A Randomized, Double-blind, Placebo-controlled Study of Tumor Necrosis Factor-α Blockade in Severe Persistent Asthma

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***Rationale*: The treatment effect of golimumab, a human monoclonal antibody against tumor necrosis factor (TNF)-α, in severe persistent asthma is unknown.**

***Objectives*: To assess the safety and efficacy of golimumab in a large population of patients with uncontrolled, severe persistent asthma.**

***Methods*: From 2004 to 2006, 309 patients with severe and uncontrolled asthma, despite high-dose inhaled corticosteroids and long-acting β_2 agonists, were randomized 1:1:1:1 to monthly subcutaneous injections of placebo or golimumab (50, 100, or 200 mg) through Week 52. Coprimary endpoints were the change from baseline through Week 24 in prebronchodilator percent-predicted FEV_1 and the number of severe asthma exacerbations through Week 24.**

***Measurements and Main Results*: No significant differences were observed for the change in percent-predicted FEV_1 (least squares mean: placebo, 2.44 [95% confidence interval (CI) −0.574 to 5.461]; combined 100-mg and 200-mg, 2.91 [0.696–5.116]) or severe exacerbations (mean ± SD: placebo, 0.5 ± 1.07 vs. combined 100-mg and 200-mg 0.5 ± 0.97) through week 24. Through Week 24, 2.6% of patients treated with placebo vs. 19.5% of those treated with golimumab discontinued the study agent, and 1.3% and 7.8% discontinued study participation, respectively. An unfavorable risk–benefit profile led to early discontinuation of study-agent administration after the Week-24 database lock. Through Week 76, 20.5% of patients treated with placebo and 30.3% of patients treated with golimumab experienced serious adverse events, with serious infections occurring more frequently in golimumab-treated patients. One death and all eight malignancies occurred in the active groups.**

***Conclusions*: Overall, treatment with golimumab did not demonstrate a favorable risk–benefit profile in this study population of patients with severe persistent asthma.**

Clinical trial registered with www.clinicaltrials.gov (NCT00207740).

Keywords: golimumab; asthma; tumor necrosis factor-α

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The treatment effect of golimumab, a human monoclonal antibody against tumor necrosis factor-α, in severe persistent asthma is unknown.

What This Study Adds to the Field

The unfavorable risk-benefit profile for golimumab in the overall population suggests that this therapeutic approach may not be suitable for all patients with asthma.

Asthma is an increasingly common disease in industrialized countries. Mild forms of asthma are easily treatable such that patients are able to live normal lives with minimal pharmacologic intervention. In contrast, the relatively small subset of patients with severe asthma (5–15% depending on definition) remains difficult to treat and contributes up to half of the overall costs of the disease (1–3). Although corticosteroids, long-acting β_2-agonists (LABA), and other therapies are effective in treating the majority of patients with asthma, patients with severe asthma respond poorly to these medications, and alternative treatments are warranted (4, 5).

Tumor necrosis factor (TNF)-α has several properties that make it a potentially attractive target molecule for treating patients with severe asthma (6–10). It is produced by cells of interest in asthma (e.g., lymphocytes, macrophages, mast cells), with studies suggesting that TNF-α further polarizes Th2 cells (11). In humans, the inhalation of TNF-α results in increased bronchial hyperresponsiveness (BHR) (12), which may be a direct effect of TNF-α on airway smooth–muscle cell responsiveness to contractile stimulants such as bradykinin and carbachol (13–15). Alternatively, BHR could increase indirectly as a result of the increased neutrophils observed in sputum following TNF-α challenge (9). TNF-α also enhances expression of adhesion mol-

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†A listing of the T03 Asthma Investigators can be found at the end of this article.

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ecules, which may then contribute to the increased parenchymal and airway neutrophils observed in severe asthma (5, 16–18).

TNF-α inhibition has improved therapy for many immune-mediated inflammatory diseases, including rheumatoid arthritis, Crohn's disease, and psoriasis. Recently, small studies of an antibody to TNF-α (infliximab) (19) or the soluble TNF-α receptor (etanercept) (20–22) reported mixed results in patients with a range of asthma severity. The objective of this study was to assess the safety and efficacy of golimumab, a fully human monoclonal antibody to TNF-α similar to infliximab, in a large population of patients with uncontrolled, severe persistent asthma. Abstracts containing results of this study have been previously presented or published (23–25).

METHODS

Patients

Patients 18 years of age or older, diagnosed with asthma for 3 or more years and uncontrolled severe asthma for 1 year or more, were eligible for this study (26, 27). Patients were required to have exhibited asthma symptoms on more than one-third of days for 3 or more months before screening despite continuous treatment with high-dose inhaled corticosteroids (ICS) (fluticasone ⩾1000 μg or equivalent) and LABA, with or without continuous oral corticosteroids (OCS); two or more asthma exacerbations within the previous year; 1 or more years without smoking and a smoking history of less than 10 pack-years (i.e., 1 pack-year = 20 cigarettes smoked per day for 1 year or equivalent); and a history of at least one of the following within 5 years of screening: postbronchodilator reversibility in FEV_1 of 12% or greater, 30% or greater diurnal variation in peak expiratory flow rate (PEFR), or BHR. Exclusion criteria included any other significant respiratory or cardiac diseases, worsening of asthma symptoms requiring treatment with additional OCS within 4 weeks of screening, or a life-threatening asthma attack requiring cardiopulmonary support within 6 months of screening. The independent Ethics Committee or Institutional Review Board at each study site approved the protocol. All patients provided written informed consent.

Study Design

This phase 2, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study assessed the safety and efficacy of multiple subcutaneous injections of golimumab in patients with uncontrolled severe persistent asthma. Following a 2-week run-in phase, during which background ICS and LABA (fluticasone propionate 500 μg/salmeterol 50 μg twice daily) were standardized, patients were randomly assigned 1:1:1:1 to one of four treatment groups via an interactive voice-response system, using an adaptive allocation method stratified by investigational site and OCS use (28). Subcutaneous injections of placebo, 50 mg golimumab (75 mg loading

