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)*
Name of Finished Product: Lebrikizumab	**Volume:**	
Name of Active Ingredient: Lebrikizumab	**Page:**	

Title of Study:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-RANGING STUDY TO EVALUATE LEBRIKIZUMAB (MILR1444A) IN ADULT PATIENTS WITH ASTHMA WHO ARE NOT TAKING INHALED CORTICOSTEROIDS (MOLLY)**
Phase of Development:	II
Investigators:	There were 53 investigators. See Appendix 16.1.4 for a list of investigators.
Study Centers:	Patients were enrolled at 53 sites in the United States, South Africa, Poland, Ukraine, Hungary, and Russia.
Publications:	No publications have resulted from this study.
Study Period:	25 November 2009 to 21 February 2011.

Objectives

Primary:

- To evaluate the efficacy of different doses of lebrikizumab compared with placebo as measured by relative change in pre-bronchodilator forced expiratory volume in 1 second (FEV_1)
- To evaluate the safety and tolerability of different doses of lebrikizumab

Secondary:

- To compare the efficacy among different doses of lebrikizumab as measured by relative change in pre-bronchodilator FEV_1
- To evaluate the efficacy of different doses of lebrikizumab compared with placebo in a subgroup of interleukin-13 (IL-13) signature surrogate positive patients, as measured by relative change in pre-bronchodilator FEV_1
- To evaluate the efficacy of different doses of lebrikizumab compared with placebo as measured by change in morning peak flow, peak flow variability, rescue medication use, and time to treatment failure
- To characterize the pharmacokinetics of lebrikizumab

Methodology

This was a randomized, double-blind, placebo-controlled, four-arm, dose-ranging study.
The purpose was to evaluate the relationship between the dose of lebrikizumab and the response in terms of the efficacy, safety, and tolerability in patients with asthma who were not on inhaled corticosteroid (ICS) therapy. Patients must have had a bronchodilator response of $\geq 15\%$ and a pre-bronchodilator $FEV_1 \geq 60\%$ and $\leq 85\%$ predicted, with protocol-defined disease stability demonstrated during the run-in period. Patients previously managed with ICS therapy could not have received ICS medication for ≥ 30 days prior to the first study visit (Visit 1). The study had no withdrawal period; patients were not to be taken off corticosteroids for the sole purpose of becoming eligible for the study.

Name of Sponsor/Company: Genentech, Inc.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
Name of Finished Product: Lebrikizumab	**Volume:**	
Name of Active Ingredient: Lebrikizumab	**Page:**	

The first study-related procedure at Visit 1 began the approximately 2-week run-in period. During the run-in period (Visits 1–3), asthma control (as measured by the Asthma Control Questionnaire [ACQ] score) and pulmonary function were assessed. Patients' asthma was further characterized with skin prick testing and relevant biomarkers, including IgE and peripheral blood eosinophils. The IgE and eosinophil levels were used to classify patients according to their IL-13 signature surrogate status. At the end of the run-in period, eligible patients were randomly allocated (1:1:1:1) to receive one of three doses (500 mg, 250 mg or 125 mg) of lebrikizumab or placebo via subcutaneous (SC) administration. Study drug was administered four times during the 12-week treatment period. After the final dose of study drug, patients were monitored for an additional 8-week follow-up period. Therefore, most patients participated in the study for a total of approximately 22 weeks after Visit 1, during which time intermittent pharmacokinetic (PK) samples were obtained. Intensive PK sampling was performed, with additional PK samples obtained during the study and follow-up periods and a final sample obtained 16 weeks after the last study drug administration, until 70 patients had completed the intensive PK sampling. Therefore, study participation for the patients in the intensive PK subset lasted for approximately 26 weeks after Visit 1. Safety was assessed throughout the study. Prespecified thresholds for treatment failure were defined; patients were to be taken off study drug to resume standard therapy if they experienced clinically significant deterioration.

Number of Patients (Planned and Analyzed):

Planned: approximately 200 patients

Randomized: 212 patients

Modified intent-to-treat population: 210 patients

Diagnosis and Main Criteria for Inclusion:

Patients ≥ 18 and ≤ 65 years of age with stable asthma were eligible for enrollment. Stable asthma was defined as diagnosis of asthma ≥ 12 months prior to Visit 1, bronchodilator response at Visit 1, 2, or 3 (a bronchodilator response required a minimum 15% relative increase in the volume of FEV_1 after bronchodilator), pre-bronchodilator $FEV_1 \geq 60\%$ and $\leq 85\%$ predicted at Visit 3, relative change in pre-bronchodilator FEV_1 (volume) from Visit 2 to Visit 3 had to be $< 15\%$ (increase or decrease), Relative change in mean morning pre-bronchodilator peak flow between Visits 1 and 2 had to be $< 20\%$ (increase or decrease) of the mean pre-bronchodilator peak flow between Visits 2 and 3, daily use of albuterol metered dose inhaler (or equivalent) had to be < 10 puffs or ≤ 2 non-scheduled administrations (or any new use) of nebulized short-acting β-agonist therapy, and no required inhaled or oral or parenteral corticosteroids.

