

MEMORANDUM

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TOPIC Briefing Document:
Biologic License Application STN BL 125075/0 for efalizumab for
the treatment of moderate to severe chronic plaque psoriasis

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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 a recombinant humanized IgG1 kappa isotype monoclonal antibody that selectively 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 $\beta 2$ integrin, and is expressed on all leukocytes. Efalizumab binds specifically 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), tazarotene (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. The relative increase in risk of a person with sun-sensitive skin (e.g. Fitzpatrick Type I or II skin; always burn; tan never/sometime) developing squamous cell carcinoma is at least 5 times greater than that of control.

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 PK, 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 1 st Time With	
				XOMA	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	12	NA	339
		1.0–2.0 SC	≥ 48		
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					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 Psoriasis 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 (EI + TI + SI) AI

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

Score	Category	Description
0	Clear	Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale) Erythema = \pm (hyperpigmentation, pigmented macules, diffuse faint pink or red coloration)
1	Minimal	Plaque elevation = \pm (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = \pm (<i>surface dryness with some white coloration</i>) 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 (<i>very bright red coloration</i>)
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.

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 |

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 $\geq 75\%$ 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:

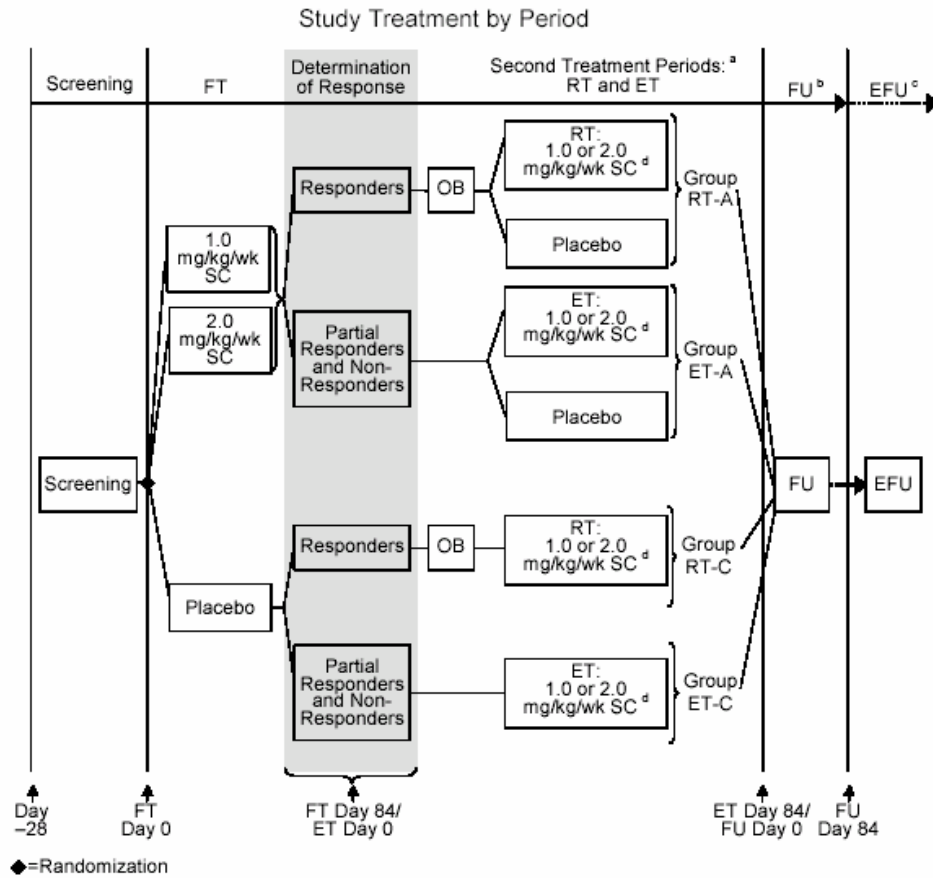
- optimization of dose
- duration of treatment-free response
- potential for treatment-withdrawal phenomena (e.g. flaring, psoriasis variants)
- safety and efficacy of retreatment following relapse
- safety and activity of extended treatment for partial responders and non-responders

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 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

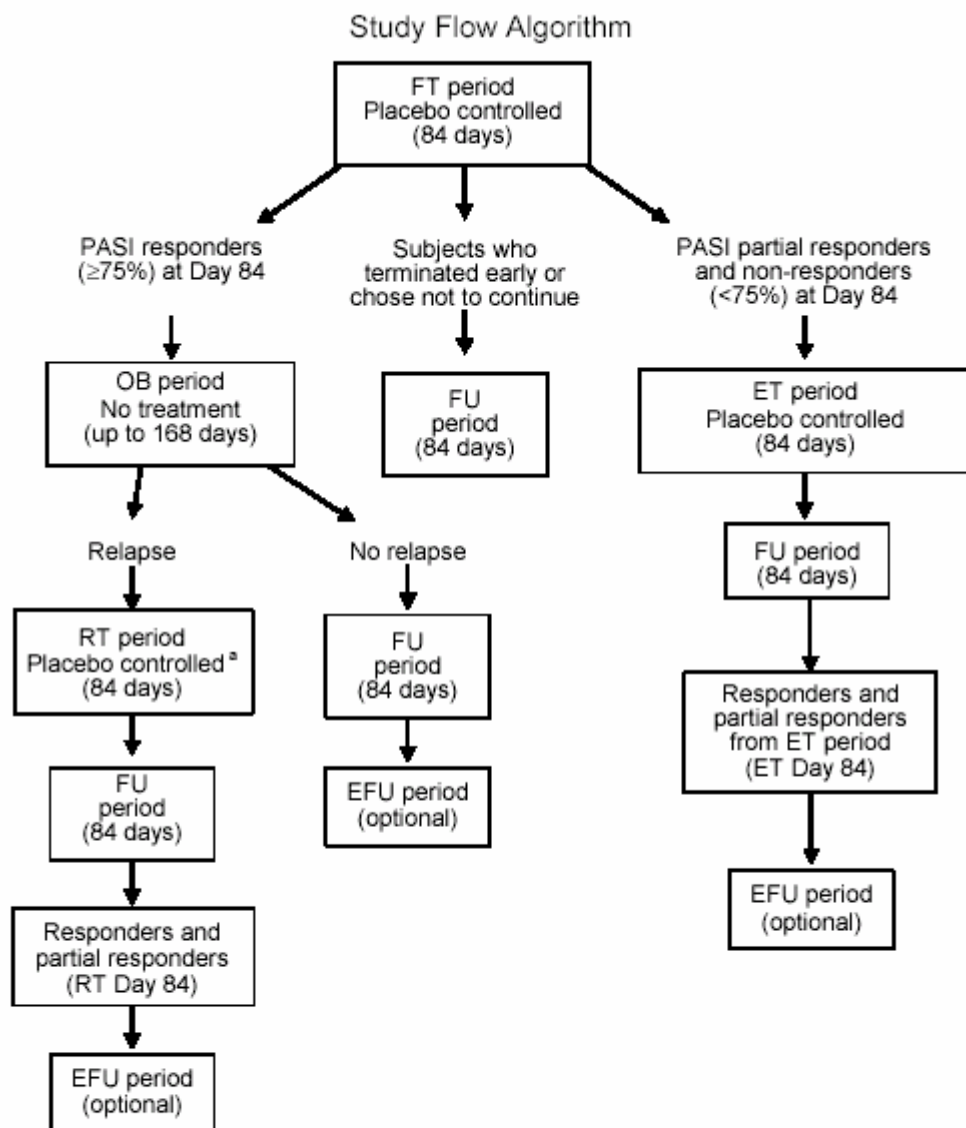


^a Subjects had the option of transferring to the open-label study, [ACD2062g](#), if they were non-responders between Day 56 of the second treatment period and FU Day 28.

^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.



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 $\geq 50\%$ 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 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 balanced for subjects who were partial responders and non-responders.

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 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
- 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.

4.3.3.5 Disallowed treatments

The following were not allowed: 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, 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.

4.3.3.6 Eligibility

Inclusion

- Plaque psoriasis covering $\geq 10\%$ 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 $3\times$ the upper limits of normal (ULN) Subjects with hepatic enzymes elevated above the ULN but $<3\times$ 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 $<4000/\mu\text{L}$ or $>14,000/\mu\text{L}$
- Serum creatinine $\geq 2\times$ 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

4.3.3.7 Efficacy Outcomes

The primary efficacy outcome measure was the proportion of subjects with a $\geq 75\%$ improvement in PASI score between FT Day 0 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.

4.3.3.8 Assessment of Safety

The following were performed: 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. 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)

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 excluded from the summary.

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 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 $\geq 75\%$ from FT Day 0 to FT Day 84
- Partial responder: Any subject whose PASI score decreased $\geq 50\%$ 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. 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.

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 $\alpha=0.049$ (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.

4.3.3.10 Protocol Amendments

The protocol was amended twice. 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 3.

Table 3 Disposition of Subjects and Reasons for Discontinuation during the FT Period

	Placebo	Efalizumab	
		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 4 below depicts the demographics of subjects during the first treatment period of the study.

Table 4 Demographic Characteristics of Subjects in the FT Period

Characteristic, n	FT Placebo (n=170)	FT Efalizumab	
		1.0 mg/kg/wk (n=162)	2.0 mg/kg/wk (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. 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 5 below contains the baseline disease characteristics for the study population.

Table 5 Baseline Psoriasis Characteristics of Subjects in the FT Period

Characteristic	FT Placebo (n=170)	FT Efalizumab	
		1.0 mg/kg/wk (n=162)	2.0 mg/kg/wk (n=166)
Duration of psoriasis (yr)			
Mean	18.5	19.1	16.7
Median	17	19	15
Range	1–56	1–58	1–60
Prior systemic therapy			
Yes	91 (53.5%)	89 (54.9%)	93 (56.0%)
No	79 (46.5%)	73 (45.1%)	73 (44.0%)
PASI			
Mean	19.02	18.63	18.86
Median	16.5	16.9	16.8
Range	9.6–57.6	11.9–50.1	10.0–55.6
PASI category			
≤ 16.0	79 (46.5%)	74 (45.7%)	74 (44.6%)
16.1–30.0	78 (45.9%)	77 (47.5%)	79 (47.6%)
>30	13 (7.6%)	11 (6.8%)	13 (7.8%)
PASI thickness component			
Mean	6.26	6.07	6.08
Median	5.6	5.5	5.5
Range	2.4–19.2	2.1–18.2	3.0–18.6
Physician's Global Assessment			
Mild	6 (3.5%)	4 (2.5%)	4 (2.4%)
Moderate	86 (50.6%)	90 (56.3%)	86 (51.8%)
Severe	67 (39.4%)	61 (38.1%)	70 (42.2%)
Very severe	11 (6.5%)	5 (3.1%)	6 (3.6%)
% BSA of psoriasis			
Mean	29.4	29.6	29.9
Median	25.6	24.3	24.2
Range	10–85	10–72	10–83
Itching Scale			
Mean	5.9	5.8	6.1
Median	6	6	7
Range	0–10	0–10	0–10

The median duration of disease was 17 years (range 1–60 years). Approximately 55% of all subjects had a history of prior systemic therapy; however, for a substantial proportion of the study subjects, efalizumab was the first systemic therapy received. The median baseline PASI score was approximately 16.7. The treatment groups were well-balanced in all the measures of baseline disease activity. Overall, the baseline psoriasis characteristics indicate the study population had moderate-to-severe psoriasis.

Table 6 below contains information with regard to treatment compliance with study drug by treatment group.

Table 6 Treatment Compliance for Subjects during the FT Period

No. of Doses	Placebo	Efalizumab	
		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 7 PASI Response to Treatment during the FT Period: All Randomized Subjects

PASI Response at FT Day 84	Placebo (n=170)	Efalizumab	
		1.0 mg/kg/wk (n=162)	2.0 mg/kg/wk (n=166)
Responders, 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.

Table 8 Mean Percent Improvement in PASI Thickness, Erythema, and Scaling Components during the FT Period

PASI Component	FT Placebo (n=170)	FT Efalizumab	
		1.0 mg/kg/wk (n=162)	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 9 Mean Improvement in Percent BSA of Psoriasis during the FT Period

	FT Placebo (n=170)	FT Efalizumab	
		1.0 mg/kg/wk (n=162)	2.0 mg/kg/wk (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 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 10 below.

Table 10 PASI Responders by Subsets of Randomized Subjects: FT Period

Subject Subset	Placebo n=170	Efalizumab	
		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.

The data below show the response rate by geographic latitude by treatment group (see Table 11). 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 11 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 12 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.

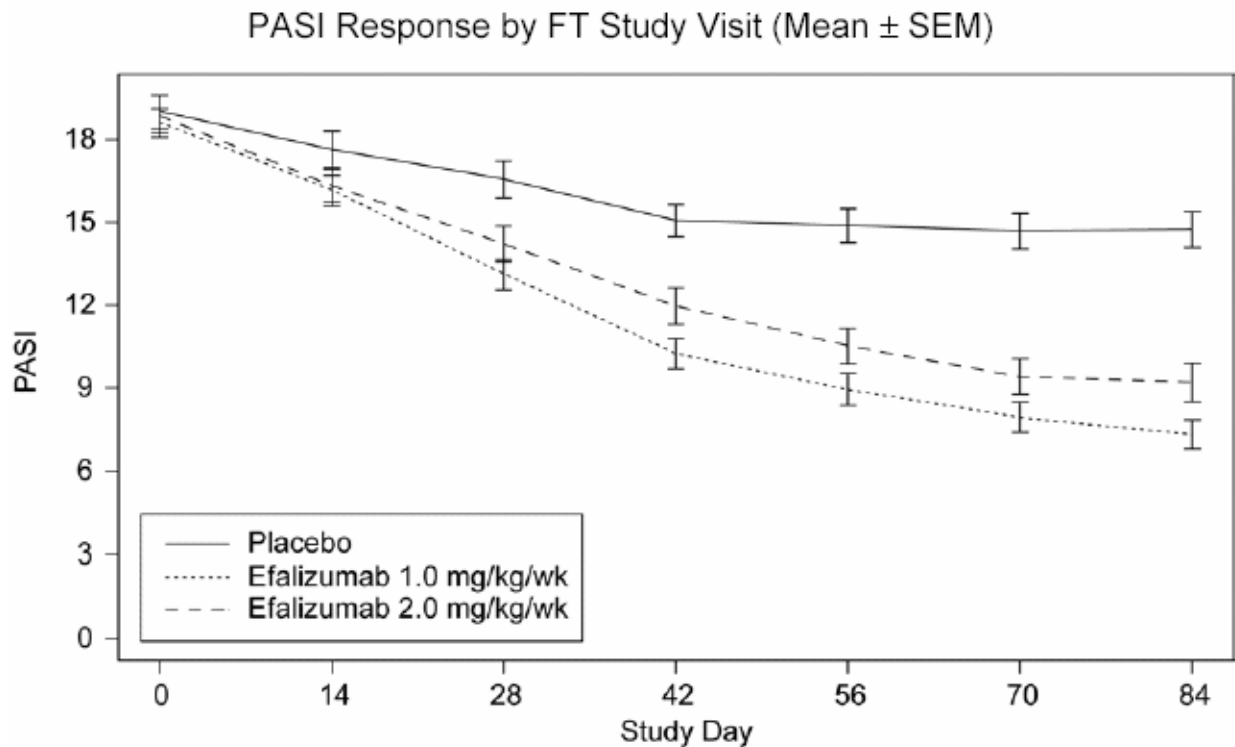
4.3.4.6 Secondary Efficacy Outcomes

Table 13 Principal Secondary Efficacy Endpoint: FT Period

OLS Response at FT Day 84	FT Efalizumab		
	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.

The secondary efficacy outcomes also showed that efalizumab was superior to placebo.



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

The PGA, a physician's global assessment, was used to measure the dynamic response of patients as compared baseline (See Table 14 below).

Table 14 PGA Response for Subjects during the FT Period

	Placebo	FT Efalizumab	
		1.0 mg/kg/wk	2.0 mg/kg/wk
PGA 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.

4.3.4.7 Time-to-response and duration of treatment response

Time-to-onset of PASI-75 response was analyzed and the results are shown in Table 15 below.

Table 15 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.

4.3.4.8 Duration

Time-to-relapse defined as a loss of $\geq 50\%$ improvement in PASI score achieved between baseline and the end of the 84-day treatment period was summarized by treatment group for treatment responders (\geq PASI 75 at day 84). The results are shown in Table 16 below.

Table 16 Time (days) to Relapse during the OB Period, Using Kaplan-Meier Estimates: Subjects Treated with Efalizumab during the FT Period

Characteristic	Efalizumab	
	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

^aData 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.

An analysis of the distribution of percent improvement in PASI achieved during the first 84 days of treatment is shown in Table 17 below.

Table 17 PASI Response by Percent Improvement from Baseline for Subjects during the FT Period (% of total)

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

^aSubjects 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.

4.3.4.9 The OB Period

Patients who achieved PASI 75 at the end of the first treatment period could enter the observation period. A total of 111 patients entered the OB Period. Of these, 4 received placebo in the first treatment period and the remainder received treatment with efalizumab. Overall, 83% of the patients who discontinued the observation period met the endpoint of relapse during the observation period and entered retreatment. Overall, 9.9% of patients did not experience relapse during the 84-day observation period.

Table 18 Disposition of Subjects and Reasons for Discontinuation during the OB Period

Subject Status	FT Efalizumab			
	FT Placebo (n=4)	1.0 mg/kg/wk (n=63)	2.0 mg/kg/wk (n=44)	All Subjects (n=111)
Completed OB, n	1 (25.0%)	5 (7.9%)	5 (11.4%)	11 (9.9%)
Enrolled in Study ACD2062g	0	0	1	1
Entered RT	0	1	1	2
Entered FU	1	3	3	7
Discontinued from study	0	1	0	1
Discontinued OB, n	3 (75.0%)	58 (92.1%)	39 (88.6%)	100 (90.1%)
Enrolled in Study ACD2062g	0	1	2	3
Entered RT	3	49	31	83
Entered FU	0	2	2	4
Discontinued from study	0	6	4	10
Reason for discontinuation from OB				
Adverse event	0	1	1	2
Lost to follow-up	0	1	1	2
Subject's decision	0	2	1	3
Investigator's decision	0	1	4	5
Pregnancy	0	1	1	2
Relapse of psoriasis	3	52	31	86

A protocol amendment made it possible for patients experiencing severe psoriasis upon relapse to enter Study ACD2062g. Of the 100 patients who discontinued the observation period, 86 patients experienced a relapse of psoriasis. Of these patients, 83 entered the retreatment period and 3 entered Study ACD2062g. Among the 14 patients listed as having discontinued for reasons other than relapse of psoriasis, several discontinued for psoriasis variants and worsening of psoriasis.

Table 19 Psoriasis-Related Concomitant Medications Initiated during the OB Period:

	FT Period Responders							
		Placebo	Drug		Drug		All Subjects	
USAN Class	Generic Name	(N=4)	1.0 mg/kg/wk (N=63)		2.0 mg/kg/wk (N=44)		(N=111)	
Subjects with completed medication forms		4	63		44		111	
Subjects initiated at least one psoriasis-related medication		2 (50.0%)	12 (19.0%)		13 (29.5%)		27(24.3%)	
Dermatologic agents	- Total -	(0.0%)	2	(3.2%)	2	(4.5%)	4	(3.6%)
	Acitretin	(0.0%)		(0.0%)	1	(2.3%)	1	(0.9%)
	Calcipotriene	(0.0%)	1	(1.6%)		(0.0%)	1	(0.9%)
	Coal tar	(0.0%)	1	(1.6%)	1	(2.3%)	2	(1.8%)
Steroids	- Total -	2 (50.0%)	11 (17.5%)		12 (27.3%)		25 (22.5%)	
	Betamethasone valerate	(0.0%)		(0.0%)	1	(2.3%)	1	(0.9%)
	Cortisone acetate	(0.0%)		(0.0%)	1	(2.3%)	1	(0.9%)
	Dexamethasone	(0.0%)		(0.0%)	1	(2.3%)	1	(0.9%)
	Fluocinolone acetonide	(0.0%)		(0.0%)	1	(2.3%)	1	(0.9%)
	Fluticasone propionate	(0.0%)	2	(3.2%)		(0.0%)	2	(1.8%)
	Halobetasol propionate	(0.0%)	1	(1.6%)		(0.0%)	1	(0.9%)
	Hydrocortisone	1 (25.0%)	5	(7.9%)	5	(11.4%)	11	(9.9%)
	Mometasone furoate	(0.0%)	4	(6.3%)	1	(2.3%)	5	(4.5%)
	Prednisolone acetate	(0.0%)		(0.0%)	1	(2.3%)	1	(0.9%)
	Prednisone	1 (25.0%)		(0.0%)	2	(4.5%)	3	(2.7%)
	Triamcinolone acetonide	(0.0%)	1	(1.6%)	3	(6.8%)	4	(3.6%)

Overall, 24% of patients entering the observation period initiated at least one psoriasis-related medication (See Table 19). The majority of these patients initiated treatment with topical steroids. Three patients initiated treatment with systemic steroids (prednisone).

Reviewer's comment: It is possible that the use of the disallowed concomitant medications during the observation period may have affected the estimate of the duration of response. Analyses are ongoing to evaluate.

4.3.4.10 Response to Second Treatment Course in Patients who Responded to the First Treatment

The only study which examined the response to retreatment was Study ACD2058. In this study, patients who were responders (achieved $\geq 75\%$ improvement in PASI) at day 84 were eligible to enter an observation period, no treatment for up to 168 days during which they were followed until relapse, and then rerandomized to a second treatment course.

Upon relapse, placebo patients received a second course of efalizumab, while efalizumab-treated patients were rerandomized centrally to receive either the same dosage of efalizumab or placebo in a 2:1 ratio.

Subjects not responding to the second course of treatment by RT Day 56 were eligible to transfer to the open label study, ACD2062g. As discussed on page 33, the majority of both placebo- and efalizumab- treated patients discontinued the observation period due to relapse of their psoriasis.

Table 20 below reflects the disposition of the subset of patients who responded to treatment with efalizumab (active drug) during the first 84 days of treatment and were rerandomized during the observation period to retreatment.

Table 20 Disposition of RT-A Subjects and Reasons for Discontinuation

	Placebo	Efalizumab	
		1.0 mg/kg	2.0 mg/kg
Subject Status	(n=27)	(n=32)	(n=23)
Completed RT	8 (29.6%)	26 (81.2%)	16 (69.6%)
Entered FU	5	23	13
Entered Study ACD2062g	2	3	1
Discontinued from study	1	0	2
Discontinued RT	19 (70.4%)	6 (18.8%)	7 (30.4%)
Entered FU	1	0	2
Entered Study ACD2062g	18	6	5
Reason for RT discontinuation	(n=19)	(n=6)	(n=7)
Subject's decision	1	0	1
Investigator's decision	1	0	0
Non-response to RT	16	6	6
Non-response to ET ^a	1	0	0

^a One subject should have been classified as a non-responder to retreatment, making the total number of non-responders 29 (90.6%).

Eighty-six subjects were eligible to enter RT. Of these, 82 were rerandomized to RT. Most of the patients who were rerandomized to receive efalizumab completed the course of retreatment, while fewer than one-third (29.6%) of the patients who were rerandomized to placebo completed the retreatment period. Most of the latter patients discontinued due to non-response to retreatment.

Table 21 below shows the psoriasis characteristics of the subset of responders who entered retreatment upon relapse.