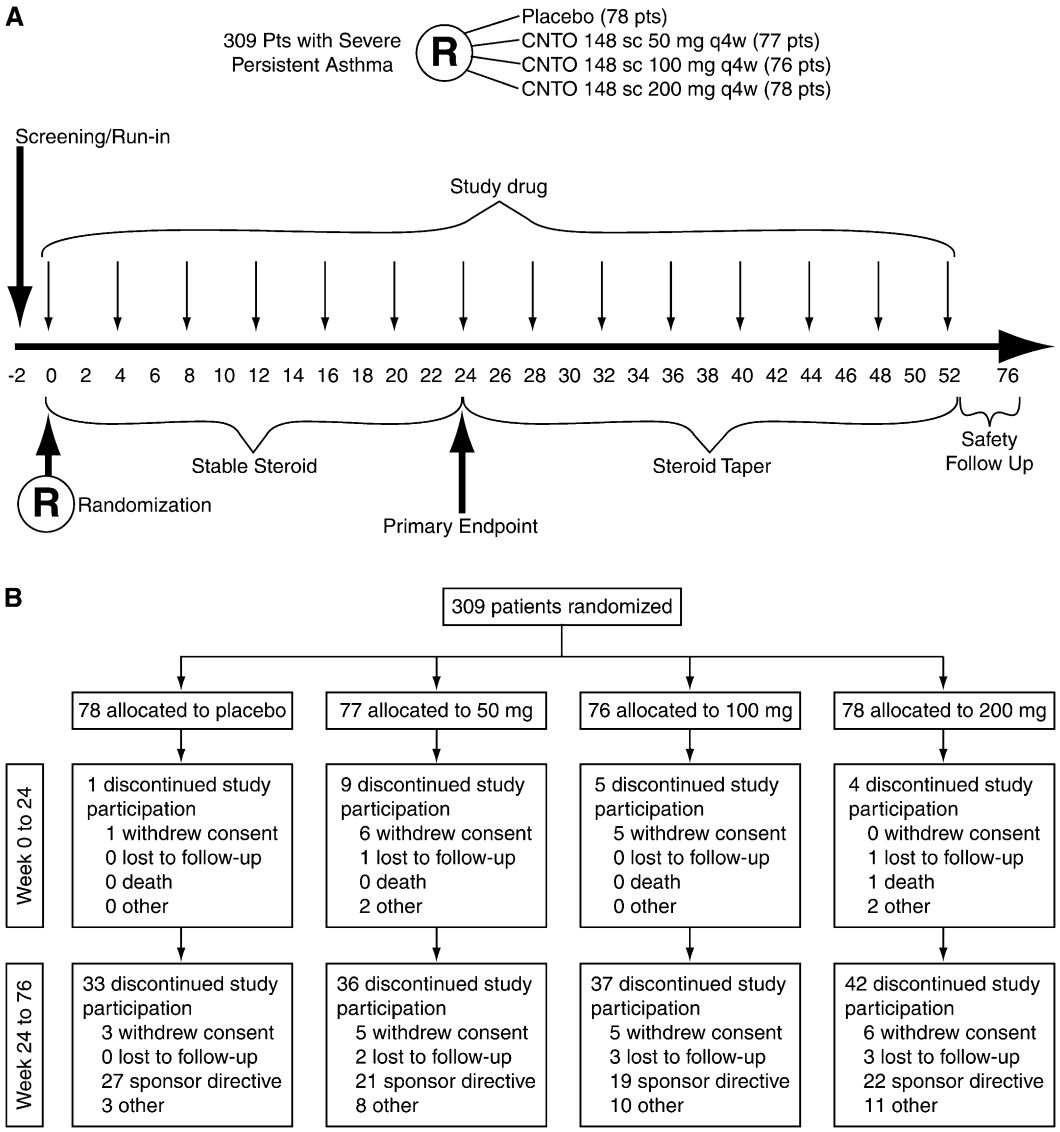


Figure 1. (*A*) Study design and (*B*) patient flow. R = randomization; pts = patients; sc = subcutaneous; q4w = every 4 weeks.

dose at baseline), 100 mg golimumab (150 mg at baseline), or 200 mg golimumab (300 mg at baseline) were given every 4 weeks for 52 weeks. All patients were provided with fluticasone 500 mcg/salmeterol 50 mcg for use during the first 52 weeks of the study. From Weeks 0 to 24, patients were required to remain on their initial OCS and/or ICS doses established during the run-in phase. From Weeks 24 to 52, a reduction in CS was attempted, per protocol. Patients were followed through Week 76 (Figure 1A).

Coprimary endpoints were (*1*) change in prebronchodilator percent-predicted FEV_1 and (*2*) number of severe asthma exacerbations from baseline through Week 24. Major secondary endpoints included the change from baseline through Week 24 in the Asthma Quality of Life Questionnaire (AQLQ) (29) score, rescue medication use (short-acting β_2 agonists), and domiciliary morning PEFR.

Study data were locked for analysis at Weeks 24 and 76. Group-level data were unblinded to the Steering Committee and the sponsor for the Week-24 database lock. Patient-level data remained blinded through Week 76. Efficacy data through Week 24 and safety data through Week 76 are reported here.

Efficacy Evaluations

The coprimary efficacy endpoints of FEV_1 and number of severe asthma exacerbations were assessed every 4 weeks from baseline through Week 64 and again at Week 76. Bronchodilator reversibility was based on the FEV_1 response 15 to 30 minutes after administration of 4 puffs of albuterol/salbutamol via metered dose inhaler with a spacer. AQLQ score was assessed at Weeks 0, 12, 24, 36, 52, 64, and 76. Domiciliary PEFR, rescue medication use, and symptoms were recorded daily by an electronic peak-flow meter/e-diary device.

The coprimary endpoint of severe asthma exacerbation was defined as an episode of worsening asthma requiring treatment with intravenous (IV) or OCS (an addition or increase of OCS ⩾20 mg/d from baseline). A mild asthma exacerbation was defined as a greater than 20% decrease in morning PEFR or more than three additional inhalations of rescue medication per 24 hours on two consecutive days compared with baseline or an increase in nocturnal awakenings due to asthma on two consecutive nights compared with baseline.

Safety Evaluations

Safety was assessed during each study visit and by monitoring adverse events (AEs) and serious adverse events (SAEs). Routine laboratory tests were assessed at baseline and Weeks 12, 24, 36, and 52. An independent Safety Monitoring Committee periodically reviewed all data and made recommendations to the Steering Committee regarding study continuation.

Statistical Design

The primary efficacy analyses used the intention-to-treat population. The coprimary endpoints were the change in prebronchodilator

