CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN/BLA 125075/0

Medical Review(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
Food and Drug Administration
Center for Drug Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852

Memorandum

Division of Therapeutic Biologics
Internal Medicine Products
HFM-582

Date: October 27, 2003

From: Elektra J. Papadopoulos, M.D. /S/ 10/27/03
Medical Officer
Division of Therapeutic Biologics Internal Medicine Products
Office of New Drug Evaluation VI, CDER, FDA

Subject: Clinical Review

Biologic License Application: STN 125075/0
Product: Efalizumab
Indication: Moderate to Severe Chronic Plaque Psoriasis
Sponsor: Genentech Corporation

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To: STN 125095/0

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1 INTRODUCTION

1.1 Filing of License Application

On December 27, 2002 Genentech submitted to the Center for Biologics Evaluation and Research a Biologics License Application (STN BL 125075/0) for efalizumab for the treatment of psoriasis.

1.2 Drug Product

Efalizumab is an immunosuppressive recombinant humanized IgG1 kappa isotype monoclonal antibody that binds to human CD11a and has an approximate molecular weight of 150 kD. The protein is produced by Chinese hamster ovary cells.

The drug product is provided as a sterile lyophilized powder to deliver 125 mg of efalizumab. Reconstitution with 1.3 mL of supplied Sterile Water for Injection yields a clear to slightly opalescent solution containing 100 mg/mL efalizumab, 0.2% polysorbate 20, 40 mM histidine, 240 mM sucrose, and SWFI at a pH of 6.2. Although the drug is produced in a suspension culture containing gentamicin, gentamicin is not detectable in the final product.

1.3 Rationale and Hypothesis

CD11a is the α subunit of lymphocyte function-associated antigen (LFA-1), a β2 integrin, and is expressed on all leukocytes. Efalizumab binds to the CD11a alpha chain of LFA-1 and blocks the binding of LFA-1 to its ligand intercellular adhesion molecule 1 (ICAM-1). Binding of CD11a by efalizumab results in saturation of available CD11a binding sites and down-modulation of cell surface CD11a expression. This event is believed to decrease the activation of lymphocytes and reduce their translocation to peripheral tissues (such as in psoriatic plaques).

Activated T lymphocytes may play a role in autoimmune diseases including plaque-type psoriasis. Blocking or reducing T lymphocyte activation and migration may improve the clinical manifestations of psoriasis.

1.4 Proposed Indication: Plaque Psoriasis

Psoriasis is a chronic skin disorder characterized by erythematous, scaly papules and plaques with a predisposition for the scalp, extensors of the limbs, lumbosacral area and genitalia. The condition affects between 1 and 3% of the general population. However, it is relatively infrequent among African-Americans, in Japanese populations and in the Native American population. Men and women are equally affected.

Psoriasis has a bimodal peak of onset, one in adolescents and young adults (at 16 to 22 years of age) and the second in older persons (at age 57-60). Onset is before the age of 15 in 27% of cases. Early onset disease is strongly linked to HLA -Cw6 and DR7, while late onset disease is linked to HLA-Cw2. The predisposition to psoriasis is thought to be polygenic with expression triggered by environmental factors such as streptococcal infection, stress, certain drugs, and HIV. The cause of psoriasis is not fully known.

Psoriasis is characterized by excessive proliferation of keratinocytes and inflammation. There is evidence that activated T cells are involved in the pathogenesis of psoriasis. In addition,

abnormalities in cytokine expression, intracellular signaling, and polyamine metabolism may mediate psoriasis.

Plaque psoriasis is the most common form. The lesions are indurated/raised, erythematous and scaly. Approximately 1/3 of patients have moderate to severe disease. The disease waxes and wanes. Spontaneous remissions and relapses are the rule. Spontaneous durable remissions may occur.

Guttate (drop-like) psoriasis is sometimes triggered by streptococcal infection and is associated with development of chronic psoriasis. Pustular psoriasis varies in severity from localized to generalized forms with fever, malaise, and a relatively high mortality after prolonged courses. Erythroderma can be complicated by sepsis, temperature instability and high output cardiac failure. Psoriatic arthritis is a complication in approximately 10% of all psoriasis patients.

Patients with psoriasis report reduction in mental and physical functioning comparable to that seen in patients with cancer or arthritis. The chief complaints of patients with psoriasis are scaling, itching, redness and tightness of the skin, bleeding and burning sensations. In a 1998 National Psoriasis Foundation Patient-Membership survey, patients reported depression, difficulties in the workplace and socialization caused by psoriasis. -

The goal of treatment of psoriasis is to decrease the severity and extent of psoriasis to the point that it no longer interferes with the patient's occupation, personal or social life, or well-being.

1.5 Licensed Therapies for Psoriasis

Topical Therapy

The initial treatment of stable plaque psoriasis affecting less than 10-20% of body surface area is topical. Topical therapies include emollients, corticosteroids, anthralin, tar, retinoids, calcipotriene, and salicylic acid. The mainstay of treatment is topical corticosteroids. Topical corticosteroids induce skin atrophy, striae, purpura and may be absorbed systemically leading to suppression of the hypothalamic-pituitary-adrenal axis. Another possible limiting factor to their use is tachyphylaxis. Other commonly used topical agents include calcipotriene (a vitamin D analogue), tazarotine (a retinoid prodrug) and anthralin. Salicylic acid is used as a keratolytic agent. Skin irritation is the most common adverse effect of these topical agents.

Phototherapy

Phototherapy for psoriasis includes UVB, narrow band UVB, and psoralen, a photosensitizer, plus UVA (PUVA). PUVA induces responses in a high proportion of patients and can induce long-term remissions. PUVA causes premature aging of skin and increases the risk of cutaneous malignancy in a dose-related fashion.

Systemic Therapy

Methotrexate, cyclosporin, and retinoids, in general, induce moderate improvement in the majority of treated patients. These products are recommended for severe and/or recalcitrant psoriasis because they induce serious toxicities. Methotrexate, an antimetabolite folate analogue, may cause bone marrow toxicity with leukopenia, dose-dependent development of cirrhosis of the liver, severe pneumonitis and lymphomas. Methotrexate is also fetotoxic and an

abortifacient. Cyclosporine, an immunosuppressant calcineurin inhibitor, induces hypertension, nephrotoxicity, increased risk of malignancy (especially B cell lymphoma) and infection. Retinoids are the treatment of choice for pustular psoriasis and have also been used in the treatment of erythrodermic psoriasis. Of major consideration in women of childbearing potential is teratogenicity of retinoids. Other serious adverse events are hepatotoxicity, pancreatitis, depression, visual impairment, and hyper-triglyceridemia.

Alefacept, an immunosuppressive and the first biologic agent to receive FDA approval for the treatment of moderate-to-severe psoriasis, results in 75% clearing in 10% (by IV route) 16% (by IM route) of patients. Remissions may last for months. The drug induces lymphopenia and requires monitoring of CD4+ T lymphocyte counts on a regular basis.

Immunosuppressive Agents and Anti-metabolites: Risk/benefit in Psoriasis
Psoriasis is a serious chronic disease associated with significant morbidity and impairment. The disease is usually not life threatening and does not induce irreversible injury to skin or other organs, with the exception of psoriatic arthritis. A number of serious toxicities are associated with the use of immunosuppressants and antimetabolites. These include serious infections, and neoplasms. In the case of neoplasms there may be a lag in the time to clinical detection and long-term follow-up of treated patients may be required to assess the excess risk. Therapies associated with significant risk of serious irreversible toxicity or mortality should be reserved for patients with severe, recalcitrant psoriasis. The goal of therapy is to bring disease under control and change to the least toxic therapy.

1.6 Licensing Status of Drug Product
At the time this application was submitted, efalizumab was not licensed in any country, nor had it been withdrawn from the market in any country.

1.7 Disclosure of Financial Interests and Arrangements of Clinical Investigators
At the time this application was submitted, none of the clinical investigators (from whom a response was received) disclosed financial interest in either Genentech or Genentech's partner, XOMA, Ltd.

1.8 Debarment Certification
Genentech has provided certification that it did not and will not use the services of anyone debarred under Subsections A or B of Section 306 of the Food, Drug and Cosmetics Act in connection with this application.

2 CLINICAL STUDIES OF EFALIZUMAB AND REGULATORY HISTORY

Two sponsors, XOMA, Ltd. and Genentech, Inc., participated in the development of efalizumab for moderate to severe plaque psoriasis.

- XOMA sponsored the phase 1 and 2 clinical studies and manufactured efalizumab used in those studies.
- Genentech sponsored the phase 3 studies and is the current manufacturer of the to-be-marketed efalizumab product.

- Study ACD2058g, the first phase 3 study, studied exclusively efalizumab manufactured by XOMA.
- Most of the patients in study ACD2059g, received XOMA-manufactured efalizumab. In the latter part of the study Genentech-manufactured product was introduced.
    - In this study, the pharmacokinetic (PK), pharmacodynamic (PD) and clinical activity of the XOMA-manufactured and Genentech-manufactured efalizumab products were compared.
- Subsequent phase 3 studies, ACD2390g and ACD2600g, studied exclusively the Genentech-manufactured product.

September 2001:
The agency expressed concerns about the comparability of the efalizumab manufactured by XOMA and Genentech and recommended that a PK comparability study (ACD2389) be performed in healthy volunteers.

