SYNOPSIS OF CLINICAL STUDY REPORT

Name of Sponsor/Company: Genentech, Inc.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
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Title of Study:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND EFFICACY OF LEBRIKIZUMAB (MILR1444A) IN ADULT PATIENTS WITH ASTHMA WHO ARE INADEQUATELY CONTROLLED ON INHALED CORTICOSTEROIDS (MILLY)**
Phase of Development:	II
Investigators:	There were 54 investigators. See Appendix 16.1.4 for a list of investigators.
Study Centers:	Patients were enrolled at 54 sites in the United States, Czech Republic, Poland, and Hungary.
Publications:	Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. N Engl J Med 3-Aug-2011 (10.1056/NEJMoa1106469).
Study Period:	11 July 2009 to 10 September 2010.

Objectives

Primary:

- To assess the efficacy of lebrikizumab in improving lung function in patients with asthma who remain inadequately controlled despite therapy with inhaled corticosteroids (ICS)
- To evaluate the safety of lebrikizumab in patients with asthma who remain inadequately controlled despite therapy with ICS

Secondary:

- To assess the efficacy of lebrikizumab in improving asthma control in patients with asthma who remain inadequately controlled despite therapy with ICS
- To assess the efficacy of lebrikizumab in reducing the rate of exacerbations in patients with asthma who remain inadequately controlled despite therapy with ICS

Methodology

This was a randomized, double-blind, placebo-controlled study to evaluate the effects of lebrikizumab in patients with asthma whose disease remains inadequately controlled while on chronic therapy with ICS. Patients continued their standard-of-care therapy (as permitted in the protocol), which must have included an ICS and may have included a long-acting β-agonist (LABA) and/or a leukotriene receptor antagonist (LTRA). In this two-arm study, patients were randomly allocated to receive six monthly doses of either lebrikizumab or placebo for 6 months. During a 14-to 20-day run-in period (Visit 1 to Visit 3), patients must have demonstrated compliance with ICS therapy and their ability to use the equipment necessary for daily monitoring throughout the study. Patients were then assessed for study eligibility and randomly allocated (1:1) to study drug (lebrikizumab or placebo), with stratification based on interleukin-13 (IL-13) signature surrogate status, LABA use, and study site.

The first subcutaneous (SC) dose occurred within 24 hours of random allocation (Day 1, i.e., the day of random allocation, regardless of first study drug administration date). Administration of study drug was repeated once every 4 weeks for the next 20 weeks (for a total of six study drug doses,

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providing a protocol-specified 24-week treatment period). Measures of the efficacy of lebrikizumab were assessed during this treatment period. The primary analysis was conducted after all (approximately 200) patients had been treated and followed for 24 weeks after random allocation (Day 1). Safety was assessed throughout the study. After the final dose (Week 20) of study drug, patients were monitored for an additional 12 weeks; the first 4 weeks after the final dose were considered part of the (24-week) treatment period, and the final 8 weeks constituted the follow-up period. The 8-week follow-up period, together with the last 4 weeks of the treatment period, allowed monitoring of patients for 3–4 half-lives following the last dose. Therefore, patients participated in the study for a total of approximately 34 weeks.

Number of Subjects (Planned and Analyzed):

Planned: 200 patients

Randomized: 219 patients

Modified intent-to-treat population: 218 patients

Diagnosis and Main Criteria for Inclusion:

Patients ≥ 18 and ≤ 65 years of age whose asthma was inadequately controlled on ICS therapy, with or without LABA therapy, were eligible for enrollment. Uncontrolled asthma was defined as diagnosis of asthma > 12 months, bronchodilator response required a minimum 12% relative improvement in the volume of the forced expiratory volume in 1 second (FEV_1) after bronchodilator at Visit 1 or 2, pre-bronchodilator FEV_1 ≥ 40% and ≤ 80% predicted at Visit 3, Required daily use of ICS ≥ 200 μg and ≤ 1000 μg total daily dose of fluticasone propionate or equivalent for a minimum of 6 consecutive months prior to Visit 1, and demonstrated ongoing asthma symptoms assessed at the end of the run-in period by Asthma Control Questionnaire (ACQ) score ≥ 1.5 (for symptoms over the 7 days prior to Visit 3) despite ICS compliance.

Test Product, Dose and Mode of Administration, Batch Number:

Each patient was to receive six doses of study drug (lebrikizumab or placebo) administered by SC injection, on Day 1 and at Weeks 4, 8, 12, 16, and 20. Each dose of lebrikizumab was 250 mg.

Product code and lot number information is provided in Appendix 16.1.6.

