# Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids

**Michael Noonan, MD,[a] Phillip Korenblat, MD,[b] Sofia Mosesova, PhD,[c] Heleen Scheerens, PhD,[c] Joseph R. Arron, MD, PhD,[c] Yanan Zheng, PhD,[c] Wendy S. Putnam, PhD,[c] Merdad V. Parsey, MD, PhD,[d] Sean P. Bohen, MD, PhD,[c] and John G. Matthews, MB, BS, PhD[c]** *Portland, Ore, St Louis, Mo, and South San Francisco and Menlo Park, Calif*

**Background: Asthma is a disease with marked heterogeneity in its clinical course and response to treatment. IL-13 is central to type 2 inflammation, which contributes to many key features of asthma. Lebrikizumab is an anti–IL-13 mAb previously reported to significantly improve lung function in patients with inadequately controlled asthma despite inhaled corticosteroid therapy, especially in periostin-high patients.**

**Objective: This phase II study investigated the efficacy and safety of IL-13 blockade with different doses of lebrikizumab in asthmatic patients not receiving inhaled corticosteroids.**

**Methods: Patients were randomized to receive 125, 250, or 500 mg of lebrikizumab or placebo subcutaneously monthly for 12 weeks with an 8-week follow-up period. The primary efficacy end point was the relative change in prebronchodilator $FEV_1$ from baseline to week 12.**

**Results: A total of 212 patients were randomized. The mean relative change in $FEV_1$ was numerically higher in all lebrikizumab dose groups versus the placebo group, although the difference was neither statistically nor clinically significant. There were no meaningful differences in changes in $FEV_1$ between the dose groups and the placebo group by the periostin subgroup. Lebrikizumab treatment was associated with a reduced risk of treatment failure at all doses versus placebo ($P < .001$), and results were similar by the periostin subgroup, with no apparent differences between doses of lebrikizumab. Lebrikizumab was generally well tolerated.**

**Conclusion: Blocking IL-13, a single cytokine, in this population of asthmatic patients is insufficient to improve lung function. There is evidence that IL-13 blockade may improve disease control, as measured by prevention of protocol-defined treatment failure in these patients. (J Allergy Clin Immunol 2013;132:567-74.)**

***Key words:*** *Asthma, lebrikizumab, IL-13, type 2 inflammation, periostin, uncontrolled, antibody, $FEV_1$*

Asthma is a complex disease with marked heterogeneity in its clinical course and response to treatment.[1-3] Inhaled corticosteroids (ICSs), along with $\beta_2$-agonist therapy, are the cornerstones of asthma treatment and provide effective control in the majority of patients. Yet because of poor response or potential side effects in some patients, additional therapies are still required.

IL-13 is believed to be central to type 2 inflammation, which contributes to many key features of asthma, including mucus production, IgE synthesis, bronchial fibrosis, and airway hyperresponsiveness.[4-7] Lebrikizumab is a novel, humanized, stabilized $IgG_4$ mAb with high binding affinity to human IL-13, neutralizing its functional activities with high potency.[8-10] Periostin is a matricellular protein the expression of which is inducible in bronchial epithelial cells by IL-13 and that is detectable in peripheral blood. Periostin was shown to be the best independent predictor of airway eosinophilia among multiple $T_H2$-associated biomarkers (IgE levels, blood eosinophil numbers, and fraction of exhaled nitric oxide [FENO] levels).[11] Furthermore, lebrikizumab has been demonstrated to result in a greater improvement in $FEV_1$ in symptomatic asthmatic patients despite ICS treatment and who had periostin levels greater than the median compared with patients with periostin levels of less than the median.[8]

Corticosteroids have been noted to inhibit IL-13 activity[12] and therefore could affect interpretation of data when investigating IL-13 blockade on a background of ICS therapy. The effects of IL-13 blockade in patients with mild asthma not taking ICSs have been demonstrated in allergen challenge studies.[13] In addition, a recent study with a novel IL-13 mAb described dose-dependent reductions in FENO levels,[14] but the effects of IL-13 blockade on airway function ($FEV_1$) in this population have not been evaluated. Other asthma therapies have been investigated in patients not receiving ICSs.[15,16]

From [a]Allergy Associates Research, Portland; [b]Clinical Research Center LLC, St Louis; [c]Genentech, South San Francisco; and [d]3-V Biosciences, Menlo Park.

Supported by F. Hoffmann–La Roche Ltd.

