HJ, Puri KD, Lee YC. Phosphoinositide 3-kinase δ inhibitor suppresses interleukin-17 expression in a murine asthma model. *Eur Respir J* 2010;36:1448–1459.
- Molet S, Hamid Q, Davoine F, Nutku E, Taha R, Pagé N, Olivenstein R, Elias J, Chakir J. IL-17 is increased in asthmatic airways and induces human bronchial fibroblasts to produce cytokines. *J Allergy Clin Immunol* 2001;108:430–438.
- Al-Ramli W, Préfontaine D, Chouiali F, Martin JG, Olivenstein R, Lemièrre C, Hamid QT. T(H)17-associated cytokines (IL-17A and IL-17F) in severe asthma. *J Allergy Clin Immunol* 2009;123:1185–1187.
- Sergejeva S, Ivanov S, Lötvall J, Lindén A. Interleukin-17 as a recruitment and survival factor for airway macrophages in allergic airway inflammation. *Am J Respir Cell Mol Biol* 2005;33:248–253.
- Chakir J, Shannon J, Molet S, Fukakusa M, Elias J, Laviolette M, Boulet LP, Hamid Q. Airway remodeling-associated mediators in moderate to severe asthma: effect of steroids on TGF- β , IL-11, IL-17, and type I and type III collagen expression. *J Allergy Clin Immunol* 2003;111:1293–1298.
- Al-Alwan LA, Chang Y, Baglione CJ, Risse PA, Halayko AJ, Martin JG, Eidelman DH, Hamid Q. Autocrine-regulated airway smooth muscle cell migration is dependent on IL-17-induced growth-related oncogenes. *J Allergy Clin Immunol* 2012;130:977–985.e6.
- Rickel EA, Siegel LA, Yoon BR, Rottman JB, Kugler DG, Swart DA, Anders PM, Tocker JE, Comeau MR, Budelsky AL. Identification of functional roles for both IL-17RB and IL-17RA in mediating IL-25-induced activities. *J Immunol* 2008;181:4299–4310.
- Papp KA, Reid C, Foley P, Sinclair R, Salinger DH, Williams G, Dong H, Krueger JG, Russell CB, Martin DA. Anti-IL-17 receptor antibody AMG 827 leads to rapid clinical response in subjects with moderate to severe psoriasis: results from a phase I, randomized, placebo-controlled trial. *J Invest Dermatol* 2012;132:2466–2469.
- Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, Aras G, Li J, Russell CB, Thompson EH, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 2012;366:1181–1189.
- Pavelka K, Chon Y, Newmark R, Erondy N, Lin S. A randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety, tolerability, and efficacy of brodalumab (AMG 827) in subjects with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Rheum* 2012;64:S362.
- Targan S, Feagan B, Vermeire S, Panaccione R, Melmed G, Bloch C, Newmark R, Zhang N, Chon Y, Lin S, et al. A randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of AMG 827 in subjects with moderate to severe Crohn's disease. 2012 Digestive Disease Week Annual Meeting. May 19–22, 2012, San Diego, CA.
- Busse WW, Holgate ST, Kerwin EM, Chon Y, Feng J, Lin JH, Lin S-L. A randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety, tolerability, and efficacy of brodalumab (AMG 827) in subjects with moderate to severe asthma [abstract]. *J Allergy Clin Immunol* 2013;131:AB230.
- Juniper EF, Bousquet J, Abetz L, Bateman ED, Committee G; GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100:616–621.
- Holgate ST. Trials and tribulations in identifying new biologic treatments for asthma. *Trends Immunol* 2012;33:238–246.
- Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R Jr, Castro M, Curran-Everett D, Fitzpatrick AM, et al; National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315–323.
- Advair [United States prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; September 2011.
- Aun MV, Ribeiro MR, Costa Garcia CL, Agondi RC, Kalil J, Giavina-Bianchi P. Esophageal candidiasis—an adverse effect of inhaled corticosteroids therapy. *J Asthma* 2009;46:399–401.
- Flovent [United States prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; September 2011.
- Fukushima C, Matsuse H, Tomari S, Obase Y, Miyazaki Y, Shimoda T, Kohno S. Oral candidiasis associated with inhaled corticosteroid use: comparison of fluticasone and beclomethasone. *Ann Allergy Asthma Immunol* 2003;90:646–651.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.