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: TBD	**Volume:**	
Name of Active Ingredient: Quilizumab (Anti-M1 Prime, MEMP1972A)	**Page:**	

Title of Study:	A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Intravenous MEMP1972A in the Prevention of in Allergen-Induced Airway Obstruction in Patients with Mild Asthma
Phase of Development:	II
Investigators:	There were 6 investigators in this study. See Appendix 11.1.4.
Study Centers:	There were six study centers in this study, five in Canada and one in Sweden. See Appendix 11.1.4.
Publications:	No publications have resulted from this study.
Study Period:	9 December 2010 (first randomized patient) to 5 January 2012 (last patient visit)

Objectives

Primary:

The primary objective of this study was to evaluate if quilizumab decreased the allergen-induced late asthmatic response (LAR) after 12 weeks of exposure.

Secondary:

- To assess the safety and tolerability of quilizumab
- To evaluate whether quilizumab decreased allergen-induced early asthmatic response (EAR) after 12 weeks of exposure
- To evaluate whether quilizumab decreased bronchial hyper-responsiveness in response to methacholine challenge 24 hours after the airway allergen challenge
- To characterize the pharmacokinetics of quilizumab

Methodology

This study was designed to evaluate the efficacy, safety, and tolerability of quilizumab when administered to patients by intravenous (IV) infusion for the treatment of allergen-induced asthma. Patients with stable, mild allergic asthma with a history of episodic wheeze and shortness of breath and with spirometry conducted according to Miller et al. (2005) were eligible for enrollment.

This study was conducted at study sites in Canada and Sweden that were experienced in conducting clinical trials using allergen-challenge methodology and that were able to follow a standard operating procedure (SOP) manual describing the methodology (Canadian Investigator Collaborative Procedures, [redacted]). Individuals were screened (Days −35 to −1) to obtain a cohort of patients with documented EAR and LAR to inhaled incremental allergen challenge (see Figure 1 of Clinical Study Report MOP4843g).

Patients received study drug (quilizumab or placebo equivalent) every 28 days (i.e., Days 1, 29, and 57) for a total of three doses at 5 mg/kg IV starting on Day 1. At screening, clinical data, spirometric data, and a set of blood samples were taken. Patients underwent a non-invasive measurement of fractional exhaled nitric oxide (FeNO) in exhaled breath. Patients were randomized in a 1:1 ratio to receive quilizumab or placebo by employment of an interactive response system. Patients were followed for approximately 20 additional weeks after the last dose and completed clinic visits for the assessment of safety, efficacy, pharmacokinetic (PK), and pharmacodynamics (PD) measures according to the study flowchart (see Table 2 of Clinical Study Report MOP4843g).

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The post-treatment allergen challenge was conducted on Day 86, 29 days after the last and third infusion. Methacholine challenges were performed 24 hours before and 24 hours following allergen challenges. The sputum-induction procedure was performed 24 hours before the allergen challenge and 7 hours and 24 hours following each allergen challenge. The methacholine challenge preceded sputum induction. The skin sensitivity to allergen by titration was repeated on Day 87 and Day 141. The end of the study was defined as the last patient's last visit or the last key datapoint received.

Number of Patients (Planned and Analyzed):

Up to 36 patients were to be recruited into the study. Twenty-nine patients were randomized to receive either quilizumab (15) or placebo (14).

Diagnosis and Main Criteria for Inclusion:

Patients with stable, mild allergic asthma with a history of episodic wheeze and shortness of breath were eligible to participate in this study. See Section 3.4.1 for the full listing of inclusion criteria.

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

Quilizumab at 5 mg/kg was administered intravenously on Days 1, 29, and 57. See Appendix 11.1.6 for product codes and lot numbers.

Duration of Treatment:

Study drug was administered on Days 1, 29, and 57. The study was completed after 197 days.

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

Placebo at 5 mg/kg was administered intravenously on Days 1, 29, and 57. See Appendix 11.1.6 for product codes and lot numbers.