TABLE 1. BASELINE DEMOGRAPHICS, DISEASE CHARACTERISTICS, AND CONCOMITANT MEDICATIONS

		Golimumab		
	Placebo	50 mg	100 mg	200 mg
N	78	77	76	78
Female	42 (53.8)	46 (59.7)	39 (51.3)	46 (59.0)
Age, yr	49.4 ± 12.0	49.4 ± 11.3	49.1 ± 12.9	52.7 ± 12.3
Race				
Caucasian	66 (84.6)	66 (85.7)	69 (90.8)	71 (91.0)
Black	12 (15.4)	8 (10.4)	7 (9.2)	6 (7.7)
Asian	0 (0)	0 (0)	0 (0)	1 (1.3)
Other	0 (0)	3 (3.9)	0 (0)	0 (0)
Body mass index, kg/m^2	31.0 ± 8.36	30.3 ± 6.75	29.9 ± 7.68	29.4 ± 7.31
Disease duration, yr	24.4 ± 16.2	23.4 ± 16.5	22.9 ± 13.0	24.3 ± 14.5
Patients with ⩾1 asthma-related emergency room visits within the previous year	31 (39.7)	26 (33.8)	15 (19.7)	22 (28.2)
Patients with ⩾1 asthma-related hospitalizations within the previous year	18 (23.1)	18 (23.4)	14 (18.4)	13 (16.7)
Patients with a history of smoking*	19 (24.4)	20 (26.0)	26 (34.2)	16 (20.5)
FEV_1% predicted prebronchodilator	60.9 ± 11.11	59.6 ± 11.46	58.9 ± 12.11	59.8 ± 11.16
FEV_1% predicted postbronchodilator	69.6 ± 11.08	69.2 ± 14.09	68.9 ± 14.32	68.8 ± 12.39
FEV_1 BD reversibility	15.6 ± 15.32	16.9 ± 16.03	17.8 ± 14.73	15.6 ± 13.90
Patients with ⩾12% FEV_1 BD reversibility	36 (46.2)	40 (51.9)	47 (61.8)	41 (52.6)
PEFR, L/min	303 ± 123.6	288 ± 107.6	299 ± 112.9	269 ± 114.0
AQLQ (1–7 scale)	4.3 ± 1.2	4.0 ± 1.1	4.0 ± 1.2	4.4 ± 1.0
ACQ (0–6 scale)	3.0 ± 0.8	3.0 ± 0.8	3.1 ± 0.8	2.9 ± 0.7
Patients receiving concomitant medications at study entry†				
CS	78 (100)	77 (100)	76 (100)	78 (100)
ICS only	53 (67.9)	52 (67.5)	51 (67.1)	54 (69.2)
OCS only	0 (0)	0 (0)	0 (0)	0 (0)
ICS and OCS	25 (32.1)	25 (32.5)	25 (32.9)	24 (30.8)
Theophylline	23 (29.5)	12 (15.6)	19 (25.0)	18 (23.1)
β_2-agonists	78 (100)	77 (100)	76 (100)	78 (100)
Long-acting	78 (100)	77 (100)	76 (100)	78 (100)
Leukotriene modifiers	25 (32.1)	31 (40.3)	25 (32.9)	22 (28.2)
Anticholinergics	16 (20.5)	16 (20.8)	9 (11.8)	12 (15.4)
Long-acting	7 (9.0)	6 (7.8)	5 (6.6)	3 (3.8)
Short-acting	10 (12.8)	11 (14.3)	4 (5.3)	9 (11.5)

Definition of abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BD = bronchodilator; CS = corticosteroids; ICS, inhaled corticosteroids; OCS, oral corticosteroids; PEFR, peak expiratory flow rate.

Data presented as n (%) or mean ± SD.

* All patients had not smoked for at least 1 year before study entry and had a smoking history of fewer than 10 pack-years.

† Patients were to remain on the same dose of asthma controller medications through Week 52, except for the treatment of exacerbations.

percent-predicted FEV_1 from baseline through Week 24 for the number of severe asthma exacerbations from baseline through Week 24 for the combined 100 and 200 mg golimumab group compared with the placebo group. The Hochberg step-up procedure (30) was used to maintain a 0.05 or less type I error rate. Analysis of covariance (ANCOVA) adjusted for investigator region, OCS use, and FEV_1 at baseline was used to compare the change from baseline in FEV_1. The "last observation carried forward" method was used to impute missing FEV_1 values at Week 24. The Cochran Mantel-Haenszel Row Mean Scores test, stratified for investigator region, OCS use, and FEV_1 at baseline, was used to compare the number of severe asthma exacerbations. Using an implicit modeling method (31), the number of exacerbations for patients who withdrew early was imputed from the worst outcome of a "similar" patient who did not withdraw. A similar patient was defined as one whose exacerbations during the same observation period were less than or equal to that observed in the patient who withdrew. If a similar patient could not be identified, the maximum number of asthma exacerbations observed in the entire study population was used.

A sample size of 300 patients (75 patients per treatment group) was planned with 86% power to detect a 10% improvement in FEV_1 and 79% power to detect a 35% reduction in severe asthma exacerbations relative to placebo at a 0.05 significance level, assuming that the change in FEV_1 from baseline through Week 24 had a standard deviation of 23% predicted and the rate of severe asthma exacerbation was 2 per year in the placebo group.

Predefined subgroup analyses were planned to support the coprimary endpoints. Subgroups were defined by age ($\geq$ median or $<$ median), weight ($\geq$ median or $<$ median), sex, race (Caucasian or non-Caucasian), baseline OCS use (yes or no), investigational-site region (Eastern Europe, Western Europe, or North America), baseline FEV_1 ($\geq$ median or $<$ median), age of asthma onset ($\geq$12 yr or $<$12 yr) and number of hospitalizations or emergency room visits within 1 year before screening. Within each subgroup, the odds ratio (OR) for having 1 or more severe asthma exacerbations was calculated to assess the treatment effect between placebo and golimumab (100 and 200 mg). Post-hoc exploratory analyses without adjustment for multiple comparisons were performed for the following subgroups: baseline FEV_1 reversibility ($\geq$12% or $<$12%), current or historical sinusitis (yes or no). To support the validity of the sinusitis categorization, a subset of patients completed a sinusitis questionnaire, a 27-item instrument measuring sinusitis symptoms (scale 0–108) (32); overall scores were compared between patients with and without a reported history of sinusitis.

Role of the Funding Source

This study sponsor, Centocor, Inc., designed the protocol, which was approved by the Steering Committee. Study data were collected by the investigators and transmitted to a central database. All authors participated in the data interpretation, writing of the manuscript, and decision to submit the manuscript for publication.

RESULTS

Patient Characteristics and Disposition

Between October 2004 and July 2006, 309 patients were randomized at 53 study sites in the United States and Europe. A total of 78 patients were randomly assigned to the placebo, 77 to 50-mg, 76 to 100-mg, and 78 to the 200-mg golimumab group. Baseline demographics, disease characteristics, and concomitant medications were similar across all groups (Table 1).