June 2002:
Study ACD2389g showed that the XOMA- and Genentech- produced efalizumab were equivalent pharmacodynamically, but were not pharmacokinetically equivalent. The Genentech-manufactured efalizumab appeared to have higher bioavailability and/or slower clearance. The ratio of geometric means for AUC_{inf} of Genentech and XOMA efalizumab was 1.32, with a 90% confidence interval of 1.19–1.47, above the 0.80–1.25 range specified for comparability.

These results prompted the FDA to request additional phase 3 studies for safety and efficacy of the Genentech-manufactured product.

November 2002:
Study ACD2390g showed that 1 mg/kg/wk SC of the Genentech-manufactured efalizumab was superior to placebo. The Agency agreed that the data were adequate for filing a licensing application and recommended that the XOMA- and Genentech-manufactured efalizumab databases be analyzed separately and also be pooled for the BLA submission.

Table 1 provides a listing of the clinical studies of efalizumab in patients with psoriasis and summarizes the number of patients treated and the duration of treatment as of May 2003.

Table 1 Efalizumab Studies: Psoriasis Subjects Receiving at Least One Dose of Efalizumab

Study	Phase and Design	Dose (mg/kg) and Route	Treatment Duration (wk)	No. of Subjects Treated 1st Time With XOMA	No. of Subjects Treated 1st Time With GNE
HU9602	1, open-label	0.03–10.0 IV	1	31	NA
HUPS249	1, open-label	0.1–1.0 IV	7	39	NA
HUPS252	2, placebo-controlled	0.1, 0.3 IV	8	97	NA
HUPS254	1, open-label	0.5–2.0 SC	1–8	52	NA
HUPS256	1, open-label	0.3–1.0 IV	12	11	NA
		1.0–4.0 SC	12	57	NA
ACD2058g	3, placebo-controlled	1.0–2.0 SC	12–24	462	NA
ACD2059g	3, placebo-controlled	1.0–4.0 SC	12–24	442	137
ACD2062g	3, open-label extension study to ACD2058g	1.0–2.0 SC	12	28	6
ACD2142g	1, open-label	1.0–2.0 SC	12	NA	70
ACD2243g	3, open-label	2.0 SC, then 1.0–2.0 SC	12 ≥ 48	NA	339
ACD2390g	3, placebo-controlled	1.0 SC	12	NA	368
ACD2391g	3, open-label extension to ACD2390g	1.0 SC	24	NA	174
ACD2600g	3, placebo-controlled	1.0 SC	12	NA	449
Subjects with psoriasis receiving efalizumab by manufacturer				1219	1543
Subjects with psoriasis receiving efalizumab (Total)				2762	

In addition to phase 1 and 2 trials, four phase 3 double blinded, randomized, placebo controlled trials were conducted. Long-term exposure data were provided by studies ACD2058g and ACD2059g (24 weeks of treatment), by study ACD2243g (48 weeks of treatment), and by the open-label extension studies. The total safety database consisted of over 2500 patients exposed to efalizumab.

3 SUMMARY OF THE PHASE 1 AND 2 CLINICAL EXPERIENCE

XOMA conducted the Phase 1 studies (trials HU9602, HUPS249, HUPS254, and HUPS256), which characterized efalizumab's intravenous (IV) and subcutaneous (SC) pharmacokinetic and pharmacodynamic properties in patients with psoriasis and obtained preliminary evidence of activity in psoriasis. XOMA also conducted one Phase 2 clinical study (HUPS252). It was determined from single-dose studies that adverse events including fever, headache and nausea were seen shortly after the intravenous infusion of efalizumab. In multiple-dose studies, these adverse events were most common after the first dose, hence the phenomenon was called a "first-dose" effect. These adverse events were also dose-related. This led to the development of an initial low "tolerization dose" that decreased the incidence and severity of the adverse events associated with dosing.

An efalizumab-treated patient experienced acute unilateral hearing loss in the phase 2 study. This finding led to the inclusion of audiologic testing during the first of the phase 3 trials, Study ACD2058g (See Appendix 1).

4 PHASE 3 CLINICAL TRIALS

The four Phase 3, placebo-controlled studies were as follows:

- Study ACD2058g: a randomized, double-blind study evaluating 12 weeks of therapy with SC administered XOMA efalizumab, followed by a placebo-controlled period with either continued treatment for 12 additional weeks or retreatment for an additional 12 weeks after relapse

- Study ACD2059g: a randomized, placebo-controlled, double-blind study evaluating 12 weeks of therapy with SC administered efalizumab (~75% XOMA, ~25% Genentech), followed by a second placebo-controlled period with either continued active treatment or placebo for 12 weeks

- Study ACD2390g: a randomized, double-blind study evaluating 12 weeks of therapy with SC administered Genentech efalizumab

- Study ACD2600g: a randomized, double-blind, placebo-controlled trial, was conducted to provide additional controlled safety data with the Genentech-manufactured efalizumab.

The sponsor has also conducted two open-label phase 3 clinical trials.

- Study ACD2062 was an open-label trial to assess the safety and efficacy of retreatment with efalizumab.

- Study ACD2243g is an ongoing trial to evaluate the safety and efficacy of long-term maintenance with efalizumab. The interim data from this study provide the 1-year safety data to support this BLA submission.

4.1 Issues Explored in the Efficacy Trials

Some of the issues explored in the efficacy trials were as follows:

- The lack of comparability of the pharmacokinetics of the XOMA-manufactured and the Genentech-manufactured efalizumab made it necessary to further study the Genentech material for safety and efficacy.
- The safety and efficacy of long-term continuous treatment and retreatment upon relapse were explored.
- The safety of treatment discontinuation was evaluated.
- Correlations of efficacy as measured by PASI and other measures such as static and dynamic physician's global assessment were performed.

Studies ACD2058g and ACD2059g were designed to evaluate the safety and efficacy of continuous therapy for a total of 6 months. In addition, retreatment upon relapse among patients classified as responders after the first treatment course was studied in Study ACD2058g.

4.2 Outcomes used in the Clinical Efficacy Trials

4.2.1 Primary efficacy outcome

A 75% improvement from baseline in the PASI (Psoriasis Area and Severity Index) score (Fredriksson et al, 1978) was the primary efficacy outcome used in the clinical trials. PASI scoring is discussed below.

PASI Scoring

PASI can range from 0 to 72. Dermatologic disease severity is scored as follows:

Body Areas

Four main body areas are assessed, the head (h), the trunk (t), the upper extremities (u), and the lower extremities (l) corresponding to 10%, 30%, 20%, and 40% of the total body surface area, respectively.

The area of psoriatic involvement for each body area (Ah, At, Au, Al) is assigned a numerical value according to degree of involvement as follows:

0 = no involvement
1 = <10% involvement
2 = 10% to <30% involvement
3 = 30% to <50% involvement
4 = 50% to <70% involvement
5 = 70% to <90% involvement
6 = 90% to 100% involvement

The severity of the psoriatic lesions in three main signs—erythema (E), thickness (T), and scaling (S)—are assessed for each body area according to a scale (0–4) in which 0 represents a complete lack of cutaneous involvement and 4 represents the most severe possible involvement.

Calculating PASI

To calculate the PASI, the sum of the severity rating for the three main signs are multiplied with the numerical value of the area affected and with the various percentages of the four body areas. These values are then added to complete the formula as follows:

$$PASI = 0.1\,(Eh + Th + Sh)\,Ah + 0.3\,(Et + Tt + St)\,At + 0.2\,(Eu + Tu + Su)\,Au + 0.4\,(El + Tl + Sl)\,Al$$

4.2.2 Secondary efficacy outcomes

The principal secondary efficacy outcome used in the clinical efficacy trials was a static physician's global assessment, the Overall Lesion Severity (OLS) Scale. The scoring system is depicted in the following table (Table 2).

Table 2 Overall Lesion Severity Scale (also called Static Physician's Global Assessment, sPGA)

Score	Category	Description
0	Clear	Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale) Erythema = ± (hyperpigmentation, pigmented macules, diffuse faint pink or red coloration)
1	Minimal	Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) *Scaling = ± (surface dryness with some white coloration)* Erythema = up to moderate (up to definite red coloration)
2	Mild	Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (coarse scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (coarse, non-tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)
5	Very severe	Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)

Clinical response was defined as "clear" or "minimal" at 12 weeks.

A dynamic Physician's Global Assessment (dPGA) was also used. Patients were evaluated using the following categories (Table 3).

Table 3 Dynamic Physician's Global Assessment

Category	Percent Improvement	Category Description
Cleared	100%	Remission of all clinical signs and symptoms as compared with baseline, except for residual manifestations such as mild erythema
Excellent	75%–99%	Improvement of all clinical signs and symptoms as compared with baseline, except for residual manifestations such as mild erythema
Good	50%–74%	Improvement of all clinical signs and symptoms as compared with baseline
Fair	25%–49%	Improvement of all clinical signs and symptoms as compared with baseline
Slight	1%–24%	Improvement of all clinical signs and symptoms as compared with baseline
Unchanged		Clinical signs and symptoms unchanged from baseline
Worse		Clinical signs and symptoms deteriorated from baseline

Physicians were instructed to perform the PGA rating using the baseline medical photographs for comparison. The PGA score were to reflect a global consideration of erythema, scaling, plaque thickness, and percentage total body surface area affected by psoriasis and were to be performed after the determination of the PASI score, the OLS, and the other clinical assessments. The evaluator could reference the case report forms, or other relevant documents to assist in determination of the PGA.

