CLINICAL STUDY REPORT

TITLE:	**PHASE II RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF rhuMAb BETA7 IN PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS**
STUDY DRUG:	Etrolizumab (formerly known as rhuMAb Beta7)
INDICATION:	Ulcerative Colitis
REPORT NUMBER:	CSR ABS4986g
IND:	100,366
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
SPONSOR'S MEDICAL OFFICER:	[redacted]
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REPORT PREPARED BY:	[redacted]
RECORDS RETENTION:	Genentech Central Records
STUDY DATES:	Initiation: 23 August 2011 Completion: 20 January 2013
REPORT DATE:	13 November 2013

SYNOPSIS OF CLINICAL STUDY REPORT

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Title of Study: Phase II Randomized Double-Blind Placebo-Controlled Study to Evaluate the Efficacy and Safety of rhuMAb BETA7 in Patients with Moderate to Severe Ulcerative Colitis

Phase of Development: II

Investigators: Thirty-nine Investigators participated in the study (see Appendix 12.1.4 for investigator listing).

Study Centers: Forty global sites participated in the study (see Appendix 12.1.4 for investigator listing).

Publications: No publications have resulted from this study.

Study Period: 23 August 2011 to 20 January 2013.

Objectives

Primary

The primary objective of this study was to evaluate the efficacy of different doses of etrolizumab (formerly known as rhuMAb Beta7 [PRO145223]) compared with placebo in patients with moderately to severely active ulcerative colitis (UC); evidence of efficacy was defined as induction of clinical remission defined by a Mayo Clinic Score (MCS) ≤ 2 with no individual subscore exceeding 1 point by Week 10.

Secondary

The secondary objectives for this study were as follows:

- To evaluate the safety and tolerability of etrolizumab over a treatment period of 10 weeks and a follow-up period of 18 weeks
- To characterize the pharmacokinetic (PK) and immunogenicity [anti–therapeutic antibody (ATA) profile] of etrolizumab when administered subcutaneously (SC) across dose levels (Groups A and B)
- To evaluate the effect of etrolizumab on clinical remission (defined above) at Week 6
- To evaluate the effect of etrolizumab on clinical response as defined by at least a 3-point decrease and 30% reduction in MCS from baseline and a ≥ 1-point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1
- To evaluate the effect of etrolizumab as indicated by obtaining both an endoscopy score and a rectal bleeding score of 0 at Weeks 6 and 10

Methodology

This Phase II study was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety across two etrolizumab dose levels compared with placebo in patients with moderate to severe UC. The primary efficacy endpoint was evaluated at Week 10 (2 weeks after the final dose of study drug was administered). In the study, 124 patients were enrolled across 40 global sites.

Patients were planned to be randomized in a 1:1:1 ratio across a dose range of etrolizumab 100 mg SC at Weeks 0, 4, and 8, with placebo at Week 2; 420 mg SC at Week 0 followed by 300 mg SC at Weeks 2, 4, and 8; or matching placebo SC (40 patients per arm). The study was divided into a screening period of 0–35 days, a double-blind treatment period of 10 weeks, a safety follow-up period of 18 weeks, and a progressive multifocal leukoencephalopathy (PML) follow-up period of 17 months (2 years after randomization).

If patients experienced persisting or increasing disease activity at any time during the study, rescue therapy in the form of an increase in steroids and/or immunosuppressant dose or these

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therapies could have been initiated according to the investigator's clinical judgment. Patients who required rescue therapy were permitted to remain in the study but discontinued study drug and were classified as having experienced treatment failure for the data analysis.

Regular blinded reviews with an Internal Monitoring Committee (IMC; Clinical Scientist, Safety Scientist, and Biostatistician) were conducted during the course of the study to monitor safety data, including adverse events, serious adverse events, and laboratory abnormalities.

Number of Patients (Planned and Analyzed)

The study was expected to enroll approximately 120 patients at up to 55 global sites.
The actual enrollment included 124 patients from 40 participating global sites.

Diagnosis and Main Criteria for Inclusion

Eligible patients must have had a minimum of 12-weeks duration of UC diagnosed according to the American College of Gastroenterology (ACG) practice guidelines with clinical and endoscopic evidence corroborated by a histopathology report; evidence of moderate to severe disease as evidenced by an MCS of ≥ 6 (MCS of ≥ 5 for sites outside of the United States), including an endoscopy subscore of ≥ 2; a rectal bleeding subscore of ≥ 1; and endoscopic evidence of disease activity within a minimum distance of 25 cm from the anal verge.