Through Week 24, 2 patients in the placebo, 14 in the 50-mg, 17 in the 100-mg, and 13 in the 200-mg golimumab group discontinued the study agent, most commonly due to AEs (Table 2). Per

TABLE 2. SAFETY ASSESSMENTS FROM BASELINE THROUGH WEEK 76* BY MeDDRA PREFERRED TERM, TREATED PATIENTS

		Golimumab		
	Placebo	50 mg	100 mg	200 mg
N	78	75	78	78
Patients who discontinued study agent due to adverse events through Week 24	1 (1.3)	7 (9.1)	11 (14.5)	9 (11.5)
Patients with $\geq$1 adverse events	75 (96.2)	69 (92.0)	77 (98.7)	78 (100)
Patients with adverse events occurring $\geq$3% more frequently in the combined golimumab groups than placebo				
Sinusitis	9 (11.5)	19 (25.3)	17 (21.8)	10 (12.8)
Pneumonia	4 (5.1)	7 (9.3)	8 (10.3)	5 (6.4)
Nausea	1 (1.3)	2 (2.7)	6 (7.7)	3 (3.8)
Injection site erythema	0 (0)	2 (2.7)	4 (5.1)	4 (5.1)
Patients with $\geq$1 infections	54 (69.2)	50 (66.7)	55 (70.5)	56 (71.8)
Patients with $\geq$1 serious adverse events	16 (20.5)	24 (32.0)	24 (30.8)	22 (28.2)
Patients with common serious adverse events occurring in $>$2 patients in the combined golimumab groups				
Asthma exacerbation†	7 (9.0)	12 (16.0)	6 (7.7)	9 (11.5)
Pneumonia	1 (1.3)	3 (4.0)	5 (6.4)	2 (2.6)
Cellulitis	0 (0)	1 (1.3)	1 (1.3)	2 (2.6)
Sepsis	0 (0)	1 (1.3)	0 (0)	2 (2.6)
Chest pain	0 (0)	0 (0)	1 (1.3)	2 (2.6)
Patients with $\geq$1 serious infections	7 (9.0)	14 (18.7)	12 (15.4)	10 (12.8)
Patients with malignancies	0 (0)	1 (1.3)	2 (2.6)	5 (6.4)
B-cell lymphoma	0 (0)	0 (0)	1 (1.3)	0 (0)
Basal cell carcinoma	0 (0)	0 (0)	0 (0)	2 (2.6)
Breast cancer	0 (0)	1 (1.3)	0 (0)	0 (0)
Cervix carcinoma	0 (0)	0 (0)	0 (0)	1 (1.3)
Colon cancer (stage 0)	0 (0)	0 (0)	0 (0)	1 (1.3)
Malignant melanoma	0 (0)	0 (0)	1 (1.3)	0 (0)
Renal cell carcinoma	0 (0)	0 (0)	0 (0)	1 (1.3)

Definition of abbreviation: MedDRA, Medical Dictionary for Regulatory Activities.

Data presented as n (%).

* Unless noted otherwise.

† Asthma exacerbations reported here are based on the standard definition of a serious adverse event, which does not indicate the severity of exacerbation or describe whether or which medications were required to treat. Most severe asthma exacerbations that met the criteria for the coprimary efficacy endpoint of severe did not meet the criteria for a serious adverse event.

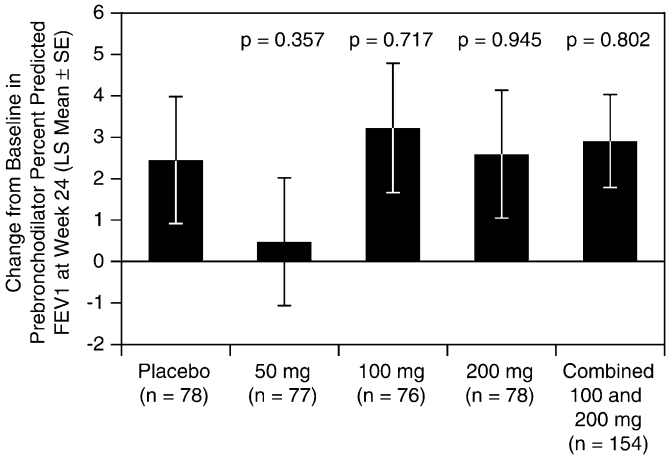


Figure 2. Change from baseline in prebronchodilator percent-predicted FEV_1 through Week 24. LS = least squares.

protocol, patients discontinuing study treatment before Week 24 were to complete all study assessments though Week 36. However, 19 patients discontinued study follow-up before Week 24 (1 in the placebo, 9 in the 50-mg, 5 in the 100-mg, and 4 in the 200-mg golimumab group) (Figure 1B). Concomitant medication use remained generally consistent from baseline through Week 24, with all patients continuing on high-dose ICS and LABA (data not shown).

Efficacy

No significant differences between placebo and active treatment were observed for either coprimary endpoint. All treatment groups demonstrated small increases in prebronchodilator percent-predicted FEV_1 at Week 24 without significant differences between groups (least squares [LS] mean: placebo, 2.44 [95% CI −0.574 to 5.461] vs. combined 100-mg and 200-mg, 2.91 [0.696–5.116]) (Figure 2). The mean (± SD) number of severe exacerbations from baseline through Week 24 was 0.5 ± 1.07 for placebo and 0.5 ± 0.97 for the combined 100-mg and 200-mg group. The majority of patients were free from severe asthma exacerbations through Week 24 (patients with severe exacerbations in the placebo, 50-mg, 100-mg, and 200-mg groups: 32.1, 31.2, 19.7, and 24.4%, respectively) (Figure 3). Although there were no significant differences in the coprimary endpoint of the number of severe exacerbations in the first 24 weeks ($P = 0.1$ for 100-mg golimumab), both the 100-mg and 200-mg groups showed a trend toward increased time-free-from-exacerbation through Week 24 compared with placebo (hazard ratio [HR]: 0.63; 95% CI, 0.377–1.060; $P = 0.08$ for the combined 100-mg and 200-mg group) (Figure 4A).

All groups demonstrated clinically meaningful improvement in mean AQLQ score at Week 24 (placebo, 0.54 ± 0.91; 100-mg and 200-mg golimumab, 0.71 ± 1.02) without significant treatment effect. There was no meaningful difference between groups from baseline through Week 24 in mean rescue medication use (placebo, −0.62 ± 1.93 puffs/d; 100-mg and 200-mg, −0.74 ± 2.19 puffs/d), PEFR (placebo, 4.73 ± 60.91 L/min; 100-mg and 200-mg, 2.98 ± 59.77 L/min), Asthma Control Questionnaire score (placebo, −0.76 ± 0.89; 100-mg and 200-mg, −0.83 ± 0.94), or Short Form-36 Health Survey component summary scores (physical: placebo, 3.16 ± 8.13; 100-mg and 200-mg, 4.14 ± 8.19; mental: 0.31 ± 8.76 and 1.18 ± 9.19, respectively).

Safety

After reviewing safety data at the Week-24 database lock, the SMC recommended, and the Steering Committee agreed, to discontinue study-agent administration due to an unfavorable risk-benefit profile observed in the patients treated with golimumab. At the time of this recommendation, approximately half of those patients remaining in the study had completed the Week-52 visit.

