

SYNOPSIS OF CLINICAL STUDY REPORT

Title of Study:	AN OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 1.0 mg/kg SUBCUTANEOUSLY ADMINISTERED EFALIZUMAB FOLLOWED BY EFALIZUMAB TAPER IN ADULTS WITH PLAQUE PSORIASIS PREVIOUSLY ENROLLED IN STUDY ACD2390g
Phase of Development:	IIIb
Investigators:	Thirty investigators participated in the study.
Study Centers:	There were 30 investigative sites in the United States and Canada.
Publications:	No publications have resulted from this study.
Study Period:	18 January 2002 to 18 April 2003

Objectives

Primary:

The primary objectives were examined during the Extended Treatment (ET) period in subjects who received efalizumab during Study ACD2390g. The objectives were the following:

- The rate of response at 24 weeks in subjects originally randomized to receive 1.0 mg/kg/wk subcutaneous (SC) efalizumab for 12 weeks in Study ACD2390g. Response to treatment was measured by the proportion of subjects with $\geq 75\%$ improvement in Psoriasis Area and Severity Index (PASI) score (PASI-75) on ET Day 84 relative to Day 0 in Study ACD2390g (hereafter referred to as ACD2390g Day 0)
All subjects who received efalizumab during Study ACD2390g, including subjects who did not enter the ET period of Study ACD2391g (referred to as Group 2390-A), were included in this analysis.
- The safety and tolerability of extended treatment with 1.0 mg/kg/wk SC efalizumab following an initial 12 weeks of exposure to efalizumab in Study ACD2390g
All subjects who received efalizumab during Study ACD2390g, completed the study, and received at least one dose of efalizumab during the ET period of Study ACD2391g (referred to as Group ET-A) were included in this analysis.

Secondary:

The secondary objectives examined during the ET period for Group 2390-A are listed below in order of importance:

- To determine the proportion of subjects achieving an Overall Lesion Severity (OLS) scale rating of Minimal or Clear at ET Day 84
- To determine the proportion of subjects attaining a rating of Excellent or Cleared on the Physician's Global Assessment (PGA) of change at ET Day 84
- To determine the change in the Dermatology Life Quality Index (DLQI) from ACD2390g Day 0 to ET Day 84
- To determine the change in the Psoriasis Symptom Assessment (PSA) from ACD2390g Day 0 to ET Day 84

Secondary objectives examined during the ET period for Group ET-A are listed below in order of importance:

- To determine the proportion of subjects with $\geq 75\%$ improvement in the PASI score on ET Day 84 relative to ACD2390g Day 0 categorized by PASI response at ACD2390g Day 84
- To determine the proportion of subjects achieving an OLS scale rating of Minimal or Clear at ET Day 84 categorized by PASI response at ACD2390g Day 84

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- To determine the change in the DLQI from ACD2390g Day 0 to ET Day 84 categorized by PASI response at ACD2390g Day 84

Secondary objectives examined during the ET period for subjects who received placebo during Study ACD2390g and efalizumab in Study ACD2391g (referred to as Group ET-C) are listed below in order of importance:

- To determine the proportion of subjects with $\geq 75\%$ improvement in the PASI score on ET Day 84 relative to ET Day 0
- To determine the proportion of subjects achieving an OLS scale rating of Minimal or Clear at ET Day 84
- To determine the change in the DLQI from ET Day 0 to ET Day 84
- To characterize the safety and tolerability of an initial 12-week course of treatment with 1.0 mg/kg/wk SC efalizumab

Secondary objectives examined during the Taper Treatment (TT) and Follow-Up (FU) periods were the following:

- To determine the incidence of psoriasis relapse in subjects receiving one of two taper regimens of efalizumab
- To characterize psoriasis in subjects who relapse

Methodology

This was an open-label, multicenter study designed to evaluate the efficacy and safety of efalizumab administered at weekly SC doses of 1.0 mg/kg followed by efalizumab taper in subjects with plaque psoriasis who previously participated in Study ACD2390g.

The study consisted of three periods: ET, TT, and FU. Each period lasted 12 weeks.