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

Each patient was to receive four doses of study drug (lebrikizumab or placebo) administered by SC injection, on Days 1, 8, 29, and 57. Patients assigned to the lebrikizumab group received the same dose of lebrikizumab (125 mg, 250 mg, or 500 mg) at each of the specified visits. Regardless of study drug dose (including patients in the placebo group), all patients receive the same volume of fluid (1 mL per injection, four injections per dose) to maintain the blind.

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

Duration of Treatment:

Study drug was administered four times during the 12-week treatment period.

Name of Sponsor/Company: Genentech, Inc.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
Name of Finished Product: Lebrikizumab	**Volume:**	
Name of Active Ingredient: Lebrikizumab	**Page:**	

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

Each patient was to receive four doses of study drug (lebrikizumab or placebo) administered by SC injection, on Days 1, 8, 29, and 57. Regardless of study drug dose (including patients in the placebo group), all patients receive the same volume of fluid (1 mL per injection, four injections per dose) to maintain the blind.

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.

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 efficacy endpoint was the relative change in pre-bronchodilator FEV_1 (volume in liters) from baseline to 12 weeks, where the relative change in FEV_1 from baseline was calculated by the FEV_1 change (L) divided by the baseline FEV_1 (L). The baseline FEV_1 measurement was determined from the last spirometry evaluation performed before the first dose of study drug (Visit 3).

The primary endpoint was analyzed by reporting the mean relative changes from baseline to Week 12 by treatment group, along with the treatment effect size, p-value, and corresponding two-sided 95% confidence interval. Treatment effect size was defined as the difference between the mean changes in pre-bronchodilator FEV_1 in lebrikizumab-treated patients versus placebo-treated patients.

All analyses were performed for periostin high and periostin low patients, as well as for IL-13 signature surrogate positive and negative patients. Because the lebrikizumab program will use periostin status to define patient populations, only the subgroup analyses based on periostin status are included in this report. Periostin high patients were defined as those with a baseline periostin concentration that was ≥ 50 ng/mL, and periostin low patients were defined as those with a baseline concentration < 50 ng/mL.

Primary Efficacy Endpoint:

The primary efficacy outcome measure was the relative change in pre-bronchodilator FEV_1 (volume) from baseline to Week 12.

Secondary Efficacy Endpoints:

The secondary efficacy outcomes measures were the change from baseline to Week 12 in the following:

- Relative change in pre-bronchodilator FEV_1 (volume) in patients who were IL-13 signature surrogate positive
- Relative change in pre-bronchodilator morning peak flow value
- Change in peak expiratory flow (PEF) variability
- Change in rescue medication use
- Time-to-treatment failure

Name of Sponsor/Company: Genentech, Inc.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use Only)*
Name of Finished Product: Lebrikizumab	**Volume:**	
Name of Active Ingredient: Lebrikizumab	**Page:**	

Pharmacokinetic Endpoints:

- Maximum serum lebrikizumab concentration after the fourth dose
- Time to maximum serum lebrikizumab concentration after the fourth dose
- Predose serum lebrikizumab concentrations at Weeks 4 and 8
- Serum lebrikizumab concentration at Week 12
- Elimination half-life

Summary of Results and Conclusions

Efficacy and Pharmacokinetic/Pharmacodynamic Conclusions:

- The relative change in pre-bronchodilator FEV_1 (L) from baseline to Week 12 was not different between placebo- and lebrikizumab-treated patients in the 125-mg, 250-mg, or 500-mg dose groups: 3.5% (95% CI: −1.1%, 8.1%; p=0.13), 4.8% (95% CI: −0.1%, 9.7%; p=0.05), and 2.3% (95% CI: −2.6%, 7.3%; p=0.35), respectively.
- At all doses, lebrikizumab treatment was associated with a reduction in the rate of treatment failure compared with placebo (hazard ratio of 0.21; 95% CI: 0.09, 0.47). Patients who met the criteria for treatment failure during the study discontinued study drug and then began treatment with currently available asthma therapies.
- There was evidence of benefit from lebrikizumab compared with placebo in reducing FeNO and improving PEF.
- No difference was observed in the effect of treatment with lebrikizumab compared with placebo on change from baseline in the ACQ score or change in use of rescue medication.
- The study provided evidence that lebrikizumab inhibits the Th2 inflammatory pathway, as reflected by a 10%–40% reduction from baseline in median total IgE, CCL17, CCL13, and FeNO levels.
- No dose–response relationship was observed in the efficacy data, despite using three doses, with a 4-fold increase in the total dose, and achieving steady-state concentrations. In addition, no apparent dose response was observed in the 125-mg, 250-mg, and 500-mg dose groups in the biomarker analyses, indicating that all three dose levels achieved maximal biomarker responses in these patients with mild asthma.
- Following four SC administrations, lebrikizumab concentrations reached a maximum approximately 1 week after the last dose (125, 250, or 500 mg), with a mean half-life of approximately 25 days. The observed mean maximum concentrations were dose proportional, with values of 25.9, 52.9, and 102 μg/mL in the main group and 24.0, 45.1, and 96.3 μg/mL in the intensive PK subset for the 125-, 250-, and 500-mg dose groups, respectively.
- One of the 145 lebrikizumab-treated patients (0.7%) with adequate samples had a positive anti–therapeutic antibody (ATA) result at the posttreatment visit. This patient may have developed an ATA response to lebrikizumab [redacted]. While there were no irregularities in safety or mean PK profile, this individual experienced "treatment failure." It is unknown whether there was a causal relationship between the ATA response and the treatment failure. Four patients tested positive predose, but were negative posttreatment and thus were not considered ATA positive.