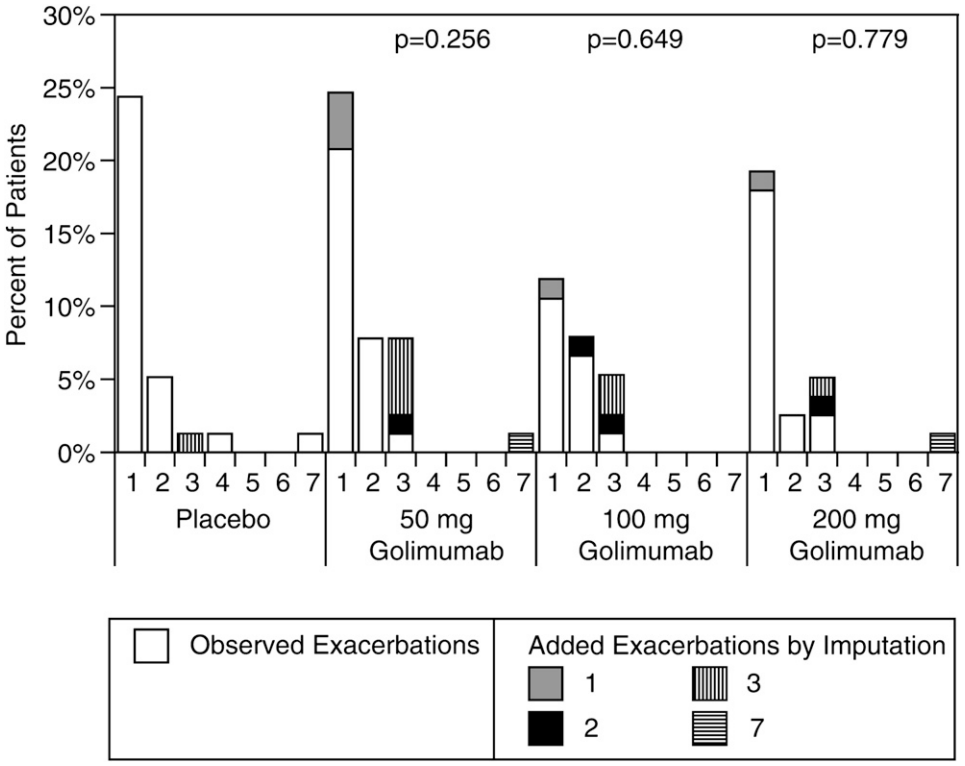


Figure 3. Number of severe asthma exacerbations from baseline through Week 24. *Open bars* represent exacerbations observed in patients who completed study participation through Week 24. *Shaded bars* represent additional exacerbations calculated for patients who withdrew early, imputed from the worst outcome of a "similar" patient whose exacerbations during the same observation period was less than or equal to that observed in the patient who withdrew. If a similar patient could not be identified, the maximum number of exacerbations observed in the entire study population was used.

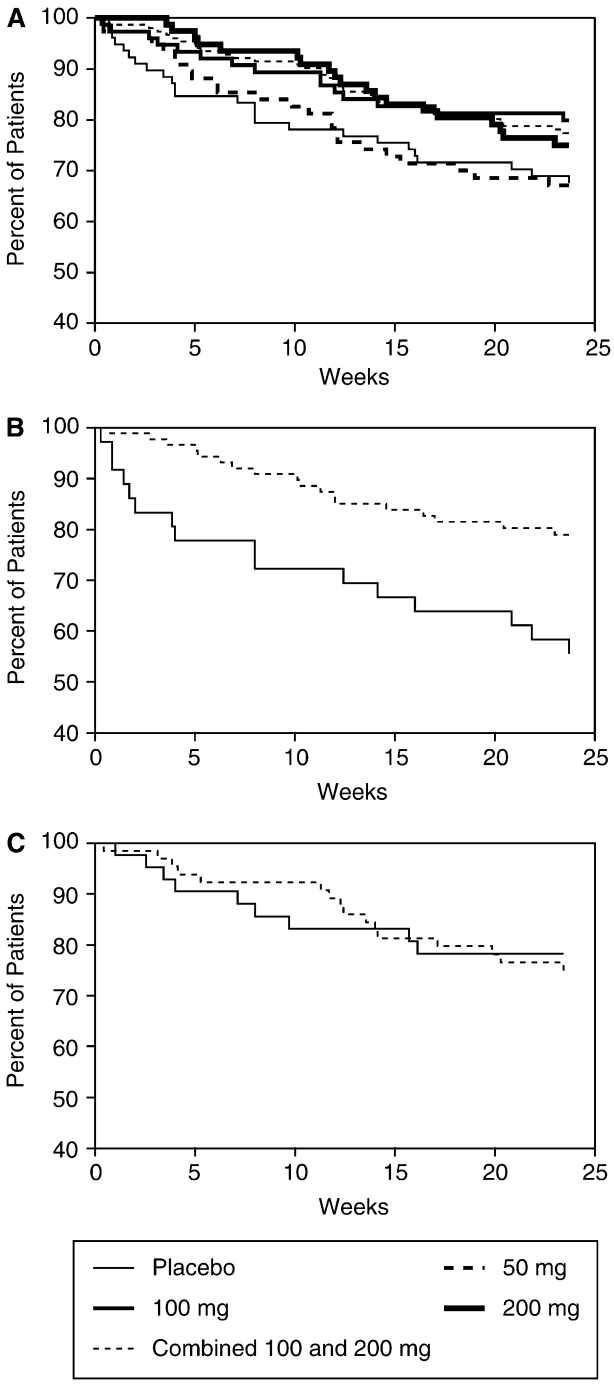


Figure 4. Percent of patients free from severe asthma exacerbation. (*A*) All patients: all groups. (*B*) Patients with 12% or greater reversibility in baseline FEV_1: placebo versus combined 100-mg and 200-mg golimumab group. (*C*) Patients with less than 12% reversibility in baseline FEV_1: placebo versus combined 100-mg and 200-mg golimumab group.

Through Week 76, asthma exacerbation was the most frequently reported AE across all groups (placebo, 91.0%; golimumab, 89.2%). AEs classified as infections occurred at a similar rate in the placebo and golimumab groups overall, with sinusitis, upper respiratory tract infection, nasopharyngitis, and bronchitis being the most commonly observed. Sinusitis, pneumonia, nausea, and injection-site erythema occurred greater than or equal to 3% more frequently in the golimumab groups compared with the placebo (Table 2).

SAEs occurred more frequently in the golimumab (50-mg [32.0%], 100-mg [30.8%], and 200-mg [28.2%]) groups than in placebo (20.5%) (Table 2). Asthma exacerbation was the most common SAE across all groups, followed by pneumonia, cellulitis, sepsis, and chest pain. An increased incidence of SAEs of an infectious nature was observed in the active groups. A 73-year-old patient, treated with 100 mg, was diagnosed with tuberculosis (class 3) 189 days after the Week-48 dose; this patient had lived in a region with endemic tuberculosis and had received a BCG vaccination on an unknown date. One death occurred in the 200-mg group. This patient was hospitalized in an unresponsive state 1 week after receiving the fourth golimumab dose. The patient's respiratory status declined, requiring ventilatory support, and the patient died from septic shock following diagnosis of small bowel pneumatosis. Eight malignancies were reported in golimumab-treated patients: breast cancer in the 50-mg group; B-cell lymphoma and malignant melanoma in the 100-mg group; and cervical carcinoma, renal cell carcinoma, colon cancer (stage 0), and two basal cell carcinomas in the 200-mg group. Details regarding these malignancies are presented in Table 3.