Reviewer's comment: The PGA is not an independent assessment because the investigator was instructed to utilize data from PASI and other scales in performing the PGA rating. Also, note that where five categories of improvement exist, only one category of worsening exists; therefore, this highly asymmetric scale is strongly biased to sense improvement.

The Dermatology Life Quality Index (DLQI) (Finlay et al,1994) was one of the secondary efficacy outcomes. The DLQI is a 10-item questionnaire that attempts to assess how much a skin condition has affected the subject's quality of life during the previous 7 days. Each question has four possible responses: "not at all," "a little," "a lot," or "very much," with scores of 0, 1, 2, and 3, respectively. The DLQI represents the sum of the scores, ranging from 0 to 30 points.

Dermatology Life Quality Index Questionnaire

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	Not relevant
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	Not relevant
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	Not relevant
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	Not relevant
7.	Over the last week, has your skin prevented you from **working** or **studying**? If "No," over the last week how much has your skin been a problem at **work** or **studying**?	Yes No A lot A little Not at all	Not relevant
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	Not relevant
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	Not relevant
10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not much at all	Not relevant

Psoriasis Symptoms Assessment (PSA). The PSA is a 16-item patient-reported measure of psoriasis-related symptoms, using a 2-week recall period. The PSA contains two subscales, one measuring the frequency of psoriasis symptoms (eight items) and the other measuring the severity of psoriasis symptoms (eight items). The PSA has been used in prior efalizumab studies. The PSA is an adaptation of a skin disorder instrument, the Skindex (Chren et al. 1996; Chren et al. 1997) with two additional questions related to the frequency and severity of skin scaling. The questions are shown below. A decrease in PSA score represents improvement.

Reviewer's comment: According to the sponsor, the PSA is not currently a validated research tool. Therefore, it is this reviewer's recommendation that results obtained using the PSA not be considered for use in the package insert.

PSA Questionnaire

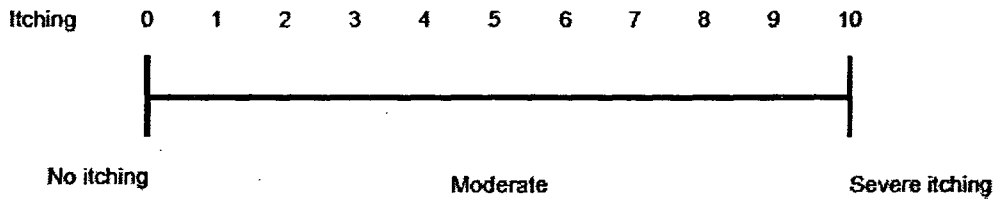
During the past 2 weeks, indicate how often:

	Always	Often	Sometimes	Never
1. Your skin hurt	☐	☐	☐	☐
2. Your skin condition felt like it was burning or stinging	☐	☐	☐	☐
3. Your skin itched	☐	☐	☐	☐
4. Water bothered your skin condition (e.g., bathing, washing hands)	☐	☐	☐	☐
5. Your skin was irritated	☐	☐	☐	☐
6. Your skin was sensitive	☐	☐	☐	☐
7. Your skin condition bled	☐	☐	☐	☐
8. Your skin was scaling	☐	☐	☐	☐

During the past 2 weeks, indicate how troublesome/bothersome each of the following symptoms has been:

	A Great Deal	Somewhat	A Little	Not at All
1. Your skin hurt	☐	☐	☐	☐
2. Your skin condition felt like it was burning or stinging	☐	☐	☐	☐
3. Your skin itched	☐	☐	☐	☐
4. Water bothered your skin condition (e.g., bathing, washing hands)	☐	☐	☐	☐
5. Your skin was irritated	☐	☐	☐	☐
6. Your skin was sensitive	☐	☐	☐	☐
7. Your skin condition bled	☐	☐	☐	☐
8. Your skin was scaling	☐	☐	☐	☐

The Itching Scale is a modified visual analog scale and is shown below.



4.3 Protocol ACD2058g

4.3.1 Study Title

"A Phase III, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter, Multidose Study to Evaluate the Efficacy and Safety of Subcutaneously Administered Anti-CD11a in Adults with Moderate to Severe Plaque Psoriasis"

4.3.2 Study Objectives

- To investigate the efficacy of weekly subcutaneous (SC) dosing with either 1.0 mg/kg or 2.0 mg/kg efalizumab relative to placebo as measured by the proportion of subjects achieving a ≥75% decrease from baseline in PASI at the end of the initial 12-week treatment period (First Treatment, or FT Day 84)
- To evaluate the safety and tolerability of 12 weekly SC doses of 1.0 mg/kg or 2.0 mg/kg efalizumab relative to placebo

The primary objective of the study was to assess the safety and efficacy of a 12-week treatment of efalizumab. The study was also designed to explore a number of secondary safety and efficacy questions with special emphasis on issues relevant to patients with psoriasis. These questions included:

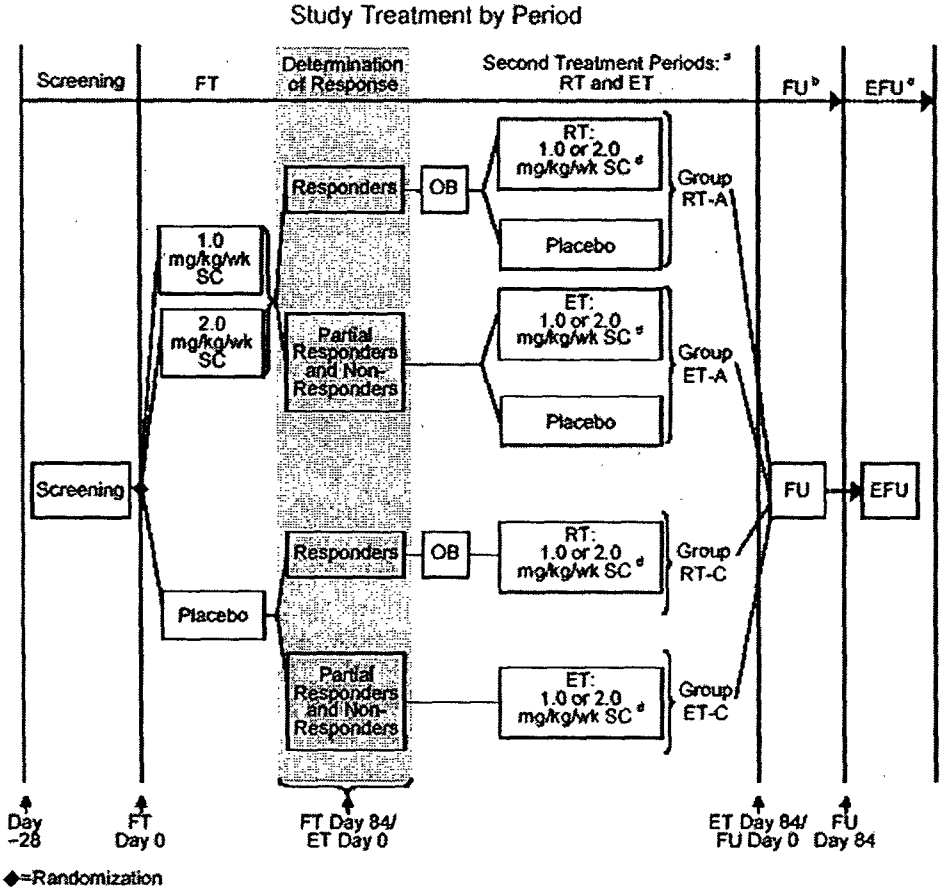
- optimization of dose
- duration of treatment-free response
- potential for treatment-withdrawal phenomena (e.g. flaring, psoriasis variants)
- safety and efficacy of retreatment following relapse
- safety and activity of extended treatment for partial responders and non-responders

4.3.3 Study Design

Study ACD2058g was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of efalizumab in subjects with moderate to severe psoriasis. Following the initial 84-day randomized blinded placebo-controlled treatment period, responders were observed on no treatment until they relapsed or until 168 days (OB period). Upon relapse, patients who had initially received efalizumab were rerandomized to receive placebo or efalizumab at the same dose previously received. Responding patients in the placebo arm who relapsed during the OB period were treated with efalizumab during retreatment. Patients who were initially randomized to receive efalizumab who had no response or a partial response at Day 84 were rerandomized to continue efalizumab at the same dose they had received previously or to receive placebo in the extended treatment regimen (ET) protocol for an additional

contiguous 84 days. Partial responders and non-responders who received placebo initially went on to receive efalizumab in the ET period. The study also included a follow-up period (FU) and an extended follow-up period (EFU), for people who had not relapsed by the FU Day 84, to assess duration of effect and safety. Figure 1 below shows the study schema.