Criteria for Evaluation

Efficacy:

Efficacy analyses included all patients who were randomized and who completed the baseline and Week 12 allergen-challenge tests, with patients allocated to the treatment arm to which they were randomized. There were 28 patients in the efficacy-evaluable population, 13 in the placebo group and 15 in the quilizumab group. One placebo patient ([redacted]) did not perform the Day 86 allergen challenge, and this patient was excluded from the efficacy analyses.

Safety:

Safety analyses included all patients who were included in the randomization and who received at least one dose of study drug, with patients allocated to the treatment arm associated with the regimen actually received. The safety population consisted of all treated patients, which was a total of 29 patients: 14 in the placebo group and 15 in the quilizumab group.

Statistical Methods

Primary Endpoint:

The primary efficacy analysis for this study was to determine a 90% CI on the ratio of mean late asthmatic response forced expiratory volume in 1 second area under the concentration-time curve (LAR FEV_1 AUC) on Day 86 between active and placebo patients. LAR FEV_1 AUC was calculated as the area under the curve of percent decline in FEV_1 (L) 3–7 hours post–allergen challenge.

Point estimates and 90% CIs on treatment effect sizes, along with descriptive summary statistics for each treatment group overall, were calculated for the primary and secondary efficacy outcome measures.

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Secondary Endpoints:

Safety was assessed through summaries of adverse events, concomitant medications, changes in laboratory test results, and changes in vital signs.

Individual and mean serum quilizumab concentration-time data were tabulated and plotted. The serum pharmacokinetics of quilizumab were summarized by maximum observed serum concentration (C_{max}) after each dose (i.e., $C_{max,1}$, $C_{max,29}$, $C_{max,57}$), by trough serum concentration (C_{min}) prior to the second and third doses ($C_{min,29}$ and $C_{min,57}$), and by serum concentration at 28 days after the last dose, on nominal Study Day 85 (C_{85}). Non-compartmental PK analysis was performed to estimate the $t_{1/2}$. Accumulation ratios (ARs), calculated as the ratio of $C_{min,57}$ to $C_{min,29}$ (C_{min}-based $AR_{57/29}$) and the ratio of $C_{max,57}$ to $C_{max,1}$ (C_{max}-based $AR_{57/1}$), were also reported. All parameters were tabulated and summarized by descriptive statistics (mean, standard deviation, coefficient of variation, median, geometric mean, minimum, and maximum).

Serum total and allergen-specific immunoglobulin E (IgE) levels were summarized over time.

FeNO assessments were performed for only a small number of patients ($n = 10$).

Summary of Results and Conclusions

Efficacy Conclusions:

- At Week 12, when compared with placebo, quilizumab reduced the LAR AUC by 36% (90% CI: -14, 69) and the EAR AUC by 26% (90% CI: 6, 43).
- In an exploratory, post-hoc subgroup analysis, a greater reduction in the LAR AUC at Week 12 was observed for patients with higher values of LAR AUC after the baseline allergen challenge: Patients ($n = 20$) with a baseline LAR AUC of ≥ 10%/hr had a 54% (90% CI: 10, 84) reduction versus placebo in the Week 12 LAR AUC.
- The maximum percentage decline in FEV_1 (L) at Week 12 when compared with placebo during the early (0–2 hr) and late (3–7 hr) phases were 11% and 13%, respectively.
- At Week 12, there was no difference in the change from pre-challenge (Day 85) to post-challenge (Day 87, 24 hours after the post-dosing allergen challenge) in methacholine PC_{20} between the two treatment groups (ratio of geometric means of 1.02).