Subgroup Analyses

Prespecified. Although the majority of prespecified subgroups did not show treatment difference, trends toward a lower risk of exacerbations with golimumab versus placebo were seen in the following subgroups: those with an age greater than or equal to the median (49.0 yr), those with greater than or equal to one hospitalization or emergency room visit within 1 year before screening, those with baseline prebronchodilator percent-predicted FEV_1 less than the median (60.5), and those with asthma onset at 12 years of age or greater (Figure 5). No prespecified subgroup analyses demonstrated any treatment effect on FEV_1.

Post-hoc. Post-hoc subgroup analysis based on baseline FEV_1 reversibility ($\geq$12% [n = 164, mean change = 26.1%] vs. <12% [n = 144, mean change = 5.5%]) indicated that reversible ($\geq$12%) patients receiving 100-mg or 200-mg golimumab were less likely than those receiving placebo to experience severe asthma exacerbations through Week 24 (20.5 vs. 44.4%; OR, 0.3; 95% CI, 0.13–0.81; $P = 0.014$) (Figure 5). Kaplan-Meier analysis of time-to-first-exacerbation through Week 24 was significantly longer for patients in the combined 100-mg and 200-mg golimumab group versus placebo in the reversible subgroup ($P = 0.005$; Figure 4B); no significant differences were observed in the less than 12% subgroup (Figure 4C). Multivariate analyses indicated that percent-predicted FEV_1 reversibility was an independent predictor of golimumab response, and that, in patients with 12% or more FEV_1 reversibility (n = 164, 53% of total study population), golimumab treatment demonstrated the greatest reduction in the number of severe asthma exacerbations through Week 24 (mean ± SD: 100-mg and 200-mg golimumab, 0.32 ± 0.72; placebo, 0.75 ± 1.36; $P = 0.010$).

Further post-hoc subgroup analysis based on history of sinusitis also showed a similar treatment difference (Figure 5). The validity of the current or past sinusitis data was supported by the sinusitis questionnaire data (n = 145) that measured a 50% or higher baseline score in patients with a reported history of sinusitis than those without (mean ± SD, 38.4 ± 19.9 vs. 24.0 ± 18.2; $P < 0.001$).

DISCUSSION

This is the only large-scale, double-blind, placebo-controlled, dose-ranging study to date of a monoclonal antibody to TNF-α

TABLE 3. MALIGNANCY

Malignancy	Age/Sex	Treatment	Doses Prior to Diagnosis	Study Day of Diagnosis	Comments
Breast carcinoma	63/F	50 mg	5	Day 139	History of a benign tumor in right breast, surgically excised 12 yr before study entry. Histopathology of current tumor: carcinoma praccipue tubullare invasium. Patient underwent radical mastectomy. Subsequent treatment unknown.
Metastatic melanoma	78/F	100 mg	5	Day 159	History of nasal polyps. Resection of extremely fast-growing nasal polyp resulted in diagnosis of sinonasal melanoma. PET scan 2 mo later revealed metastases to right hilum and both lungs.
B-cell lymphoma	59/F	100 mg	10	Day 281	Enlargement of left inguinal lymph node and swelling of left leg 2 mo prior to diagnosis of follicular lymphoma, grade IIIA. Patient prescribed 8 cycles of IV chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone).
Renal cell carcinoma	67/M	200 mg	3	Day 76	Diagnosed with advanced metastatic disease. Right kidney surgically removed. Metastases of liver, bones, and lungs documented 6 mo later.
Cervical carcinoma	49/F	200 mg	6	Day 160	Prestudy cytology of concern. Patient experienced metrorrhagia, which led to a diagnosis of cervical planoepithelial carcinoma subsequently treated with moderate intensity brachytherapy.
Basal cell carcinoma	76/M	200 mg	2	Day 225	History of basal cell carcinomas on face and head.
Colon cancer (stage 0)	71/F	200 mg	14	Day 374	Adenocarcinoma in situ diagnosed following routine colonoscopy with polypectomy. Colonoscopy 3 mo later without any clinical signs/symptoms.
Basal cell carcinoma	63/M	200 mg	14	Day 448	Basal cell carcinoma of the head.

in severe asthma. An unfavorable risk-benefit profile observed in patients who received golimumab led to early discontinuation of study agent after the Week-24 database lock. Treatment with golimumab failed to achieve significant treatment effect on either of the two coprimary endpoints of FEV_1 or severe asthma exacerbation.

Several previous, but more limited, studies suggested that inhibition of TNF-α might improve outcomes in patients with severe asthma. In particular, a 10-subject crossover study comparing etanercept with placebo demonstrated significant improvements in bronchial hyperresponsiveness, FEV_1, and asthma-related quality of life; however, the study was not of sufficient duration or size to determine any effect on exacerbations (20). An additional parallel group study in 39 subjects with the same compound demonstrated a small but significant improvement in the Asthma Control Questionnaire score but no improvement in other endpoints (22).

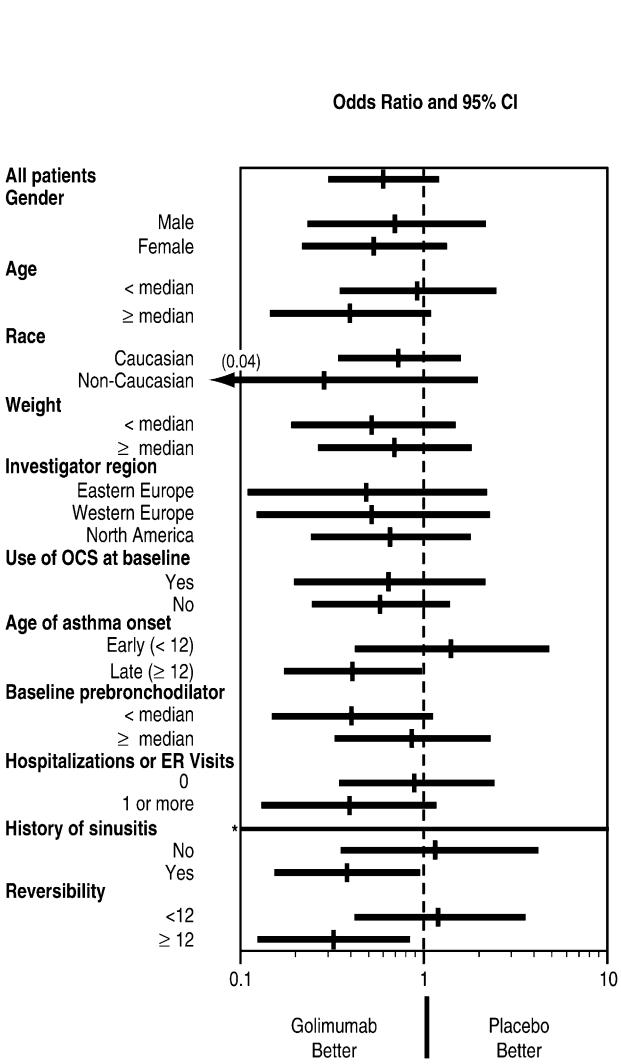
In the study presented here, after the Week-24 database lock, the SMC recommended discontinuation of further dosing based on the lack of a sufficient risk-benefit profile in the overall population. Infections, including serious and life-threatening infections, were more common in the golimumab groups. Specifically, there were increases in respiratory SAEs, including pneumonia, that were not commonly observed in anti-TNF-α trials in other diseases (33). All patients in this study were taking high-dose ICS and approximately one-third were taking additional OCS. There was a higher incidence of infections in patients receiving OCS that appeared to be dose-related. Several recent studies suggest ICS therapy (and asthma itself) is associated with an increased risk for pneumonia (4, 34). The findings from this study suggest that inhibiting TNF-α in patients with asthma taking ICS or OCS may further increase the risk of pneumonia.