All treatments during the ET and TT periods were open label. During the ET period, all subjects received 1.0 mg/kg/wk efalizumab SC for 12 weeks. For the purpose of stratification for randomization to TT regimens and for the purpose of defining relapse used in monitoring the TT and FU periods, response at the end of the ET period was determined as follows:

- Responder: any subject whose PASI score decreased $\geq 75\%$ on ET Day 84 relative to ACD2390g Day 0
- Partial responder: any subject whose PASI score decreased $\geq 50\%$ but $< 75\%$ on ET Day 84 relative to ACD2390g Day 0
- Non-responder: any subject whose PASI score decreased $< 50\%$ on ET Day 84 relative to ACD2390g Day 0

After completion of the ET period, all subjects entered the TT period. Subjects were randomized in a 1:1 ratio to receive one of two taper regimens. Randomization was stratified based on treatment assignment in Study ACD2390g and on response status at ET Day 84, as determined by an interactive voice response system using PASI data entered by study site personnel. The taper regimens were Taper Regimen A, 0.5 mg/kg/wk SC efalizumab for 6 weeks followed by 0.25 mg/kg/wk SC efalizumab for 6 weeks, and Taper Regimen B, 1.0 mg/kg every other week (qow) SC efalizumab for 6 weeks followed by 0.5 mg/kg/qow SC efalizumab for 6 weeks.

After completing the TT period, subjects entered the FU period. During the FU period, subjects were monitored for safety following discontinuation of efalizumab treatment.

Number of Subjects (Planned and Analyzed):

For the ET period, the planned enrollment was 450 subjects; 516 subjects were analyzed. For the TT period, the planned enrollment was 400 subjects; 458 subjects were analyzed.

Diagnosis and Main Criteria for Inclusion:

Subjects with plaque psoriasis who previously participated in Study ACD2390g were eligible to enroll in Study ACD2391g.

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

During the ET period, each subject received a conditioning dose of 0.7 mg/kg efalizumab followed by 11 weekly SC doses of 1.0 mg/kg efalizumab. During the TT period, subjects received one of two taper regimens: Taper Regimen A (0.5 mg/kg/wk SC efalizumab for 6 weeks followed by 0.25 mg/kg/wk SC for 6 weeks) or Taper Regimen B (1.0 mg/kg/qow SC efalizumab for 6 weeks followed by 0.5 mg/kg/qow SC efalizumab for 6 weeks). See Appendix 16.1.6, for efalizumab product codes and lot numbers.

Duration of Treatment:

Up to 24 weeks of continuous treatment followed by 12 weeks of taper treatment

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

Not applicable.

Criteria for Evaluation

Efficacy:

For the ET period, the proportion of subjects with an improvement of $\geq 75\%$ in PASI score at ET Day 84 relative to ACD2390g Day 0 (responders) in Group 2390-A was summarized. For the ET period, the proportion of subjects achieving an OLS rating of Minimal or Clear at ET Day 84 (the principal secondary endpoint), the proportion of subjects achieving $\geq 50\%$ in PASI score at ET Day 84, and the proportion of subjects achieving a PGA rating of Excellent or Cleared at ET Day 84 were summarized. For the TT period, the proportion of subjects achieving $\geq 75\%$ in PASI score, the proportion of subjects achieving an OLS rating of Minimal or Clear, the proportion of subjects achieving $\geq 50\%$ in PASI score, and the proportion of subjects achieving a PGA rating of Excellent or Cleared were summarized.

The incidence of psoriasis relapse during the TT and FU periods was summarized by period and taper regimen. The analysis was based on subjects who received any amount of study drug during Study ACD2390g and/or the ET period and who subsequently entered the TT or FU period.

Safety:

Safety was assessed through the summary of adverse events, deaths, laboratory test results, vital signs, antibodies to efalizumab, and psoriasis relapse. These summaries were produced separately for each study period. For comparison with baseline, baseline was ACD2390g Day 0 for subjects who received efalizumab in Study ACD2390g and was ET Day 0 for subjects who received placebo in Study ACD2390g and efalizumab in Study ACD2391g. Baseline for subjects who entered the FU period directly from Study ACD2390g was ACD2390g Day 0 regardless of treatment.

Three cohorts were defined for subjects who entered the FU period:

- FU-FT: subjects who entered the FU period from the First Treatment (FT) period of Study ACD2390g
- FU-ET: subjects who entered the FU period from the ET period
- FU-TT: subjects who entered the FU period from the TT period

Subjects were analyzed according to the actual treatment received.

Primary Endpoint:

The primary efficacy outcome measure for this study was the proportion of subjects with a $\geq 75\%$ improvement in PASI score at ET Day 84 relative to ACD2390g Day 0 in all subjects who received efalizumab during Study ACD2390g (Group 2390-A).

Principal Secondary Endpoint:

The principal secondary outcome measure was the proportion of subjects achieving an OLS rating of Minimal or Clear at ET Day 84 (Group 2390-A).

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Other Endpoints:

Other outcome measures examined were the Patient's Global Psoriasis Assessment (PGPA) and the mean improvement in the DLQI, the Itching Scale, and the PSA over time.