Pharmacodynamic/Pharmacokinetic Conclusions:

- The allergen challenge appeared to induce an increase in serum total IgE levels in the placebo group at baseline and after Week 12. This increase was not detected in the quilizumab group.
- Quilizumab serum concentrations appeared to be at steady state by the third dose.
- The pre-dose mean serum concentrations, $C_{min,29}$ and $C_{min,57}$, were 19.0 ± 3.56 and 25.7 ± 5.40 μg/mL, respectively. The mean serum concentration on Day 57 was similar to that on Day 85 (29.5 ± 10.4 μg/mL), consistent with the drug reaching steady state by the third dose. The post-dose mean C_{max}, $C_{max,1}$, $C_{max,29}$, and $C_{max,57}$, were 120 ± 16.7, 138 ± 21.8, and 150 ± 24.9 μg/mL, respectively.
- The C_{min}-based mean AR was 1.35 ± 0.168 and the C_{max}-based mean AR was 1.23 ± 0.176, suggesting that accumulation of the drug was low.
- Quilizumab exhibited the expected PK characteristics for an IgG1 monoclonal antibody, with a slow clearance (CL) and a long terminal elimination half-life ($t_{1/2}$). The mean total serum CL of quilizumab was 1.87 ± 0.385 mL/day/kg and the $t_{1/2}$ averaged 20.2 ± 2.91 days. The mean V_{ss} was 82.1 ± 24.7 mL/kg, approximately equal to that of blood volume (74 mL/kg). The mean AUC_{57-85} and mean AUC_{1-last} were 2500 ± 413 and 7710 ± 1080 μg • day/mL, respectively. AUC_{1-last} captured over 99% of AUC_{1-inf}, indicating that the follow-up period was sufficient to adequately characterize elimination of quilizumab.

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Safety Conclusions:

Quilizumab administered at 5 mg/kg IV monthly on Days 1, 29, and 57 was well tolerated and had an acceptable safety profile:

- No deaths, serious adverse events, severe adverse events, or adverse events leading to discontinuation of study drug were reported.
- No treatment-related adverse events were reported in quilizumab-treated patients.
- The most frequent treatment-emergent adverse events were headache (5 patients, 3 [21%] on placebo and 2 [13%] on quilizumab) and nasopharyngitis (5 patients, 1 [7%] on placebo and 4 [27%] on quilizumab). These events were all mild, Grade 1 in severity except for an event of headache and one of nasopharyngitis in the placebo group, which were moderate, Grade 2 in severity.
- Moderate, Grade 2 adverse events occurred in 5 (36%) patients on placebo and 3 (20%) patients on quilizumab.
- Infections occurred in 3 (21%) patients on placebo and 6 (40%) patients on quilizumab, with nasopharyngitis comprising the majority of events.
- Infusion reactions occurred in 1 (7%) placebo- and 2 (13%) quilizumab-treated patients, and the events were all mild, Grade 1 in severity.
- No clinically meaningful mean changes in vital signs or chemistry or hematologic laboratory parameters over time were observed in quilizumab-treated patients compared with placebo-treated patients.
- ECG results were reported as normal in all quilizumab-treated patients.
- Anti-therapeutic antibody (ATA) levels were negative for all patients.

Overall Conclusions:

This study was designed to evaluate the efficacy, safety, and tolerability of quilizumab treatment in patients with mild bronchial asthma who underwent a controlled exposure to an allergen in a clinical setting after 12 weeks of treatment.

No notable differences between treatment groups were observed in the frequency and type of adverse events. The adverse events reported during the study were mild or moderate in severity. There were no deaths, pregnancies, serious adverse events, or patients withdrawn from study treatment due to adverse events. Overall, quilizumab was well tolerated.

Quilizumab exhibited the expected PK characteristics of an IgG1 monoclonal antibody, with a slow CL and a long mean $t_{1/2}$ of approximately 20 days.

The expected pharmacological activity of quilizumab was observed. Serum total IgE levels were gradually reduced in the quilizumab group, starting as early as Week 8 and sustained through the end of the study (Week 28), reaching a mean reduction of approximately 25%. Quilizumab appeared to prevent an increase in allergen-specific IgE observed in the placebo patients following the allergen challenge.

Quilizumab treatment reduced the early and late asthmatic responses (as measured by the AUC of the FEV_1 percent decline) by approximately 26% and 36%, respectively, compared with placebo.

All these findings are consistent with the mechanism of action of quilizumab, and the depletion of the M1 prime-expressing B-cell lineage may be effective for the treatment of allergic asthma.

Date of the Report:

16 November 2012