Figure 1 Design of Study ACD2058g

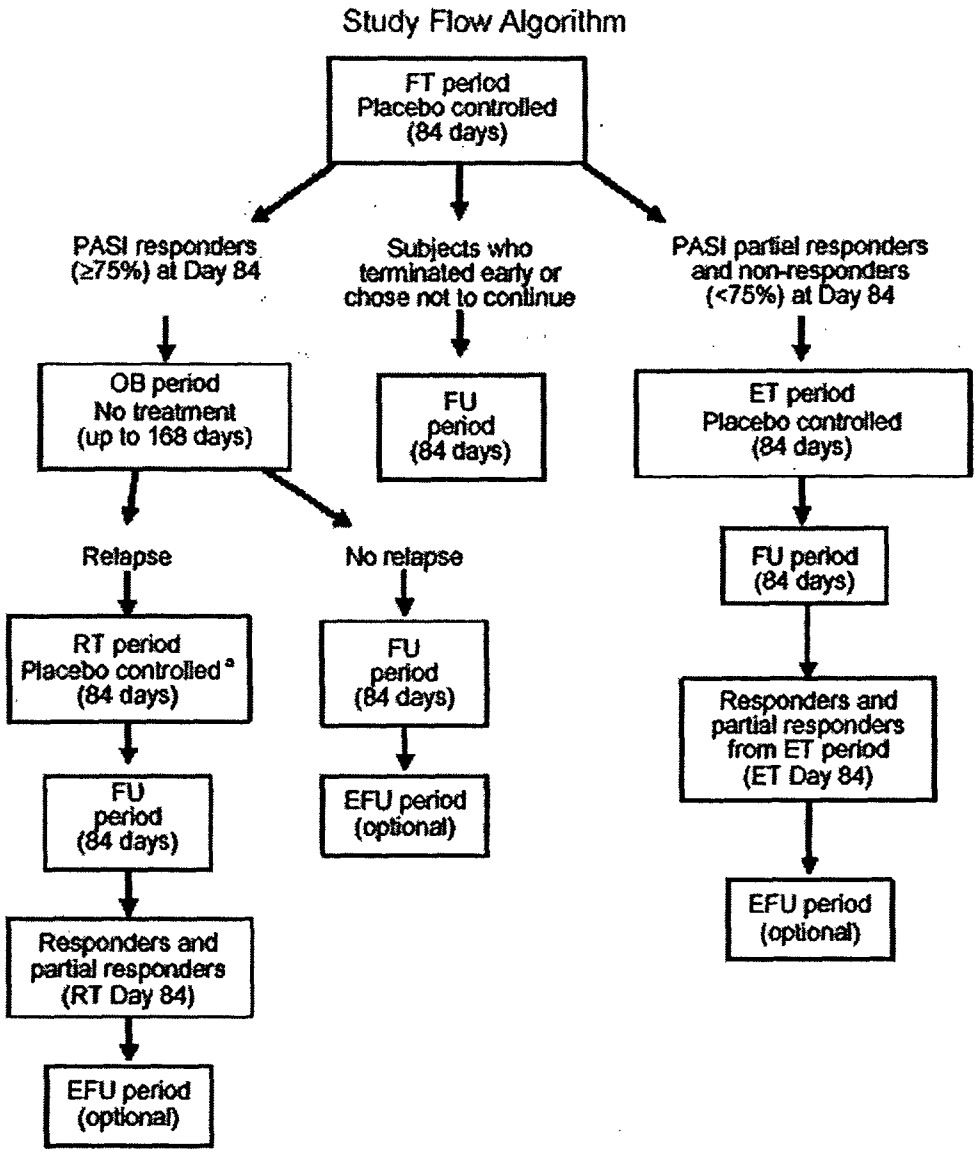


[a] Subjects had the option of transferring to the open-label study, ACD2062g, if they were non-responders between Day 56 of the second treatment period and FU Day 28.

[b] Upon relapse, subjects who were responders and partial responders to second treatment had the option of transferring to Study ACD2062g.

[c] The EFU period was an optional period for individuals who had not relapsed during the FU period.

[d] Subjects remained in the same dose group in which they were randomized for the FT period.



a Only for subjects in the efalizumab arms of the FT period. Placebo-treated subjects received efalizumab.

4.3.3.1 Open Label Extension Study

Protocol ACD2062g served as the open-label extension for Study ACD2058g. Subjects who did not experience a ≥50% improvement in PASI by ET day 56 (as compared to FT day 0) could transfer to open-label treatment.

4.3.3.2 Study Drug

Subjects in the active group received XOMA-manufactured efalizumab. Dosing volumes and schedules were identical during the FT, RT, and ET periods. Subjects received an initial conditioning dose of 0.7 mg/kg study drug followed by 11 weekly doses of 1.0 or 2.0 mg/kg SC study drug (efalizumab or equivalent volume of placebo).

4.3.3.3 Randomization

During the FT period, subjects were randomized to low-dose (1.0 mg/kg) efalizumab, high dose (2.0 mg/kg) efalizumab or low dose or high dose placebo in a 2:2:1:1 ratio. Randomization was stratified by FT Day 0 PASI (≤ 16, ≥ 16.1), by prior treatment for psoriasis (naïve to systemic treatment vs. history of prior systemic therapy) and by study site through an IVRS. The random assignment to efalizumab or placebo was blinded to subjects, investigators and the sponsor.

At the start of the ET period, subjects who previously received efalizumab were rerandomized within the low- or high- dose group to active therapy or placebo in a 2:1 ratio. Randomization was stratified by response to the first treatment period, partial response (PASI ≥ 50 and <75) and non-response (PASI <50).

All patients assigned to placebo in the FT period were reassigned to receive efalizumab, whether they participated in the RT or ET periods and regardless of response status during the first treatment period.

4.3.3.4 Blinding

Subjects, investigators, and the Sponsor were blinded to subject assignment to placebo or active study drug. Dose level and dose frequency were not blinded.

Efalizumab produces an elevation of lymphocyte counts and total WBC counts in most subjects. Therefore, only absolute neutrophil and eosinophil counts from the leukocyte portion of the complete blood count (CBC) were made available to investigators and monitors on samples drawn during any of the treatment periods.

4.3.3.5 Withholding Treatment

Subjects were discontinued from efalizumab treatment if they met any of the following criteria: diagnosis of any cancer; anaphylaxis; opportunistic infection; or any medical condition that the investigator determined could jeopardize the subject's safety if he or she continued in the study. Other reasons for discontinuation included pregnancy, administration of live virus or bacteria vaccine, or concurrent treatment with an excluded systemic or topical therapy.

If a subject had an atypical severe relapse or emergence of a new psoriatic morphology (e.g., pustular, rupioid, guttate), the investigator was to contact the Medical Monitor. If, in the judgment of the investigator, this flare required treatment, the subject had to discontinue from the study.

Treatment options for these subjects included the following:

- Immediate transfer to the open-label study, ACD2062g, for treatment with efalizumab upon approval from the Medical Monitor

4.3.3.2 Study Drug

Subjects in the active group received XOMA-manufactured efalizumab. Dosing volumes and schedules were identical during the FT, RT, and ET periods. Subjects received an initial conditioning dose of 0.7 mg/kg study drug followed by 11 weekly doses of 1.0 or 2.0 mg/kg SC study drug (efalizumab or equivalent volume of placebo).

4.3.3.3 Randomization

During the FT period, subjects were randomized to low-dose (1.0 mg/kg) efalizumab, high dose (2.0 mg/kg) efalizumab or low dose or high dose placebo in a 2:2:1:1 ratio. Randomization was stratified by FT Day 0 PASI (≤ 16, ≥ 16.1), by prior treatment for psoriasis (naïve to systemic treatment vs. history of prior systemic therapy) and by study site through an IVRS. The random assignment to efalizumab or placebo was blinded to subjects, investigators and the sponsor.

At the start of the ET period, subjects who previously received efalizumab were rerandomized within the low- or high- dose group to active therapy or placebo in a 2:1 ratio. Randomization was stratified by response to the first treatment period, partial response (PASI ≥ 50 and <75) and non-response (PASI <50).

All patients assigned to placebo in the FT period were reassigned to receive efalizumab, whether they participated in the RT or ET periods and regardless of response status during the first treatment period.

4.3.3.4 Blinding

Subjects, investigators, and the Sponsor were blinded to subject assignment to placebo or active study drug. Dose level and dose frequency were not blinded.

Efalizumab produces an elevation of lymphocyte counts and total WBC counts in most subjects. Therefore, only absolute neutrophil and eosinophil counts from the leukocyte portion of the complete blood count (CBC) were made available to investigators and monitors on samples drawn during any of the treatment periods.

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Subjects were discontinued from efalizumab treatment if they met any of the following criteria: diagnosis of any cancer; anaphylaxis; opportunistic infection; or any medical condition that the investigator determined could jeopardize the subject's safety if he or she continued in the study. Other reasons for discontinuation included pregnancy, administration of live virus or bacteria vaccine, or concurrent treatment with an excluded systemic or topical therapy.

If a subject had an atypical severe relapse or emergence of a new psoriatic morphology (e.g., pustular, rupioid, guttate), the investigator was to contact the Medical Monitor. If, in the judgment of the investigator, this flare required treatment, the subject had to discontinue from the study.

Treatment options for these subjects included the following:

- Immediate transfer to the open-label study, ACD2062g, for treatment with efalizumab upon approval from the Medical Monitor

- Early discontinuation from the study to begin excluded psoriasis medications. Subjects were to undergo end-of-treatment-period evaluations and immediately enter the follow-up period.

Concomitant Medications

The only concomitant psoriasis treatments that could be used until study Day 84 were Eucerin cream and tar or salicylic acid preparations (for scalp psoriasis only). Potency Group VII topical corticosteroids could be used in small amounts on psoriatic lesions on the face, hands, feet, groin, or axillae, if required (except for the day of the scheduled visit).

After FU Day 84, any topical or systemic psoriasis therapies could be used at the investigator's discretion, even for subjects continuing in the extended follow-up EFU period through FU Day 252.