Table 21 Psoriasis Characteristics of RT-A Subjects

Characteristic, n	Efalizumab			All Efalizumab- Treated Subjects (n=55)
	Placebo (n=27)	1.0 mg/kg/wk (n=32)	2.0 mg/kg/wk (n=23)	
Duration of psoriasis (yr)				
Mean	20.6	20.0	18.9	19.5
Median	21	20	18	20
Range	3–46	3–43	2–43	2–43
Prior systemic therapy				
Yes	15 (55.6%)	19 (59.4%)	13 (56.5%)	32 (58.2%)
No	12 (44.4%)	13 (40.6%)	10 (43.5%)	23 (41.8%)
Baseline PASI (FT Day 0)				
Mean	18.7	17.7	19.2	18.3
Median	17.5	15.4	17.1	15.6
Range	11.9–29.7	12.0–35.3	12.1–36.0	12.0–36.0
RT Day 0 PASI				
Mean	14.8	13.2	13.7	13.4
Median	12.4	11.9	11.6	11.6
Range	7.5–39.0	7.4–29.2	8.5–28.7	7.4–29.2
Baseline (FTDay 0) PASI category				
≤16.0	12 (44.4%)	19 (59.4%)	11 (47.8%)	30 (54.5%)
16.1–30.0	15 (55.6%)	10 (31.3%)	8 (34.8%)	18 (32.7%)
>30	0	3 (9.4%)	4 (17.4%)	7 (12.7%)
Baseline (FT Day 0) OLS				
Moderate	18 (66.7%)	21 (65.6%)	12 (52.2%)	33 (60.0%)
Severe	9 (33.3%)	10 (31.3%)	11 (47.8%)	21 (38.2%)
Very severe	0	1 (3.1%)	0	1 (1.8%)

The rerandomized patients were reasonably well balanced in terms of the baseline disease severity. This subset had moderate-to-severe psoriasis at Day 0 of the first treatment period according to the static physician's global assessment and a median baseline PASI of 15.6. As would be expected, the overall median PASI score at the beginning of retreatment, 11.6, was lower than that at Day 0 of the first treatment period.

Psoriasis Characteristics of RT-A Subjects (cont)

Characteristic, n	Efalizumab			All Efalizumab- Treated Subjects (n=55)
	Placebo (n=27)	1.0 mg/kg/wk (n=32)	2.0 mg/kg/wk (n=23)	
RT Day 0 OLS				
Mild	0	1 (3.2%)	4 (17.4%)	5 (9.3%)
Moderate	23 (85.2%)	25 (80.6%)	15 (65.2%)	40 (74.1%)
Severe	4 (14.8%)	4 (12.9%)	4 (17.4%)	8 (14.8%)
Very severe	0	1 (3.2%)	0	1 (1.9%)
% BSA of psoriasis				
Mean	31.7	29.1	31.5	30.1
Median	32.0	24.6	28.0	24.8
Range	13.0–63.0	11.0–59.0	11.0–81.0	11.0–81.0
RT Day 0 % BSA of psoriasis				
Mean	24.0	17.1	21.8	19.1
Median	20.0	14.0	15.5	14.8
Range	5.0–74.0	6.2–43.0	7.0–54.0	6.2–54.0
FT Day 84 PGA				
Cleared	1 (3.7%)	2 (6.3%)	0	2 (3.6%)
Excellent	23 (85.2%)	27 (84.4%)	20 (87.0%)	47 (85.5%)
Good	2 (7.4%)	2 (6.3%)	3 (13.0%)	5 (9.1%)
Fair	1 (3.7%)	0	0	0
Missing	0	1 (3.1%)	0	1 (1.8%)
RT Day 0 PGA				
Good	1 (3.7%)	2 (6.3%)	0	2 (3.6%)
Fair	12 (44.4%)	17 (53.1%)	7 (30.4%)	24 (43.6%)
Slight	4 (14.8%)	5 (15.6%)	12 (52.2%)	17 (30.9%)
Unchanged	2 (7.4%)	2 (6.3%)	1 (4.3%)	3 (5.5%)
Worse	8 (29.6%)	6 (18.8%)	3 (13.0%)	9 (16.4%)

Unless otherwise stated baseline was FT Day 0.

The subset of patients who subsequently received retreatment had moderate to severe psoriasis at baseline (FT Day 0). The baseline characteristics were comparable to the ITT population as a whole. The patients' retreatment baseline were, as would be expected, better than their original baseline in all measures of disease severity including PASI and baseline BSA affected by psoriasis.

Treatment compliance in the patients randomized to retreatment is shown in

Table 22 below.

Table 22 Treatment Compliance for RT-A Subjects

No. of Doses	Placebo	Efalizumab	
		1.0 mg/kg/wk	2.0 mg/kg/wk
Received	(n=27)	(n=32)	(n=23)
All 12	8 (30%)	24 (75%)	16 (70%)
10–11	0	2 (6.3%)	1 (4.3%)
<10	19 (70%)	6 (19%)	6 (26%)

Whereas, the majority of patients in the efalizumab groups received all 12 doses in the RT period, less than one-third of the placebo patients received all 12 doses. Again, the reasons for missed doses are probably reflective of the reasons for discontinuing the retreatment period. In the case of the placebo patients the most common reason was non-response to treatment.

Response to retreatment is described below. These were patients who responded to the first treatment period and then were rerandomized to either efalizumab or placebo upon relapse (loss of 50% of improvement in PASI). In this analysis, responses were compared to the original baseline at FT Day 0.

Table 23 PASI Response to Retreatment (% Improvement from FT Day 0)

Response Category	Placebo (N=27)	Efalizumab (Combined) (N=55)
≥ 75%	0	17 (31%)
≥ 50% -< 75%	5 (19%)	20 (36%)
0-50%	2 (7%)	4 (7%)
<0%	1 (4%)	1 (2 %)
Missing	19 (70%)	13 (24%)

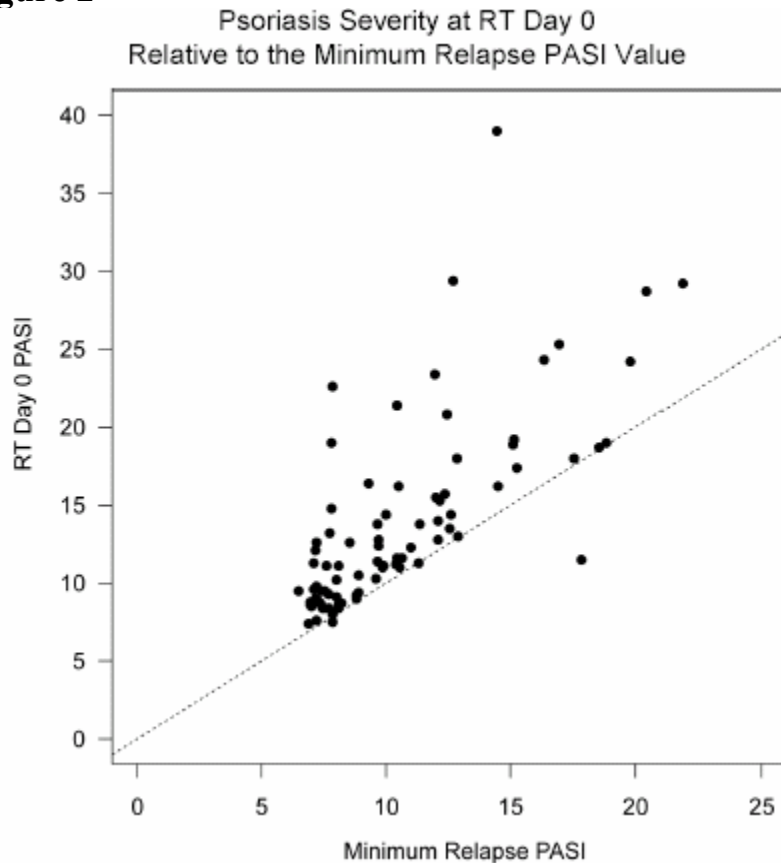
Among patients who received retreatment with efalizumab, 34% of the 1 mg/kg group and 25% of the 2 mg/kg group responded at the PASI 75 level at the end of the retreatment period. This was in contrast to patients rerandomized to placebo who had no responders to retreatment. The majority of the patients receiving efalizumab upon retreatment, 72% and 61% the 1 mg/kg group and 2 mg/kg group, respectively, responded at the PASI 50 level.

While all patients had achieved a 75% improvement in PASI at Day 84 of the first treatment period, less than one-third of the combined efalizumab-treated patients achieved this level of response at Day 84 of retreatment. The patients' state of active

relapse at the beginning of the retreatment period may have contributed to the lower response rate to retreatment.

Figure 2 below depicts the PASI score at retreatment in relation to the minimum relapse PASI defined as a loss of 50% of the improvement achieved during the first treatment period.

Figure 2



Since PASI assessments were scheduled for OB Days 14, 28, 56, 84, 112, 140 and 168, in most cases the retreatment baseline PASI score exceeded the minimum retreatment score. The magnitude of the difference between retreatment PASI and the minimum requirement ranged from 0 to nearly 25 points. In most cases the difference did not exceed 10 PASI points. (Of note one patient, entered retreatment with less than the minimum required PASI score.)

Reviewer's comment: It is not known whether the severity of relapse may have played a role in inhibiting the ability of the drug to recapture PASI responses comparable to those achieved during the first treatment period.

Of note, there was a considerable proportion of patients in each group for whom these data are missing. The majority of the patients in the placebo group had missing data. The high proportion of missing data reflects the number of patients who transferred to Study ACD2062g with our completing the retreatment period, due to non-response.

The responses to retreatment when compared to the new baseline are shown in Table 24 below.

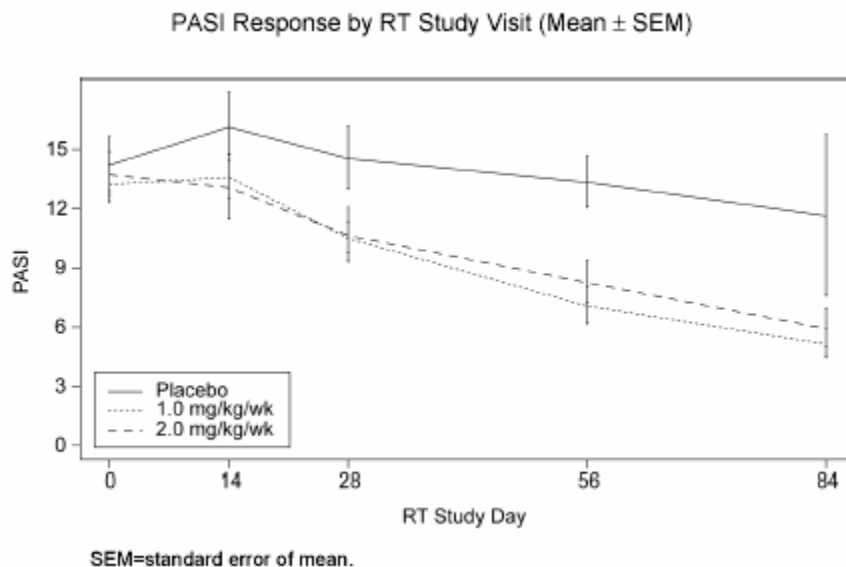
Table 24 PASI Response to Retreatment (% Improvement from RT Day 0)

Response Category	Placebo (N=27)	Efalizumab (Combined) (N=55)
≥ 75%	0	12 (22%)
≥ 55%	3 (11%)	27 (49%)
0-50	3 (11%)	12 (22%)
< 0	2 (7.4%)	3 (5%)
Missing	19 (70%)	13 (24%)

By comparison to the most recent baseline, the proportions of patients achieving PASI 50 and PASI 75 are fewer than when the comparison is to the patient's own original baseline as would be expected.

The time course of response to retreatment is shown in Figure 3 below. Separation of the efalizumab curves from that of placebo took place by 28 days of retreatment.

Figure 3



The proportion of patients responding at retreatment day 84 by OLS minimal to clear was approximately 23.6% higher in the combined efalizumab group as compared to the placebo group. See Table 25 below.

Table 25 OLS Response to Treatment for RT-A Subjects

RT Day 84 Characteristic	Placebo (n=27)	Efalizumab		All Efalizumab- Treated Subjects (n=55)	All Efalizumab vs. Placebo
		1.0 mg/kg/wk (n=32)	2.0 mg/kg/wk (n=23)		
Minimal or Clear	1 (3.7%)	9 (28.1%)	6 (26.1%)	15 (27.3%)	0.016

4.3.4.11 Response to Extended Treatment in Patients who were Non-responders or Partial Responders to the First Treatment Period

The group of non-responders and partial responders from the first treatment period who were re-randomized to extended treatment or placebo for the extended treatment period was also analyzed.

The patient disposition of this group is shown below.

Table 26 Disposition of ET-A Subjects and Reasons for Discontinuation

Subject Status	Withdrawal/ Placebo (n=60) ^a	Efalizumab	
		1.0 mg/kg/wk (n=57)	2.0 mg/kg/wk (n=66)
Completed ET, n	24 (40.0%)	36 (63.2%)	48 (72.7%)
Entered FU	15	28	36
Entered Study ACD2062g	8	8	12
Discontinued from study	1	0	0
Discontinued ET, n	35 (58.3%)	21 (36.8%)	18 (27.3)
Entered FU	8	5	5
Entered Study ACD2062g	26	13	11
Discontinued from study	1	3	2
Reason for ET discontinuation			
Adverse event	6	2	4
Lost to follow-up	0	2	0
Subject's decision	3	3	2
Investigator's decision	0	1	2
Non-response to ET	26	13	10

^a One subject (11010) was randomized to the withdrawal/placebo group, but never received treatment

The demographics of the ET patients were similar to the ITT population for first treatment. There were no significant differences among treatment groups (data not shown). Median age was 44 (range 19-72). As in the first treatment group, there was a higher proportion of males than females (73%: 27%).

Baseline psoriasis characteristics of ET patients were comparable across treatment groups (Table 27).

Table 27 Baseline Psoriasis Characteristics of ET-A Subjects

Characteristic, ^a n	Efalizumab			All Efalizumab- Treated Subjects
	Placebo (n=60)	1.0 mg/kg/wk (n=57)	2.0 mg/kg/wk (n=66)	
Duration of psoriasis (yr)				
Mean	17.3	20.0	15.0	17.3
Median	12	19	15	17
Range	1–60	2–58	1–42	1–58
Prior systemic therapy				
Yes	31 (51.7%)	35 (61.4%)	40 (60.6%)	75 (61.0%)
No	29 (48.3%)	22 (38.6%)	26 (39.4%)	48 (39.0%)
Baseline PASI				
Mean	19.5	17.3	18.2	17.8
Median	18.1	16.6	15.9	16.3
Range	10.0–40.0	12.0–27.3	12.2–55.6	12.0–55.6
FT Day 84 PASI				
Mean	12.4	10.0	11.8	10.9
Median	9.8	9.8	9.3	9.3
Range	3.5–31.6	3.4–23.5	3.6–53.3	3.4–53.3
Baseline PASI category				
≤16.0	24 (40.0%)	25 (43.9%)	34 (51.5%)	59 (48.0%)
16.1–30.0	30 (50.0%)	32 (56.1%)	28 (42.4%)	60 (48.8%)
>30.0	6 (10.0%)	0	4 (6.1%)	4 (3.3%)
FT Day 84 PASI category				
≤16.0	45 (75.0%)	50 (87.7%)	55 (83.3%)	105 (85.4%)
16.1–30.0	13 (21.7%)	7 (12.3%)	9 (13.6%)	16 (13.0%)
>30.0	2 (3.3%)	0	2 (3.0%)	2 (1.6%)

^a The FT Day 84 characteristics were based on FT Day 84/ET Day 0 values.

The efficacy results of extended treatment in non-responders and partial responders to the first treatment period are shown below (Table 28).

Table 28 Proportion of ET-A Subjects Who Achieved PASI Response

	Efalizumab			All Efalizumab-Treated Subjects (n=123)	All Efalizumab vs. Placebo
	Placebo (n=60)	1.0 mg/kg/wk (n=57)	2.0 mg/kg/wk (n=66)		
ET Day 84 Responders	4 (6.7%)	12 (21.1%)	13 (19.7%)	25 (20.3%)	0.018

These results demonstrate that an additional 13.6% of patients achieved PASI 75% response in the combined efalizumab group compared to placebo when treated with a three-month extended treatment beyond the first treatment period.

Reviewer's comment:

The use of intermittent treatment upon 50% relapse does not recapture response in the majority of patients. Response was 31% at the PASI 75 level. However, the evidence suggests that extended treatment does result in an additional 14% response in those patients who failed to respond to the first course.

4.3.5 Summary of Efficacy: Study ACD2058g

- After 3 months of efalizumab treatment (1 mg/kg/wk SC), a 37% treatment effect was observed (95% CI 28-46%) by PASI 75 response criteria.
- The secondary endpoints confirmed the efalizumab treatment effect
 - The principal secondary endpoint, “minimal or clear” by static physician’s global assessment was achieved by 29% (absolute difference) of treated patients.
 - A PASI 50 response was achieved by 46% (absolute difference) of treated patients.
- The mean thickness, erythema and scaling components of the PASI score decreased by approximately 50%. All three components, thickness, erythema and scaling, changed to a similar extent. The mean affected surface area decreased by 14%.
- Baseline variables and demographics including PASI score and history of previous systemic therapy did not influence response to treatment.
- There was a general shift towards improvement in the entire efalizumab-treated group; however, a small proportion of patients developed clinically significant worsening of psoriasis (see safety assessments).
- For efalizumab-treated patients who had a response, the time to PASI 75 response was approximately 2 months.
- Duration of response after treatment discontinuation was variable, but estimated as a median of 67 days until time to relapse, or loss of 50% of the improvement obtained in responders during the first treatment period.

- Only one-third of patients who responded to the first treatment period and were followed until relapse responded to retreatment with efalizumab.
- Among the patients who did not respond to the initial 12-week treatment period, an additional 14% achieved PASI 75% response in the combined efalizumab group compared to placebo when treated with an additional contiguous three-month extended treatment of efalizumab.
- The 2 mg/kg/wk SC dose was not superior to the 1 mg/kg/wk SC dose.

4.4 Protocol ACD2059g

4.4.1 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 Who Are Candidates for Systemic Therapy”

4.4.2 Study Objectives

Primary

- To investigate the efficacy of weekly 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 $\geq 75\%$ 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

Secondary

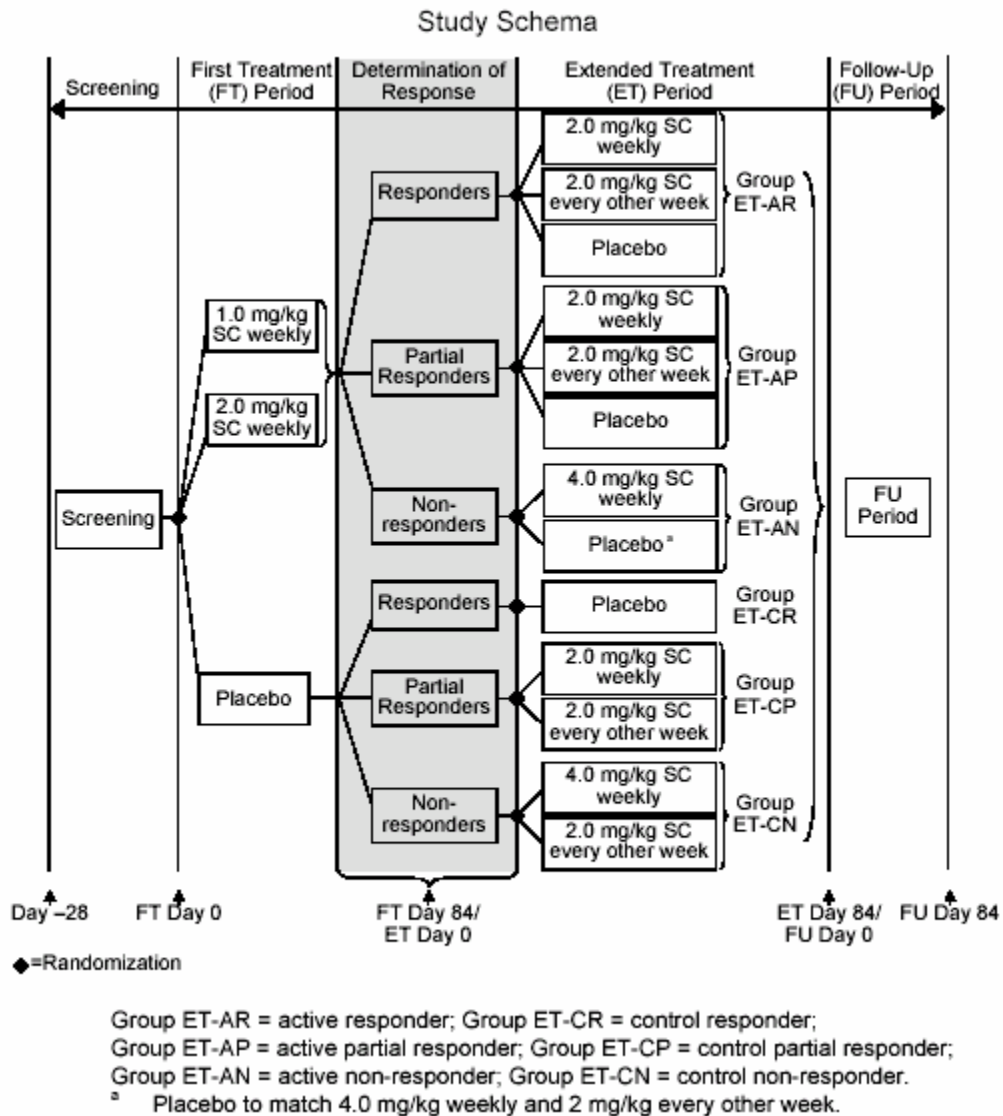
- To evaluate the safety and tolerability of 24 weeks of continuous treatment with SC efalizumab FT responders
- To investigate the efficacy of SC efalizumab as measured by the frequency of relapse during 12 weeks of “maintenance” treatment with one of two regimens of efalizumab compared with placebo
- To investigate the efficacy of SC efalizumab administered for 24 weeks compared with 12 weeks followed by placebo for 12 weeks as measured by PASI, Overall Lesion Severity (OLS), and Physician’s Global Assessment, with particular attention to the proportion of subjects who became “cleared” or “almost cleared.”

4.4.3 Study Design

This was a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter, multidose study designed to evaluate the efficacy and safety of efalizumab administered at weekly SC doses of 1.0 mg/kg or 2.0 mg/kg in subjects with moderate to severe plaque psoriasis who were candidates for systemic therapy.

The study consisted of three periods, each of which lasted ~3 months (84 days): FT, ET, and FU (see Figure 4).

Figure 4 Study ACD 2059 Schema



The treatment regimens in the three study periods were the following:

- FT period: Day -28 through FT Day 84
 All subjects entered the FT period, which included a screening period and an initial 12- week course of 1.0 mg/kg/wk efalizumab, 2.0 mg/kg/wk efalizumab, or placebo.
- ET period: FT Day 84 (ET Day 0) through ET Day 84
 Responders and partial responders who received efalizumab during the first treatment period, received an additional 12 weeks of treatment with 2.0

mg/kg/wk efalizumab, 2.0 mg/kg/qow efalizumab, or placebo. Non-responders from the FT period received an additional 12 weeks of treatment with 4.0 mg/kg/wk efalizumab, 2.0 mg/kg/qow efalizumab, or placebo.

- Patients who received placebo during the first treatment period were rerandomized differently from those who received efalizumab during the first treatment period. If a patient received placebo during the first treatment period and was classified as a responder, he/she continued to receive placebo during the extended treatment period. However, if a patient received placebo during the first treatment period and was considered a partial responder, he/she could be rerandomized to 2 mg/kg SC weekly or 2 mg/kg SC every other week. Finally, if a placebo patient was a nonresponder during the first treatment period, then he/she was rerandomized to 2 mg/kg SC weekly or 4 mg/kg SC weekly. Therefore, a partial responder or a nonresponder who received placebo during the first treatment period would receive active drug in the extended treatment period.
- FU period: ET Day 84 (FU Day 0) to FU Day 84
All subjects completed three monthly safety visits after the last dose of study drug.

4.4.3.1 Randomization

Subjects were randomized through an interactive voice response system in a 4:4:1:1 ratio to high-dose (2.0 mg/kg) efalizumab, low-dose (1.0 mg/kg) efalizumab, high-dose placebo, or low-dose placebo.

Randomization was stratified by the FT Day 0 PASI score (≤ 16.0 , ≥ 16.1), by prior treatment for psoriasis (naive to systemic treatment vs. prior systemic treatment), and by study site.

Re-randomization on ET Day 0 was dependent on response status at FT Day 84 and whether the subject received active drug or placebo in FT. For subjects who received active drug, randomization was balanced within categories defined by the FT dose (i.e., 1.0 mg/kg or 2.0 mg/kg SC weekly) using static randomization tables.

Patients were assigned an ID number at screening. If the patient was determined to be a candidate for therapy at screening, he/she was randomized centrally as described. The patient was considered to be enrolled at the time he/she was randomized.