Prior to randomization, patients must have been on stable doses of concomitant medications for UC. Oral 5-ASA and immunosuppressant (AZA, 6-MP, or methotrexate) doses must have been kept stable for at least 4 weeks prior to randomization on Day 1. Patients who were receiving topical 5-ASA or corticosteroids must have discontinued use 2 weeks prior to randomization on Day 1. Oral corticosteroid doses were required to be kept stable for 2 weeks prior to randomization on Day 1. Patients receiving high-dose steroids had to have the dose reduced to ≤ 20 mg/day for 2 weeks prior to randomization on Day 1. For patients receiving oral corticosteroids during the study treatment period, the dose was kept stable until Week 10 (timepoint for the primary endpoint), at which time tapering of corticosteroid dose was mandatory at a rate of a 5-mg prednisone or prednisone equivalent per week for 2 weeks and then at a rate of 2.5 mg prednisone or prednisone equivalent per week to discontinuation. In the United States, for patients receiving oral immunosuppressants (other than oral corticosteroids), tapering of immunosuppressants was commenced at Week 8, and patients must have completely discontinued immunosuppressants by Week 10. All patients must have discontinued anti–tumor necrosis factor (anti-TNF) therapy for a minimum of 8 weeks prior to randomization on Day 1.

Test Product, Dose and Mode of Administration, Batch Number

See Appendix 12.1.6 for the etrolizumab product code and lot numbers.

Group A: Etrolizumab 100 mg monthly SC at Weeks 0, 4, and 8

Group B: Etrolizumab 420 mg SC at Week 0 followed by 300 mg SC at Weeks 2, 4, and 8

Patients were randomly allocated (1:1:1) to Groups A, B, or C. All doses were delivered SC to the abdomen. If the abdomen was not available for injection, patients received SC injection in the thigh. Each patient received four injections of 0.7 mL at Week 0 followed by three SC injections of 0.7 mL at Weeks 2, 4, and 8.

Duration of Treatment

The study included a 5-week screening period, 10-week double-blind treatment period, and a safety follow-up to Week 28 or rollover to the open-label extension.

Reference Therapy, Dose and Mode of Administration, Batch Number

See Appendix 12.1.6 for the reference product code and lot numbers.

Group C: Placebo SC at Weeks 0, 2, 4, and 8

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Patients randomized to Group C received placebo. Placebo and etrolizumab were administered via the same route and according to the same procedures.

Criteria for Evaluation

Efficacy

The efficacy population was defined as all patients who received at least one dose of study drug and had a central endoscopic score of at least 2 at baseline, which included 119 patients: 39 in the etrolizumab 100-mg arm, 39 in the etrolizumab 300-mg + loading dose (LD) arm, and 41 in the placebo arm.

Safety

The safety population was defined as all patients who received at least one dose of study drug.

Statistical Methods

Primary Endpoint

The primary endpoint was the proportion of patients in clinical remission (clinical remission defined by a MCS ≤ 2 with no individual subscore exceeding 1 point) at Week 10. The difference between each etrolizumab arm and placebo was evaluated using the Mantel-Haenszel test statistic, stratified by concomitant treatment with corticosteroids, concomitant treatment with immunosuppressants, and previous anti-TNF exposure. Additionally, the difference between treatment groups was evaluated by constructing 80% confidence intervals for the primary efficacy endpoint. Descriptive summary statistics are provided for each treatment group.

Secondary Endpoints

The secondary efficacy endpoints were as follows:

- The proportion of patients with clinical response at Week 6 and Week 10

  Clinical response was defined by at least a 3-point decrease and 30% reduction from baseline in MCS and a ≥ 1-point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1.
- The proportion of patients in clinical remission (defined above) at Week 6
- The proportion of patients who achieve an endoscopic score and rectal bleeding score of 0 at Weeks 6 and 10

Summary of Results and Conclusions

Efficacy Conclusions:

- In the efficacy evaluable population, etrolizumab showed clinical meaningful activity for both doses relative to placebo for the primary endpoint—proportion of patients in clinical remission at Week 10 (20.5% [100 mg] and 10.3% [300 mg + LD] vs. 0% [placebo]; p=0.004, 80% CI: 12.5%, 29.9% in 100 mg vs. placebo; and p=0.048, 80% CI: 4.2%, 18.2% in 300 mg + LD vs. placebo, respectively).
- Exploratory subgroup analysis of the study established that both etrolizumab 100 mg and etrolizumab 300 mg + LD led to a higher proportion of clinical remission at Week 10 than placebo in the TNF-naive population (43.8%, 25%, and 0% in the 100 mg, 300 mg + LD, and placebo arms, respectively, in TNF-naive population; p = 0.007, 80% CI: 26.1%, 59.5% in etrolizumab 100 mg vs. placebo and p = 0.075, 80% CI: 9.2%, 43.3% in etrolizumab 300 mg + LD vs. placebo).