4.3.3.6 Disallowed treatments

The following were not allowed until after Day 84 of the follow-up period: Systemic treatments for psoriasis (e.g., PUVA, cyclosporine, corticosteroids, methotrexate, oral retinoids, MMF, thioguanine, hydroxyurea, sirolimus, azathioprine, 6-MP, etanercept) and immunosuppressive medications for any indication other than psoriasis.

Treatment with UVB phototherapy and all other topical treatments for psoriasis (e.g., topical corticosteroids, calcipotriene, tazarotene, anthralin, tar) were excluded from Day –14 through Day 84 of the follow-up period, with the exceptions noted previously. Tanning booths or nonprescription UV light sources were not to be used.

Use of live virus or bacteria vaccines were prohibited.

4.3.3.7 Eligibility

Inclusion

- Plaque psoriasis covering ≥ 10% of total BSA
- A minimum PASI score of 12.0 at screening
- Plaque psoriasis diagnosed for at least 6 months
- Plaque psoriasis clinically stable for at least 3 months prior to screening
- Candidate for systemic therapy for psoriasis who had not been previously treated or history of prior treatment with systemic therapy for psoriasis (e.g., PUVA, cyclosporine, corticosteroids, methotrexate, oral retinoids
- Body weight ≤ 140 kg
- 18 to 70 years old
- Women of childbearing potential had to use an acceptable method of contraception to prevent pregnancy and agree to continue to practice an acceptable method of contraception for the duration of their participation in the study.
- Willingness to hold sun exposure reasonably constant and to avoid use of tanning booths or other UV light sources for the duration of the trial

Exclusion

Subjects who met any of the following exclusion criteria were ineligible for study entry:

- Guttate, erythrodermic, or pustular psoriasis as sole or predominant form of psoriasis
- History of severe allergic or anaphylactic reactions to humanized monoclonal antibodies
- Clinically significant psoriasis flare during screening or at the time of enrollment
- History of or ongoing uncontrolled bacterial, viral, fungal, or atypical mycobacterial infection
- History of opportunistic infections (e.g., systemic fungal infections, parasites)
- History of hepatitis B or C infection
- Hepatic enzymes 3× the upper limits of normal (ULN) Subjects with hepatic enzymes elevated above the ULN but <3× the ULN had to be tested for hepatitis B and C. Only subjects with negative viral tests could be enrolled.
- Active tuberculosis (TB) or currently undergoing treatment for TB. Purified protein derivative (PPD) testing and/or a chest X-ray were required for high-risk subjects.
- Presence or history of malignancy within the past 5 years, including lymphoproliferative disorders. Subjects with a history of fully resolved basal cell or squamous cell skin cancer could be enrolled.
- Previous treatment with efalizumab
- Initiation or change in treatment regimen of β-blockers, angiotensin-converting enzyme (ACE) inhibitors, interferons, quinidine, antimalarial drugs, or lithium within the past month
- Seropositivity for human immunodeficiency virus (HIV). Subjects underwent mandatory testing at screening.
- Pregnancy or lactation
- White blood cell (WBC) count <4000/μL or >14,000/μL
- Serum creatinine ≥ 2× the ULN
- Progressive hearing loss
- Any medical condition that, in the judgment of the investigator, could have jeopardized the subject's safety following exposure to study drug

4.3.3.8 Study Assessments

The study assessments obtained during the first treatment period are shown in the following table.

Table 4 Assessments during the FT Period

Evaluation	FT Day 0	7	14	21	28	35	42	49	56	63	70	77	84
Review of eligibility criteria	x												
Medical history	x												
DLQI and PSA[a]	x								x				x
Complete physical examination													x
Vital signs	x	x	x		x		x		x		x		x
Body weight	x	x	x	x	x	x	x	x	x	x	x	x	
PASI	x		x		x		x		x		x		x
OLS	x								x				x
Itching Scale	x		x		x		x		x		x		x
Psoriatic BSA	x								x				x
PGA[b]			x		x		x		x		x		x
Hematology[c]	x								x[d]				x
Chemistries[e]	x								x				x
Urinalysis	x								x				x
Serum antibody	x												x
Pregnancy test	x				x				x				x
TB test													x
Medical photographs	x												x
Audiogram[f]	x												x
Concomitant meds.	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x

[a] The DLQI and PSA were performed prior to the complete physical examination, PASI, PGA, BSA, OLS, Itching Scale, and medical photographs.

[b] The PGA was performed after the PASI, BSA, OLS, and Itching Scale; the FT Day 0 photographs were used for comparison.

[c] Included CBC with differential and platelet count.

[d] The leukocyte portion of hematology profile included only absolute neutrophil count and absolute eosinophil count.

[e] Included sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid.

[f] Audiograms by air and bone conduction were assessed prior to study drug administration and at the end of the first treatment period.

The frequency of assessments of PASI, OLS, PGA, PSA, DLQI, Itching scale and psoriatic BSA took place at every two weeks for two visits and subsequently at monthly intervals during retreatment and extended treatment periods. Laboratory tests and frequency of assessment during the retreatment and extended treatment periods were similar to those obtained during the first treatment period. Assessments of adverse events and concomitant medications were at days 7, 14, 28, 56 and 84 during the retreatment and extended treatment periods compared with weekly during the first treatment period.

Assessments during the observation period and the follow up period are shown in the following tables.

Table 5 Assessments during the OB Period

Evaluation	OB Day 14	28	56	84	112	140	168
DLQI and PSA [a]				x			x
Vital signs		x		x			x
PASI	x	x	x	x	x	x	x
OLS				x			x
Itching Scale	x	x		x			x
Psoriatic BSA				x			x
PGA	x	x		x			x
Hematology [b]				x			
Chemistries [c]				x			
Urinalysis with microscopic examination				x			
Serum antibody sample		x		x			x
Pregnancy test [d]		x		x			
Concomitant medications	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x
IVRS contact [e]	x	x	x	x	x	x	x

[a] The DLQI and PSA were performed prior to the PASI, PGA, BSA, and OLS.
[b] Included CBC with differential and platelet count.
[c] Included sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid.
[d] If the urine test results were positive, results were confirmed with a serum pregnancy test. If the serum test result was positive, the subject was transferred to the FU period.
[e] If a subject appeared to have relapsed, study personnel contacted the IVRS with the subject's PASI score for confirmation.

Table 6 Assessments during the FU and EFU Periods

Evaluation	FU Day 28	56	84	EFU Day 112	140	168	196	224	252
DLQI and PSA			x						
Complete physical exam			x						
Vital signs	x	x	x						
PASI	x	x	x	x	x	x	x	x	x
OLS			x						
Itching Scale			x						
Psoriatic BSA			x						
PGA	x	x	x						
Hematology			x						
Chemistries			x						
Urinalysis with microscopic examination			x						
Serum antibody sample	x		x						
Pregnancy test	x		x						
Concomitant medications	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x

As shown in the tables above, the following were performed during the observation and follow-up periods: physical examinations (including vital signs and body weight); monitoring for adverse events; blood chemistry, hematology (CBC, platelet, differential); urinalysis; antibodies to efalizumab (HAHA) and urine pregnancy test (females of childbearing potential). TB skin testing was done for high risk subjects only at day 84 of the FT, ET, and RT periods. Audiograms were also performed in this study prior to the first study drug administration and at the end of FT (FT Day 84) ET and RT. (See appendix 1)

Reviewer's comment: According to the tables above, serum samples for antibodies to efalizumab were collected at timepoints both during treatment and after drug washout.

Drug concentration measurements, steady-state trough concentration, were performed on samples collected on FT Day 84 for HAHA analysis. Patients who were positive for anti-efalizumab antibodies were initially excluded from the summary of pharmacokinetics.

Reviewer's comment: Although the sponsor excluded HAHA positive patients from the summary of pharmacokinetics, it is important to understand how HAHA positivity might have affected the pharmacokinetic measurements (Please refer to Dr. Rajpal's Pharamacology review).

Adverse events and concomitant medications were recorded. Adverse events were defined as any sign, symptom, data or medical diagnosis, regardless of relationship to study drug, that began or worsened after the start of study drug treatment and were recorded in the subject's adverse event case report form. Definitions of seriousness, severity and causality were included in the protocol. Provisions were made for reporting serious adverse events to sponsor, to IRB, and to FDA.

4.3.3.9 Efficacy Outcomes

The primary efficacy outcome measure was the proportion of subjects with a ≥ 75% improvement in PASI score between FT Day 0 (baseline) and FT Day 84 (the end of the FT period).

The principal secondary efficacy outcome measure was the proportion of subjects who achieved an OLS rating of Minimal or Clear at FT Day 84.

The remaining secondary efficacy outcome measures listed in the order of ranking were the following:

- Proportion of subjects attaining a rating of Excellent or Cleared on the Dynamic Physician's Global Assessment, the PGA, at FT Day 84
- Time to relapse after FT Day 84 for subjects who achieved a ≥ 75% improvement in PASI score at FT Day 84

  Minimum relapse PASI= $PASI_{FTDay\ 84} + (PASI_{FTDay\ 0} - PASI_{FTDay84})/2$

- Change from baseline in the thickness component of the PASI at FT Day 84

- Change from baseline on the Itching Scale at FT Day 84
- Change from baseline in percentage of BSA affected by psoriasis at FT Day 84

Reviewer's comment: The DLQI was not a primary or secondary endpoint, but a tertiary endpoint.