4.4.3.2 Blinding

During both the FT and ET periods, subjects, investigators, and the Sponsor were blinded to subject assignment to placebo or active study drug. Dose level and dose frequency were not blinded during the FT and ET periods.

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 after FT Day 0 until FU Day 84.

4.4.3.3 Open Label Extension study

No open label extension study existed.

4.4.3.4 Study Drug(s)

Actively treated subjects received either XOMA-manufactured efalizumab or Genentech-manufactured efalizumab. Each subject received only one product throughout the study. There was a matching placebo for each product (manufactured by XOMA or Genentech).

FT: Each subject received an initial conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 1.0 mg/kg or 2.0 mg/kg study drug.

ET: On ET Day 0, all subjects received a conditioning dose of 0.7 mg/kg study drug. Subjects assigned to receive 2.0 mg/kg weekly or every other week received 2.0 mg/kg on ET Day 7. Subjects assigned to receive 4.0 mg/kg weekly, received a second conditioning dose of 2.0 mg/kg on ET Day 7 and their first full dose of 4.0 mg/kg on ET Day 14.

4.4.3.5 Withholding Treatment

Subjects were discontinued from efalizumab treatment if they met any of the following criteria: diagnosis of any cancer, lymphoma, or leukemia; 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 excluded systemic or topical therapy.

If a subject had an atypical severe relapse or emergence of a new psoriatic morphology, 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 study drug treatment and enter the FU period.

4.4.3.6 Concomitant Medications

The only topical psoriasis treatments that could be used during the screening, FT, ET, and FU periods 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, groin, or axillae, if required.

Itching could be treated with oral, not topical, hydroxyzine hydrochloride or diphenhydramine hydrochloride during the study. However, these medications and other antihistamines were not to be used within 24 hours prior to a clinic visit with a scheduled PASI evaluation.

If a subject relapsed during the ET period (lost of $\geq 50\%$ of the improvement in the PASI score achieved between FT Day 0 and FT Day 84), he/she could receive topical psoriasis therapies or UVB phototherapy.

If a subject relapsed during the FU period (lost $\geq 50\%$ of the improvement in the PASI score achieved between FT Day 0 and ET Day 84), he/she could receive topical psoriasis therapies, UVB phototherapy, or systemic psoriasis therapies (e.g., PUVA, cyclosporine, corticosteroids, methotrexate, oral retinoids).

4.4.3.7 Disallowed treatments

Disallowed treatments were similar to those described in Study ACD2058g (See page19).

4.4.3.8 Eligibility

The eligibility criteria of Protocol ACD2059g were similar to those of Protocol ACD2058g. (Progressive hearing loss was no longer an exclusion criterion in ACD 2059g as it was in ACD2058g.)

Efficacy Outcomes

The primary efficacy outcome measure for this study was the proportion of subjects with a $\geq 75\%$ improvement in PASI score between FT Day 0 and FT Day 84.

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

Clinical and Laboratory Assessments

Assessments of Efficacy

The following were measured: PASI, OLS, psoriatic BSA, target lesion assessment, PGA, DLQI, Itching scale. Patient photography was performed.

4.4.3.9 Safety Assessments

The following were performed: physical examinations (including vital signs and body weight); monitoring for adverse events; blood chemistry, hematology (CBC, platelet, differential); urinalysis; antibodies to efalizumab and urine pregnancy test (females of childbearing potential), RPR at baseline. PPD and/or chest X-ray were done at screening for high risk subjects only. MHA-TP test was monitored in patients RPR+ at baseline.

4.4.3.10 Protocol Amendments

The protocol was amended on 14 March 2001, to allow for the use of topical psoriasis therapies and/or UVB phototherapy for subjects who relapsed during the ET period the use of topical therapies, UVB phototherapy and systemic therapies if a patient relapsed during the ET period.

4.4.4 Study Results

4.4.4.1 Patient Disposition

The study ACD2059g included 51 study centers in the United States and Canada. A total of 597 patients were randomized and treated. The following table shows the subject disposition (Table 29).

Table 29 Subject Disposition and Reasons for Discontinuation during the FT Period

Subject Status	FT Placebo (n=122)	FT Efalizumab	
		1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
Completed FT	111 (91.0%)	211 (90.9%)	227 (93.4%)
Entered ET	110 (90.2%)	210 (90.5%)	224 (92.2%)
Entered FU	0	1 (0.5%)	3 (1.3%)
Discontinued from study	1 (0.9%)	0	0
Discontinued from FT	11 (9.0%)	21 (9.1%)	16 (6.6%)
Entered FU	5	12	9
Discontinued from study	6	9	7
Reason for discontinuation from FT			
Subject's decision	4	8	5
Adverse event	1	7	6
Use of excluded medication	2	2	3
Lost to follow-up	2	2	2
Investigator's decision	2	2	0

A total of 597 subjects were enrolled and randomized, 122 in the placebo group, 232 in the 1.0 mg/kg/wk group and 243 in the 2.0 mg/kg/wk group. A total of 40 subjects (8.0 %) discontinued treatment during the first treatment period. The proportions of patients completing the first treatment course were comparable across treatment groups. The proportion of patients who discontinued the FT for an adverse event was higher in the active treatment arms than in placebo.

Demographics and baseline disease characteristics in this study were similar to those in Study ACD2058g and are shown in Table 30 and in Table 31 below.

Table 30 Demographic and Baseline Characteristics of Randomized Subjects in the FT Period

Characteristic	FT Placebo (n=122)	FT Efalizumab	
		1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
Sex, n			
Male	79 (64.8%)	151 (65.1%)	157 (64.6%)
Female	43 (35.2%)	81 (34.9%)	86 (35.4%)
Race/ethnicity, n			
White	106 (86.9%)	197 (84.9%)	204 (84.0%)
Hispanic	7 (5.7%)	16 (6.9%)	22 (9.1%)
Other ^a	9 (7.4%)	19 (8.2%)	17 (7.0%)
Age group (yr), n			
18–40	45 (36.9%)	75 (32.3%)	99 (40.7%)
41–64	68 (55.7%)	138 (59.5%)	123 (50.6%)
≥65	9 (7.4%)	19 (8.2%)	21 (8.6%)
Age (yr)			
Mean	45.4	46.3	44.9
Range	18–72	18–74	18–74
Weight (kg)			
Mean	93.0	91.6	93.3
Range	54–140	55–140	43–143
BMI (kg/m ²)			
Mean	31.25	31.44	31.50
Range	18.7–52.3	17.9–55.2	18.7–51.1

^a Pacific Islander, Black, American Indian or Alaskan Native, or Other.

Males constituted 65% of patients and Caucasians 85%. The median age was 46 with 8% of patients over age 65. Overall the treatment groups were comparable with regard to demographic characteristics. The study population's demographic characteristics are reflective of the general population of patients with psoriasis, with the exception that more male than female patients were enrolled. In general psoriatic population, the sex ratio is one to one, male to female. Of note, the population is heavier than the average US population and this probably reflects the psoriasis population as a whole.

The range of ages shows that some patients were enrolled who were older than the entry criteria allowed. In addition, some patients exceeded the protocol specified weight limit of 140 kg.

Table 31 Baseline Psoriasis Characteristics of Subjects in the FT Period

Characteristic	FT Efalizumab		
	FT Placebo (n=122)	1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
Duration of psoriasis (yr)			
Mean (SD)	19.6 (12.3)	19.3 (12.3)	18.2 (11.6)
Range	0–62	1–60	1–70
Prior systemic therapy, n			
Yes	86 (70.5%)	160 (69.0%)	152 (62.6%)
No	36 (29.5%)	72 (31.0%)	91 (37.4%)
PASI category, n			
≤16.0	52 (42.6%)	95 (40.9%)	100 (41.2%)
16.1–30.0	54 (44.3%)	107 (46.1%)	120 (49.4%)
>30.0	16 (13.1%)	30 (12.9%)	23 (9.5%)
PASI score			
Mean (SD)	20.43 (8.72)	19.98 (8.25)	19.83 (8.28)
Range	11.7–49.6	11.7–53.4	5.6–53.4
OLS, n			
Minimal	0	4 (1.7%)	0
Mild	5 (4.1%)	12 (5.2%)	23 (9.5%)
Moderate	59 (48.4%)	128 (55.2%)	127 (52.3%)
Severe	52 (42.6%)	76 (32.8%)	81 (33.3%)
Very severe	6 (4.9%)	12 (5.2%)	12 (4.9%)
Percent BSA of psoriasis			
Mean (SD)	31.11 (18.87)	31.97 (18.12)	30.44 (17.75)
Range	10.0–90.0	10.0–98.0	7.0–94.0
Patient's Assessment of Itch			
Mean (SD)	3.1 (1.5)	3.0 (1.4)	3.1 (1.4)
Range	0–5	0–5	0–5

The overall baseline disease severity was moderate to severe plaque psoriasis with a large percentage of subjects (66.7%) having a history of prior systemic therapy. The mean duration of psoriasis was 19 years. The mean PASI score upon entry was 20 and ranged from 5.6 to 53.

The proportion of placebo patients classified as moderate or higher by the OLS score was 95.9% vs. 91.8% of the combined active treatment arm. Overall baseline disease severity was comparable between treatment groups.

STUDY CONDUCT

4.4.4.2 Adequacy of the blind

No instances were identified with regard to inadequate maintenance of the study blind.

Protocol Deviations

A total of 33 subjects were treated with excluded medications for psoriasis during the FT period. These consisted of 4 subjects in the placebo arm (3.3%), 19 subjects in the 1.0 mg/kg/wk efalizumab arm (8.2%), and 10 subjects in the 2.0 mg/kg group (4.1%). The most frequently used excluded treatments were desonide followed by fluocinolone acetone, prednisone, and triamcinolone. No subjects used phototherapy.

Table 32 Protocol Deviations during the FT Period

Protocol Deviation	FT Placebo (n=122)	FT Efalizumab	
		1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
Total ^a	34 (27.9%)	71 (30.6%)	58 (23.9%)
Missing laboratory data	20 (16.4%)	37 (15.9%)	29 (11.9%)
PASI performed outside of the FT Day 84 window ^b			
<82 Days	10 (8.2%)	17 (7.3%)	22 (9.1%)
>86 Days	2 (1.6%)	6 (2.6%)	2 (0.8%)
OLS performed outside of the FT Day 84 window ^b			
<82 Days	8 (6.6%)	11 (4.7%)	20 (8.2%)
>86 Days	10 (8.2%)	17 (7.3%)	22 (9.1%)
Use of excluded medication	2 (1.6%) ^{c, d}	19 (8.2%)	10 (4.1%)
Incorrect dosing level	4 (3.3%)	0	1 (0.4%) ^e
Incorrect study drug	2 (1.6%) ^f	0	1 (0.4%) ^g

^a Represents the number of subjects with at least one protocol deviation.

^b For subjects who completed the FT period only.

^c Subject 66801 was assigned to 2.0 mg/kg/wk placebo and received 1.0 mg/kg/wk placebo throughout the FT period.

^d Subject 77604 was assigned to 1.0 mg/kg/wk placebo and received 2.0 mg/kg placebo on FT Days 7 and 14.

^e Subject 66809 was assigned to the 2.0 mg/kg/wk efalizumab group and received 1.0 mg/kg/wk efalizumab throughout the FT period.

^f Subject 70410 received 2.0 mg/kg efalizumab on FT Day 70, and Subject 68843 received 2.0 mg/kg efalizumab on FT Day 77.

^g Subject 73207 received placebo on FT Day 21.

Comparable numbers of patients were noted to have protocol deviations in each treatment group, 24-30% of patients depending on the treatment group. The most common protocol violation noted was missing baseline laboratory data. These protocol deviations were in general minor and were judged to have not affected the outcome of the clinical study.

4.4.4.3 Primary Efficacy Outcomes

Response to first treatment course are shown in Table 33 below.

Table 33 PASI Response to Treatment for Randomized Subjects during the FT Period

PASI Response at FT Day 84	FT Placebo (n=122)	FT Efalizumab	
		1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
Responders	6 (4.9%)	52 (22.4%)	69 (28.4%)
Partial responders and non-responders ^a	116 (95.1%)	180 (77.6%)	174 (71.6%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001	<0.001

^a Included subjects who discontinued.

The proportion of responders was higher in each of the treatment groups than in placebo. The absolute differences were 17.5% for the 1.0 mg/kg/wk group and 23.5% in the 2.0 mg/kg/wk group. These results were statistically significant. In study ACD2058g, the 2mg/kg/wk group had a numerically lower response rate than the 1.0 mg/kg/wk group. In this study the response rate was numerically higher in the 2 mg/kg/wk group. However, there is no evidence that the 2 mg/kg/wk dose is superior to the 1 mg/kg/wk dose.

The following table shows the mean improvement in the components of the PASI score during the first treatment period (Table 34).

Table 34 Mean Percent Improvement in PASI Thickness, Erythema, and Scaling Components during the FT Period

PASI Component at FT Day 84	FT Placebo (n=122)	FT Efalizumab	
		1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
Thickness ^a	13.6	47.2	48.7
Erythema ^a	13.8	44.5	46.0
Scaling ^a	13.1	49.6	51.5
PASI total ^b	(n=111) 17	(n=213) 51	(n=227) 51.7

Note: Improvement in each component was reflected by a decrease in score.

^a The last observation carried forward was used to impute missing Day 84 PASI data.

^b Values from the early termination visits were assigned to the next scheduled visit for PASI evaluation.

All of the components of the PASI -thickness, erythema and scaling- showed improvement. Therefore, all of the components appear to contribute similarly to improvement in the overall score.

Mean changes in percentage of body surface area during the first treatment period are shown below (Table 35).

Table 35 Mean Improvement in Percent BSA of Psoriasis during the FT Period

Percent BSA	FT Efalizumab		
	FT Placebo (n=122)	1.0 mg/kg (n=232)	2.0 mg/kg (n=243)
FT Day 0	31.1	32.0	30.4
FT Day 84 ^a	30.8	22.1	19.1
Improvement ^b	0.3	9.9	11.3
Two-sample t-test p-value ^c efalizumab vs. placebo	—	<0.001	<0.001

^a The last observation carried forward was used to impute missing Day 84 PASI data.

^b Improvement was reflected by a decrease in the percent BSA score.

^c Using the pooled error term from an ANOVA of all three treatment groups.

The percent improvement in the percentage body surface area affected was greater in both of the efalizumab-treated groups compared to placebo and was approximately 9% higher in the 1.0 mg/kg dose group at than placebo at the end of the first treatment period.

Reviewer's comment: The percentage change in BSA is smaller than the percentage improvements in the cardinal manifestations of psoriasis-erythema, scale and elevation.

The table below shows the distribution of improvement by treatment group during the first treatment period (Table 36).

Table 36 PASI Response by Percent Improvement from Baseline for Subjects in the FT Period

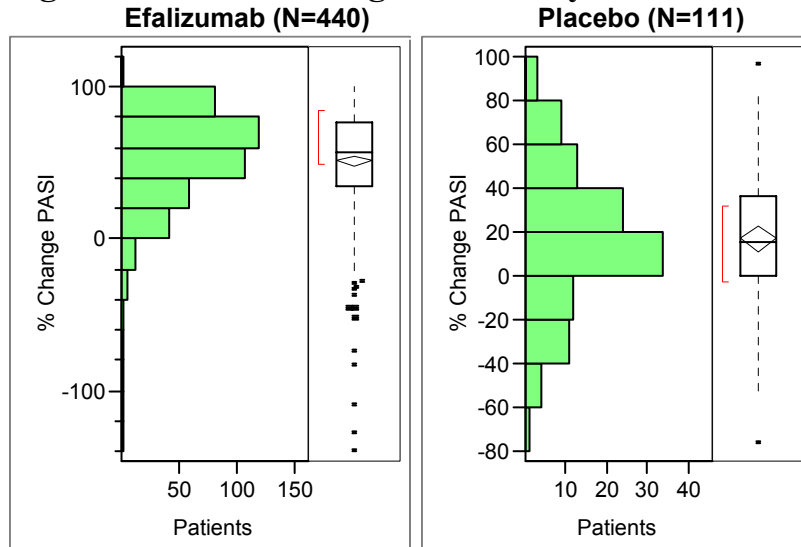
Percent Improvement from Baseline	FT Efalizumab		
	FT Placebo (n=122)	1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
≥90%	1 (0.8%)	10 (4.3%)	15 (6.2%)
≥75% to <90%	5 (4.1%)	42 (18.1%)	54 (22.2%)
≥50% to <75%	13 (10.7%)	68 (29.3%)	69 (28.4%)
≥25% to <50%	21 (17.2%)	51 (22.0%)	48 (19.8%)
<25%	71 (58.2%)	42 (18.1%)	41 (16.9%)
Missing ^a	11 (9.0%)	19 (8.2%)	16 (6.6%)

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

The groups which received active treatment showed a general shift towards improvement in PASI response from baseline. The treatment effect by the PASI 50 criterion (efalizumab-placebo) was 36% for the 1.0 mg/kg/wk dose.

Figure 5 below depicts the distribution of the response to treatment by percent change in PASI. A positive change is improvement and a negative change indicates deterioration. The two efalizumab treatment groups (1 and 2 mg) were combined for this analysis.

Figure 5 Percent Change in PASI by Treatment Group



Percent Change in PASI by Treatment Group

	Efalizumab	Placebo
maximum	100.0	96.97
quartile	76.3	36.70
median	56.9	15.36
quartile	34.6	-0.25
minimum	-139.0	-76.04

Of note, a few patients worsened by over 100% within the active treatment group.

Table 37 PASI Responders by Subsets of Randomized Subjects during the FT Period

Subject Subset	FT Placebo (n=122)	FT Efalizumab	
		1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
Sex			
Female, n	43	81	86
Responders, n	3 (7.0%)	19 (23.5%)	30 (34.9%)
95% CI	0.015, 0.191	0.148, 0.342	0.249, 0.459
Male, n	79	151	157
Responders, n	3 (3.8%)	33 (21.9%)	39 (24.8%)
95% CI	0.008, 0.107	0.155, 0.293	0.183, 0.324
Age group (yr)			
18–40, n	45	75	99
Responders, n	0	12 (16.0%)	25 (25.3%)
95% CI	0.000, 0.079	0.086, 0.263	0.171, 0.350
41–64, n	68	138	123
Responders, n	3 (4.4%)	36 (26.1%)	36 (29.3%)
95% CI	0.009, 0.124	0.190, 0.342	0.214, 0.381
≥65, n	9	19	21
Responders, n	3 (33.3%)	4 (21.1%)	8 (38.1%)
95% CI	0.075, 0.701	0.061, 0.456	0.181, 0.616
Baseline PASI score			
≤16.0, n	52	95	100
Responders, n	2 (3.8%)	20 (21.1%)	25 (25.0%)
95% CI	0.005, 0.132	0.134, 0.306	0.169, 0.347
16.1–30.0, n	54	107	120
Responders, n	3 (5.6%)	24 (22.4%)	35 (29.2%)
95% CI	0.012, 0.154	0.149, 0.315	0.212, 0.382
>30.0, n	16	30	23
Responders, n	1 (6.3%)	8 (26.7%)	9 (39.1%)
95% CI	0.002, 0.302	0.123, 0.459	0.197, 0.615
Prior systemic therapy			
Yes, n	86	160	152
Responders, n	4 (4.7%)	37 (23.1%)	47 (30.9%)
95% CI	0.013, 0.115	0.168, 0.304	0.237, 0.389
No, n	36	72	91
Responders, n	2 (5.6%)	15 (20.8%)	22 (24.2%)
95% CI	0.007, 0.187	0.122, 0.320	0.158, 0.343

The results for the primary endpoint in subsets defined by gender, age group, baseline PASI score and history of prior systemic therapy are consistent with the results of the ITT population as a whole. Treatment effect was seen in each of the subgroups analyzed.

The median time to onset of PASI 75 response is shown below (Table 38).

Table 38 Time (days) to PASI-75 Response, Using Kaplan Meier Estimates Study ACD2059g (FT Period)

Characteristic	Placebo	Efalizumab 1.0 mg/kg/wk	Efalizumab 2.0 mg/kg/wk
Subjects Who Achieved PASI-75 at Any Time	8	66	77
Median	63.0	57.5	58.0
95% C.I. for Median	(42.0, 71.0)	(57.0, 70.0)	(57.0, 71.0)
25-75 %ile	42.5 - 70.5	45.0 - 72.0	57.0 - 77.0
Minimum - Maximum	30.0 - 72.0	13.0 - 109.0	29.0 - 92.0

As in study ACD2058g, the median time to onset of PASI 75 in patients who responded at any time was approximately 2 months.

4.4.4.4 First Treatment Course: Secondary Outcomes

The principal secondary endpoint, the static physician's global assessment is shown below (Table 39).

Table 39 Principal Secondary Efficacy Endpoint for the FT Period

	FT Efalizumab		
	FT Placebo (n=122)	1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
OLS Response at FT Day 84			
Minimal or Clear	4 (3.3%)	45 (19.4%)	55 (22.6%)
Mild to Very Severe ^a	118 (96.7%)	187 (80.6%)	188 (77.4%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001	<0.001

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

Using the physician's static global assessment, the proportions of responders, those achieving minimal or clear on the OLS scale was higher in each of the active treatment arms than placebo. The absolute difference was 16.1% in the 1.0 mg/kg/wk group and 19.3 in the 2.0 mg/kg/wk group. Therefore, the principal secondary outcome supports the primary efficacy outcome. Of note, the percentages of responders by the OLS are comparable to those by the PASI 75 criteria.

An additional secondary efficacy outcome was the proportion of patients achieving excellent or cleared on the PGA, the physician's dynamic scale (See Table 40).

Table 40 PGA Response of Subjects during the FT Period

PGA Response at FT Day 84	FT Placebo (n=122)	FT Efalizumab	
		1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
Excellent or Cleared	5 (4.1%)	52 (22.4%)	69 (28.4%)
Good to Worse ^a	117 (95.9%)	180 (77.6%)	174 (71.6%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001	<0.001

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

The proportions of responders, those achieving excellent or cleared on the PGA scale was higher in each of the active treatment arms than placebo. The absolute differences were 18% for the 1 mg/kg/wk group and 24% for the 2.0 mg/kg/wk group. Therefore, the response by physician's dynamic scale also supports the primary analysis.

4.4.4.5 Response to Second Treatment Course

The outcome of patients who responded to the first treatment period to a subsequent contiguous treatment period was evaluated. Comparisons of the proportion of subjects who experienced relapse of psoriasis in the withdrawal/placebo group versus the 2.0 mg/kg/qow efalizumab group and the 2.0 mg/kg/wk efalizumab group is shown in Table 41 below.

Table 41 Proportion of ET-AR Subjects Experiencing Psoriasis Relapse

Response	ET-AR Withdrawal/ Placebo (n=40)	ET-AR Efalizumab	
		2.0 mg/kg/qow (n=40)	2.0 mg/kg/wk (n=39)
Subjects who relapsed ^a	27 (67.5%)	3 (7.5%)	3 (7.7%)
Subjects who did not relapse	13 (32.5%)	37 (92.5%)	36 (92.3%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001	<0.001

Note: Relapse during the FU period was defined as the loss of $\geq 50\%$ of the improvement in the PASI score achieved between FT Day 0 and ET Day 84.

^a Included subjects who discontinued early during the ET period.

Of the patients who remained on active treatment, 92% did not relapse; whereas, the majority of patients who received placebo for the second 12 weeks of therapy, 67%, experienced loss of 50% of the improvement that they achieved in the first treatment period of efalizumab therapy.

The proportion of patients who maintained a $\geq 75\%$ improvement in PASI at the end of the extended treatment period is shown in Table 42 below.

Table 42 Proportion of ET-AR Subjects Who Maintained PASI Response at ET Day 84

Response	ET-AR Withdrawal/ Placebo (n=40)	ET-AR Efalizumab	
		2.0 mg/kg/qow (n=40)	2.0 mg/kg/wk (n=39)
Responders	8 (20.0%)	31 (77.5%)	30 (76.9%)
Partial responders and non-responders ^a	32 (80.0%)	9 (22.5%)	9 (23.1%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001	<0.001

^a Included subjects who discontinued early during the ET period.