Duration of Treatment:

Administration of study drug was repeated once every 4 weeks for the next 20 weeks (for a total of six study drug doses, providing a protocol-specified 24-week treatment period).

Reference Therapy, Dose and Mode of Administration, Batch Number:

Each patient was to receive six doses of study drug (lebrikizumab or placebo) administered by SC injection, on Day 1 and at Weeks 4, 8, 12, 16, and 20. Each placebo dose was 2 mL of the same fluid without lebrikizumab.

Product code and lot number information is provided in Appendix 16.1.6.

Criteria for Evaluation

Efficacy:

All efficacy analyses were based on the modified intent-to-treat (mITT) population, including all patients who were randomized and received at least one dose of study drug. For the efficacy analysis, the treatment groups were based on the treatment assigned at randomization.

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Safety:

All safety analyses included all randomized patients who received any study drug. For these analyses, patients were grouped according to the treatment actually received.

Statistical Methods

The primary endpoint was analyzed by reporting the mean of individual patients' relative change in pre-bronchodilator FEV_1 (L) from baseline to Week 12 by treatment group, along with the treatment effect size and corresponding two-sided 95% confidence interval (CI). Treatment effect size was defined as the difference between the mean change in pre-bronchodilator FEV_1 in lebrikizumab-treated patients and placebo-treated patients.

A parametric analysis of covariance (ANCOVA) model comparing the relative change in pre-bronchodilator FEV_1 between treatment groups after adjustment for key baseline characteristics was also fit to the data as a sensitivity analysis. LABA status (prescribed or not), IL-13 signature surrogate status (positive or negative), and baseline pre-bronchodilator FEV_1 (L) were included in the model as covariates, and the mean change from baseline over time was estimated for each treatment group. LABA status was determined on the basis of concomitant medication data, and IL-13 signature surrogate status was determined on the basis of the laboratory data at Visit 1.

All analyses were performed for periostin high and periostin low patients as well as on IL-13 signature surrogate positive and negative patients. As IL-13 signature surrogate status will not be used in the lebrikizumab development program, the focus of this report is on the analyses by periostin status, as prespecified in the informal analysis plan, with periostin high and periostin low defined by the median periostin concentration (≥ 50.2 ng/mL and < 50.2 ng/mL respectively) for the study population. Analyses by IL-13 signature status are provided in the appendices.

Primary Efficacy Endpoint:

Relative change in pre-bronchodilator FEV_1 (volume) from baseline to Week 12

Secondary Efficacy Endpoints:

- Relative change in pre-bronchodilator FEV_1 (volume) from baseline to Week 24
- Relative change in pre-bronchodilator FEV_1 (volume) from baseline to Week 12 for patients with IL-13 signature surrogate positive status
- Change in ACQ score from baseline to Week 12
- Change in Asthma Symptom Score as measured by the ACDD from baseline to Week 12
- Change in morning pre-bronchodilator peak flow value from baseline to Week 12
- Rate of asthma exacerbations during the 24-week treatment period
- Rate of severe asthma exacerbations during the 24-week treatment period
- Change in rescue medication use (measured by number of puffs per day of rescue medication or nebulized rescue medication) from baseline to Week 12

Pharmacokinetic Endpoints:

- Maximum serum lebrikizumab concentrations after first and last dose
- Time to maximum serum lebrikizumab concentrations after first and last dose
- Predose serum lebrikizumab concentrations at Weeks 4, 12, and 20
- Serum lebrikizumab concentration at Week 24

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- Accumulation ratios based on the maximum concentrations after the first and last dose and trough concentrations prior to the second and last dose
- Elimination half-life

Summary of Results and Conclusions

Efficacy and Pharmacokinetic/Pharmacodynamic Conclusions:

This study met its primary endpoint as measured by Week 12 relative change in FEV_1 in all lebrikizumab patients compared with those treated with placebo. The robustness of the primary endpoint was demonstrated by the consistent results from sensitivity analyses (ANCOVA model adjusted for baseline characteristics). In addition, the treatment benefit of lebrikizumab, as measured by relative FEV_1 change at Week 12, was greater in the subgroup of patients with baseline periostin levels ≥ 50.2 ng/mL than in those with levels < 50.2 ng/mL. Point estimates for the reduction in exacerbations rates and severe exacerbation rates trended in favor of lebrikizumab.