4.3.3.10 Statistical Considerations

Two treatment comparisons were of interest during the FT period of this study: 1.0 mg/kg efalizumab versus placebo and 2.0 mg/kg efalizumab versus placebo. The placebo groups for each of the two dose levels were combined for all statistical comparisons following investigation of baseline comparability of the two placebo groups.

Analysis of Treatment Group Comparability:
Treatment groups were assessed for comparability at the beginning of the FT, RT and ET periods with respect to demographic (i.e., age, sex, race/ethnicity) and baseline characteristics. The baseline value of any variable was defined as the last available value prior to the first administration of study drug. Continuous variables were analyzed using ANOVA, and categorical variables were assessed using appropriate contingency table methodology.

Efficacy Analyses: First Treatment Period
Analysis Population:
The intent-to-treat (ITT) population consisted of all subjects who were randomized, whether or not they received any study drug or completed the full course of treatment. The ITT population was the primary analysis population for the primary and secondary endpoints.

Primary Endpoint:
Response status at the end of the FT period was determined as follows:

- Responder: Any subject whose PASI score decreased ≥ 75% from FT Day 0 to FT Day 84
- Partial responder: Any subject whose PASI score decreased ≥ 50% but <75% from FT Day 0 to FT Day 84
- Non-responder: Any subject whose PASI score decreased <50% from FT Day 0 to FT Day 84

The evaluation of the primary endpoint consisted of the pairwise comparison of the proportion of responders in each efalizumab dose group (1.0 mg/kg efalizumab and 2.0 mg/kg efalizumab) versus placebo by Fisher's exact test for the ITT population. Fisher's exact test was used in the comparison between treatment groups for the static PGA, the dynamic PGA and the PASI 50 responses. Partial responder and non-responder categories were combined for the primary analysis. The placebo groups from the FT period for each of the two dose levels were also combined for all statistical comparisons. A pair-wise comparison of change from baseline in the DLQI overall score by treatment group was also to be performed via the Wilcoxon rank sum test.

Conventions for missing data imputation were as follows:
For all study endpoints, if a subject discontinued from the study prior to FT Day 84 but after receiving the final scheduled dose of study drug on FT Day 77, data from the early termination

visit were to be used for analysis, i.e., the Day 84 data was not considered to be missing in this case.

A formal interim analysis of the primary efficacy endpoint was performed by an independent data monitoring committee (DMC) once approximately half (~225) of the projected 450 subjects completed the FT period. The stopping rules established prior to review of the results by the DMC allowed the trial to be stopped for futility only; stopping for efficacy was not allowed. Nonetheless, a penalty rule adjusting the critical value for the final analysis was established. Therefore, the analysis of the primary efficacy endpoint was carried out at the 0.049 level rather than at the 0.05 level. To maintain a type I error rate for the primary analysis of α=0.049 (two sided), the Hochberg-Bonferroni multiple comparisons procedure was used to adjust for the two comparisons. If both comparisons had $p<0.049$ in favor of efalizumab over placebo, both active treatment groups were considered significantly different from placebo. If one comparison had a $p>0.049$, the other active treatment was considered statistically significantly different from placebo only if its associated p-value was <0.0245 in favor of efalizumab over placebo.

4.3.3.11 Protocol Amendments

The protocol was amended twice (on 12 May 2000 and on 14 March, 2001 after initiation of the clinical study in 4 January 2000). The first amendment was to ensure that only patients who were clinically stable could enroll. The principal secondary objective was changed from the dynamic physician's global assessment to the static physician's global assessment scale based on discussions with the FDA. This change was also reflected in the secondary and other endpoints. In the second protocol amendment, the unblinding of treatment assignment was allowed to be performed separately for the FT period and the RT and ET periods because the availability of the primary efficacy results at the earliest possible time was necessary to justify the continued exposure to efalizumab in the ongoing open-label studies.

4.3.4 Study Results

4.3.4.1 Patient Disposition

The first subject was enrolled into the study on January 4, 2000, and the last subject completed the study on October 15, 2001. Twenty nine sites in the United States and Canada participated. A total of 498 patients were enrolled into this study (planned enrollment 450). The disposition of the patients who enrolled is shown in Table 7.

Table 7 Disposition of Subjects and Reasons for Discontinuation during the FT Period

		Efalizumab	
	Placebo	1.0 mg/kg	2.0 mg/kg
Subject Status	(n=170)	(n=162)	(n=166)
Completed FT, n	151 (89%)	149 (92%)	145 (87%)
Entered ET	144	83	99
Entered OB	4	63	44
Entered FU	1	2	2
Discontinued from study	2	1	0
Discontinued FT, n	19 (13%)	13 (8%)	21 (13%)
Entered FU	7	5	8
Discontinued from study	12	8	13
Reason for discontinuation from FT	(n=19)	(n=13)	(n=21)
Adverse event	5	5	8
Lost to follow-up	3	3	5
Subject's decision	8	2	5
Investigator's decision	2	3	2
Use of excluded medication	1	0	1

During the first treatment period, the most common reason for discontinuation in the efalizumab treatment arm was for adverse events. In the placebo treatment arm, the most common reason for discontinuation was "subject's decision." Several, but not all, of the patients who discontinued the study due to "subject's decision" were noted to have worsening of both the PASI score and the dynamic physician's global assessment including some of the patients who were randomized to study drug and others to placebo (data not shown).

4.3.4.2 Demographics

Table 8 below depicts the demographics of subjects during the first treatment period of the study.

Table 8 Demographic Characteristics of Subjects in the FT Period

		FT Efalizumab	
	FT Placebo	1.0 mg/kg/wk	2.0 mg/kg/wk
Characteristic, n	(n=170)	(n=162)	(n=166)
Age (yr)			
Mean	42	45	46
Median	43	45	44
Range	18–68	18–75	20–74
Age group (yr)			
18–40	73 (42.9%)	53 (32.7%)	63 (38.0%)
41–64	94 (55.3%)	98 (60.5%)	87 (52.4%)
≥ 65	3 (1.8%)	11 (6.8%)	16 (9.6%)
Sex			
Male	124 (73%)	118 (73%)	118 (71%)
Female	46 (27%)	44 (27%)	48 (29%)
Race/ethnicity			
White	157 (92.4%)	147 (90.7%)	152 (91.6%)
Black	3 (1.8%)	5 (3.1%)	1 (0.6%)
Asian/ Pacific Islander	6 (3.5%)	6 (3.7%)	3 (1.8%)
Hispanic	4 (2.4%)	2 (1.2%)	8 (4.8%)
Other	0	2 (1.2%)	2(1.2%)
Weight (kg)			
Mean	93	92	94
Median	91	90	91
Range	45–144	50–138	53–144
BMI (kg/m^2)			
Mean	31	31	31
Median	30	30	30
Range	14.8–60.2	18.7–52.0	18.5–53.6

More male than female patients participated in the study, whereas, in the general psoriasis population, men and women are equally affected. The population tends to have higher than average median weight and body mass index probably reflecting the overall U.S. psoriatic population.

Other than the gender distribution, the characteristics are reflective of the general psoriasis population in the United States. The median age was 44 years and ranged from 18-75 years. A higher proportion of patients were age 65 or older in the active treatment arms than in placebo. The numbers of patients older than 70 years of age are limited because this age group was excluded per the eligibility criteria (data not shown). The other baseline characteristics were well-balanced among the treatment groups.

4.3.4.3 Disease Characteristics at Baseline

Table 9 below contains the baseline disease characteristics for the study population.

Table 10 Treatment Compliance for Subjects during the FT Period

		Efalizumab	
No. of Doses	Placebo	1.0 mg/kg/wk	2.0 mg/kg/wk
Received	(n=170)	(n=162)	(n=166)
All 12	122 (72%)	129 (80%)	119 (72%)
10–11	27 (16%)	20 (12%)	29 (18%)
<10	21 (12%)	13 (8%)	18 (11%)

Twenty-one subjects (4.2%) received two or more conditioning doses: 5.9% of subjects in the placebo group, 3.1% in the 1.0 mg/kg/wk efalizumab group, and 3.6% in the 2.0 mg/kg/wk efalizumab group.

The proportion of patients who received ≤ 10 doses, in part, reflects the proportion of patients discontinuing the first treatment period.

4.3.4.4 Use of Concomitant Medications

A total of 30 subjects, 6.0% of all patients, received an excluded medication or phototherapy during the first treatment period. Eight of these patients were in the placebo group, 14 in the 1.0 mg/kg dose efalizumab group, and 8 were in the 2.0 mg/kg efalizumab group.

4.3.4.5 Primary Efficacy Outcomes

Table 11 PASI 75 Response to Treatment during the FT Period: All Randomized Subjects

		Efalizumab	
PASI 75 Response at FT Day 84	Placebo (n=170)	1.0 mg/kg/wk (n=162)	2.0 mg/kg/wk (n=166)
Responders (≥ PASI 75), n	4 (2%)	63 (39%)	44 (26%)
Partial and non-responders, n *	166 (98%)	99 (61%)	122 (74%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001	<0.001

* Included subjects who discontinued.

The proportion of responders was statistically higher in the treatment groups than in placebo. The absolute difference was 37% for the 1.0 mg/kg/wk group and 24% for the 2 mg/kg/wk group. The response rate was not higher with the 2.0 mg/kg/wk vs. the 1.0 mg/kg/wk dose of efalizumab.

Reviewer's comment: CD11a receptors of circulating lymphocytes are saturated at the 1.0 mg/kg/wk dose and would probably explain the lack of dose response.