Approximately 77% of responders to the first treatment period maintained at least a PASI 75 level of improvement during the second 12 weeks of continuous blinded therapy; whereas, 20% of patients who received placebo during this period maintained responder status. Of the subjects in the 2.0 mg/kg/qow and 2.0 mg/kg/wk efalizumab groups, 95.0% and 89.8%, respectively, maintained a $\geq 50\%$ improvement in PASI at ET Day 84 compared with FT Day 0, whereas 40% of subjects in the withdrawal/placebo group maintained this level of response (data not shown). Therefore, the ability of efalizumab to maintain treatment response in responders is better than its ability to recapture response in patients in a state of active relapse (See Study ACD2058g, Response to Second Treatment Course in Patients who Responded to the First Treatment, p. 34).

Reviewer's comments

It is noteworthy that following discontinuation of efalizumab, treatment response is maintained for ≥ 3 months in some patients (20%). Moreover, a small proportion of patients (7%) experiences relapse of psoriasis (loss of 50% of response) despite continued efalizumab therapy.

4.4.4.6 Response to an additional 12-week treatment course in patients who were non-responders during the first treatment course

The response status by treatment group during extended treatment with either efalizumab or placebo in the group of patients who were non-responders to active drug in the first treatment period is shown below.

Table 43 Proportion of ET-AN Subjects Who Achieved PASI Response at ET Day 84

Response	ET-AN Withdrawal/Placebo (n=59)	ET-AN Efalizumab 4.0 mg/kg/wk (n=118)
Responders	1 (1.7%)	15 (12.7%)
Partial responders and non-responders ^a	58 (98.3%)	103 (87.3%)
Fisher's exact p-value efalizumab vs. placebo	—	0.023

^a Included subjects who were missing ET Day 84 evaluations.

These results show that treatment with a second contiguous 12 week period of therapy can result in 11% of patients achieving response status at the end of the extended treatment period. This result is consistent with the finding in study ACD2058g. Of note, the dose used in the extended treatment group is higher than the one for which the sponsor is seeking approval.

4.4.4.7 Duration of Response

The median time to relapse for the withdrawal/placebo group was 64 days after the last dose for subjects who received 1.0 mg/kg/wk during the first treatment period. These results are consistent with those obtained in Study ACD2058g (see page 32).

4.4.4.8 Quality of Life

DLQI was designated as an exploratory outcome measure in Study ACD2059g. Results of change in DLQI during the first treatment period are shown below.

**Table 44 DLQI, Mean Improvement from Baseline(FT Period):
Randomized Subjects**

		Placebo (N=122)	Efalizumab 1.0 mg/kg/wk (N=232)	Efalizumab 2.0 mg/kg/wk (N=243)
Baseline	N	120	228	238
	Mean	12.2	11.9	12.4
	Median	10.0	11.0	11.0
	25-75 %ile	7.0 - 17.0	7.0 - 16.0	7.0 - 17.0
	Range	1 - 30	0 -30	0 -30
Improvement from Baseline	N	120	228	238
	Mean	1.7	5.5	6.0
	Median	1.0	5.0	5.0
	25-75 %ile	-1.0 -4.0	2.0 -9.0	1.0 - 10.0
	Range	-13 -19	-12 -24	-15 -30

Pairwise p values for improvement from baseline are ≤ 0.001 for both efalizumab dose levels vs. placebo.

Efalizumab-treated patients demonstrated a mean change in DLQI of 5.5 and 6.0 in the 1.0 mg/kg/wk and 2.0 mg/kg/wk treatment groups vs. 1.7 in the placebo-treated patients. These changes represented a significant difference in favor of the efalizumab-treated patients vs. placebo and are consistent with the results seen in Study ACD2390g (see page 77).

Reviewer's comment

The DLQI self-assessment questionnaire attempts to determine how much a skin condition affects a patient's quality of life. A response of "not at all" for all 10 questions yields a score of 0, and a response of "a little" yields a score of 10. The median score across the study arms was 11 at baseline. The clinical significance of the shift in score from 11 to approximately 6 is not clear.

4.4.5 Summary of Efficacy: Study ACD2059g

- Study ACD 2059g confirmed the efficacy of efalizumab in plaque psoriasis. In the 1.0 mg/kg/wk treatment group, the proportion of patients achieving a PASI 75 was 18% higher than that of the placebo group.
- The numbers of responders in the 2.0mg/kg/wk group tended to be higher than that of the 1.0 mg/kg/wk, although the differences were not statistically significant. In both treatment groups the numbers of responders were statistically higher than placebo. Considering the results of Study ACD2058g and Study ACD2059g together, there is no evidence that the 2 mg/kg/wk dose is superior to the 1 mg/kg/wk dose.
- The secondary efficacy outcomes also showed evidence of treatment response (absolute increase in proportion of responders) including the physician's static

- global assessment of “minimal or clear” (16%), PASI 50 (36%), physician’s dynamic global assessment of “excellent or cleared” (18%).
- A small proportion of patients experienced worsening of psoriasis during efalizumab treatment (see also safety assessment).
 - In patients treated with 1mg/kg efalizumab the duration of response off-treatment (64 days) and time to onset of response (58 days) were similar to those observed in study ACD2058 g.
 - Continuous treatment with efalizumab beyond the initial twelve-week treatment period maintained clinical response in 77% of patients; whereas, among patients who responded to the first treatment period with efalizumab and who received placebo during the extended treatment period a substantially lower proportion, 20%, maintained their treatment response.
 - Treatment with a second contiguous 12- week period of therapy can result in additional patients achieving response status, e.g. 11% in this study. This result is consistent with the findings in study ACD2058g

4.5 Protocol ACD2390g

4.5.1 Study Title

“A Phase IIIb, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of 1.0 mg/kg Subcutaneously Administered Efalizumab in Adults with Moderate to Severe Plaque Psoriasis”

4.5.2 Study Objectives

To evaluate the efficacy of a 12-week course of 1.0 mg/kg/wk subcutaneous (SC) efalizumab relative to placebo as measured by the proportion of subjects achieving a \geq 75% improvement in Psoriasis Area and Severity Index (PASI) on Day 84 relative to Day 0.

To evaluate the safety and tolerability of a 12-week course of 1.0 mg/kg/wk SC efalizumab relative to placebo.

Reviewer’s comment

The main objective of Study ACD2390g was to show the safety and efficacy of Genentech-manufactured efalizumab. Previous studies had shown that the 2 mg/kg/wk dose was not superior to the 1 mg/kg/wk dose. Given the potential for dose-dependent toxicity of efalizumab, the study only evaluated the 1 mg/kg dose.

4.5.3 Study Design

This was a Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study (approximately 30 sites) designed to evaluate the efficacy and safety of efalizumab administered at weekly SC doses of 1.0 mg/kg in subjects with moderate to severe plaque psoriasis who were candidates for systemic therapy.

4.5.3.1 Randomization

Subjects were randomized (centrally) in a 2:1 ratio to receive either 12 weeks of 1.0 mg/kg/wk SC efalizumab or placebo.

Randomization was stratified by the Day 0 PASI score (≤ 16.0 , ≥ 16.1), by prior treatment for psoriasis (naive to systemic treatment vs. prior systemic treatment), and by study center. A random permuted block design was used to obtain approximately a 2:1 ratio within categories defined by the stratification variables.

4.5.3.2 Blinding

Efalizumab produces an elevation of lymphocyte counts and total WBC counts in most subjects that could result in unblinding. Therefore, from Day 0 to Day 84 only absolute neutrophil and eosinophil counts from the leukocyte portion of the complete blood count (CBC) were made available to investigators and monitors. An independent assessor monitored the entire leukocyte panel and notified the investigator and Medical Monitor of any findings relevant to subject safety.

The pharmacokinetic, pharmacodynamic, and HAHA test results also had the potential to unblind investigators and monitors. These data were available only to laboratory staff until all subjects had completed the study through Day 84. These data were not shared with investigators or clinical monitors until after the completion of Study ACD2390g and until the data were cleaned and frozen.

4.5.3.3 Study Drug

Each subject received an initial conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 1.0 mg/kg study drug (efalizumab or placebo equivalent). Study drug was administered by SC injection by a trained member of the research team. Subjects randomized to the efalizumab group received the to-be-marketed formulation of efalizumab.

4.5.3.4 Open Label Extension Study

Study ACD2391g served as the open-label extension study for Study ACD2390g. This study allowed evaluation of response after an extended treatment with efalizumab for up to 24 weeks. The incidence of psoriasis relapse in patients receiving a tapering regimen of efalizumab was also analyzed.

Reviewer's comment: The results of Study ACD2391g were not available at the time of the original BLA submission.

4.5.3.5 Criteria for Discontinuation of Treatment

Subjects were discontinued from efalizumab treatment if they met any of the following criteria: pregnancy, any medical condition that the investigator determined could jeopardize the subject's safety if he or she were to continue in the study, or diagnosis of

severe or serious arthritis with evidence of joint inflammation upon examination for any subject without a history of arthritis.

Other reasons for discontinuation included initiation of any excluded topical or systemic treatment for psoriasis or excluded medication or vaccine. Subjects who required concomitant treatment with systemic psoriasis therapies had to discontinue from study drug immediately. For subjects who withdrew early, the Day 84 assessments were to be completed and the subject entered Study ACD2391g for follow-up.

4.5.3.6 Concomitant treatments

The only concomitant psoriasis treatments that could be used during the entire study (screening and treatment period) were Eucerin cream and tar or salicylic acid preparations (for scalp psoriasis only). Potency Group VI or VII topical corticosteroids could be used in small amounts on psoriatic lesions on the face, hands, feet, groin, or axillae, if required.

4.5.3.7 Disallowed treatments

The following were not allowed:

Systemic treatments for psoriasis (e.g., PUVA, cyclosporine, corticosteroids, methotrexate, oral retinoids) 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, with the exceptions noted previously. Tanning booths or nonprescription UV light sources were not to be used .

Use of live virus vaccines or live bacteria vaccines was prohibited.

4.5.3.8 Eligibility

Patients were required to have plaque psoriasis, diagnosed for at least 6 month, over at least 10% BSA and a PASI of at least 12 at screening. The eligibility criteria were similar to Study ACD 2058g.

4.5.3.9 Efficacy Outcomes

Primary Efficacy Endpoint

The proportion of patients with $\geq 75\%$ improvement in PASI score at the end of the treatment period (Day 84) was the primary efficacy endpoint.

Principal Secondary Efficacy Endpoint

The proportion of subjects who achieved an OLS rating of “Minimal or Clear” at Day 84 was compared between treatment groups.

4.5.3.10 Other Secondary Efficacy Outcome Measures

Secondary efficacy outcome measures in support of the primary efficacy outcome measure are in order of importance:

- Proportion of subjects with a $\geq 50\%$ improvement in PASI score at Day 84 relative to Day 0
- Mean percentage improvement from baseline (Day 0) in PASI over time
- Mean improvement from baseline (Day 0) in the DLQI at Day 84
- Mean improvement from baseline (Day 0) in the Itching Scale at Day 84
- Mean improvement from baseline (Day 0) in the PSA at Day 84
- Proportion of subjects attaining a PGA rating of Excellent or Cleared at Day 84
- Mean improvement from baseline (Day 0) in the thickness component of the PASI at Day 84
- Mean improvement from baseline (Day 0) in the percentage of body surface area (BSA) affected by psoriasis at Day 84

4.5.3.11 Clinical and Laboratory Assessments

At baseline, physical examinations (including vital signs and body weight) were performed. Concomitant medications and adverse events were monitored weekly during the treatment period. Vital signs were monitored pre-dose on days 0, 28, 56 and 84. Hematology, chemistries and urinalysis were monitored on days 0, 56 and 84. Serum antibody and serum PK were assessed and blood for PD (including lymphocyte subsets and CD11a expression) was collected at selected treatment sites. In females of childbearing potential, urine pregnancy testing was performed.

The following psoriasis assessments were done monthly: PASI, OLS, psoriatic BSA, PGA, DLQI, Itching scale. Patient photography was performed.

4.5.3.12 Planned Statistical Analyses

Sample size considerations

The sample size for this study was based primarily on safety considerations. The planned accrual was up to 333 subjects in the active treatment group (1.0 mg/kg efalizumab) and up to 167 subjects in the placebo group for a total of up to 500 subjects. The probability of observing one or more instances of an adverse event with a background rate of 1% or 2% over the period of observation in a treatment group containing 333 subjects was 0.965 and 0.999, respectively.

Missing Data

For the all study endpoints, if a subject discontinued from the study prior to Day 84 but after receiving the final scheduled dose of study drug on Day 77, data from the early termination visit were used for analysis in place of Day 84.

For the primary and principal secondary efficacy endpoints (PASI 75, OLS, and PASI 50) subjects with a missing data at Day 84 were classified as non-responders for analysis of this endpoint (worst outcome imputation).

Baseline Data

Data were summarized for each treatment group. Subjects were stratified by baseline PASI, history of prior systemic therapy and center.

Efficacy Analyses

All statistical tests were two sided and were performed at the 5% level of significance.

Primary Endpoint

Response status at the end of the study was determined as follows:

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

The treatment effect was defined as the difference in the proportion of responders between the active group (1.0 mg/kg SC efalizumab) and the placebo group. The primary endpoint was evaluated by comparing the proportion of responders between the active group and the placebo group using Fisher's exact test for the ITT population; the exact 95% confidence interval (CI) for response rate within each treatment group and the difference in response rate between the active and placebo group were calculated. Partial responders and non-responders were combined for the primary analysis.

4.5.4 Study Results

4.5.4.1 Disposition, Demographics and Baseline Disease Characteristics

The first subject was enrolled into the study on 25 January 2002, and the last subject completed the study on 30 July 2002. Thirty investigators in United States and Canada enrolled a total of 556 patients into this study.

Table 45 Subject Disposition and Reasons for Discontinuation

Subject Status	Placebo (n=187)	Efalizumab (n=369)
Completed treatment	175 (93.6%)	345 (93.5%)
Entered Study ACD2391g ET	174	342
Entered Study ACD2391g FU	1	2
Discontinued study	0	1
Discontinued treatment	12 (6.4%)	24 (6.5%)
Entered Study ACD2391g FU	3	11
Discontinued study	9	13
Reason for discontinuation		
Subject's decision	3	7
Adverse event	2	7
Lost to follow-up	5	4
Use of excluded medication	0	5
Investigator's decision	2	1

ET=Extended Treatment period.

FU=Follow-Up period.

A total of 556 subjects were randomized, 187 in the placebo group and 369 in the 1.0 mg/kg/wk group. One subject (33602) who was randomized into the efalizumab group never received any drug. Data from this subject were included in the efficacy analysis, but excluded from the safety analysis. The proportion of patients who discontinued due to use of an excluded medication was higher in the efalizumab group than placebo.

Demographics: Populations Enrolled and Analyzed

Demographic characteristics were balanced among the treatment groups

Table 46 Demographic and Baseline Characteristics of Randomized Subjects

Characteristic		Placebo (n=187)	Efalizumab (n=369)
Sex, n	Male	132 (71%)	251 (68%)
	Female	55 (29%)	118 (32%)
Race/ethnicity, n	White	167 (89%)	331 (89.7%)
	Hispanic	7 (4%)	17 (4.6%)
	Other ^a	13 (7%)	21 (5.7%)
Age group (yr), n	18–40	68 (36%)	140 (38%)
	41–64	106 (57%)	206 (56%)
	≥ 65	13 (7%)	23 (6%)
Age (yr)	Mean	45	45
	Range	20–75	18–75
Weight (kg)	Mean	94	94
	Range	50–143	45–160
Height (cm) ^b	Mean	173	173
	Range	147–196	123–198
BMI (kg/m ²) ^b	Mean	32	31
	Range	30–48	19–56

^aThe “Other” group included individuals who described their race/ethnicity as Asian or Pacific Islander, Black, American Indian or Alaskan Native, or Other.

^bData available for 551 subjects: 185 in the placebo group and 366 in the efalizumab group.

Overall, the treatment groups were comparable with regard to demographic characteristics. The study population’s demographic characteristics are reflective of the general population of patients with psoriasis, with the exception that more male than female patients were enrolled. Psoriasis is estimated to affect males and females in a one to one ratio. Of note, the population is heavier than the average US population.

Randomization stratified by baseline PASI score (≤ 16.0 , ≥ 16.1) and by history of prior systemic treatment for psoriasis, was performed to allow for a comparable baseline level of disease severity in each treatment group. Characteristics of psoriasis at baseline are shown in Table 47.

Table 47 Baseline Psoriasis Characteristics of Treated Subjects

Characteristic	Placebo (n=187)	Efalizumab (n=369)
Duration of psoriasis (yr)		
Mean	19	19
Range	1–53	1–62
Prior systemic therapy, n		
Yes	139 (74%)	283 (77%)
No	48 (26%)	86 (23%)
PASI category, n		
≤16.0	83 (44.4%)	155 (42.0%)
16.1–30.0	88 (47.1%)	181 (49.1%)
>30.0	16 (8.6%)	33 (8.9%)
PASI score		
Mean	19	19
Range	11–50	10–59
PASI thickness component		
Mean	6.2	6.2
Range	3–15	2.4–19
OLS, n		
Minimal	1 (0.5%)	1 (0.3%)
Mild	12 (6.4%)	23 (6.2%)
Moderate	96 (51.3%)	206 (55.8%)
Severe	69 (36.9%)	121 (32.8%)
Very severe	9 (4.8%)	18 (4.9%)
DLQI		
Mean	12	12
Range	0–30	0–30
Itching Scale		
Mean	6.2	6.4
Range	0–10	0–10
PSA frequency		
Mean	14	14
Range	2–24	2–24
PSA severity		
Mean	15	15
Range	2–24	0–24
Percent BSA of psoriasis		
Mean	27	28.
Range	10–90	10–95

The baseline disease severity is moderate to severe with the mean disease duration 19 years and the mean PASI score 19. The majority (approximately 3 out of 4) of patients enrolled with a history of prior systemic therapy.

The two treatment groups were well-balanced with respect to the baseline disease characteristics, including PASI, OLS, and BSA.

4.5.4.2 Study Conduct

Table 48 below shows protocol deviations noted in Study ACD2390g.

Table 48 Protocol Deviations Study 2390

Protocol Deviation	Placebo (n=187)	Efalizumab (n=369)
Total ^a	38 (20.3%)	84 (22.8%)
Missing laboratory data ^b	16 (8.6%)	38 (10.3%)
PASI performed outside of the Day 84 window ^c	19 (10.2%)	32 (8.7%)
<82 Days	7 (3.7%)	11 (3.0%)
>86 Days	12 (6.4%)	21 (5.7%)
OLS performed outside of the Day 84 window	19 (10.2%)	33 (8.9%)
<82 Days	7 (3.7%)	11 (3.0%)
>86 Days	12 (6.4%)	22 (6.0%)
Use of excluded medication	6 (3.2%)	18 (4.9%)
Incorrect study drug administration	1 (0.5%)	3 (0.8%)
Incorrect dosing level	0	2 (0.5%)

^a Represents the number of subjects with at least one protocol deviation.

^b Missing laboratories (hematologic assessments, chemistries, urinalysis, HIV serology, serum antibody, pregnancy).

^c For subjects who completed the treatment period.

One subject (33602) who was randomized into the efalizumab group never received any drug.

Twenty-four subjects were treated with an excluded medication for psoriasis during the treatment period: 6 subjects (3%) in the placebo group and 18 subjects (5%) in the efalizumab group. One efalizumab-treated patient received UVB. Also, among the disallowed therapies were systemic steroids. Systemic steroids were used for different indications including nonpsoriasis-related indications. One patient received systemic steroids for psoriatic erythroderma (34229) and other patients received either systemic steroids or intralesional steroid injections for worsening psoriatic arthritis (33424, 34415). Therefore, the use of systemic steroids indicated worsening of psoriasis and/or psoriatic arthritis in some, but not all patients.

Treatment compliance is shown in Table 49 below.

Table 49 Compliance for Subjects

Number of Doses Received	Placebo (n=187)	Efalizumab (n=369)
All 12	146 (78.1%)	271 (73.4%)
10–11	29 (15.5%)	74 (20.1%)
<10	12 (6.4%)	24 (6.5%)

Treatment compliance was comparable between the two treatment groups. Approximately 3 of 4 patients in each group received all 12 treatments.

4.5.4.3 Primary Efficacy Outcome

Table 50 PASI Response to Treatment for Randomized Subjects

PASI Response at Day 84	Placebo (n=187)	Efalizumab (n=369)
Responders	8 (4.3%)	98 (26.6%)
Partial responders and non- responders ^a	179 (95.7%)	271 (73.4%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001
Treatment effect	22.3%	
95% CI for treatment effect	15.8%, 29.5%	

^a Included subjects whose Day 84 PASI score was missing.

The proportion of responders was higher in the treatment group than in placebo. The absolute difference was 22.3%. These results were statistically significant. Therefore, Study ACD2390g was successful in establishing the efficacy of Genentech-manufactured efalizumab.

A more detailed examination of the percentage change in PASI at the end of the first treatment period is shown in Table 51 below.

Table 51 PASI Response by Percent Improvement from Baseline

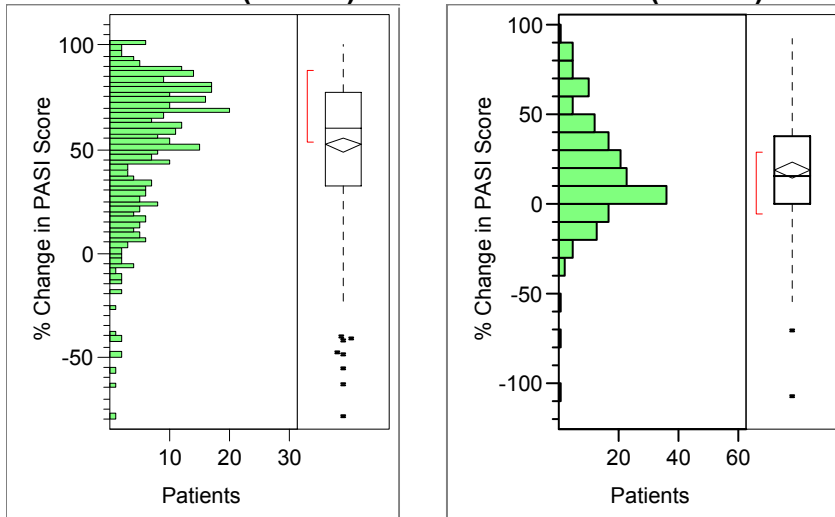
Percent Improvement from Baseline at Day 84	Placebo (n=187)	Efalizumab (n=369)
≥90%	1 (0.5%)	19 (5.1%)
≥75% to <90%	7 (3.7%)	79 (21.4%)
≥50% to <75%	18 (9.6%)	118 (32.0%)
≥25% to <50%	39 (20.9%)	59 (16.0%)
≥0% to <25%	70 (37.4%)	48 (13.0%)
≥ -25% to <0%	32 (17.1%)	15 (4.1%)
≥ -50% to < -25%	5 (2.7%)	6 (1.6%)
< -50%	3 (1.6%)	3 (0.8%)
Missing ^a	12 (6.4%)	22 (6.0%)

^a Subjects with missing Day 84 PASI scores were classified as non-responders.

The efalizumab-treated group showed a general shift towards improvement in PASI response from baseline. Efalizumab treatment effect was 45% using as criterion ≥ 50% improvement in PASI score. The proportion of patients who experienced worsening of the PASI score was higher in the placebo group (27.8%) than in the efalizumab group (12.5%).

Figure 6 below shows the distribution of the change in PASI score at day 84 by treatment group. The histograms reflect data from 347/369 patients in the efalizumab group and 175/187 of the placebo group for whom the data were available. A positive percentage change reflects improvement from baseline and a negative score is deterioration.

Figure 6 Percent Change in PASI Score at Day 84 by Treatment Group
Efalizumab (N=347) **Placebo (N=175)**



From this distribution, one can see that a small number of patients in both treatment groups worsened during treatment.

Table 52 depicts the percentage changes in PASI score by quantiles. The mean percentage changes in PASI score were 52 and 19, respectively in the efalizumab and placebo groups, while the median changes were 60 and 16.

Table 52 Percent Change in PASI by Treatment Group

	Efalizumab	Placebo
maximum	100	92
quartile	78	38
median	60	16
quartile	32	0.0
minimum	-79	-107

There is a general shift towards higher PASI improvement within each quartile in the efalizumab-treated group as compared to placebo.

4.5.4.4 Treatment Response in Patient Subgroups

Treatment responses were examined in various patient subgroups based on demographic factors, baseline PASI and prior history of systemic therapy (Table 53).