Disclosure of potential conflict of interest: P. Korenblat has been supported by one or more grants from Clinical Research Center, LLC; has consultancy arrangements with Targacept; is employed by Associated Specialists in Medicine, PC, and the Clinical Research Center, LLC; has received one or more payments from the Washington University School of Medicine (CME Allergy for the Practicing Physician, Program Director); and owns stock/stock options in Dendreon Corporation, Johnson & Johnson, GlaxoSmithKline, and Stereotaxis. S. Mosesova is employed by Genentech; has one or more patents (planned, pending, or issued) with Genentech and Roche; and owns stock/stock options in Roche. H. Scheerens has been provided with writing assistance, medicines, equipment, or administrative support by MTM; is employed by Genentech; has one or more patents (planned, pending, or issued) with Genentech and Roche; and owns stock/stock options in Roche. J. R. Arron is employed by Genentech, has one or more patents (planned, pending, or issued) with Genentech and Roche, and owns stock/stock options in Roche. Y. Zheng is employed by Genentech; has one or more patents (planned, pending, or issued) with Genentech and Roche; and owns stock/stock options in Roche. W. S. Putnam is employed by and owns stock/stock options in Genentech and has received one or more payments for travel/accommodations/meeting expenses from the American Association of Pharmaceutical Scientists. M. V. Parsey is employed by and owns stock/stock options in Genentech. S. P. Bohen has been provided with writing assistance, medicines, equipment, or administrative support by MTM and is employed by Genentech. J. G. Matthews has been provided with writing assistance, medicines, equipment, or administrative support by MTM; is employed by Genentech; has one or more patents (planned, pending, or issued) with Genentech and Roche; and owns stock/stock options in Roche. M. Noonan declares that he has no relevant conflicts of interest.

Received for publication October 19, 2012; revised March 21, 2013; accepted for publication March 27, 2013.

Available online May 29, 2013.

Corresponding author: John G. Matthews, MB, BS, PhD, Principal Medical Director, Product Development Immunology, Genentech, Inc, 1 DNA Way, South San Francisco, CA 94080-4990. E-mail: matthews.john@gene.com.

0091-6749/$36.00



http://dx.doi.org/10.1016/j.jaci.2013.03.051

*Abbreviations used*
AE: Adverse event
FENO: Fraction of exhaled nitric oxide
HR: Hazard ratio
ICS: Inhaled corticosteroid
mITT: Modified intent-to-treat
PEF: Peak expiratory flow
SABA: Short-acting $\beta_2$-agonist

The current dose-response study investigated the efficacy and safety of IL-13 blockade with different doses of lebrikizumab in asthmatic patients not receiving ICSs.

## METHODS

### Study design/patients

This phase II, randomized (1:1:1:1), double-blind, placebo-controlled, dose-ranging study (NCT00971035) evaluated the efficacy and safety of lebrikizumab. The study consisted of a 2-week screening period, a 12-week treatment period, and an 8-week safety follow-up period. During the 12-week treatment period, patients received 125, 250, or 500 mg of lebrikizumab or placebo subcutaneously every 28 days on days 1, 29, and 58 (plus an additional loading dose at day 8) for a total of 4 doses. At randomization patients were classified with available blood tests, serum IgE and eospinophil count into IL-13 signature surrogate status and stratified across the treatment arms; patients were designated IL-13-signature-surrogate-positive with IgE levels of greater than 100 IU/mL and a peripheral blood eosinophil count of $0.14 \times 10^9$ cells/L or greater, and IL-13-signature-surrogate-negative for the remaining combinations (IgE low or eosinophil count low).[8,17] IgE and eosinophil levels were used because the periostin assay was unavailable at the start of the trial. Periostin status was ascertained before unblinding and prospectively assessed by using the baseline samples (day 1 before treatment).

All patients provided written informed consent, and the protocol was approved by applicable independent review committees or institutional review boards.

### Inclusion criteria

Asthmatic adults (18-65 years old) not receiving ICSs were enrolled (Fig 1). Patients had to have a bronchodilator response of 15% or greater and a prebronchodilator $FEV_1$ of 60% to 85% of predicted value, with protocol-defined disease stability demonstrated during the run-in period. Stable asthma was defined as diagnosis of asthma 12 or more months before enrollment, a bronchodilator response, and relative change in prebronchodilator $FEV_1$ the week before treatment of less than 15%. Prebronchodilator peak expiratory flow (PEF) also had to be stable before treatment, and daily use of short-acting $\beta_2$-agonist (SABA) therapy had to be less than 10 inhalations or 2 or fewer nonscheduled administrations of nebulized SABA therapy. ICSs or oral or parenteral corticosteroids were not permitted (see the Methods section in this article's Online Repository at www.jacionline.org for more detail on the definition of stable asthma and exclusion criteria).