Eight malignancies were reported in the active groups, five of which were observed in the highest dose group. Notably, seven of the eight malignancies occurred in patients without a bronchodilator (BD) response, suggesting that malignancies may be more common in certain phenotypes. The single malignancy in the BD responsive group was a colonic polyp. Although the incidence of malignancies per 100 patient-years in this study was 0.00 (95% CI, 0.00–2.94) in placebo-treated patients and 3.09 (95% CI, 1.33–6.08) in golimumab-treated patients, the confidence intervals for the placebo and golimumab groups overlapped.

Asthma has not been clearly associated with an increased risk of cancer. Conflicting data from cohort studies have suggested either a protective effect of asthma or a slightly elevated risk of cancer associated with asthma (35–38). In comparison, current published data do not exclude the possibility that there is an increased risk of malignancies due to anti-TNF antibody therapy. In a meta-analysis of patients with rheumatoid arthritis treated with infliximab or adalimumab, there was evidence of a dose-dependent increased risk of malignancy (39). In contrast, other reports suggest that inhibition of TNF-α may represent a promising therapeutic option in the treatment of pancreatic tumors and renal cell carcinoma (40, 41). Data from several large golimumab studies in rheumatologic indications will soon be available and may help elucidate if golimumab therapy is associated with an increased risk of malignancy.

Although the overall study population did not improve in either coprimary endpoint, subsequent post-hoc analyses for age of onset and BD responsiveness suggest that this result may be due to the well-recognized heterogeneity of this population (18, 42, 43) and the possibility that certain phenotypes may be responsive to TNF-α blockade, (e.g., subjects with the highest TNF expression on peripheral mononuclear cells who responded best in the study by Berry and colleagues [20]). First, based on a prespecified analysis, greater efficacy was shown in 72% of patients with asthma onset later in life (at 12 yr of age or older), a phenotype of severe asthma different from those with early-age onset (4, 42). Although the reasons for the better efficacy in the prespecified late-onset asthma group are unclear, compared with early-onset asthma, late-onset asthma is less atopic (42) and may be associated with viral or atypical bacterial infections (44, 45), aspirin sensitivity (46), occupational exposures (47), gastroesophageal reflux (48), and neutrophilic inflammation (42).

Second, post-hoc analysis of patients with 12% or greater BD response at study entry (53% of all patients) showed efficacy for prevention of exacerbations. A 12% or greater BD response was not required at study entry because it is known that some patients with severe asthma, who may have shown a BD response in the past, develop fixed airway limitation over time; and that older patients have been reported to demonstrate less BD response (49). It is conceivable that these patients with fixed airflow limitation represent a different severe asthma phenotype that is less responsive to anti-TNF agents.



Proportion of Patients with At Least 1 Severe Asthma Exacerbation from Baseline through Week 24

	Placebo n	Placebo (%)	Golimumab 100/200 Combined n	Golimumab 100/200 Combined (%)	Odds Ratio	95% CI	p-value
All patients	78	(32.1)	154	(22.1)	0.6	(0.31, 1.16)	0.112
Gender							
Male	36	(25.0)	69	(18.8)	0.7	(0.24, 2.10)	0.461
Female	42	(38.1)	85	(24.7)	0.5	(0.22, 1.28)	0.147
Age							
< median	39	(30.8)	69	(29.0)	0.9	(0.36, 2.40)	1.000
≥ median	39	(33.3)	85	(16.5)	0.4	(0.15, 1.05)	0.059
Race							
Caucasian	66	(27.3)	140	(21.4)	0.7	(0.35, 1.53)	0.380
Non-Caucasian	12	(58.3)	14	(28.6)	0.3	(0.04, 1.88)	0.233
Weight							
< median	32	(34.4)	84	(21.4)	0.5	(0.20, 1.43)	0.159
≥ median	46	(30.4)	69	(23.2)	0.7	(0.27, 1.75)	0.396
Investigator region							
Eastern Europe	24	(25.0)	43	(14.0)	0.5	(0.11, 2.12)	0.324
Western Europe	22	(27.3)	43	(16.3)	0.5	(0.13, 2.21)	0.336
North America	32	(40.6)	68	(30.9)	0.7	(0.25, 1.73)	0.371
Use of OCS at baseline							
Yes	25	(36.0)	49	(26.5)	0.6	(0.20, 2.09)	0.430
No	53	(30.2)	105	(20.0)	0.6	(0.25, 1.33)	0.168
Age of asthma onset							
Early (< 12)	28	(28.6)	39	(35.9)	1.4	(0.44, 4.66)	0.604
Late (≥ 12)	50	(34.0)	115	(17.4)	0.4	(0.18, 0.94)	0.025
Baseline prebronchodilator							
< median	34	(38.2)	80	(20.0)	0.4	(0.15, 1.08)	0.059
≥ median	44	(27.3)	74	(24.3)	0.9	(0.34, 2.22)	0.827
Hospitalizations or ER Visits							
0	40	(25.0)	105	(22.9)	0.9	(0.36, 2.34)	0.828
1 or more	38	(39.5)	49	(20.4)	0.4	(0.13, 1.13)	0.060
History of sinusitis							
No	39	(15.4)	75	(17.3)	1.2	(0.37, 4.05)	1.000
Yes	39	(48.7)	79	(26.6)	0.4	(0.16, 0.92)	0.023
Reversibility							
<12	42	(21.4)	65	(24.6)	1.2	(0.44, 3.46)	0.817
≥ 12	36	(44.4)	88	(20.5)	0.3	(0.13, 0.81)	0.014

Figure 5. Subgroup analysis of patients with at least one severe asthma exacerbation from baseline to week 24. All calculations were based on the combined 100-mg and 200-mg golimumab treatment group versus placebo. *Subgroups above the line were prespecified analyses; subgroups below (history of sinusitis, reversibility) were post-hoc analyses. CI = confidence interval; OCS = oral corticosteroids.