Table 53 PASI Responders by Subsets of Randomized Subjects

Subject Subset	Placebo (n=187)	Efalizumab (n=369)
Gender		
Women	2/55 (3.6%)	33 /118 (28%)
Men, n	6 /132 (4.5%)	65 /251 (26%)
Age group (yr)		
18–40, n	4 /68 (5.9%)	43 /140 (31%)
41–64, n	4 /106(3.8%)	51 /206 (25%)
≥ 65, n	0 /13	4 /23(17%)
Baseline PASI score		
≤ 16.0, n	4 /83 (5%)	40 /155 (26%)
16.1–30.0, n	4 /88(4.5%)	48 /181 (27%)
>30.0, n	0 /16	10 /33 (30%)
Prior systemic therapy		
Yes, n	7 /139 (5%)	75 /283 (27%)
No, n	1 /48 (2.1%)	23 /86 (27%)

The results for the primary endpoint in subsets defined by sex, age group, baseline PASI score and history of prior systemic therapy are consistent with the results of the ITT population as a whole.

A logistic regression analysis did not show baseline PASI score, age, sex, and prior systemic therapy to be significantly predictive of response.

Responses in the components of the PASI score are shown in Table 54 below.

Table 54 Mean Percent Improvement in PASI Thickness, Erythema, and Scaling Components

PASI Component at Day 84	Placebo (n=187)	Efalizumab (n=369)
Thickness ^a	16.8	50.7
Erythema ^a	16.8	45.6
Scaling ^a	19.2	50.7
PASI total ^b	(n=175) 19	(n=347) 52

Note: Improvement in each component was reflected by a decrease in score.

^a The last observation carried forward was used to impute missing Day 84 PASI data.

^b Values from the early termination visits were assigned to the next scheduled visit for PASI evaluation.

As in Studies ACD2058g and ACD2059g, each of the three components of the PASI score appear to contribute similarly to improvement in the overall score.

Table 55 Mean Improvement in Percentage of BSA of Psoriasis

Percentage of BSA	Placebo (n=187)	Efalizumab (n=369)
Day 0	27	28
Day 84 ^a	25	17
Improvement ^b	2.6	11
Two-sample t-test p-value efalizumab vs. placebo	—	<0.001

^a The last observation carried forward was used to impute missing Day 84 BSA value.

^b Improvement was reflected by a decrease in the percent BSA value.

In addition to the improvements in each of the components of the PASI score (thickness, erythema, scale), efalizumab-treated patients demonstrated mean improvements in percentage body surface area affected by psoriasis.

4.5.4.5 Secondary Efficacy Outcome

The principal secondary outcome results are shown in Table 56 below.

Table 56 Principal Secondary Efficacy Endpoint

OLS Response at Day 84	Placebo (n=187)	Efalizumab (n=369)
Minimal or Clear	6 (3.2%)	95 (25.7%)
Mild to Very Severe ^a	181 (96.8%)	274 (74.3%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001

^a Included subjects who were classified as Mild, Moderate, Severe, and Very Severe and those whose Day 84 OLS rating was missing.

The proportion of patients with an OLS rating of “Minimal or Clear” in the efalizumab group was higher than in the placebo group. The absolute difference from placebo was 22.5%. These results are supportive of the primary efficacy analysis.

A more detailed examination of the distribution of Day 84 OLS categories is presented in Table 57 below.

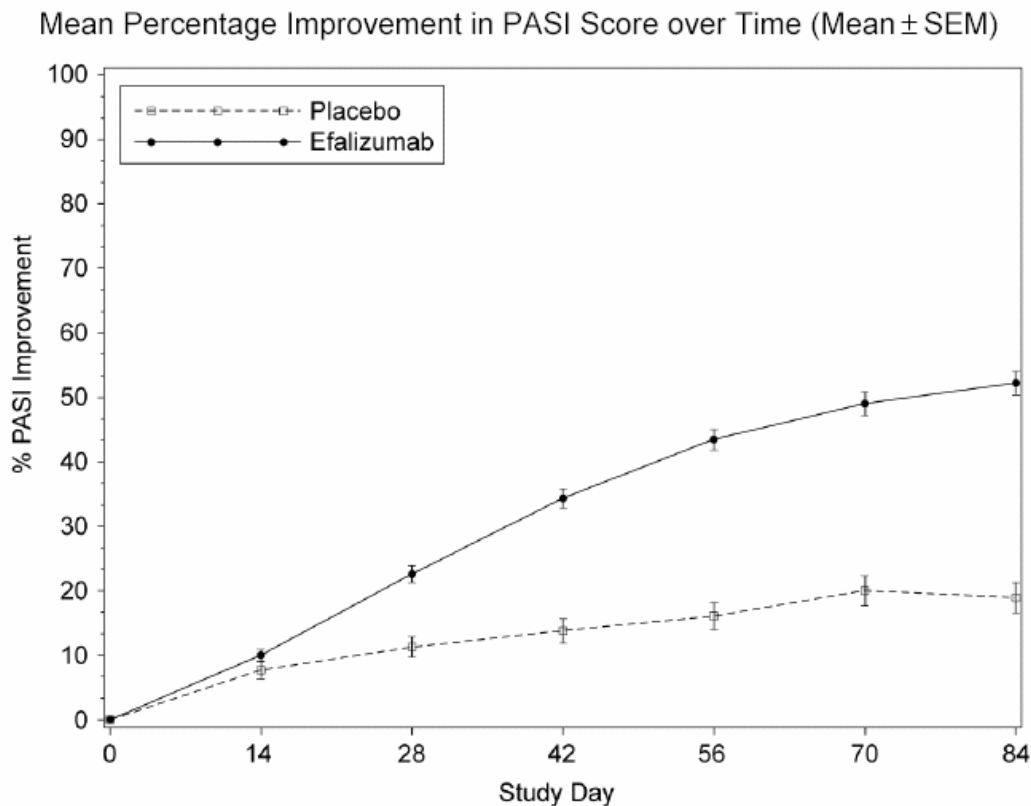
Table 57 OLS Response to Treatment at Day 84

OLS Response at Day 84	Placebo (n=187)	Efalizumab (n=369)
Clear	0	7 (1.9%)
Minimal	6 (3.2%)	88 (23.8%)
Mild	32 (17.1%)	125 (33.9%)
Moderate	92 (49.2%)	99 (26.8%)
Severe	40 (21.4%)	25 (6.8%)
Very Severe	6 (3.2%)	7 (1.9%)
Missing	11 (5.9%)	18 (4.9%)

The distribution of the OLS scores shows a higher overall shift towards milder scores in the efalizumab group than placebo. Higher numbers of patients were classified as severe and very severe in the placebo group as compared to the efalizumab-treated group. The proportions of patients with missing data were comparable between treatment groups.

4.5.4.6 Onset of treatment effect

Figure 7 below shows the mean percentage improvement in PASI score over time.

Figure 7

Statistically significant differences between treatment groups in favor of efalizumab were noted by 28 days of therapy.

4.5.4.7 Quality of life measures

The Dermatology Life Quality Index (DLQI) mean change from baseline at Day 84 was designated in a protocol amendment as a secondary efficacy outcome measure. The DLQI, consists of a 10-item questionnaire and is dermatology-specific measure of quality of life. The score ranges from 0-30. Decreases in the DLQI represent improvement in functionality and subject well being.

Table 58 Improvement from Baseline in DLQI Overall Score

DLQI		Placebo (n=187)	Efalizumab (n=369)
Day 0			
	n	183	363
	Mean	11.8	12.0
	Median	11.0	11.0
	Range	0 to 30	0 to 30
Day 84 ^a			
	n	187	368
	Mean	10.2	6.4
	Median	9.0	4.0
	Range	0 to 30	0 to 30
Improvement from baseline ^b			
	n	183	363
	Mean	1.6	5.6
	Median	1.0	5.0
	Range	-13 to 25	-22 to 25
Wilcoxon rank-sum test p-value efalizumab vs. placebo		—	<0.001

^a The last observation carried forward was used to impute missing Day 84 DLQI values.

^b Improvement was reflected by a decrease in DLQI overall score.

The baseline median score was 11 in both treatment groups, the baseline mean score was 12, and the range was from 0-30. The mean improvement from baseline was 5.6 in efalizumab-treated patients vs. 1.6 in placebo-treated patients. This represents a statistically significant difference between treatment groups in favor of the efalizumab-treated group.

Reviewer's comment

The clinical significance of a 4-point absolute improvement in score in a scale ranging from 0-30 is not clear.

4.5.5 Summary of Efficacy: Study ACD2390g

This study demonstrated the efficacy of Genentech-manufactured efalizumab

- Approximately 22% more patients in the efalizumab-treated group had a 75% improvement in PASI score at the end of the first treatment period than placebo-treated patients.
- Clinical responses as measured by the physician's static global assessment was consistent with those obtained by PASI 75 criteria. The absolute difference from placebo was 22.5%.
- Onset to treatment effect was by 4 weeks.
- Duration of response was not evaluated in this study.

4.6 Protocol ACD2600g

4.6.1 Study Title

"A phase IIIb, randomized, double- blind, parallel- group, placebo-controlled, multicenter study to evaluate the safety of 1.0 mg/kg subcutaneously administered efalizumab in adults with moderate to severe plaque psoriasis who are candidates for systemic therapy"

4.6.2 Study Objectives

The primary objective of this study was to evaluate the safety and tolerability of a 12-week course of 1.0 mg/kg SC Genetech-manufactured efalizumab relative to placebo.

The secondary objectives of this study were to evaluate the efficacy of a 12-week course of 1.0 mg/kg SC efalizumab relative to placebo as measured by:

- The proportion of subjects achieving a $\geq 75\%$ improvement in Psoriasis Area and Severity Index (PASI)
- The Overall Lesion Severity (OLS) scale
- The proportion of subjects achieving a $\geq 50\%$ improvement in PASI
- The Psoriasis Symptom Assessment (PSA)

4.6.3 Study Design

4.6.3.1 Randomization

Subjects were randomized (centrally) in a 2:1 ratio to receive either 12 weeks of 1.0 mg/kg/ SC efalizumab or placebo. Randomization was stratified within each study center by the Day 0 PASI score (≤ 16.0 , ≥ 16.1) and by prior treatment for psoriasis (naive to systemic treatment vs. prior systemic treatment). A random permuted block design was used to obtain approximately a 2:1 ratio within categories defined by the stratification variables.

4.6.3.2 Blinding

This was double-blind study. Subjects, investigators, and the Sponsor were blinded regarding treatment assignment to placebo or active study drug. Efalizumab produces elevations of lymphocyte and total white blood cell counts. Therefore, to minimize the potential for unblinding, only the absolute neutrophil count and the eosinophil count were

to be made available to the investigators and monitors from the CBC. Similarly, anti-efalizumab antibody results were not to be shared with investigators or the contract research organization until Study ACD2600g has been unblinded.

4.6.3.3 Open-label extension

The open-label extension for this study was Study ACD2601g.

4.6.3.4 Study Drug

The study drug, route and dose was the same as Study ACD2390g.

4.6.3.5 Criteria for Discontinuation of Treatment

The criteria for discontinuation of treatment included the following:

- Pregnancy
- Administration of a live virus or bacteria vaccine
- Initiation of excluded systemic treatment for psoriasis
- Initiation of excluded immunosuppressive treatment for any indication
- Initiation of excluded experimental medication or other treatment
- Diagnosis of severe or serious arthritis with evidence of joint inflammation (i.e., pain, swelling, stiffness, heat, and/or redness) upon examination for any subject without a history of arthritis
Subjects with a history of arthritis (such as, but not limited to, psoriatic arthritis) may have had variations in the severity of arthritis during the study; this did not require early discontinuation of study drug treatment.
- Any medical condition (e.g., opportunistic infections, malignancies, immune complex disorders) that the investigator determined may jeopardize the subject's safety.

4.6.3.6 Concomitant Therapy

Allowed concomitant therapies were similar to those in study ACD2390g. The concomitant therapies that were excluded were also similar to those in study ACD2390g.

4.6.3.7 Eligibility Criteria

The eligibility criteria were similar to those in Studies ACD2390g and ACD2058g.

4.6.3.8 Endpoints

4.6.3.9 Safety

The study's designated primary objective was to evaluate safety.

4.6.3.10 Efficacy

The principal secondary endpoint consisted of the comparison of the proportion of subjects whose PASI score has decreased by $\geq 75\%$ on Day 84 relative to Day 0 between the active group (1.0 mg/kg/wk efalizumab) and the placebo group for the ITT population using Fisher's exact test.

4.6.3.11 Study Assessments

Analyses for anti-efalizumab antibody assessments were performed on serum samples collected on Days 0 and 56. An unscheduled antibody sample was to be obtained from subjects who discontinued prior to Day 56.

Dermatologic evaluation (PASI, psoriatic BSA, and static physicians global assessment) and complete examination took place at baseline, Day 28, Day 56 and Day 84 of the study.

Screening laboratory evaluations consisted of hematology, chemistry (electrolytes, glucose, creatinine, bilirubin, albumin, total protein, liver function tests, creatine phosphokinase, and uric acid, urinalysis, HIV serology, hepatitis B antigen, and hepatitis C serology.

In addition to urinalysis, hematology and chemistries, other tests were performed at baseline and at day 84 of the study which were not performed in prior phase 3 studies. These consisted of C-reactive protein, fibrinogen, complement 3a and complement 5a.

4.6.4 Study Results

A total of 686 subjects were enrolled and randomized, 236 in the placebo group and 450 in the 1.0 mg/kg/wk group. The study was conducted at 58 study centers in the United States and Canada. The study was completed February 19, 2003.

One subject randomized to efalizumab group was never dosed and was removed from safety summaries

Table 59 ACD2600g: Subject Disposition and Reasons for Premature Discontinuation in Randomized Subjects

Subject Status	Placebo (N=236)	Efalizumab (N=450)
Completed FT	218 (92%)	421 (93%)
Entered ACD2601g ET	218	418
Entered ACD2601g FU	0	2
Discontinued study	0	1
Discontinued FT	18 (7.6%)	29 (6.4%)
Entered ACD2601g FU	5	10
Discontinued study	13	19
Reasons for FT discontinuation		
Death	1	0
Adverse event	6	11
Lost to follow-up	3	3
Subject's decision	6	9
Physician's decision	2	3
Pregnancy	0	1
Use of excluded rx	0	2

The proportions of patients completing the first treatment course were comparable across treatment groups. The proportion of patients who discontinued the FT for an adverse event was similar in the active treatment arms and in the placebo arm.

A total of 47 subjects (6.9%) discontinued treatment. One subject assigned to placebo died during the study. Seventeen patients overall discontinued due to adverse events, the most common reason given for discontinuation. The proportions discontinuing for adverse events were comparable between treatment groups. The second most common reason for discontinuation was “subject’s decision” accounting for 15 patients who discontinued prematurely.

The demographic and other baseline characteristics of the studied population are displayed in Table 60 below.

Table 60 ACD2600g: Demographic and Baseline Characteristics of Randomized Subjects

Characteristic	Placebo (N=236)	Efalizumab (N=450)
Sex		
Male	140 (59.3%)	303 (67.3%)
Female	96 (40.7%)	147 (32.7%)
Race/ethnicity		
White	215 (91.1%)	412 (91.6%)
Hispanic	8 (3.4%)	18 (4.0%)
Other ^a	13 (5.5%)	20 (4.4%)
Age group (yr)		
18–40	74 (31.4%)	160 (35.6%)
41–64	149 (63.1%)	252 (56.0%)
≥ 65	13 (5.5%)	38 (8.4%)
Age (yr)		
Mean	46.4	45.6
Range	20 - 77	18 - 74
Weight (kg)		
Mean	92.5	93.1
Range	46 - 159	51 - 159

^a The “Other” group included individuals who described their Asian or Pacific Islander, Black, American Indian or Alaskan Native, or race/ethnicity as Other.

Overall the two treatment groups were comparable in demographics and baseline psoriasis characteristics, except that there was a higher ratio of male to female patients in the efalizumab group than in placebo. Aside from this gender imbalance, the patient population enrolled is representative of the US population with moderate-to-severe chronic plaque psoriasis.

Reviewer’s comment: The range of ages shows that some patients were enrolled who were older than the entry criteria allowed.

The baseline psoriasis characteristics of the study population are displayed in Table 61 below.

Table 61 ACD2600g: Baseline Psoriasis Characteristics of Randomized Subjects

Characteristic	Placebo (N=236)	Efalizumab (N=450)
Prior systemic therapy, n		
Yes	174 (73.7%)	328 (72.9%)
No	62 (26.3%)	122 (27.1%)
PASI category, n		
≤ 16.0	112 (47.5%)	201 (44.7%)
16.1–30.0	105 (44.5%)	210 (46.7%)
>30.0	19 (8.1%)	39 (8.7%)
PASI score		
Mean (SD)	18.69 (7.01)	19.14 (7.47)
Range	10.5 - 49.6	10.2 - 54.6
Percent BSA of psoriasis		
Mean (SD)	26.8(15.2)	27.7(15.8)
Range	10.0 - 83.0	10.0 - 85.0

The overall baseline disease severity was moderate to severe plaque psoriasis and was comparable between treatment groups. Most of the patients, 73%, had a prior history of systemic therapy.

The tabulation of certain types of protocol deviations follows (Table 62).

Table 62 Study ACD2600g: Protocol Deviations

Protocol Deviation	Placebo (n=236)	Efalizumab (n=450)
Total ^a	49 (20.8%)	91 (20.2%)
OLS performed outside of the Day 84 window ^b	22 (9.3%)	44 (9.8%)
<82 Days	10 (4.2%)	12 (2.7%)
>86 Days	12 (5.1%)	32 (7.1%)
PASI performed outside of the Day 84 window ^b	22 (9.3%)	43 (9.6%)
<82 Days	10 (4.2%)	11 (2.4%)
>86 Days	12 (5.1%)	32 (7.1%)
Missing laboratory data ^c	19 (8.1%)	28 (6.2%)
Use of excluded medication	10 (4.2%)	22 (4.9%)
Incorrect study drug administration	2 (0.8%)	4 (0.9%)
Incorrect dosing of study drug	1 (0.4%)	1 (0.2%)
Incorrect treatment assignment ^d	1 (0.4%)	1 (0.2%)

^a Represents the number of subjects who had at least one protocol deviation.

^b For subjects who completed the treatment period.

^c Missing laboratory results (hematologic assessments, chemistries, urinalysis, C-reactive protein, fibrinogen, complement 3a, complement 5a, serum antibody, pregnancy, HIV, hepatitis B antigen, and hepatitis C serology).

^d Incorrect treatment assignment (subjects received incorrect study drug at the site).

The most frequent protocol deviation was performance of the Day 84 OLS and PASI assessments outside of the ± 2 day visit window. Most of these PASI assessments were performed within ± 7 days of Day 84. The second most common deviation was missing laboratory data. Six subjects were administered study drug from the single-use vials on two consecutive visits on one or two occasions; Subjects 42208 and 42209 were in the placebo group, and Subjects 42202, 42204, 42206, and 42207 were in the efalizumab group. One placebo-treated subject (41202) and one efalizumab-treated subject (45408) were administered a 1.0 mg/kg dose instead of the conditioning dose of 0.7 mg/kg on Day 0. Subject 40816 was randomized to receive placebo but was administered efalizumab on Day 77. Subject 41613 was randomized to receive efalizumab but was administered placebo on Day 42.

Reviewer's comment: These protocol deviations were not deemed to have an effect on the study outcome.

The efficacy results at the end of the 12-week treatment period are summarized below (Table 63).

Table 63 ACD2600g: Efficacy Results of Randomized Subjects

	Placebo (N=236)	Efalizumab (N=450)
PASI 75	7 (3.0%)	106 (23.6%)
PASI 50	33 (14.0%)	234 (52.0%)
OLS Clear/Minimal	10 (4.2%)	91 (20.3%)

The Fisher's exact test p-value was <0.001% for each comparison.

The proportion of PASI 75 responders was higher in the treatment group than in placebo. The absolute difference was 20.6%. In addition, the absolute difference in proportions of patients achieving PASI 50 response was 38% in favor of the efalizumab-treated group. Finally, the efficacy outcome based on the response by physician's static global assessment was also supportive of the response data as measure by PASI outcomes.

These results were statistically significant.

4.6.5 Summary of Efficacy: Study ACD2600g

- The efficacy results of this study were consistent with those of the earlier phase 3 studies.
- The treatment effect was 21% by the PASI 75 criterion and 38% by the PASI 50 criterion.
- Clinical responses as measured by the physician's static global assessment was consistent with those obtained by PASI 75 criteria. The absolute difference from placebo was 16%.

5 EXPLORATORY EFFICACY ANALYSES

5.1 Effect of Use of Excluded Therapies

The possible influence of excluded concomitant medications on PASI response during FT in Studies ACD2058g, ACD2059g, and ACD2390g was assessed for each study, by material, by recomputing the proportion of FT responders in each study after conservative re-categorization of each user of excluded medication as a non-responder (<PASI-75 response). Accordingly, a list of all protocol-proscribed medications for FT was compiled that included all topical high- and mid-potency corticosteroids, systemic corticosteroids, and all other systemic agents stated as prohibited by the protocols. This sensitivity exclusion list included some medications conservatively considered potentially efficacious but not proscribed previously in the protocols, including two low-potency topical corticosteroids, alclometasone and desonide. All of these excluded medications were flagged in the database such that for the sensitivity analysis, a total of 24, 46, and 30 primary analysis randomized subjects (total of 100) in Studies ACD2058g, ACD2059g, and ACD2390g, respectively, were considered non-responders for the purpose of this sensitivity exercise, based solely on the use of excluded medications. Fourteen of these 100 subjects who had received excluded medication had been FT responders in the primary analysis and were re-categorized as non-responders in the sensitivity analysis.

The results of the sensitivity analysis are shown in Table 64 and are compared with the results of the primary PASI-75 efficacy analysis. This comparison of the primary and conservatively reclassified sensitivity results revealed only minor differences in percent PASI response during FT, and this result was ascribed to the very small number of subjects who used prohibited medications.

Table 64 Sensitivity Analysis of FT PASI Response (Primary Endpoint) for Usage of Excluded, Possibly Efficacious Concomitant Medications in the Phase III Trials: Comparison to Results of Primary Analysis

Study	Placebo		Efalizumab (1.0 mg/kg/wk)		Efalizumab (2.0 mg/kg/wk)	
	Primary	Sensitivity	Primary	Sensitivity	Primary	Sensitivity
Genentech Material						
ACD2390g						
n	187	187	369	369	—	—
Responder	8 (4.3%)	7 (3.7%)	98 (26.6%)	95 (25.7%)	—	—
Treatment effect	—	—	22.3%	22.0%	—	—
95% CI	—	—	15.8, 29.5	15.6, 29.1	—	—
ACD2059g, (GNE)						
n	32	32	52	52	61	61
Responder	0 (0.0%)	0 (0.0%)	5 (9.6%)	5 (9.6%)	13 (21.3%)	11 (18.0%)
Treatment effect	—	—	9.6%	9.6%	21.3%	18.0%
95% CI	—	—	-7.2, 29.7	-7.2, 29.7	3.5, 42.2	0.5, 38.4
XOMA Material						
ACD2059g (XOMA)						
n	90	90	180	180	182	182
Responder	6 (6.7%)	6 (6.7%)	47 (26.1%)	46 (25.6%)	56 (30.8%)	55 (30.2%)
Treatment effect	—	—	19.4%	18.9%	24.1%	23.6%
95% CI	—	—	8.7, 31.0	8.2, 30.4	13.7, 35.9	13.1, 35.4
ACD2058g						
n	170	170	162	162	166	166
Responder	4 (2.4%)	4 (2.4%)	63 (38.9%)	60 (37.0%)	44 (26.5%)	41 (24.7%)
Treatment effect	—	—	36.5%	34.7%	24.2%	22.3%
95% CI	—	—	27.8, 46.2	26.0, 44.3	16.0, 33.4	14.3, 31.6

The sensitivity analysis did not appreciably alter either the clinical or statistical significance of the response rates in any dose group in any studies, nor did it affect the magnitude of significance of the treatment effects as corrected for placebo response.