Last observation carried forward and other sensitivity analyses for missing data did not change the estimate of the treatment effect.

An analysis of the distribution of percent improvement in PASI achieved during the first 84 days of treatment is shown in Table 12 below.

Table 12 Percent Improvement in PASI from Baseline for Subjects during the FT Period (% of total)

Percent Improvement from Baseline	Placebo (n=170)	Efalizumab 1.0 mg/kg/wk (n=162)	Efalizumab 2.0 mg/kg/wk (n=166)
≥ 90%	1.2%	12.3%	4.8%
≥75% to < 90%	1.2%	26.5%	21.7%
≥ 50% to < 75%	12.4%	22.2%	24.7%
≥ 25% to < 50%	20.0%	16.7%	21.1%
< 25%	54.1%	14.2%	15.7%
Missing [a]	11.2%	8.0%	12.0%

[a]Subjects who were missing the FT Day 84 score were classified as non-responders for the analysis of the primary efficacy endpoint.

This analysis demonstrates a general shift toward improvement in the efalizumab groups compared with the placebo group. Additionally, a trend toward higher percentage improvements in PASI in the low dose group than in the high dose group exists.

Table 10 below shows the mean percentage improvement of the three components of the PASI score by treatment group.

Table 13 Mean Percent Improvement in PASI Thickness, Erythema, and Scaling Components during the FT Period

PASI Component	Placebo (n=170)	Efalizumab 1.0 mg/kg/wk (n=162)	Efalizumab 2.0 mg/kg/wk (n=166)
Thickness [a]	17.4	55.9	45.4
Erythema [a]	16.4	50.9	43.0
Scaling [a]	17.4	58.6	51.2
PASI total [b]	19.8	60.1	50.5

Note: Improvement in each component was reflected by a decrease in score.
a The last observation carried was used to impute missing FT Day 84 PASI data.
b Values from the early termination visits were assigned to the next scheduled visit for PASI evaluation.

The components of the PASI - thickness, erythema, scaling- each show higher mean percentage improvement in the efalizumab-treated patients as compared to placebo-treated patients. Therefore, the all of the components appear to contribute similarly to improvement in the overall score.

The effect on affected body surface area is shown below.

Table 14 Mean Improvement in Percent BSA of Psoriasis during the FT Period

	Placebo	Efalizumab	
		1.0 mg/kg/wk	2.0 mg/kg/wk
	(n=170)	(n=162)	(n=166)
Percent BSA affected at FT Day 0	29.4	29.6	29.9
Percent BSA affected FT Day 84	27.6	15.8	19.9
Improvement [a] from baseline	1.8	13.8	10.0

[a] Improvement was reflected by a decrease in the percent BSA score.

The mean percentage body surface area affected at the end of the 84-day treatment period improved more in the 1.0 mg/kg/wk group and 2.0 mg/kg/wk efalizumab groups than in in the placebo-treated patients.

Reviewer's comment: The mean percentage improvement in affected BSA is smaller than that of the other measures of disease severity- erythema, thickness and scale.

The response among various subsets of the studied population is show in Table 15 below.

Table 15 PASI Responders by Subsets of Randomized Subjects: FT Period

	Placebo	Efalizumab	
Subject Subset	n=170	1.0 mg/kg n=162	2.0 mg/kg n=166
Gender			
Men	1/124 (0.8%)	43/118 (36%)	29/118 (25%)
Women	3/46 (6.5%)	20/44 (46%)	15/48 (31%)
Age group (yr)			
18–40	3/73 (4.1%)	17/53 (32%)	17/63 (27%)
41–64	1/94 (1.1%)	40/98 (41%)	24/87 (27%)
≥ 65, n	0/3 (0%)	6/11 (55%)	3/16 (19%)
Baseline PASI category			
≤ 16.0	1/79 (1.3%)	32/74 (43%)	20/74 (27%)
16.1–30.0, n	2/78 (2.6%)	25/77 (33%)	20/79 (25%)
>30.0, n	1/13 (7.7%)	6/11 (55%)	4/13 (31%)
Prior systemic therapy			
Yes, n	1/91 (1.1%)	32/89 (36%)	27/93 (29%)
No, n	3/79 (3.8%)	31/73 (43%)	17/73 (23%)

The results of the primary efficacy analysis are generalizable across gender, age, baseline PASI and history of prior systemic therapy subsets. There was a trend towards higher response rates in patients in the low dose group than the high dose group of efalizumab.

Efficacy was also analyzed by study site; a total of 498 patients were randomized and treated in 29 study centers. The results are summarized in Table 16 below.

Table 16 PASI 75 Response by Treatment Group and Site

Site	Placebo (N=170)	Efalizumab 1.0 mg/kg/wk (N=162)	Efalizumab 2.0 mg/kg/wk (N=166)
0066	0/5	1/4	0/2
0969	0/3	0/3	1/4
1981	0/7	3/4	3/7
2957	0/7	1/6	0/7
6282	0/4	0/4	2/4
6313	0/6	1/3	0/4
6315	0/8	2/7	1/8
6316	0/5	3/7	1/4
6319	1/26	16/24	9/28
6321	0/4	1/3	1/3
6324	1/13	9/12	3/11
6328	0/3	2/4	2/4
6330	0/4	5/6	2/5
6334	1/7	1/7	3/8
6336	0/8	6/9	1/9
6338	1/18	4/17	7/19
6346	0/7	2/8	0/5
6349	0/7	1/5	2/7
6396	0/5	1/7	2/7
6451	0/6	2/8	0/6
Combined*	0/17	2/14	4/14

* Sites that enrolled fewer than 10 patients were combined.

Among the sites shown in this table, it appears that with a few exceptions, trends towards higher response rates in the efalizumab-treated patients were seen when analyzed by study site. Nine sites were combined for this analysis because they enrolled less than 10 patients per site.

The data below show the response rate by geographic latitude by treatment group (see Table 17). The Northern U.S. sites included those in the Northeast, Northcentral, and Northwest regions (Washington, Oregon, Utah, Colorado, and northern California). The Southern U.S. sites included those in the south and southwest regions (Arizona, New Mexico, and southern California).

Table 17 PASI Response to Treatment by Latitude (FT Period)

Latitude	FT Day 84 Response	Placebo (N=170)	Efalizumab 1.0 mg/kg/wk (N=162)	Efalizumab 2.0 mg/kg/wk (N=166)
Canada	N	47	45	46
	Responder	2 (4.3%)	14 (31.1%)	11 (23.9%)
	95% Confidence Interval	[0.005, 0.145]	[0.182, 0.466]	[0.126, 0.388]
Northern United States	N	76	77	74
	Responder	2 (2.6%)	34 (44.2%)	19 (25.7%)
	95% Confidence Interval	[0.003, 0.092]	[0.328, 0.559]	[0.162, 0.372]
Southern United States	N	47	40	46
	Responder	(0.0%)	15 (37.5%)	14 (30.4%)
	95% Confidence Interval	[0.000, 0.075]	[0.227, 0.542]	[0.177, 0.458]

Clinical responses did not differ by geographic latitude.

Table 18 Covariates Potentially Predictive of PASI Response: FT Period

Model Predictor	Odds Ratio	95% CI
Sex		
Female vs. male	1.725	1.021, 2.912
Prior systemic therapy		
No vs. yes	1.108	0.689, 1.779
Geographic region		
Canada vs. western United States	0.612	0.314, 1.186
North central vs. western United States	1.186	0.620, 2.276
Northeastern vs. western United States	0.205	0.045, 0.676
Southern vs. western United States	0.622	0.287, 1.312

The following covariates were examined in the model and did not have any relationship to treatment response: baseline PASI score, age, history of prior systemic therapy and season (spring vs. summer). There was a suggestion of higher responses in women, but this was not supported in subsequent studies. Also, a comparison of response by geographic region suggested a higher response in the Western United States vs. that seen in the Northeastern United States.

4.3.4.6 Secondary Efficacy Outcomes

The analysis of the principal secondary efficacy outcome, the static Physician's Global Assessment (OLS), is shown in Table 19 below.