Summary of Results and Conclusions

Efficacy Results:

Extending the duration of efalizumab treatment to 24 weeks increases clinical efficacy as demonstrated by an increase in PASI-75 and PASI-50 response rates. By the end of 24 weeks of continuous efalizumab treatment, 43.8% of subjects (161 of 368 subjects) in the 2390-A cohort achieved a PASI-75 response and 66.6% (245 of 368 subjects) achieved a PASI-50 response.

The PASI-75 and PASI-50 response rates (24.1% of subjects achieved a PASI-75 and 60.3% achieved a PASI-50) at the end of the first 12-week exposure of efalizumab in the ET-C cohort are consistent with the treatment effect observed in previous Genentech-sponsored placebo-controlled efalizumab studies. With the second 12-week course of efalizumab treatment, 80.6% of 2390-A responders maintained a PASI-75 at Day 84 in Study ACD2391g, 49.6% of subjects advanced to PASI responders from partial responders, and 44.9% of subjects advanced to partial responders from non-responders. Additionally, 18.9% of FT Day 84 non-responders achieved PASI-75 at ET Day 84.

The percentage of subjects achieving an OLS of Minimal or Clear was 35.9% for 2390-A subjects, 38.6% and 28.7% for ET-A and ET-C subjects, respectively, and 67.3%, 38.5%, and 16.5% for ACD2390g responders, partial responders, and non-responders, respectively.

The percentage of 2390-A subjects achieving a PGA of Excellent or Cleared was 33.2%.

Patient-reported outcomes included the DLQI, the Itching Scale, and the PSA (frequency and severity). For subjects who were treated with efalizumab for up to 24 weeks, improvements in all the patient-reported outcomes were maintained through ET Day 84. For ET-C subjects, improvements at ET Day 84 were similar to those previously observed in placebo-controlled trials.

The two taper regimens demonstrated similar efficacy profiles. There appeared to be no benefits derived from the taper regimens in preventing psoriasis worsening upon discontinuation of efalizumab. At TT Day 84, the proportion of subjects with $\geq 75\%$ PASI improvement was 28.0% and 29.2% in the Taper A and Taper B groups, respectively. The proportion of subjects with $\geq 50\%$ PASI improvement was 49.1% (which was a reduction from the end of the ET period) and 48.2% in the Taper A and Taper B groups, respectively.

The taper regimens did not appear to prevent relapse during washout of the drug (FU period). By TT Day 84, 24.4% (42 of 172) and 30.8% (53 of 172) of subjects experienced protocol-defined relapse in the Taper A and Taper B groups, respectively. By FU Day 84, 66.5% (109 of 164) and 62.0% (101 of 163) of subjects experienced relapse either in the TT or FU period in the Taper A and Taper B groups, respectively. The median time to relapse during the TT and FU periods was approximately 140 days in both taper groups.

Safety Results:

The most frequently observed adverse events in all treatment periods were acute adverse events, which occurred most frequently in the ET-C group (27.2%). As in the previous studies, most of the acute adverse events were mild and self-limited, occurred with initial dose(s), and were of limited clinical significance.

Other adverse events occurred at low frequencies ($< 10\%$ of subjects in a treatment period), were similar between the groups and across treatment periods, and were consistent with results seen in previous studies. Severe and serious adverse events occurred infrequently and at a similar rate across the groups.

The rate of serious adverse events ranged between 0.9% and 4.6% during the ET and TT periods, and serious adverse events were reported in 13 subjects during the FU period (1 of 16 [6.3%] FU-FT subjects; and 12 of 428 [2.8%] FU-TT subjects).

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Conclusions:

Strong efficacy results were shown in this study of up to 24 weeks of continuous treatment with efalizumab. An intent-to-treat analysis showed that after 24 weeks of treatment, 44% of subjects were PASI responders. The PASI responder rate was 47% of subjects who received a second 12-week treatment course and 24% for subjects who received their first 12-week treatment course. All secondary endpoints, including PGA, Itching Scale, and DLQI, were consistent with the primary analysis. After 12 weeks of taper, the response rate fell to approximately 30%, suggesting that doses lower than 1.0 mg/kg/wk of efalizumab are less efficacious than 1.0 mg/kg/wk.

The overall safety profile seen in the study was consistent with the results of previous efalizumab studies. Efalizumab was well tolerated, and the most common adverse events were acute adverse events in the ET-C group. Serious adverse events were infrequent. The rate of psoriasis adverse events was low during the ET period and slightly higher during the TT period. Psoriasis adverse events in general and serious psoriasis adverse events in particular were low overall.

Efalizumab is well tolerated for up to 24 weeks of continuous treatment, and treatment with efalizumab for up to 24 weeks appears to incrementally improve psoriasis. Taper of the efalizumab dose over 12 weeks appears to decrease but not abrogate the occurrence of psoriasis adverse events.

Date of the Report:

25 February 2004