6 SUMMARY OF EFFICACY AND PATIENT POPULATION

- The patient population was representative of the general population with chronic stable moderate to severe plaque psoriasis with the exception of the gender imbalance (fewer women than men were studied).
- Primary efficacy outcome
 - In patients receiving 1 mg/kg/wk SC, treatment effect ranged from 18% to 37% (depending on the study) by PASI 75 criteria.
 - There was no meaningful difference in response by age, gender, race, baseline disease severity or history of previous systemic therapy for psoriasis.
- Secondary efficacy outcomes
 - Other efficacy outcomes, including PASI 50 and static physician's global assessment showed statistically significant differences from placebo in favor of efalizumab-treated patients and were supportive of the primary efficacy outcome.
- Quality of life outcomes showed small degrees of improvement (3-4 points on a scale from 0-30) in favor of the efalizumab-treated patients. The clinical significance of the degree of change is not known.
- Median time to response in patients achieving PASI 75 was approximately 2 months (57 days). Statistically significant differences in the mean PASI scores between patients receiving efalizumab and those receiving placebo were seen by 2-4 weeks of therapy.
- The median duration of treatment effect based on the time to loss of 50% of improvement was 67 days following discontinuation of treatment.
- A second 12-week course of treatment upon 50% relapse does not recapture response in the majority of patients who responded to the first 12 weeks of treatment. Response was 31% at the PASI 75 level, even though 100% of these patients responded to efalizumab during the first treatment period.
- Among treatment responders during the initial 12 weeks of therapy, extended treatment for an additional 12 weeks can maintain treatment response in 77% of patients.
- In patients who were nonresponders or partial responders during the first 12 weeks of efalizumab treatment, extended treatment with a contiguous 3 month treatment course can result in an additional 11%-14% PASI 75 response (depending on the study).

7 INTEGRATED SAFETY REVIEW

7.1 Safety Database

Approximately 2400 patients received efalizumab weekly for 12 weeks of continuous treatment, 939 for 24 weeks of continuous treatment, and 218 for 1 year of continuous treatment. In all, 1,620 patients received efalizumab in the 12-week, placebo-controlled portion of the four phase 3 studies (ACD2058g, ACD2059g, ACD2390g and ACD2600g).

Of the 1115 subjects who entered the first extended treatment period from 12–24 weeks (see Table 65 below), 939 completed 24 weeks of treatment.

The population of patients who received the Genentech manufactured product for the first time in controlled studies ranged in age from 18-75 years and included 67% men and 33% women. A high proportion of the patients were Caucasian (88%) reflecting the general patient population with psoriasis. The mean body weight was 93 kg. The disease severity at baseline was moderate-to-severe psoriasis, with a mean PASI of 19 and affected body surface area of 29%.

As stated previously, due to the differences in pharmacokinetics between the XOMA and Genentech manufactured efalizumab, the FDA requested that the safety data be analyzed separately according to manufacturer. No differences in safety were found between the patients treated with XOMA-manufactured vs. the Genentech-manufactured efalizumab (data not shown). Therefore, for the purposes of this summary of the integrated safety review, the databases will be pooled.

Table 65 Subjects with Moderate to Severe Plaque Psoriasis Receiving SC Efalizumab Treatment beyond the Initial 12-Week Course (EE)

Source (Manufacturer)	Efalizumab Treatment Segment			
	EE-1 12–24 Wk	EE-2 24–36 Wk	EE-3 36–48 Wk	EE-4 48–60 Wk
Original BLA				
XOMA	360	13	NA	NA
Genentech	389	292	243	149
Original total	772 ^a	318 ^b	243	149
BLA Amendment:				
Study ACD2243g (Genentech)	1	0	4	79
BLA Amendment:				
Study ACD2391g (Genentech)	342	NA	NA	NA
BLA Amendment				
XOMA	360	13	NA	NA
Genentech	732	292	247	228
Current total	1115^a	318^b	247	228

^a Includes an additional 23 subjects who received both XOMA and Genentech efalizumab during EE-1 in Study ACD2062g.

^b Includes an additional 13 subjects who received both XOMA and Genentech efalizumab in Study ACD2062g during EE-2.

Analyses of Adverse Events

7.2 Serious Adverse Events

A serious adverse event is defined as: (1) Any death; (2) Any life-threatening event (one which places the subject at immediate risk of death); (3) Any event that requires or prolongs in-patient hospitalization; (4) Any event that results in significant or persistent disability/incapacity; (5) Any congenital anomaly/birth defect diagnosed in the child of a subject who participated in this study and received study drug; or (6) Other medically important event that, in the opinion of the investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

The overall incidence of serious adverse events during the first twelve weeks of treatment for the placebo-controlled studies was 2.2% among 1,620 efalizumab-treated patients and 1.7% among 715 placebo-treated patients.

7.2.1.1 Deaths in Clinical Trials for Psoriasis

Death was reported in 7 of 2762 efalizumab treated patients (0.3%) and 3 of the 715 (0.4%) placebo-treated patients. Two subjects died while receiving efalizumab and 5 after completing treatment. None of the deaths was attributed by the investigator to efalizumab treatment. A description of the patients who died during the clinical trials is provided in Table 66 below.

Table 66 Deaths during the Clinical Trials of Efalizumab for Psoriasis

Subject no./Study	Treatment group	Age (yr)/ Gender	Duration study drug (wk)/time since last dose (wk)	Diagnosis	History and risk factors
11520/ ACD2058g	Efalizumab (XOMA) 1.0 mg/kg/wk	60/ M	12/~27	Metastatic rectal cancer	Noted to be jaundiced during first treatment period. Noted change in bowel habits, nausea and vomiting and 20 lb weight loss over the previous 2 months. No mention of family history in the report. Died during the OB period.
81601/ ACD2059g	Efalizumab (XOMA) 4.0mg/kg/wk	58/ M	~10	Atherosclerotic cardiovascular disease	Event occurred after the ninth dose of efalizumab during the treatment period. Risk factors: Type 2 diabetes, hypertension, Hypercholesterolemia, history of coronary artery bypass (1982 and 1996)
33007/ ACD2391g	Efalizumab (Genentech) 1.0mg/kg/wk	52/ M	23/~7	Myocardial infarction	Hypertension and smoking
68812/ ACD2059g	Efalizumab (XOMA)	56/ M	12/~72	Accidental death (plane crash)	N/A
17907/ ACD2062g	Efalizumab (XOMA)	68/ F	12/~41 (Patient died after completion of follow-up period)	Atherosclerotic cardiovascular disease	Angina, diabetes, hypertension, peripheral vascular disease, chronic anemia
28913/ ACD2243g	Efalizumab (Genentech)	68/ M	11/~27	"Micronodular cirrhosis of the liver"	Elevated SGOT and total and direct bilirubin
12062/ ACD2062g	Efalizumab (XOMA)	68/ F	20/~38 (2.0 mg/kg/w SC for total of 33 doses) (Patient died after completion of follow-up period)	Unconfirmed report of possible diagnosis of pneumonia: cause of death classified as unknown	Stroke (1972), Hypertension and depression (1980), hypercholesterolemia, diabetes
81235/ ACD2059g	placebo	70/ M	N/A	Accidental drowning	N/A
41011/ ACD2600g	placebo	53/ F	N/A	Sudden cardiac death	Patient had right sided congestive heart failure resulting from chronic obstructive pulmonary disease (COPD) and Pickwickian syndrome. (Subject was discontinued due to exacerbation of COPD prior to death.)
42208/ ACD2600g	placebo	47/ F	N/A	Seizure	History of seizures and bipolar disorder

None of the deaths was attributed to infection. However, the possibility of pneumonia at the time of death in patient 12062 was reported, but unconfirmed. This patient died after completion of the follow-up period.

All four of the patient deaths attributed to cardiac causes (3 in the efalizumab-treated patients and 1 in a placebo-treated patient) took place in patients \geq age 50 and in whom were known pre-existing cardiovascular risk factors.

Reviewer's note:

For patients 28913 and 12062 the details of the causes of deaths are sparse (see narratives below).

Narrative patient 28913 (death due to cirrhosis of the liver):

The subject had psoriasis for 10 years and had not received previous systemic therapy. The subject had received a total of 15 doses of efalizumab prior to the onset of the event. Medical history included migraines, arthritis of the back, hypertension, hyperlipidemia, triple bypass surgery, and alcohol use of more than 50 years and tobacco use. The patient was found to have micronodular cirrhosis of the liver after liver function tests already elevated at baseline were further elevated approximately 2 months into his treatment course. Study drug was discontinued one month later. A liver biopsy confirmed the diagnosis of micronodular cirrhosis of the liver. The subject died one month later of the "cirrhosis of the liver." The investigator determined the subject's death to be not related to study drug.

Reviewer's note: According to this report, the patient went from having elevated liver function tests to death. Report does not address whether the patient took concomitant medications. Additionally, the report does not summarize the course of manifestations or of complications related to liver disease that may have lead to the patient's death. There is no mention of whether an autopsy performed.

Narrative patient 12062 (death of unknown cause):

Six months after receiving her last dose of study drug, the subject canceled a scheduled doctor's appointment because she reportedly did not feel well. Later in the afternoon, the subject's husband found her unresponsive. She was transported to the emergency room and admitted to the hospital. The subject's husband reported that "some heart tests and dialysis were performed." He reports hearing the possible diagnosis of "pneumonia." Two days later, the subject died. The cause of death is unknown. The investigator determined the subject's death to be not related to study drug.

7.2.2 Deaths and Serious Adverse Events in Other Indications

No deaths were reported for subjects in the asthma study, ACD2017g, for healthy volunteers in Study ACD2389g, and in a study of rheumatoid arthritis.

Two deaths occurred in the renal transplant program (Study HUKT257), which were both judged by the investigators to be related to efalizumab. One death was related to posttransplant lymphoproliferative disorder (PTLD), and the other death was due to pancreatitis. All subjects in this study received efalizumab in addition to concomitant triple drug immunosuppressive therapy. In all, three cases of PTLD occurred in 38 subjects. These cases all occurred in patients treated with 2.0 mg/kg/wk efalizumab, cyclosporine, MMF, and prednisone.

7.2.3 Serious Infections

The incidence of serious infections in the combined efalizumab first exposure (FE)-controlled experience is shown in Table 67 below.

Table 67 Serious Diagnosed Infections Experienced by Subjects Who Received Study Drug (Combined Materials) in the First Exposure of Controlled Studies

Adverse Event	Placebo (n=715)	All Efalizumab (n=1620)
Total ^a	1 (0.1%)	7 (0.4%)
Cellulitis	0	3 (0.2%)
Sepsis	0	1 (<0.1%)
Gastroenteritis	1 (0.1%)	2 (0.1%)
Pneumonia	0	2 (0.1%)

The proportion of patients diagnosed with a serious infection in the first exposure of controlled clinical trials was 0.4% in the efalizumab group and 0.1% in the placebo group. Although the patient numbers are small, this represents a possible safety signal with regard to the incidence of serious infections.

Descriptions of the patients diagnosed with a serious infection during the first 12-week period of treatment with efalizumab are displayed in Table 68 below.

Table 68 Serious Infections in the First Exposure Controlled Clinical Experience (Studies 2058, 2059 and 2390)

Patient/Study	Treatment Group	Age (yr)/ Gender	Event
45225/ACD2600	Efalizumab (GNE) 1.0	70/ F	Urosepsis associated with possible kidney stone
45207/ACD2600	Efalizumab (GNE) 1.0	74/ M	Pneumonia associated with decreased neutrophil count
34229/ACD2390g	Efalizumab (GNE) 1.0	53/ F	cellulitis
76802/ACD2059g	Efalizumab (GNE) 2.0	54/ M	cellulitis
16506/ACD2058g	Efalizumab (XOMA)1.0	57/ M	pneumonia
17501/ACD2058g	Efalizumab (XOMA) 2.0	32/ M	cellulitis (hand),gastroenteritis
17512/ACD2058g	Efalizumab (XOMA) 1.0	46/ F	gastroenteritis
22006/ACD2058g	Placebo	45/ M	gastroenteritis

Serious infections were noted with both drug products (Genentech- and XOMA-manufactured efalizumab). Cellulitis accounted for three of six infectious events requiring hospitalization among patients receiving efalizumab in the FE controlled clinical experience.

The incidence rate for serious infections in the entire safety database (controlled and uncontrolled) expressed in terms of patient-years of exposure is shown by treatment group in Table 69.

**Table 69 Incidence Rate for Infection that Required Hospitalization
Total Exposure All Patients by Treatment Group**

Treatment Group	Number of Events	Subject-Years	95% CI for Observed Number of Events	Incidence Rate Per 100 Subject-Years	95% CI for Incidence Rate Per 100 Subject-Years
Efalizumab	27	1680	[17.79, 39.28]	1.61	[1.06, 2.34]
Placebo	2	185	[0.24, 7.22]	1.08	[0.13, 3.89]

The incidence of serious infections requiring hospitalization per 100 subject years is 1.61 in the efalizumab-treated group and 1.08 in the placebo-treated patients with overlapping 95% CI for the incidence rate. The numbers of individual types of serious infections were so few that a placebo comparison was not possible.

Reviewer's comment: Both the first exposure controlled clinical experience and the total exposure over the safety database as a whole show a higher incidence rate of infections requiring hospitalization in efalizumab-treated patients vs. placebo. However, given the small number of serious infections (especially in the placebo group) it is not possible to draw firm conclusions about the relative risk of serious infections.

The expected incidence rate for serious infections requiring hospitalization based on an external cohort, the Saskatchewan Health, was comparable to that seen in both treatment groups in the clinical trials (data not shown). The external cohort used for comparison, included adult patients in Saskatchewan who had a diagnosis of psoriasis between January 1995 and March 2000 and received a prescription for a systemic oral psoriasis therapy or had PUVA or ultraviolet B light therapy.

In addition to evaluating overall incidence of serious infectious adverse events, it is important to note the opportunistic infection and unusual courses of serious infections occurring in efalizumb-treated patients. Please see the following narratives.

Opportunistic Infections:

One opportunistic infection was reported, *Legionella* pneumonia.

Patient 17007: Legionella pneumonia

A 41-year-old white female with a medical history significant for tobacco use was enrolled in study ACD2058g where she received 12 weeks of therapy at the 2-mg/kg-dose level. The patient did not take any concomitant medications. After her first dose in the extended treatment period, the patient developed life-threatening *Legionella* pneumonia. She required intubation for hypoxia and marked respiratory acidosis. CXR showed bilateral pulmonary infiltrates. Her WBC count was 23 K/mm³. Bronchial

washings revealed *Legionella pneumophila*. The adverse event resolved in 19 days. Other cases of *Legionella* were seen and admitted to the same hospital, and the case was referred to the State Health Department for investigation. The investigator determined the *Legionella* pneumonia to be possibly related to study drug.

Serious infections with atypical features or unusually severe course:

The following are narratives of infections from the various studies in the BLA submission which have atypical features such as an unusually severe course. Patients 67615 and 26504 below had severe local infections with seeding to a distal site requiring surgical intervention.

67615 (Study 2059g):

A 53-year-old male was diagnosed with vertebral staphylococcal osteomyelitis and *S. aureus* sepsis. Patient had received 17 doses of study drug at the 2 mg/kg dose. The patient required hospitalization for IV antibiotics and discectomy and biopsy of infected bone. Surgical pathology revealed inflammation consistent with acute osteomyelitis. The event resolved after 43 days. The investigator determined the osteomyelitis and sepsis to be related to study drug.

Reviewer's comment: This case is notable for the severity of the osteomyelitis and that it was complicated by sepsis.

26504 (Study ACD2243): 53-year-old white male completed 2.0 mg/kg dose and received extended treatment with 1.0 mg/kg. The patient was hospitalized with bacteremia and MRI revealed bilateral ethmoid sinusitis. Chest radiographs were negative for pneumonia. Blood cultures grew Group A beta-hemolytic streptococci. The patient simultaneously experienced cellulitis of the left foot and right orbit. The patient required surgical fasciotomy for the left foot which was cultured and grew GABHS streptococci. The investigator deemed the sepsis not related to study drug.

This infection is an example of a common infection, i.e. sinusitis, which lead to serious complications, namely, orbital cellulitis and dissemination of infection to a distal site requiring surgical fasciotomy.

28008 (Study ACD2243g): A 66-year-old male was hospitalized with a severe sinus infection with a protracted course (44 days). The patient had received weekly efalizumab for approximately one year prior to event onset. Two days prior to hospitalization, the patient complained of headache and flu-like symptoms. He presented with cough, dyspnea and fever of 104°F. A chest-Xray was negative for pneumonia. The patient was hospitalized for 5 days with the diagnosis of sinus infection and treated with IV antibiotics. The event resolved after 44 days. Efalizumab was held during hospitalization

but dosing resumed 22 days after event onset. The investigator deemed the event to be unrelated to study drug.

Reviewer's comment: This case is notable for requiring hospitalization followed by a prolonged course of oral antibiotics.

25010 (Study ACD22430): The patient was a 29-year-old male who had received 7 doses of efalizumab. He developed cellulitis of the left thenar eminence and thumb that did not respond to oral antibiotics. The patient was hospitalized and received multiple antibiotics before the cellulitis resolved. The investigator deemed the event to be unrelated to study drug.

Reviewer's comment: This case is notable for requiring hospitalization including multiple antibiotics prior to resolution.

20510 (Study ACD2062): A 43 year-old male was hospitalized with an abscess of the left calf and surrounding cellulitis. Duplex ultrasonography was negative on two occasions but detected a fluid collection in the left lower extremity. The subject underwent drainage and irrigation of the abscess. Cultures performed of the fluid were negative. The abscess responded slowly to antibiotics. He was discharged from the hospital on day 20. The subject had received a total of 19 doses of efalizumab in studies 2058 and 2062 combined at the 1mg/kg/week dose level. The investigator deemed the event related to study drug.

Reviewer's comment: This is not clearly infectious in etiology as the cultures of the abscess were negative. The case is notable for requiring prolonged inpatient hospitalization after drainage of the abscess.

All infectious adverse events (serious and non-serious):

Serious and non-serious infectious adverse events are shown in Table 70 below.

Table 70 Adverse Events Diagnostic of Infection Reported within the First Exposure Period for Subjects Treated Efalizumab

Adverse Event n	FE/Controlled	
	Placebo 715	All efalizumab 1620
Infection NOS	110 (15.4%)	225 (13.9%)
Herpes simplex	24 (3.4%)	74 (4.6%)
Urinary tract infection	9 (1.3%)	27 (1.7%)
Bronchitis	9 (1.3%)	31 (1.9%)
Viral infection	8 (1.1%)	30 (1.9%)
Gastroenteritis	24 (3.4%)	34 (2.1%)
Bacterial infection	4 (0.6%)	19 (1.2%)
Otitis media	9 (1.3%)	23 (1.4%)
Fungal dermatitis	1 (0.1%)	14 (0.9%)
Cellulitis	3 (0.4%)	13 (0.8%)
Fungal infection	0	7 (0.4%)
Furunculosis	3 (0.4%)	7 (0.4%)
Periodontal abscess	2 (0.3%)	9 (0.6%)
Pneumonia	2 (0.3%)	7 (0.4%)
Abscess	0	3 (0.2%)
Herpes zoster	0	4 (0.2%)
Axillary moniliasis	0	1 (<0.1%)
Parasitic infection	0	2 (0.1%)
Hepatitis	0	1 (<0.1%)
Meningitis	0	1 (<0.1%)
Moniliasis (includes axillary, vaginal,oral)	2 (0.3%)	5 (0.3%)
Sepsis	0	1 (<0.1%)

Overall, the term infection (NOS) among efalizumab-treated patients (13.9%) did not exceed that of placebo (15.4%). However, certain types of infections occurred in a higher proportion of efalizumab-treated patients as compared to placebo. These were HSV, viral infections, bacterial infections, cellulitis, fungal infection, abscess, oral thrush, and herpes zoster among others.

During the first exposure period of controlled clinical studies, there were 13 subjects (4 subjects in the placebo group or 1.5% and 9 in the XOMA efalizumab group or 1.3%) with 14 severe infections.

7.2.4 Malignancies

Malignancies in the first course, placebo-controlled experience are shown in Table 71.

Table 71 Serious Malignancies Experienced by Subjects Who Received Study Drug in the FE/Controlled Studies

Adverse Event	Efalizumab (XOMA or Genentech)			
	Placebo (n=715)	1.0 mg/kg/wk (n=1213)	2.0 mg/kg/wk (n=407)	All Efalizumab (n=1620)
Total ^a	2 (0.3%)	2 (0.2%)	0	2 (0.1%)
Gastrointestinal carcinoma	1 (0.1%)	0	0	0
Skin carcinoma	1 (0.1%)	2 (0.2%)	0	2 (0.1%)

FE=First Exposure

The numbers of malignancies diagnosed during the placebo-controlled FE experience are very small; however, no increase is noted in the efalizumab-treated patients vs. placebo-treated patients.

Malignancies (excluding non-melanoma skin cancer) diagnosed during the clinical trials for psoriasis included the following cases: lung carcinoma, metastatic rectal carcinoma, two cases prostatic carcinoma, breast carcinoma, Hodgkin's lymphoma, B cell lymphoma, and malignant melanoma (Table 72).

Table 72 Subjects with Solid Tumors and Melanoma (updated May 2003)

Subject ID/ Study	Age (yr)/ Gender	Malignancy	Manufacturer	Dose Group (mg/kg/wk SC)	Cumulative Dose (mg/kg)
81691/ ACD2059g	70/ F	Colon cancer	XOMA	Placebo	Placebo
11520/ ACD2058g	60/ M	Metastatic rectal cancer (the subject died)	XOMA	1.0	11.7
20508/ ACD2058g	72/ F	Colon cancer	XOMA	2.0	41.4
73210/ ACD2059g	64/ F	Breast cancer	XOMA	2.0	12.7
23403/ ACD2062g	51/ M	Prostate cancer	XOMA	1.0	22.4
23512/ ACD2058g	71/ M	Prostate cancer	XOMA	1.0	22.4
25902/ ACD2243g	62/ F	Lung cancer	Genentech	2.0	22.7
28917/ ACD2243g	61/ F	Colon cancer	Genentech	1.0	64.7
25916/ ACD2243g	62/ M	Malignant melanoma (in situ)	Genentech	2.0	
30408/ ACD 2391g	75/ M	Colon Cancer	Genentech	1.0	

The patient with the melanoma reportedly had a large pigmented lesion prior to enrollment. The lesion was biopsied by the investigator after the initiation of efalizumab therapy.

Reviewer's comment: Any unexplained conditions, such as a large suspicious pigmented lesion, should have prompted exclusion of the patient into the study.

Table 73 Observed versus Expected Rate of Solid Tumors and Malignant Melanoma (updated May 2003)

Malignancy Category	Efalizumab-Treated Subjects			External Reference Cohorts		
	Observed No. of Subjects	95% CI	Observed Subject-Years	Cohort ^a	Expected No. of Subjects ^b	95% CI
Solid tumor	8	3.45, 15.76	1,790.06	SH	7.3	4.3, 11.6
				UHC	4.7	2.3, 8.1
				SEER	7.8	NA
Malignant melanoma	1	0.03, 5.57	1,790.82	SH	0.4	0.0, 2.3
				SEER	0.4	NA

^a SH=Saskatchewan Health; UHC=UnitedHealthcare; SEER=Surveillance, Epidemiology and End Results.

^b Calculation of expected number of events was based on the expected rate of events per 100 subject-years multiplied by the observed number of subject-years in the psoriasis efalizumab trials. The unadjusted expected incidence rates and number of events were given for the SH and UHC databases, whereas those derived from the SEER database were age and sex adjusted.

The point estimates for malignant melanoma and solid tumors are comparable in efalizumab-treated subjects compared to the reference groups and the 95% CI overlap. The one case of malignant melanoma may have actually been present before the start of treatment.

Table 74 Observed versus Expected Rates of Lymphoproliferative Malignancies: Efalizumab-Treated Subjects (updated July 25, 2003)

Efalizumab-Treated Subjects			External Reference Cohorts		
Observed No. of Subjects	95% CI	Observed Subject-Years	Cohort	Expected No. of Patients ^a	95% CI
2	0.24, 7.22	2203.16	SH	3.7	1.5, 7.7
			UHC	2.9	1.1, 6.2
			SEER	0.9	NA

SEER=Surveillance, Epidemiology and End Results; SH=Saskatchewan Health; UHC=UnitedHealthcare; CI=confidence interval.