### End points and analyses

**Objectives and end points.** The primary objective was to evaluate the efficacy, safety, and tolerability of different doses of lebrikizumab compared with placebo. The primary efficacy end point was the relative change in prebronchodilator $FEV_1$ from baseline to week 12. Secondary and exploratory end points included relative change in $FEV_1$ from baseline to week 12 in subjects who were periostin high and periostin low at baseline, time to treatment failure, change in morning PEF, PEF variability, and reliever medication use.

Periostin-high and periostin-low patients were defined as patients with measured predose baseline serum periostin levels of greater than and less than the median value, respectively. Serum periostin concentrations were obtained by using an Elecsys periostin immunoassay (investigational use only, currently in development).

Treatment failure was predefined as worsening of asthma symptoms in association with 1 or more of the following: relative decrease in prebronchodilator $FEV_1$ (volume) of 20% or greater compared with the baseline value; 20% decrease in morning prebronchodilator PEF on 2 consecutive days compared with baseline values; use of 10 or more inhalations of albuterol metered-dose inhaler (or equivalent) or 2 or more additional administrations (or any new use) of nebulized SABA therapy in a single day; or need for any ICS or oral or parenteral corticosteroids.

**Pharmacodynamic analyses.** Several pharmacodynamic biomarkers, including FENO levels, serum IgE levels, peripheral blood eosinophil numbers, and serum CCL13 and CCL17 levels, were measured at different time points throughout the study to provide evidence for the mechanism of action of the drug, as well as to assess the response to treatment in patient subgroups. Further details and results are available in the Methods and Results sections in this article's Online Repository.

**Pharmacokinetic analysis.** Serum lebrikizumab concentrations were measured at multiple time points throughout the study up to 12 weeks after the last dose for all subjects. Noncompartmental pharmacokinetic analysis with WinNonlin Enterprise 5.2.1 software (Pharsight, Sunnyvale, Calif) was performed to estimate the terminal elimination half-life.

### Dose selection

The doses (125, 250, or 500 mg every 4 weeks) were selected to maintain steady-state trough concentrations of at least 50-fold higher than a theoretic target concentration of approximately 0.25 μg/mL that would neutralize IL-13 and block IL-13 activity in the lung. These doses were expected to provide a wide distribution of data to develop a dose-response curve. The dosing frequency of once every 4 weeks was selected based on the half-life of lebrikizumab (approximately 25 days). A loading dose of study drug was administered 1 week after the first dose to achieve steady-state drug levels safely and rapidly.

### Statistical analysis

A total of 212 patients were equally randomized to 1 of the 4 treatment groups. This sample size (52-54 patients per group) provided greater than 90% power to detect a treatment difference of 10% in the primary end point of $FEV_1$ in the highest dose group compared with the placebo group. This sample size also provided approximately 70% power to detect a treatment difference of 10% in the primary end point of relative change from baseline in prebronchodilator $FEV_1$ in diagnostic-positive patients, assuming the prevalence of patients with a positive diagnosis is at least 50%.

All efficacy analyses were based on the modified intent-to-treat (mITT) population, including all patients who were randomized and received 1 or more doses of study drug. All safety analyses included all randomized patients who received 1 or more doses of study drug. On the basis of previous data,[8] periostin was prioritized over IL-13 signature surrogate as the subgroup of interest. All analyses were performed for periostin-high and periostin-low patients, along with a limited analysis of $FEV_1$ for IL-13 signature surrogate–positive and IL-13 signature surrogate–negative patients (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). Further statistical methods are detailed in the Methods section in this article's Online Repository.

## RESULTS

### Disposition and demographics

A total of 212 patients were randomized, and 210 received 1 or more doses of study drug. Among the 210 patients who received 1 or more doses of study drug, 26 (12.4%) discontinued the study before week 20 (n = 16 [10.1%] in the lebrikizumab group and n = 10 [19.2%] in the placebo group, Fig 1; reasons for discontinuation are detailed in Tables E3 and E4 in this article's Online