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Name of Finished Product: Lebrikizumab	**Volume:**	
Name of Active Ingredient: Lebrikizumab	**Page:**	

Safety Conclusions:

- On the basis of a similar proportion of patients having at least one adverse event (67.7% in the combined lebrikizumab groups vs. 67.3% in the placebo group), lebrikizumab-treated patients were not disproportionately affected by adverse events compared with placebo-treated patients.
- A greater proportion of lebrikizumab-treated patients had at least one adverse event in the 500-mg dose group (75%) than in the two lower dose groups (64% in both the 125-mg and 250-mg dose groups).
- Most patients who experienced at least one adverse event had events that were moderate in severity. Most patients' adverse event of the highest severity was considered not related to the study drug, though greater proportions of events of the highest severity were considered related to study drug among lebrikizumab-treated patients than placebo-treated patients.
- Four lebrikizumab-treated patients (2.5%) experienced a total of six serious adverse events, one of which was considered related to study drug by the investigators. Three of the 4 lebrikizumab-treated patients with a serious adverse event were in the lowest dose group (125 mg); there was no evidence that higher doses of lebrikizumab were associated with serious adverse events. No serious adverse events were reported among placebo-treated patients.
- Among the 15 patients who discontinued treatment because of an adverse event, a greater proportion were in the placebo group than in the combined lebrikizumab groups (17.3% vs. 3.8%, respectively), noting that patients who met the protocol-defined criteria for treatment failure were required to discontinue treatment.
- Injection-site reactions (ISRs) were reported in a greater proportion of all lebrikizumab-treated patients than placebo-treated patients (23.4% vs. 5.8%), with higher proportions of patients in the two highest dose groups (15%, 30%, and 25% in the 125-mg, 250-mg, and 500-mg dose groups, respectively).
- One patient in the [redacted] dose group appeared to have developed an ATA response to the drug. (This patient had a negative titer prior to treatment and a positive result after treatment.) There were no apparent ATA effects on the PK profile, though the patient had an asthma exacerbation with a decline in lung function and experienced treatment failure.
- [redacted].
- There was one report of drug exposure during pregnancy in a lebrikizumab-treated patient.
- There were no apparent associations of laboratory abnormalities and the dose of lebrikizumab, though a greater proportion of all lebrikizumab-treated patients (20% and 11%) had CK and ALT abnormalities compared with placebo-treated patients (12% and 4%, respectively). However, these were mostly Grade 1 abnormalities and were not associated with clinical symptoms or signs.
- No pattern of clinically significant change was seen in the results of other chemistry, hematology, or urinalysis, or ECG evaluations when comparing treatment groups or dose levels within the lebrikizumab-treated patients.
- There were no deaths reported in this study.

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Name of Finished Product: Lebrikizumab	**Volume:**	
Name of Active Ingredient: Lebrikizumab	**Page:**	

Overall Conclusions:

The study demonstrated that 12 weeks of lebrikizumab treatment (125, 250, or 500 mg administered monthly by SC injection) was associated with a 3.6% improvement in lung function (95% CI: −0.6%, 7.8%; p=0.10) in adults with asthma who were not receiving ICS therapy. The magnitude of this treatment effect is not considered clinically meaningful. Lebrikizumab treatment was associated with a significant reduction in the rate of protocol-defined treatment failure compared with placebo (hazard ratio of 0.21; 95% CI: 0.09, 0.47; p<0.001), as well as a reduction in FeNO and improvement in PEF. Placebo-treated patients who met the criteria for treatment failure received alternative available therapies and, per protocol, were followed until resolution of the event. There was no evidence of treatment benefit as measured by changes in ACQ scores and rescue medication use.

Small sample sizes and imbalances in the number of periostin high and periostin low patients in the placebo group precluded a meaningful analysis of the data by periostin status.

Overall, the MOLLY safety data did not reveal a specific safety concern. There was an increase in the number of ISRs in lebrikizumab-treated patients, but these were not persistent and in most cases did not require treatment. There were more CK and ALT elevations in lebrikizumab-treated patients than in placebo-treated patients. [redacted].

Efficacy and safety data did not demonstrate a dose response, despite using three doses, with a 4-fold increase in the total dose, and achieving steady-state concentrations. In addition, no apparent dose response was observed in the 125-mg, 250-mg, and 500-mg dose groups for biomarker analyses, indicating that all three dose levels achieved maximal biomarker responses in these patients with mild asthma.

Date of the Report

5 November 2011