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Pharmacodynamic/Pharmacokinetic Conclusions

- Etrolizumab displayed linear PK profiles in both the 100-mg and 300-mg + LD arms within the PK evaluation duration. The 300-mg + LD arm provided a 4.3-4.6-fold higher drug exposure than that from the 100-mg arm ($C_{max,last\ dose}$: 11.6±5.50 and 50.2±22.8 μg/mL for the 100-mg and 300-mg+LD arm, respectively; $AUC_{\tau\ (Days\ 56–84)}$: 265±163 and 1215±495 μg•day/mL for the 100-mg and 300-mg+LD arm, respectively). The mean elimination half-life was estimated to be approximately 13–15 days for both arms. By comparing the exposure during the last dose interval ($AUC\tau_{(Days\ 56–84)}$) to the first month exposure ($AUC\tau_{(Days\ 0–28)}$), etrolizumab accumulated 1.9-fold in the 100-mg arm following 3 doses given once every 4 weeks (q4w) and 1.4-fold in the 300-mg + LD arm given as 420 mg at Week 0 and 300 mg at Weeks 2, 4, and 8.
- Maximal/near maximal β7 receptor occupancy was observed on lymphocyte subsets both in blood and in colonic tissue following the administration of etrolizumab at 100 mg or 300 mg+LD. There was no apparent β7 receptor occupancy observed in patients dosed with placebo. These observations were consistent with the binding of etrolizumab to target cells expressing β7 integrin in peripheral blood and colonic tissue. The relationship between serum drug levels and β7 occupancy in colonic tissue, although based on limited available data (n=23), is similar to the PK/PD relationships observed in blood in Phase I and is consistent with the predicted IC_{90} for receptor occupancy (IC_{90}=1.3 μg/mL estimated by a Phase I, target-mediated, drug-disposition PK/PD model; Wei et al. 2012). This suggests that β7 receptor occupancy in blood may serve as a surrogate indicator for occupancy in colonic tissue in patients with UC.
- The overall incidence of ATAs was calculated from the total number of baseline-negative patients who subsequently (after drug administration) tested positive for ATAs against etrolizumab divided by the total number of patients who had postdose ATA samples available for the ATA analysis. Four of the 81 (4.9%) etrolizumab-treated patients had detectable ATAs that emerged after treatment, a nearly identical rate to that seen in the Phase I trial (Study ABS4262g) of etrolizumab in patients with UC (2 of 38 [5.3%] treated patients). There was no observed relationship between safety and presence of ATAs in these ATA-positive patients. There were also no observed effects of positive ATA on their PD or PK parameters or efficacy.

Safety Conclusions

- The overall safety profile in both etrolizumab arms was similar to that of placebo. No significant adverse safety signals, including any evidence of increased rates of serious or opportunistic infections, were associated with etrolizumab treatment. The most frequently reported AEs with a higher rate in the etrolizumab arms compared with the placebo arm were rash, influenza-like illness, and arthralgia (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade ≤2).
- Most AEs that patients experienced were Grade 1 and 2 (NCI CTCAE). The highest grade of AEs recorded in this study was Grade 3.
- There were no fatal adverse events reported in this study.

Overall Conclusions

The primary efficacy endpoint of this study was the proportion of patients who achieved clinical remission, defined as an MCS ≤ 2 with no individual subscore exceeding 1 point, by Week 10. The analysis of proportion of patients in clinical remission at Week 10 showed both etrolizumab 100 mg and etrolizumab 300 mg + LD led to a higher proportion of patients who achieved clinical remission than placebo. This is true for both the efficacy population and all randomized

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patients population. There was no evidence of a dose–response relationship. Exploratory subgroup analysis of the study established that both etrolizumab 100 mg and etrolizumab 300 mg + LD led to a higher proportion of clinical remission at Week 10 than placebo in the TNF-naive population. For the secondary efficacy endpoint of endoscopic remission at Week 10, a clinically significant improvement among etrolizumab-treated patients was seen.

The overall safety profile in both etrolizumab arms was similar to that of placebo. No significant adverse safety signals, including any evidence of increased rates of serious or opportunistic infections, were associated with etrolizumab treatment. There were no fatal adverse events reported in this study.

Etrolizumab displayed linear PK profiles in both 100 mg and 300 mg + LD arms within the PK evaluation period. A clear drug exposure separation was observed between the 300-mg + LD arm (4.3–4.6 fold higher) and 100-mg arm. The mean elimination half-life was estimated to be approximately 13–15 days from both arms. Four of 81 treated patients demonstrated a drug-emergent antibody response to etrolizumab. There was no observed relationship between safety and the presence of ATAs in the ATA-positive patients. There were also no apparent effects on PD or PK parameters or efficacy in ATA-positive patients.

Maximal/near maximal β7 receptor occupancy was observed on lymphocyte subsets both in blood and in colonic tissue following the administration of etrolizumab at 100 mg or 300 mg+LD. There was no apparent β7 receptor occupancy observed in patients dosed with placebo. The relationship between serum drug levels and β7 occupancy in colonic tissue, although based on limited available data ($n = 23$), is similar to the PK/PD relationships observed in blood in Phase I and is consistent with the predicted IC_{90} for receptor occupancy. This suggests that β7 receptor occupancy in blood may serve as an indicator for occupancy in colonic tissue.

Date of the Report

13 November 2013