^a Calculation of the expected number of events was based on the expected rate of events per 100 patient-years multiplied by the observed number of subject-years in the efalizumab psoriasis trials divided by 100. The unadjusted expected incidence rates and number of events were given for the SH and UHC databases, whereas those derived from the SEER database were age and sex adjusted.

The number of lymphoproliferative malignancies in the efalizumab-treated patients (2.0) was higher than the gender- and age-adjusted incidence derived from the SEER database (0.9) and lower than the incidence derived from the other reference groups (3.7 and 2.9). The confidence intervals around these point estimates overlapped.

Reviewer's comment: Overall, the incidence of solid tumors, melanoma and lymphoma is consistent with what might be expected based on external reference groups; however, the numbers of cases are too small to draw definitive conclusions about malignancy risk.

The two cases of lymphoproliferative malignancy observed among efalizumab-treated patients in clinical trials for psoriasis, were Hodgkin's disease and B cell lymphoma. Although, a third patient was diagnosed with cutaneous T-cell lymphoma after study completion, it is likely that this patient had pre-existing disease and was incorrectly enrolled with a misdiagnosis of widespread plaque-type psoriasis (See narrative below).

The patient who developed Hodgkin's disease received 4.0 mg/kg/wk SC XOMA efalizumab and had received a total of 29.4 mg/kg efalizumab over 136 days. Biopsy specimen was negative for Epstein-Barr virus. Hodgkin's disease was judged by the investigator to be related to efalizumab.

The patient who developed B cell lymphoma was a 57-year-old male. He participated in study ACD2243g, an open-label study in which prolonged maintenance treatment of efalizumab was evaluated. He had received regular dosing for approximately 2 years prior to the onset of the event with the 1-mg/kg/wk dose. He had a history of prior therapy with a 5-month course of methotrexate 4 years prior to his diagnosis of lymphoma, but had never received cyclosporine. The patient was diagnosed with B cell lymphoma after presenting with abdominal pain. CT scan revealed a ureteral stone and also mesenteric changes suggestive of a neoplastic process. Fine needle aspiration biopsy of an abdominal mass revealed atypical single cells and mixed small and large malignant cells which were LCA and CD20 positive suggestive of B cell lymphoma. EBV status was not obtained. The stage of the lymphoma was assessed as stage I bulky mixed large and small cell Non-Hodgkin's lymphoma. The investigator assessed the event of B cell lymphoma as related to efalizumab.

Cutaneous T-cell lymphoma: A 62-year-old male (Subject No. 79608) enrolled in study ACD 2059g and was randomized to 1.0 mg/kg/wk SC efalizumab during the first treatment period and re-randomized to placebo for the extended treatment period. The event occurred following completion of the study. The subject's medical history was significant for a seizure disorder, hypothyroidism, and heart disease. Concomitant medications upon entry into the study were vasotec, synthroid, and trileptal. During the retreatment period, a cutaneous infection was suspected, and a skin biopsy revealed lymphocytic atypia. Ciprofloxacin was initiated, in addition to triamcinolone acetonide for worsening psoriasis. The patient's skin disease worsened during treatment with efalizumab during the first treatment period and he was classified as a "non-responder." After completion of the study, treatment with acitretin was added for psoriasis. The following month, a repeat biopsy revealed patterns consistent with cutaneous T-cell lymphoma. Subsequent evaluations, including a full body CT scan, were negative for

metastases. Treatment included bexarotene and denileukin diftitox. At the time of this report the subject remains stable and the event is ongoing. The investigator determined the cutaneous T-cell lymphoma to be not related to study drug.

Reviewer's comment: Based upon the photographs of the patient's skin disease at baseline (violaceous annular coalescing plaques), it is the clinical impression of this reviewer that the patient likely had widespread cutaneous T-cell lymphoma rather than plaque-type psoriasis upon entry into the study. Although, the patient was not diagnosed with cutaneous T-cell lymphoma until after study completion, the diagnosis of this malignancy is typically delayed for many years, requiring multiple biopsies to differentiate from non-malignant T-cell mediated skin disorders such as psoriasis and atopic eczema. Of note, this patient's skin disease worsened during treatment with efalizumab during the first treatment period and he was classified as a "non-responder" by PASI, PGA and OLS.

7.2.5 Nonmelanomatous Skin Cancers

The most frequently occurring malignancy in clinical trial subjects was non-melanoma skin cancer (NMSC). Table 75 below shows the observed vs. expected number of non-melanomatous skin cancer by treatment group based on two reference cohorts, United Healthcare and Saskatchewan Health. The SEER database does not contain information with regard to non-melanomatous skin cancer for comparison.

Table 75 Observed vs. Expected Rate of Non-melanomatous Skin Cancer Efalizumab vs. Placebo

Treatment Group	Study Subjects			External Reference Cohorts		
	Observed No. of Subjects	95% CI	Observed Subject-Years	Cohort ^a	Expected No. of Subjects ^b	95% CI
Efalizumab	20	12.22, 30.89	1784	SH	7.0	3.9,11.2
				UHC	7.0	4.1,11.1
Placebo	2	0.24, 7.2	185	SH	0.7	0.4, 1.2
				UHC	0.7	0.4, 1.2

^a SH=Saskatchewan Health; UHC=United Healthcare

^b Calculation of expected number of events was based on the expected rate of events per 100 subject-years multiplied by the observed number of subject-years in the psoriasis efalizumab trials. The unadjusted expected incidence rates and number of events were given for the SH and UHC databases

The number of efalizumab-treated subjects with non-melanomatous skin cancer (20) exceeded the expected number based on the reference cohorts (7) with nonoverlapping confidence intervals.

Reviewer's comment: The higher incidence of non-melanomatous skin cancer than expected is possibly due to ascertainment bias. Additionally, it is important to identify an

appropriate comparator when assessing the risk of malignancies in the more severe psoriasis-population as these patients are at increased risk for both non-melanoma skin cancer as well as lymphoproliferative malignancies due to previous treatment (e.g. cyclosporine, PUVA) and, possibly, other factors relevant in this patient population.

A comparison of the NMSC incidence rates per 100 subject-years of treatment between subjects receiving efalizumab and those receiving placebo is shown below (see Table 76).

Table 76 Observed Rates for Non-Melanomatous Skin Cancer: Placebo-Treated and Efalizumab-Treated Subjects

	Observed No. Of Subjects	Observed Subject- Years	Rate/100 Patient- Years	95% CI for Rate
Placebo	2	185	1.08	0.13, 3.89
Efalizumab	20	1784	1.12	0.68, 1.73

The NMSC incidence rates per 100 subject-years of treatment between subjects receiving efalizumab and those receiving placebo are similar with overlapping confidence intervals. The point estimate was 1.08 for placebo and 1.12 for efalizumab. Although, the placebo comparison yielded similar rates between treatment groups, the small number of cases makes it difficult to exclude an increase in risk of non-melanomatous skin cancer.

For 20 efalizumab-treated subjects, 13 events of basal cell carcinoma and 13 events of squamous cell carcinoma were reported. For 2 placebo-treated patients, two events of basal cell and squamous cell carcinoma each were reported. Thus, for both efalizumab-treated and placebo-treated subjects, the ratio of basal cell to squamous cell carcinoma was 1:1. As of December 2002, the ages of patients who were diagnosed with NMSC ranged from 44 to 68 and the cumulative dose of efalizumab ranged from 1mg/kg to 68 mg/kg (data not shown).

7.2.6 CNS Adverse Events

Patient 14025: Aseptic meningitis

A 20-year-old man (14025) was randomized to receive 2.0 mg/kg/wk efalizumab, and a conditioning dose was administered. The day after receiving his first dose of study drug, the subject experienced the onset of severe meningitis. He presented to the ER with a severe throbbing bifrontal headache, nausea without vomiting, chills, and myalgia and arthralgia of 2–3 days' duration. Results of a cranial CT scan were negative. Aseptic meningitis was diagnosed with cerebrospinal fluid showing WBC count of 550/cmm (differential of 14 mononuclear cells and 86 polymorphonuclear cells), CSF glucose of

54 mg/dL, CSF protein of 55 mg/dL and negative CSF for bacterial antigens. A gram stain of CSF showed 2+ WBC counts and no organisms. Treatment included prochlorperazine, promethazine hydrochloride, ibuprofen, lidocaine, acetaminophen/hydrocodone bitartrate, butorphanol bitartrate, and sodium chloride. The event resolved after 7 days with no reported sequelae. Test results for anti-efalizumab antibodies were negative. The subject discontinued study drug treatment after the conditioning dose because of the event. He entered the follow-up period and went on to complete the study. The investigator classified the adverse event as related to study drug.

Reviewer's comment: This adverse event is possibly related to study drug due to the close temporal relationship to study drug administration and was deemed by the investigator as related. The cause of this adverse event might be a cytokine release reaction.

Patient 32425: Transverse myelitis

A 34-year-old white male (32425) received 1 mg/kg of efalizumab in study ACD2390g. Two days after the second dose, the patient experienced paresthesia and pain of right side of his body. MRI showed a central cord enhancing lesion and Chiari malformation; spinal cord biopsy with foamy macrophages was interpreted as a demyelinating process. The patient's condition progressed to involve impairment of bowel, bladder and sexual function. He discontinued from the study due to the adverse event. The investigator classified the adverse event as related to study drug.

Reviewer's comment: This case represents an example of a potentially autoimmune-mediated adverse event. The event was ameliorated with the use of systemic corticosteroids.

7.2.7 Laboratory Adverse Events/ Changes

7.2.7.1 Hematology

Thrombocytopenia

Table 90 below is a listing of patients who experienced platelet counts below 50,000 during the clinical trials with efalizumab or who had serious adverse events of thrombocytopenia. A total of 8 patients are included. Five of these patients were classified as having serious adverse events with regard to thrombocytopenia. One of the patients had a pre-existing diagnosis of idiopathic thrombocytopenia and had a below normal platelet count at baseline. Two other patients had a history of autoimmune disease, Grave's disease.

No placebo patients fell into this category. However, one must also take into consideration differences in the period of observation between placebo-treated patients and patients during treatment with efalizumab.

Table 77 Subjects with Serious Adverse Event(s) of Thrombocytopenia or a Reported Platelet Level below 50,000/cmm

Subject	Age(yr) Gender	Onset	Medical history	Concomitant Medications	Baseline platelets/ mm3	Nadir platelets/ mm3	Treatment
10501 (SAE) 2058g	61/ M	112 d (3.7 mo) post first study drug (2 mg/kg) and 20 days after last study drug (6/00)	negative	Terazosin (12/99), ibuprofen (95), aspirin (6/00)	274, 000	52,000 normocellular bone marrow biopsy	Study drug D/C, prednisone Event resolution (10/00)
23512	71/ M	During retreatment	Cardiomegaly, hyperlipidemia, fistula repair, elevated PSA	Pravastatin (97->), aspirin (97->), amoxicillin/clavilinate (12/00), Nefazodone,	213,000	40,000	Case identified retrospectively, no treatment rendered
27103 (SAE)	29/ M	145 days (4.8 mo) post first dose study drug	TMJ, seizures, migraine headaches	amoxicillin/clavulanate, PCN, cephalexin, cyclobenzaprine, methadone, divalproex sodium	176,000	30,000	Study drug D/C, prednisone Event resolved
33203 (SAE)	40/ F	84 days (3 mo)	Grave's disease	Levothyroxine (since 1995), simvastatin (since 1996)	155,000	10,000, heavy vaginal bleeding, positive antiplatelet antibody	requiring 10 unit platelet transfusion and RhoGAM for bleeding, D/C study drug, prednisone
37204	78/ F	24 weeks (6 mo) after first dose of study drug	Acid reflux ds, ruptured aortic aneurysm	none	141,000	27,000	Study drug D/C
41232 (SAE) 2601g	39/ M	168 days (5.6 mo)	Hypertension, alcohol use, asthma		242, 000	16,000, normocellular bone marrow	Prednisone, Event ongoing
44202 (SAE)	73/ F	138 days (4.6 mo)	Hypertension, Grave's disease	Thyroid, quinapril (6/97), atenolol (6/97), hydroxyzine (12/02), cephalexin, propranolol (1/03), flurazepam (1/03)	199,000	3,000 ANA >1:1280 Generalized axonal neuropathy	Prednisone Event ongoing, with recurrence of low platelets upon prednisone taper
25239 00259	63/ F	5.5 mo	ITP (dx 1998 prior to enrollment), hypertension, coronary disease	Diltiazem, glyburide, enalapril, isorbide, digoxin, furosemide, metformin, atorvastatin, acetylsalicylic acid	94,000	48,000	Discontinued from the study

Reviewer's note: Hematologic evaluation was performed only at baseline and at study day 84 in some of the clinical trials, e.g. study ACD2600g. This might partially explain why, in the table above, the onset date was not shorter than study day 84. Concomitant drugs or medical conditions could have been responsible for thrombocytopenia in certain patients, e.g. previous history of idiopathic thrombocytopenia in patient 2523900259.

Human platelets and megakaryocytes express surface CD11a and LFA-1, and the murine progenitor of the humanized antibody used in the psoriasis clinical trials has been reported to bind to human platelets. Therefore, there is a molecular basis for these adverse events of thrombocytopenia potentially linking it to the study drug. The delayed time course (at least 3 months in most cases) of the thrombocytopenia in addition to the response to systemic steroids suggests an immune-based mechanism of platelet depletion rather than direct toxicity. Furthermore, one patient (33203) tested positive for an anti-platelet antibody. It is unknown whether the other patients were tested.

Narratives for the patients with serious adverse events of thrombocytopenia are provided below.

Patient 44202:

The patient was a 73-year-old woman enrolled in Study 2601g, an open label-multicenter study for patients who previously participated in study 2600g. The patient received efalizumab (1 mg/kg/wk) for psoriasis in Study 2600g starting in September 25, 2002. On March 6, 2003, her platelet count was noted to be 3,000/ mm³ without associated symptoms. She was admitted to the hospital. Her evaluation was positive for ANA>1:1280. She was treated with IV steroids and discharged with a platelet count of 67,000/ mm³ and oral prednisone. Her medical history and concomitant medications were not reported. The investigator assessed the event as not related to efalizumab. The sponsor's assessment of causality is possibly related.

Patient 10501

A 61 year-old man patient treated with efalizumab 2 mg/kg for approximately 12 weeks prior to the onset of the event. The patient's platelet count was within the normal range from March 21, 2000 to May 17, 2000. On June 14, 2002 his platelet count was 124, 000 cells/mm³. By July 19,2000, it had dropped to 63,000 cells/mm³. He had no associated evidence of bleeding or hepatosplenomegaly. His bone marrow was normocellular on biopsy. His initial treatment was with systemic steroids. The event resolved after 112 days. The investigator's assessment was possibly related.

Patient 33203

41-year-old female treated with efalizumab 1 mg/kg for approximately 22 weeks prior to event onset. She presented with bruising and her platelet count was found to be 10, 000 cells/mm³. She was permanently discontinued from the study. On August 24, 2002, she was hospitalized with heavy vaginal bleeding and required a platelet transfusion of 10

units and RhoGam. The thrombocytopenia resolved after 41 days. The investigator assessed the event as possibly related.

Reviewer's comment: Although the event was reported to have resolved, the patient at last report was still receiving prednisone at a dose of 25 mg po per day. Therefore, more follow-up is needed to determine whether the patient remained prednisone-dependent for the treatment of her thrombocytopenia.

Patient 27103

A 29-year-old male subject with a past-medical history of thrombocytopenia and generalized seizures, controlled with medication (phenitoin and divalproex). The subject received efalizumab 1 mg/kg for 17 months and the dose increased to 2 mg/kg 10 days prior to event onset. The subject required hospitalization for diminished oral intake and his platelet count was found to be 6,000 cells/mm³. The event resolved after 35 days. The subject was permanently discontinued from the study. The investigator stated that the event was not related to efalizumab.

7.2.8 Psoriasis Flares and Rebound

Of the 2589 subjects treated with SC efalizumab (Genentech or XOMA materials), 19 (0.7%) had a serious adverse event of psoriasis. These included psoriasis flares that occurred both during treatment and after treatment discontinuation.

The following were observed in subjects treated with the to-be-marketed efalizumab (i.e. Genentech material):

- In the first exposure of controlled clinical trials of efalizumab, adverse events of psoriasis occurred in more subjects receiving efalizumab (2.4%, n=22) than placebo (1.1%, n=5).
- Only subjects receiving efalizumab experienced psoriatic erythroderma, pustular psoriasis and palmoplantar psoriasis.
- In the FE studies, <1% of subjects experienced severe psoriasis and <0.5% discontinued efalizumab treatment because of psoriasis as an adverse event.
- In the EE studies, the incidence of adverse events of psoriasis was lower during Weeks 24–60 of continuous treatment compared with Weeks 12–24 of treatment.
- Adverse events of psoriasis were similar to FE during RE.
- Adverse events of psoriasis were approximately three times as common and more likely to be serious or severe during WO compared with FE.

Table 78 below shows the proportions of patients in the first exposure controlled period with psoriasis adverse events occurring during treatment. This table includes all psoriatic adverse events by morphology, both serious and non-serious.

Table 78 Psoriasis Flares and Variants Reported for First Exposure, Controlled Period (XOMA and GNE)

Adverse Event	Placebo 479	All Efalizumab 1171
Subjects with psoriasis AEs	8 (1.7%)	42 (3.6%)
Psoriatic erythroderma	0	6 (0.51%)
Pustular psoriasis	0	4 (0.34%)
Guttate psoriasis	2 (0.4%)	13 (1.1%)
Recurrence of plaque psoriasis	4 (0.8%)	9 (0.8%)
Unusual morphology	2 (0.4%)	6 (0.51%)
Inverse psoriasis	0	3 (0.26%)
Palmo-plantar psoriasis	0	1 (0.08%)

In this analysis, all the cases of psoriatic erythroderma and pustular psoriasis occurred in the efalizumab treatment arms. One patient with erythroderma in the first exposure controlled portion required hospitalization (25609).

Table 79 below shows the serious adverse events of psoriasis in efalizumab-treated patients by treatment period.

Table 79 Serious Adverse Events of Psoriasis Flares Experienced by Subjects Treated with Efalizumab

Subject ID	Event	Exposure Period	Response to Treatment	Admitted to Hospital
25609	Erythroderma	FE	NR	Yes
16513	Erythroderma	EE	NR	Yes
82009	Exfoliative erythroderma	EE	Initial R, then lost efficacy to NR	Yes
16517	Erythroderma	RE	PR	Yes
19515	Erythroderma	WO	NR	Yes
21505	Erythrodermic pustular	WO	R	Yes
25906	Pustular von Zumbusch	WO	NR	No
27708	Pustular	WO	PR initially then lost efficacy to NR	Yes
64006	Flare	WO	NR	Yes
82024	Erythroderma	WO	R	Yes
12516	Pustular	Post-WO	NR	Yes
16533	Erythroderma	NC ^a	NR	Yes
25914	Pustular von Zumbusch	Post-WO	PR initially then lost efficacy to NR	No
28615	Pustular	Post-WO	R	No
80002	Atypical flare	Post-WO	NR	Yes
16511	Erythroderma	NC ^a	NR	Yes

NC=not classified; NR=non-responder or non-response; PR=partial responder; R=responder. WO= washout; FE= first exposure; EE= extended treatment

^a The event occurred approximately 4 weeks after early discontinuation from FE. The subject had received three doses of efalizumab. The case was also counted during WO.

Most of the psoriasis adverse events that required hospitalization occurred in the extended treatment, washout or post-washout period. Although most of the patients were classified as non-responders, some patients who were responders subsequently developed serious psoriasis-related complications.

Narratives of Psoriasis-related Adverse Events:

Subject No.: 12516

Events: Psoriasis (pustular psoriasis flare)

This 59-year-old man was randomized to 2.0 mg/kg/wk efalizumab in study ADC2058g and received his initial dose of 0.7 mg/kg on 15 May 2000. He also had had psoriasis for 6 years and had previously used systemic therapies. The patient's only medication at baseline was chlorpheniramine maleate/phenylpropanolamine hydrochloride, for sinus, since the 1960's. On FT Day 76, the patient was diagnosed with impetigo for which he was prescribed doxycycline. On FT Day 77, on the day his last dose of efalizumab, he began to experience a severe psoriasis flare accompanied by headaches, nausea and

vomiting which lead to discontinuation from the study. The patient was treated with methotrexate and corticosteroid therapy. Approximately 10 days later, while on methotrexate and corticosteroid therapy, a severe diffuse pustular psoriasis flare was diagnosed for which he was hospitalized. The pustular psoriasis flare resolved in 8 days, and the headache, malaise, and vomiting continued beyond the subject's participation in the study. The investigator determined the psoriasis flare, headache, malaise, vomiting, and the serious adverse event of pustular psoriasis flare to be not related to study drug.

Reviewer's comment: Of note, the patient had severe flare of psoriasis during the first treatment period. This was followed by the episode of pustular psoriasis while on systemic corticosteroids and methotrexate. The fact that these events followed so closely and began within 1 day of dosing would make it seem unlikely that close observation with institution of alternative treatment could have prevented the sequence of events. In addition, according to the history, the patient developed "impetigo" within one day preceding the adverse event of psoriasis flare. Pustular impetigo is in the clinical differential diagnosis of pustular psoriasis and therefore, it is conceivable that the patient had pustular psoriasis rather than the impetigo. If this were the case, the pustular psoriasis diagnosis would have taken place during the first treatment period. It is also, worth noting that the patient demonstrated improvement in his psoriasis during the first treatment period his PASI improvement was up to 82% on FT day 42, approximately mid-way through his treatment course. This reviewer disagrees with the investigator's assessment of causality as the temporal relationship of this event as well as lack of an alternative explanation would indicate that the adverse event could possibly be related to use of the study drug.

Subject No.: 16517

This 30-year-old man had had psoriasis for 12 years and had a history of systemic therapy. He initially participated in the Genentech-sponsored study ACD2058g. He received placebo for the first 12 weeks followed by 2.0 mg/kg/wk SC efalizumab for the subsequent 12 weeks (ET), for a total of 12 doses of efalizumab. The patient showed clinical response to his first exposure to study drug in the ET period and ended the treatment with a PASI score of 3.9, an 85% improvement in PASI from baseline. Within one month of discontinuing therapy, during the follow-up period, however, his PASI increased to 25.7.

Approximately 5 weeks after discontinuation of therapy, the subject entered Study ACD2062g in the Re-Exposure group with a PASI score of 61.2. The day after receiving his first dose of study drug, the subject was hospitalized for a severe erythrodermic psoriasis flare. The investigator determined the event of erythrodermic psoriasis flare to be not related to study drug.

Comments: Note, this patient's psoriasis quickly deteriorated within one month of discontinuation of therapy and the patient suffered an erythrodermic flare resulting in

hospitalization within 5 weeks of stopping therapy. Of note, this case meets the National Psoriasis Foundation's definition of rebound: a PASI of 125% of baseline or new generalized pustular, erythrodermic or more inflammatory psoriasis occurring within 3 months of stopping therapy.

Four subjects were receiving efalizumab at the time of the serious adverse event of psoriasis:

Subject No.: 25609

This 66-year-old woman had psoriasis for 15 years and a history of systemic therapy. She entered Study ACD2243g and was randomized to receive 2.0 mg/kg/wk SC efalizumab without topical corticosteroid therapy in the FT period. PASI at the time of the conditioning dose was 33. After receiving the fifth dose of study drug, the subject's PASI was 25. A total of seven doses of efalizumab were given.

Six weeks after her first dose, the subject began to develop a severe psoriasis exacerbation and discontinued efalizumab treatment and study participation. One week later, she developed a severe erythrodermic exacerbation of psoriasis and was hospitalized. PASI at this time was 31. Treatment included triamcinolone wraps, cyclosporine, and methotrexate. The subject was discharged in good condition in 4 days. The event resolved after 5 days. The investigator determined the psoriasis exacerbation and erythrodermic exacerbation of psoriasis to be related to efalizumab.

Comments: Of note, the patient's PASI score at the time of her erythrodermic flare, 31, was similar to her baseline PASI score of 33. The narrative does not address whether the patient had a positive anti-efalizumab antibody. It is unusual that the patient received both cyclosporin and methotrexate in the hospital.