- The primary efficacy analysis at 12 weeks demonstrated that lebrikizumab-treated patients had a 5.5% greater mean improvement in FEV_1 from baseline than placebo-treated patients (CI: 0.8%, 10.2%; $p = 0.02$). Lebrikizumab-treated patients in the periostin high group experienced an 8.2% improvement in FEV_1 compared with placebo-treated patients (95% CI: 1.0%, 15.4%; $p = 0.03$), whereas patients in the periostin low group had a 1.6% increase in FEV_1 compared with placebo-treated patients (95% CI: -4.5%, 7.7%; $p = 0.61$).
- At Week 24, the exacerbation rate was reduced by 32% (95% CI: -16%, 60%) in lebrikizumab-treated patients compared with placebo-treated patients. Severe exacerbation rates were reduced by 43% (95% CI: -10%, 71%). In periostin high patients, the exacerbation and severe exacerbation rates were reduced by 26% (95% CI: -50%, 64%) and 67% (95% CI: -15%, 90%), respectively, compared with the placebo-treated patients.
- No difference was detected in the effect of treatment with lebrikizumab compared with placebo on the patient-reported outcomes (Asthma Control Questionnaire score, on the Asthma Quality of Life Questionnaire score, or on daily diary measures [asthma symptom score, change in the use of rescue medication, or change in the number of well-controlled days]).
- Treatment with lebrikizumab was associated with a reduction in fractional exhaled nitric oxide (FeNO) compared with placebo. The reduction was larger in the periostin high patients than periostin low patients.
- Following six SC administrations of lebrikizumab at 250 mg every 4 weeks, mean trough concentrations rose approximately 2-fold, from 16.3 ± 5.8 μg/mL (mean $\pm$ SD) prior to the second dose to 31.6 ± 13.9 μg/mL prior to the sixth dose. The observed maximum lebrikizumab concentration (54.8 ± 20.8 μg/mL) occurred approximately a week after the last dose. Lebrikizumab was eliminated with a mean half-life of 25.4 ± 5.16 days.
- The study provided indirect evidence that lebrikizumab inhibits the activity of IL-13, as reflected by the changes in FeNO, CCL-13, CCL-17, and IgE.
- Two of the 99 (2.0%) lebrikizumab-treated patients with adequate samples had a positive anti–therapeutic antibody (ATA) result at the posttreatment visit. However, both patients were also positive predose, suggesting that the observed responses were not drug induced. In addition, neither patient had a clinically detectable response (based on pharmacokinetic, efficacy, and safety data) that could be attributed the positive ATA response before and after treatment.

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Safety Conclusions:

The results of this double-blind, placebo-controlled study in 218 adults with asthma that was inadequately controlled despite treatment with high-dose ICS, with or without additional controller medications, showed the following:

- The proportion of patients with at least one adverse event was similar in the lebrikizumab and placebo groups (74.5% in the lebrikizumab group vs. 78.6% in the placebo group).
- The majority of patients with at least one adverse event had adverse events that were mild to moderate in severity and were considered not related to study drug.
- The percentage of patients experiencing a serious adverse event was larger among the placebo-treated patients (3.8% in the lebrikizumab group vs. 6.3% in the placebo group); none of these events were attributed to study drug by the investigators.
- Musculoskeletal adverse events were more common with lebrikizumab than with placebo (13.2% vs. 5.4%). There was no clear evidence of a single pathologic process accounting for the overall increased frequency of these events observed in patients treated with lebrikizumab.
- ISRs were reported in a greater proportion of lebrikizumab-treated patients than placebo-treated patients (13.2% vs. 8.0%)
- Adverse events that led to discontinuation of study drug were reported in 4 patients in the lebrikizumab group versus 3 patients in the placebo group (3.8% vs. 2.7%).
- No deaths were reported in this study.
- No pattern of clinically significant change was seen in the hematology, chemistry, urinalysis, or ECG parameters assessed.

Overall Conclusions:

Study ILR4646g demonstrated that lebrikizumab treatment was associated with improved lung function, as measured by FEV_1 after 12 weeks of treatment. A trend toward reduction in severe exacerbation rates was also observed. Patients with pretreatment serum periostin levels above the median for the study population had greater clinical improvement (as measured by placebo-corrected change in FEV_1 at 12 weeks) with lebrikizumab than those with low periostin levels. The study provides further supportive evidence that lebrikizumab inhibits the activity of IL-13, as reflected by changes in FeNO, CCL-13, CCL-17, and IgE.

In addition to the efficacy of lebrikizumab, the reported safety data demonstrated no substantive safety risks or differences in the safety profile of lebrikizumab compared with placebo. While ISRs were seen in more lebrikizumab-treated patients than placebo-treated patients, few of them required treatment, needed to discontinue treatment, or showed any evidence of an allergic/immune-mediated reaction. In this population of patients with asthma that is uncontrolled despite ICS therapy, with or without another controller, lebrikizumab appeared to have a favorable benefit–risk profile, especially among patients in the periostin high group.

Date of the Report

5 November 2011