Although BD responsiveness was a post-hoc analysis, there were large differences between those patients who entered the study with a documented BD response versus those whose entry was based on historical criteria. In those patients with a BD response less than 12%, the mean improvement in FEV_1 postbronchodilator was 5.5% (median 6.1%). In contrast, the 164 patients with a 12% or greater reversibility had a 26.1% mean (median 21.7%) increase in postbronchodilator FEV_1. A substantially greater proportion of patients with a BD response who received placebo had one or more severe exacerbations compared with patients without a BD response (44 vs. 21%, respectively), supporting the relationship of BD responsiveness to an exacerbating and potentially different inflammatory phenotype (50). A high level of BD responsiveness may be a surrogate for BHR measured by airway challenge, with methacholine, histamine, etc., an endpoint shown to improve with anti–TNF-α therapy in earlier studies (20, 21). The significance of these findings, however, should be interpreted with caution because neither the prespecified nor the post-hoc subgroup analyses were adjusted for multiple testing.

Severe asthma, as represented in this study population, remains a challenging problem with few treatment options. Patients with severe asthma experience frequent and severe asthma exacerbations that are expensive to treat because of decreased work and school attendance and increased disability (51, 52). Long-term use of systemic corticosteroids, the standard of care in severe asthma, may lead to obesity, diabetes, cataracts, osteoporosis, and avascular necrosis of hips and other joints (4). Hence, severe asthma is associated with a much heavier overall disease burden than milder asthma, suggesting that new and innovative approaches to severe asthma, even those with some risk association, are warranted.

The unfavorable risk–benefit profile for golimumab in the overall population suggests that this therapeutic approach may not be suitable for all patients with asthma. However, the subgroup analysis lends further support to the concept that severe asthma is a heterogeneous disease. The potential presence of a clinically defined severe asthma phenotype with greater efficacy and a potentially better safety profile, in combination with ongoing studies evaluating a wide range of peripheral blood/serum markers, genetic markers, and gene array data, may combine to identify a plausible clinical-genetic-biologic subgroup for which future trials may be warranted.

Conflict of Interest Statement: S.E.W. received $27,000 in the last 3 years from Centocor in her role as Global principal investigator for this study and was the primary author of the protocol itself. In addition, she served on the steering committee. S.E.W. received an additional $4,000 from Centocor in the last 3 years for projects in which she consulted on different molecules. P.J.B. received research funding, lecture fees, and served on scientific advisory boards for GlaxoSmithKline, AstraZeneca, Boehringer-Ingelheim, Novartis, Altana, and Pfizer, and has served on a scientific advisory boards for Centocor. E.R.B. served as a scientific consultant with Centocor. The amount received for consultancy fees are as follows: 2008, $0; 2007, $4,000; 2006, $8,000; and 2005, $6,000. J.B. received honoraria from Centocor for consultancies concerning this trial. W.B. provided consultancy/advisory board services for Isis (2006–2008), Altana (2006–

2007), Hoffman-LaRoche (2006), Ception (2006), Amgen (2006–2008), Centocor (2006–2008), Alza (2006), GlaxoSmithKline (2006–2008), Johnson & Johnson (2006–2008), Wyeth (2006–2008), Takeda (2006), CV Therapeutics (2006–2008), Genentech/Novartis (2006–2008), Dynavax (2007), Abbott Laboratories (2007–2008), Millenium (2007), MAP Pharmaceuticals (2007), Merck (2006–2008), Asthmatic (2007), AstraZeneca (2007–2008), Pfizer (2006–2008), MedImmune (2007), Memory Pharmaceuticals (2007), Altair (2007–2008), PDL BioPharma (2007–2008), Schering Corporation (2008), TEVA (2008), and UCB (2008); he received lecture fees from Novartis (2007–2008), Merck, AstraZeneca (2006–2008), and GlaxoSmithKline (2006–2008); and he has received industry-sponsored grants from Novartis (2006–2008), Centocor (2006–2008), GlaxoSmithKline (2006–2008), Medicinova (2006), Dynavax (2006), Wyeth (2006–2008), Pfizer (2006), Dey (2006), Astellas (2006), Inflazyme (2006), Biowa (2006–2008), MedImmune (2007–2008), and Ception Therapeutics (2008). S-E.D. received $10,000 from Johnson & Johnson for being on advisory panels during the years 2005–2007. S.T.H. received three payments each of $1,500 for serving as a member of the Scientific Advisory Board for the Centecor trial (17 January 2005, 26 July 2005, and 19 May 2007). D.A.M. participated in a steering committee for Centocor, and received $6,000 in 2005, $8,000 in 2006, and $4,000 in 2007; she performed DNA analysis on the patient samples, with a contract from the Asthma Pharmacogenetics Laboratory Study, worth $127,027 and receiving $87,962. K.F.R. has been consulting, participating in advisory board meetings, and received lecture fees from AstraZeneca, Boehringer; Chiesi Pharmaceuticals, Pfizer, Novartis, Altana, Merck, Sharpe, and Dohme, and GlaxoSmithKline. As head of the Department of Pulmonology, K.F.R. received grants from Novartis, AstraZeneca, Boehringer Ingelheim, Roche, and GlaxoSmithKline from 2005 to 2008. A.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.B. participated in multicenter clinical trials for GlaxoSmithKline, AstraZeneca, Ivae, Medpointe, Meeta, Abbott, Shinogi, Stallergens, Schering Plough, Wyeth, Novartis, Lev Pharmaceuticals, Apieron, SkyPharms, and Alza. I.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. Z.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.B. received a grant of $180,000 from Centocor for the conduct of this study of golimumab in severe persistent asthma. E.K. received $100,000 in research grant expense reimbursement for conducting multicenter clinical trials for Centocor during 2006–2007. R.S-H. was an employee of Centocor during the conduct of the study. K.H.L. has been an employee of Centocor since May 2001 and received stocks and stock options as part of the compensation associated with employment. R.W. has been an employee of Centocor since 2002. E.S.B. is currently employed by Centocor Research and Development, Inc. and owns stock and has received stock options in the parent company Johnson & Johnson. P.C. has been reimbursed by Novartis, GlaxoSmithKline, and Astra, attending several conferences during the last three years. P.C. has participated during the last three years as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies (GlaxoSmithKline, Novartis, AstraZeneca, and Chiesi) and during the last three years, received €10,000 for serving on an advisory board for Centocor as a consultant. P.C. received €10,000 speaking at conferences sponsored by Chiesi, Novartis, and Astra during the last three years. P.C.'s institution has received an unrestricted educational grant from Schering Plough.

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