Table 19 Principal Secondary Efficacy Endpoint: FT Period

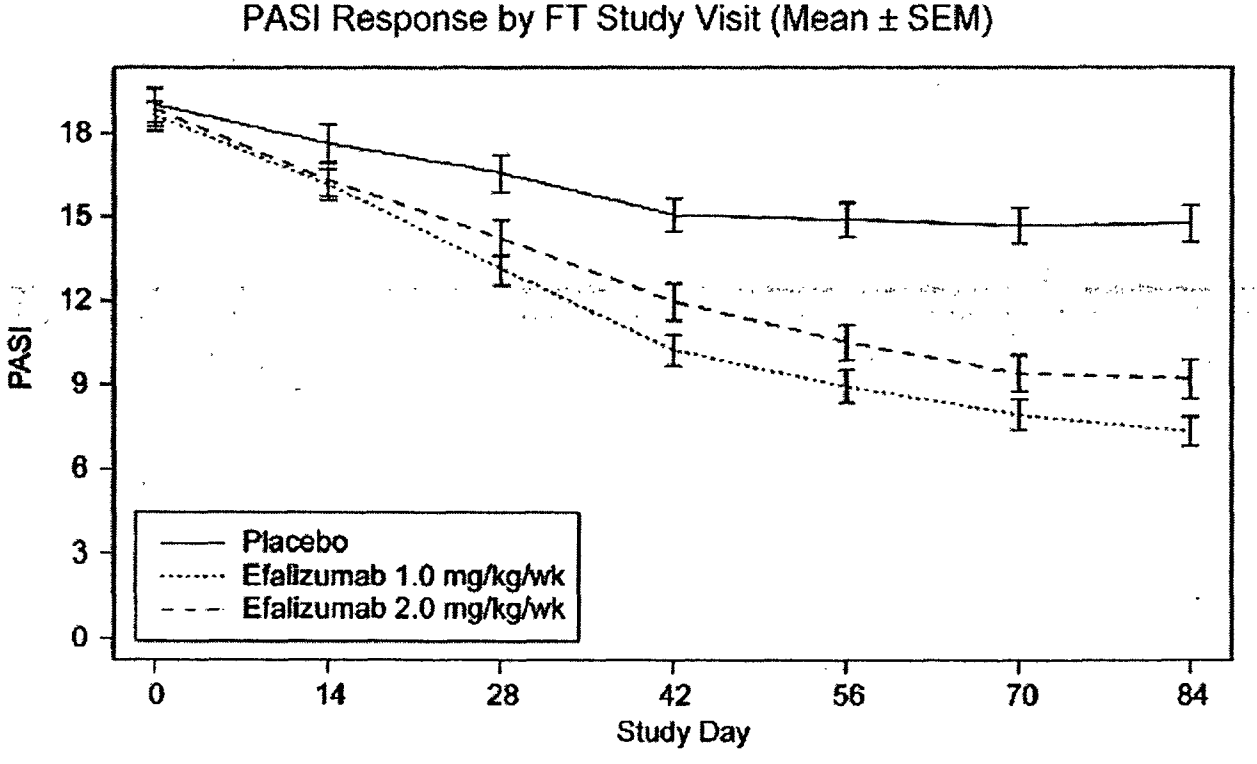
		FT Efalizumab	
OLS Response at FT Day 84	FT Placebo (n=170)	1.0 mg/kg/wk (n=162)	2.0 mg/kg/wk (n=166)
Minimal or Clear	5 (2.9%)	52 (32.1%)	37 (22.3%)
Mild to Very Severe *	165 (97.1%)	110 (67.9%)	129 (77.7%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001	<0.001

* Included subjects who were classified as Mild, Moderate, Severe, and Very Severe and those who discontinued.

By this analysis, the proportions of patients with OLS ratings of mininal or clear in each efalizumab treatment group were higher than in the placebo group. The treatment effect with the 1 mg/kg/wk dose is 25% (efalizumab-placebo).

The other secondary efficacy outcomes also showed that efalizumab was superior to placebo. Figure 2 below shows the mean PASI score over time.

Figure 2



From the figure, there is separation of the efalizumab curves from that of placebo by 14 days of treatment.

The dPGA, a dynamic physician's global assessment, was used to measure the dynamic response of patients as compared baseline (See Table 20).

Table 20 dPGA Response for Subjects during the FT Period

		FT Efalizumab	
	Placebo	1.0 mg/kg/wk	2.0 mg/kg/wk
dPGA Response at FT Day 84	(n=170)	(n=162)	(n=166)
Excellent or Cleared	7 (4.1%)	63 (38.9%)	50 (30.1%)
Good to Worse [a]	163 (95.9%)	99 (61.1%)	116 (69.9%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001	<0.001

[a] Included subjects who were classified as Good, Fair, Slight, Poor, Unchanged, or Worse and those who discontinued.

A greater proportion of patients achieved excellent or cleared in both efalizumab treatment groups compared to placebo using the dynamic physician's global assessment. The differences reached statistical significance.

Reviewer's comment:
The PGA is a dynamic assessment, which takes into account the same variables as the PASI, namely the affected body surface area, scale, plaque thickness and erythema. It is of limited additional value as it is not independent of the PASI.

DLQI (Dermatology Life Quality Index)
A pairwise comparison of change from baseline in the DLQI overall score is shown below. A decrease in score represents improvement. Change in DLQI was a tertiary endpoint in this study.

Table 21 DLQI Overall Score during the FT Period

		FT Efalizumab	
DLQI	FT Placebo (n=170)	1.0 mg/kg/wk (n=162)	2.0 mg/kg/wk (n=166)
FT Day 0, n			
Mean	11.8	11.5	12.0
Median	11.0	10.0	10.5
25th–75th Percentile	6.0–16.0	6.0–16.0	7.0–17.0
Range			
FT Day 84, n			
Mean	9.9	6.1	6.3
Median	9.0	3.0	4.0
25th–75th Percentile	5.0–14.0	1.0–9.0	2.0–9.0
Range			
Improvement from baseline, [a] n			
Mean (SD)	2.1 (6.0)	5.3 (6.5)	5.5 (7.2)
Median	2.0	5.0	5.0
25th–75th Percentile	–1.0 to 5.0	1.0 to 10.0	1.0 to 10.0
Range			
Wilcoxon rank sum test p-value efalizumab vs. placebo	—	<0.001	<0.001

All three treatment groups were found to have comparable baseline scores. The decrease in overall DLQI was greater in the efalizumab-treated groups as compared with placebo. Although, this difference reached statistical significance at the 0.001 level, the clinical significance of these results are not clear as the sponsor has provided any analysis of what degree of change represents a clinically meaningful change.

4.3.4.7 Time-to-response

Time-to-onset of PASI-75 response was analyzed and the results are shown in Table 22 below.

Table 22 Time (days) to PASI-75 Response, Using Kaplan Meier Estimates Study ACD2058g (FT Period): Subjects Who Achieved a PASI-75 Response at Any Time

Characteristic	Placebo	Efalizumab 1.0 mg/kg/wk	Efalizumab 2.0 mg/kg/wk
Subjects Who Achieved PASI-75 at Any Time	9	74	52
Median	43.0	57.0	57.0
95% C.I. for Median	(41.0, 71.0)	(56.0, 59.0)	(55.0, 71.0)
25-75 %ile	41.0 - 71.0	43.0 - 72.0	45.5 - 79.5
Minimum - Maximum	29.0 - 74.0	28.0 - 89.0	28.0 - 92.0

Median time to achieve PASI 75 in patients who achieved PASI 75 at any time was approximately 2 months. However, examination was at biweekly intervals and, therefore, it is not possible to distinguish onset more narrowly than a 14 day window.

The PASI 50 is not as stringent as the PASI 75 and therefore, the time to PASI 50 is useful in estimating the onset of clinical effect. Among the PASI 75 responders, the median time to achieve PASI 50 was analyzed in an exploratory analysis (see Table 23).

Table 23 Median Time to a PASI-50 Response for PASI-75 Responders in the First Treatment Period

Study ACD2058g	Placebo	Efalizumab 1.0 mg/kg/wk	Efalizumab 2.0 mg/kg/wk
n	4	63	44
Median (days)	35	41	43
95% CI	15, 46	29, 43	42, 46
25th–75th Percentile	21–45	29–44	31–57

For the 1 mg/kg/week dose, the median time to a PASI 50 among the patients who were classified as PASI 75 responders was 41 days. Again, the timing of examinations, at biweekly intervals, is an important consideration in this analysis.

4.3.4.8 Duration

Time-to-relapse defined as a loss of ≥ 50% improvement in PASI score achieved between baseline and the end of the 84-day treatment period was summarized by treatment group for treatment responders (≥ PASI 75 at day 84). The results are shown in Table 24 below.

Table 24 Time (days) to Relapse during the OB Period, Using Kaplan-Meier Estimates: Subjects Treated with Efalizumab during the FT Period

	Efalizumab	
Characteristic	1.0 mg/kg n=63	2.0 mg/kg n=44
Events	55	37
Censored observations [a]	8	7
Median (95% CI)	60.0 (57, 66)	59.0 (57, 82)
25th–75th Percentile	43.0–85.0	49.0–87.0

[a]Data from subjects who discontinued prior to relapse or who did not relapse during the OB period were censored.

The median time to relapse during the observation period was 60 days (67 days after the last dose of efalizumab) for the 1.0- mg/kg/wk group and 59 days for the 2-mg/kg/wk group.

Reviewer's comment: The PASI assessment took place at biweekly intervals for two visits and subsequently at monthly intervals during the observation period (e.g. OB Day 14, 28, 56, 84, 112, 140 and 168). The effect of the assessment schedule was likely the reason that observations of relapse were close to the Day 56 timepoint.

Exploratory analyses were performed in order to estimate the duration of treatment response, PASI 50 and PASI 75, in PASI 75 responders. Four different approaches were used in these analyses to determine when response was lost. In the first analysis, duration of response after 12 weeks of treatment was defined as the time (days) from FT Day 84 (1 week after the last dose) to the first visit day when efficacy was consistent with a loss of response. The second analysis used a linear interpolation between the two visits to determine the approximate date the response (either PASI-75 or PASI-50) was lost; the third method assumed that response was lost midway between the two visits; and the fourth approach assumed that response was retained only through the last visit at which the criterion (either PASI-75 or PASI-50) was met. If an excluded medication was started, the patient was assumed to have lost response at the time the medication was initiated.

Duration of response was measured from the date of last dose through the date determined by one of these four approaches. Median time to a loss of PASI-75 or PASI-50 response was determined using Kaplan-Meier estimates. The results of these analyses are summarized below.

Time to loss of PASI 75 among PASI 75 responders using the assumption of retained response during the period between observations is shown below.