Subject No.: 82009

54-year-old man. During the FT period, the subject's PASI scores had decreased from 13.6 to 2.8, and the percentage of psoriatic BSA had decreased from 12.9% to 3.0%. On 4 September (ET Day 4), the subject reported that his psoriasis had worsened. Within 1 week, his body was covered with psoriatic lesions and he was erythrodermic. On 14 September 2000, he returned for evaluation and was noted to be erythrodermic with a PASI of 59.6 and a BSA of 90% involvement. According to the investigator, the psoriasis flare was not related to efalizumab.

Comments: This patient initially improved with efalizumab therapy. However, in this case, the patient developed clinically significant worsening requiring hospitalization despite continuing the treatment and negative anti-efalizumab antibody test results.

Table 80 below shows the non-serious psoriasis-related adverse events by treatment period.

Table 80 Non-Serious Adverse Events of Erythrodermic or Pustular Psoriasis Reported for Efalizumab-Treated Subjects

Subject ID	Event	Exposure Period	Response to Treatment	Intensity
82026	Erythroderma	FE	NR	Severe
34229	Erythroderma	FE	NR	Severe
75610	Erythroderma	FE	NR	Severe
79202	Pustules in groin	FE	PR	Severe
69202	Erythroderma	WO	R	Severe
79208	Pustular lesions on groin/buttocks	WO	PR initially then lost efficacy to NR	Severe
80811	Erythroderma	WO	R	Severe
82003	Erythroderma	WO	PR	Severe

NR=non-responder or non-response; PR=partial responder; R=responder.

Each of these non-serious adverse events was listed as severe in intensity. They occurred both during treatment and after discontinuation with treatment. In some cases, the patient was classified as a responder and experienced rebound upon discontinuation of study drug. There were no cases of psoriasis variants in the control group.

Some of patients (e.g.11504, 17501) who discontinued from the study with psoriasis-related adverse events including (including some who had variants of psoriasis) were incorrectly classified as having discontinued for other causes i.e. “physician’s decision.”

7.2.9 Arthritis-Related Adverse Events

The incidence of arthritic adverse events by treatment group is shown in Table 81 below.

Table 81 Arthritis-Related Adverse Events Studies ACD2058g, ACD2059g, ACD2390g, and ACD2600g (FT Period): All Subjects

COSTART Preferred Term	Classification	Placebo (N=715)	Efalizumab 1.0 mg/kg/wk (N=1213)	Efalizumab 2.0 mg/kg/wk (N=407)	Efalizumab All Subjects (N=1620)
Subjects with completed forms		715	1213	407	1620
- Total -		16 (2.2%)	29 (2.4%)	16 (3.9%)	45 (2.8%)
Arthritis NOS		7 (1.0%)	8 (0.7%)	9 (2.2%)	17 (1.0%)
Exacerbation/flare psoriatic arthritis		2 (0.3%)	13 (1.1%)	4 (1.0%)	17 (1.0%)
Worsening/increasing psoriatic arthritis		3 (0.4%)	5 (0.4%)	2 (0.5%)	7 (0.4%)
Psoriatic arthritis		3 (0.4%)	2 (0.2%)	1 (0.2%)	3 (0.2%)
Osteoarthritis		1 (0.1%)	1 (<0.1%)	1 (0.2%)	2 (0.1%)

During the first treatment period, a higher proportion of patients in the combined efalizumab-treated group experienced exacerbation/ flares in psoriatic arthritis than placebo (1.1% vs. 0.3%). The incidence of arthritis not otherwise specified and osteoarthritis was the same in the combined efalizumab groups as in the placebo group. The incidence of arthritis-related adverse events was 2.2% in placebo, 2.4% in the 1-mg/kg/wk and 3.9% in the 2-mg/kg/wk groups.

There have been 15 cases of serious adverse events for arthritis, 0.6% of the studied population. None of the serious adverse events occurred within the first treatment period of placebo controlled studies.

Some of the serious adverse events for inflammatory arthritis are notable for occurring in association with other findings of inflammation, including neuritis, peripheral edema and bilateral cellulitis, fever and positive ANA. See the narratives below.

New onset inflammatory arthritis, accompanied by fever, peripheral edema, and neuritis: patient (28336)

The subject, a 49-year-old man, with a three-year history of psoriatic arthritis, previously treated with systemic corticosteroids, but negative history for psoriatic arthritis entered Study ACD2243g and was randomized to receive 2.0 mg/kg/wk SC efalizumab. After receiving, four doses of efalizumab, the patient experienced severe inflammatory arthritis, characterized by left ankle pain, followed by moderate bilateral lower leg peripheral edema and cellulitis of both feet. The patient was treated with nonsteroidal antiinflammatory medications and antibiotics without improvement, and continued to receive efalizumab. Approximately 7 weeks after the first dose, the subject complained of arthralgias, neuritis to feet, total body joint inflammation, and severe right knee pain associated with a right knee effusion, and increasing bilateral lower extremity peripheral edema. The patient was unable to ambulate subsequently hospitalized for further evaluation. Evaluation was negative for a deep vein thrombosis. An antinuclear antibody test done previously was positive and chemistries revealed an elevated sedimentation rate and creatine kinase. The patient received systemic corticosteroids and IV antibiotics. By the following day, the edema had markedly decreased and the subject was discharged on methylprednisolone, cephalexin, gabapentin. By 8 weeks after the first dose and 1 week after discontinuation of efalizumab, the subject experienced intermittent fevers lasting 45 days. He was re-hospitalized for three days for increased ankle edema and lower extremity pain. He underwent aspiration of a left knee effusion twice following discharge. He was hospitalized for left knee debridement, lavage, and antibiotic therapy. Laboratory results revealed an elevated sedimentation rate. During hospitalization, the subject experienced intermittent fevers, but an infectious etiology was ruled out. The subject continued to have an elevated sedimentation rate, and steroid therapy was initiated. A rheumatologist made the diagnosis of inflammatory arthritis and initiated methotrexate. The subject continued to have intermittent pain and edema to his lower extremities, while his arthritis was improved by 7 months after the onset of the adverse event. The event remains ongoing. The investigator determined the inflammatory arthritis and bilateral lower extremity cellulitis to be related to efalizumab.

Reviewer's comment: This adverse event is unusual because it resulted in hospitalization on three occasions and (as of the most recent report to the Agency) failed to resolve after discontinuation of therapy. After examining the clinical database, it was determined that the patient tested negative to anti-efalizumab antibodies during and after treatment discontinuation.

Psoriatic Arthritis and psoriasis flare (25601)

A 24-year-old Asian female assigned to 1.0 mg/kg/wk efalizumab enrolled in Study ACD2243g and received the first dose of 2.0 mg/kg/wk efalizumab on 22 March 2001. The subject's medical history was significant for adequately controlled type 1 diabetes

(since 1996) and psoriatic arthritis in the knees (since 1997). The subject experienced two events of a psoriatic arthritis flares. On 10 September 2002, the subject was evaluated by her physician for left-knee pain. Treatment included celecoxib. Within a few days she noted swelling in both knees and an X-ray of the left knee revealed a small joint effusion. One week later, the subject was unable to ambulate. She was admitted to the hospital where she was treated for 3 days. An arthrocentesis was performed, which revealed a white blood cell (WBC) count of 41,000/ μ L, with 87% segmented neutrophils, and no crystals and no organisms identified on Gram stain. The subject's Rhesus factor was 30, erythrocyte sedimentation rate was 40 mm/hr, and an antinuclear antibody test was positive. The subject noted her psoriasis started to worsen during hospitalization and continued to worsen despite having initiated treatment with methotrexate. She was subsequently hospitalized with an erythrodermic psoriasis flare. The psoriatic arthritis flare was noted to resolve on December 17, 2002. The investigator determined the psoriatic arthritis flare to be related to study drug and the psoriasis flare not to be related to study drug.

Reviewer's comment:

This case was notable for a flare in both psoriasis and psoriatic arthritis.

7.2.10 Serious Vascular and Thrombotic Events

Table 82 below presents serious cardiovascular events experienced by subjects within the first treatment period of placebo controlled studies.

Table 82 Serious Cardiovascular Adverse Events First Exposure Controlled Studies

Adverse Event n	Placebo 715	Efalizumab (combined) 1620
Subjects with at least one event	1 (0.1%)	4 (0.2%)
Coronary artery disorder	0	2 (0.1%)
Angina pectoris	0	0
Arteriosclerosis	0	0
Arteriospasm	0	1(<0.1%)
Myocardial infarct	1 (0.1%)	1(<0.1%)
Deep thrombophlebitis	0	0
Cerebral ischemia	0	0
Pulmonary embolus	0	0
Peripheral vascular disorder	0	0

The incidence of these serious cardiovascular events was low and was similar between efalizumab- and placebo-treated subjects. There was no apparent increase in incidence in serious cardiovascular events associated with efalizumab treatment. However, the numbers are too small to draw any definitive conclusions.

7.2.11 Serious Inflammatory and Autoimmune Reactions

Two cases of pneumonitis occurred in clinical development (See narratives below). One case was classified as eosinophilic pneumonitis. In addition, search of the sponsor's safety database was performed which revealed another case of pneumonitis in a 38 year old-man. One patient presented with adenopathy, fever, and arthritic symptoms which her clinician indicated was a diagnosis of a serum-sickness like reaction.

Eosinophilic pneumonitis

The patient (40011) is a 66-year-old male with a history of hypertension enrolled in trial ACD2601g. His history was negative for previous autoimmune disease, methotrexate use or lung disease. He received efalizumab 1 mg/kg/wk SC for 6 months. Concomitant medications included aspirin, hydrochlorothiazide and propranolol (dates unknown). The patient was diagnosed after having presented with flu-like symptoms and shortness of breath beginning on 31-Jan-2003, three months after his first dose of efalizumab in trial ACD2600g. The drug was temporarily stopped on 21-Feb-2003 but then resumed on 27-Feb-2003. The patient had an increased white blood cell count of $19.9 \times 10^3/\text{mm}^3$ and notable for an eosinophil count of 13%. Chest radiography and follow-up CT scan both showed cardiomegaly and bilateral diffuse interstitial lung disease. Pulmonary function tests showed significant restrictive lung disease with gas transfer defect. Lung biopsy showed mild, non-specific, chronic inflammation and interstitial thickening without atypia. The patient was treated by permanent discontinuation of efalizumab (last dose April 23, 2003) and systemic corticosteroids. The patient's symptoms resolved after the drug was discontinued. The investigator classified the event as possibly related to study drug.

Reviewer's comment: The patient continued to receive efalizumab for several months despite having had continued symptoms of a flu-like illness and dyspnea, an important protocol violation to note. If licensed, the label should advise to withhold dosing in the presence of unexplained pulmonary symptomatology such as shortness of breath.

Pneumonitis

The second patient is a 38 year-old man who was enrolled in study ACD2059g. The subject received efalizumab 1.0 mg/kg/wk in the first treatment course, first dose received on August 8, 2000. On January 15, 2003, the patient was hospitalized for a fever and ongoing dry cough and was noted to be hypoxic (pO₂ level of 52). Chest X ray revealed diffuse parenchymal changes consistent with drug-induced hypersensitivity. Bronchoscopy results were unremarkable with all cultures and diagnostic tests negative. The patient received supplemental oxygen, trimethoprim/sulfamthoxazole and methylprednisolone. The pneumonitis resolved on February 26, 2003. The investigator indicated the final diagnosis was pneumonitis of unknown etiology and assessed the event as related to study drug.

Serum-sickness-like reaction

The patient (42004) is a 35-year-old female who received treatment with efalizumab 1.0 mg/kg/wk in study ACD2600g. Three and half weeks after receiving the first dose of efalizumab, the patient presented to the emergency room with tender cervical lymphadenopathy, fever and slight chest pressure. She was admitted to the hospital and the following laboratory evaluations were negative: chest x-ray, blood cultures, EBV titer, CMV titer, monospot. The patient had psoriatic arthritis at baseline and while in the hospital she experienced febrile episodes and an exacerbation of her psoriatic arthritis accompanied with an elevation of the erythrocyte sedimentation rate. She responded to prednisone at a dose of 60 mg per day with an improvement in her lymphadenopathy and psoriatic arthritis symptoms. The investigator's assessment of relationship to study medication was potentially related while the physician responsible for the patient's care in the hospital reported the relationship as causal and advised the patient not to receive efalizumab in the future. Follow-up information revealed that the patient's adenopathy had resolved without evidence of recurrence. Similar adverse events involving adenopathy and fever of unknown origin are in the efalizumab safety database. This event possibly represents a serum sickness-like reaction to the study drug.

7.3 Severe Adverse Events

During the first treatment period of controlled clinical trials, the proportion of patients with at least one severe adverse event was higher among efalizumab-treated (11.8%) patients than placebo-treated patients (6.9%).

7.4 Common Adverse Events

The following table depicts the adverse events that occurred in $\geq 3\%$ of patients treated with the Genentech material in the 1.0 mg/kg/week group compared to placebo-treated patients in the first exposure in controlled studies.

Table 83 Adverse Events that Occurred in $\geq 3\%$ of Subjects Treated with Genentech Material in the 1.0 mg/kg/wk Group or the Placebo Group in the FE/Controlled Studies

COSTART Body System/ Preferred Term	Genentech Efalizumab		
	Placebo (n=219)	1.0 mg/kg/wk (n=420)	2.0 mg/kg/wk (n=61)
Subjects with at least one adverse event	156 (71.2%)	338 (80.5%)	56 (91.8%)
Body as a whole			
Headache	46 (21.0%)	137 (32.6%)	18 (29.5%)
Infection	31 (14.2%)	51 (12.1%)	14 (23.0%)
Chills	10 (4.6%)	52 (12.4%)	8 (13.1%)
Pain	11 (5.0%)	44 (10.5%)	9 (14.8%)
Fever	3 (1.4%)	32 (7.6%)	7 (11.5%)
Flu syndrome	7 (3.2%)	28 (6.7%)	2 (3.3%)
Asthenia	12 (5.5%)	25 (6.0%)	4 (6.6%)
Accidental injury	21 (9.6%)	19 (4.5%)	5 (8.2%)
Digestive			
Nausea	14 (6.4%)	43 (10.2%)	8 (13.1%)
Diarrhea	14 (5.9%)	21 (5.0%)	5 (8.2%)
Gastroenteritis	10 (4.6%)	5 (1.2%)	0
Metabolic/nutritional			
Peripheral edema	9 (4.1%)	16 (3.8%)	3 (4.9%)
Musculoskeletal			
Myalgia	8 (3.7%)	40 (9.5%)	9 (14.8%)
Arthralgia	7 (3.2%)	14 (3.3%)	4 (6.6%)
Nervous			
Dizziness	4 (1.8%)	16 (3.8%)	4 (6.6%)
Hypertonia	8 (3.7%)	3 (0.7%)	1 (1.6%)
Respiratory			
Pharyngitis	12 (5.5%)	30 (7.1%)	5 (8.2%)
Rhinitis	13 (5.9%)	28 (6.7%)	4 (6.6%)
Cough increased	9 (4.1%)	17 (4.0%)	5 (8.2%)
Sinusitis	8 (3.7%)	16 (3.8%)	5 (8.2%)
Skin/appendages			
Herpes simplex	8 (3.7%)	21 (5.0%)	2 (3.3%)
Acne	0	14 (3.3%)	2 (3.3%)

Adverse events with a $\geq 1\%$ higher incidence among the efalizumab-treated patients compared to placebo-treated patients are highlighted in bold.

Adverse events with a 5% or higher incidence among efalizumab-treated patients compared to placebo-treated patients were: headache, chills, pain, fever, and myalgia. The incidence of adverse events appears to be higher in the 2 mg/kg group compared to the 1 mg/kg group.

7.5 **Hypersensitivity Reactions (serious and non-serious)**

The following table provides a placebo-controlled comparison of the hypersensitivity-related adverse events predefined in the clinical protocol.

Table 84 Hypersensitivity-Related Adverse Events Studies ACD2058g, ACD2059g, ACD2390g, and ACD2600g (FT Period): All Subjects Treated with Combined Materials

		Placebo	Efalizumab 1.0 mg/kg/wk		Efalizumab 2.0 mg/kg/wk		Efalizumab All Subjects	
COSTART Body System COSTART Preferred Term		(N=715)	(N=1213)		(N=407)		(N=1620)	
Subjects with completed forms		715	1213		407		1620	
Subjects with at least one hypersensitivity-related adverse event		49 (6.9%)	95 (7.8%)		37 (9.1%)		132 (8.1%)	
Body as a Whole	TOTAL	13 (1.8%)	26 (2.1%)		10 (2.5%)		36 (2.2%)	
	Allergic reaction	6 (0.8%)	14 (1.2%)		5 (1.2%)		19 (1.2%)	
	Face edema	6 (0.8%)	6 (0.5%)		3 (0.7%)		9 (0.6%)	
	Injection site hypersensitivity	1 (0.1%)	6 (0.5%)		2 (0.5%)		8 (0.5%)	
Respiratory	TOTAL	14 (2.0%)	15 (1.2%)		7 (1.7%)		22 (1.4%)	
	Dyspnea	3 (0.4%)	9 (0.7%)		3 (0.7%)		12 (0.7%)	
	Asthma	6 (0.8%)	4 (0.3%)		3 (0.7%)		7 (0.4%)	
	Laryngismus	5 (0.7%)	1 (<0.1%)		1 (0.2%)		2 (0.1%)	
	Bronchiolitis	(0.0%)	1 (<0.1%)		(0.0%)		1 (<0.1%)	
Skin/Appendages	TOTAL	26 (3.6%)	59 (4.9%)		20 (4.9%)		79 (4.9%)	
	Rash	20 (2.8%)	37 (3.1%)		11 (2.7%)		48 (3.0%)	
	Urticaria	3 (0.4%)	16 (1.3%)		6 (1.5%)		22 (1.4%)	
	Maculopapular rash	3 (0.4%)	8 (0.7%)		2 (0.5%)		10 (0.6%)	
	Angioedema	(0.0%)	1 (<0.1%)		3 (0.7%)		4 (0.2%)	
	Erythema multiforme	(0.0%)	1 (<0.1%)		(0.0%)		1 (<0.1%)	

The proportions of patients who experienced at least one hypersensitivity-related adverse event in the combined efalizumab group and the placebo group were similar, 8.1% vs. 6.9%.

A single case of erythema multiforme and four cases of angioedema took place in efalizumab-treated patients. Urticaria was at least three times more common in efalizumab-treated patients than in control (1.4% vs. 0.4%).

7.6 Immunogenicity

7.6.1 Anti-efalizumab Antibodies

The screening test for anti-efalizumab antibodies (HAHA) is less sensitive during treatment with efalizumab, due to interference by the drug with the assay. Therefore, the preferred analysis is one using the data from screening done after patients have undergone drug washout. The incidence of anti-efalizumab antibodies is shown in Table 85.

Table 85 Incidence of Anti-Efalizumab Antibodies in Genentech Sponsored Studies by Manufacturer

	Efalizumab Manufacturer			All Subjects
	Genentech	XOMA	Both ^a	
No. of HAHA-positive subjects/no. of subjects tested (all available data)	28/904 (3.1%)	38/716 (5.3%)	17/302 (5.6%)	83/1922 (4.3%)
No. of HAHA-positive /no. of subjects with follow-up samples ^b	12/173 (6.9%)	38/623 (6.1%)	17/267 (6.4%)	67/1063 (6.3%)
^a Subjects exposed to Genentech efalizumab in Study ACD2062g after prior exposure to XOMA efalizumab (subjects who are not included in manufacturer-specific columns).				
^b Only includes data from completed studies for subjects who tested positive or who had a negative sample at least 56 days after last dose.				

The incidence of anti-efalizumab antibodies was 6.3% (67/1063) among patients treated with either Genentech or XOMA-manufactured, 56 days after discontinuation of treatment. There was little difference in the incidence of HAHA antibodies by efalizumab manufacturer.

Six subjects with local injection-site reactions tested positive for HAHA. The adverse events coded to injection-site mass, hypersensitivity reaction, or inflammation and were described as irritation, inflammation, redness, lump, or urticaria. These adverse events resolved despite continued efalizumab therapy. A potential a relationship between presence of HAHA and local cutaneous reactions exists.

Of the HAHA-positive patients, 20% achieved a PASI 75 and 53.3% achieved a PASI 50. These data are consistent with the response rate, overall. However, the response was on the low side of the range of observed values in the dose groups tested in the phase 3 and open-label studies. Titers of the antibodies were generally low.

The long-term immunogenicity of efalizumab is not known.

Reviewer's comment: The association of arthritic and other inflammatory adverse events with HAHA positivity may be underestimated given that some of the patients may have discontinued the study prematurely due to their adverse event and thus, have missing data with regard to anti-efalizumab antibody screening.

7.6.2 Other Laboratory Changes and Adverse Events Associated with Efalizumab Therapy:

Effects on Total White Blood Cell Counts

During the FE/Controlled studies, mean WBC counts increased by approximately 30%–40% relative to baseline among subjects receiving Genentech efalizumab compared with no increase in placebo-treated subjects. Table 86 below shows the absolute change in WBC counts by treatment group. Leukocytosis was sustained throughout efalizumab treatment, including the EE and RE treatment periods, and subsequently resolved during WO after efalizumab discontinuation.

Table 86 Change in White Blood Cell Counts (K/cmm) from Baseline to Day 84 of Each Period for Subjects Treated with Genentech Efalizumab

Type of Study/Period	Genentech Efalizumab, Mean				
	Placebo	2.0 mg/kg/qow	1.0 mg/kg/wk	2.0 mg/kg/wk	3.0–4.0 mg/kg/wk
FE/Controlled	-0.15	NA	2.58	3.20	NA
FE	NA	2.17	2.59	2.68	3.81
EE-1	NA	3.03	2.56	2.71	2.72
EE-2	NA	NA	2.71	3.27	2.84
EE-3	NA	NA	2.65	2.77	4.92
EE-4	NA	NA	2.21	3.05	5.23
RE-1	NA	NA	2.40	2.97	NA
WO	NA	0.20	0.06	0.32	0.09

NA=not applicable.

The maximal WBC count observed in any efalizumab-treated subject was 26.0 K/cmm during the first 12 weeks of efalizumab treatment, 24.1 K/cmm during extended treatment, and 21.5 K/cmm during retreatment. All changes were between 3 and 4-fold of the upper limit of normal. The increase in WBC count appeared to be dose dependent.

Lymphocyte Counts

Table 87 shows the change in absolute lymphocyte counts from baseline by treatment group.

Table 87 Change in Absolute Lymphocyte Counts (K/cmm) from Baseline to Day 84 of First Treatment

Treatment Group	N	Baseline				Change			
		Mean	Mdn	Min	Max	Mean	Mdn	Min	Max
Placebo	664	1.9	1.8	0.4	4.2	0.05	0.0	-2.6	2.5
Efalizumab	1538	1.9	1.8	0.5	5.1	2.10	1.9	-1.2	9.4

A mean doubling of absolute lymphocyte counts took place at the end of the first treatment period in the efalizumab group compared to negligible changes in the placebo group. The clinical significance of this finding is unknown. The changes are reversible upon discontinuation of therapy.

Segmented Neutrophils

With the emergence of adverse events of low platelets and given that segmented neutrophils (among other WBC subsets) express CD11a, it is important to consider carefully any changes that are occurring in neutrophils. Mean decreases occur in the percentages of segmented neutrophils. The percentage change is -13.6% in the efalizumab 1.0 mg/kg/wk group the minimum percentage change is -55%.

In contrast to percentage changes in neutrophil counts, mean absolute neutrophil counts increased somewhat with treatment according to mean values (See Table 88).

Table 88 Change in Absolute Neutrophil Counts (K/cmm) from Baseline to Day 84 for Subjects Treated with Genentech Efalizumab

Treatment Group	N	Baseline				Change			
		Mean	Mdn	Min	Max	Mean	Mdn	Min	Max
Placebo	417	4.7	4.4	0.9	15.9	-0.16	-0.1	-11.0	8.0
Efalizumab 1.0 mg/kg/wk	816	4.6	4.5	1.1	18.0	0.26	0.2	-10.0	10.7
Efalizumab 2.0 mg/kg/wk	60	4.7	4.3	2.1	9.8	0.62	0.7	-4.8	4.0
Efalizumab (combined)	876	4.6	4.5	1.1	18.0	0.29	0.2	-10.0	10.7

Includes Studies ACD2059g, ACD2390g and ACD2600g

Thus, while the mean absolute neutrophil counts increased, the percent neutrophils decreased because the increase in lymphocytes was relatively greater.

Shifts to low values of absolute neutrophils were also assessed. Overall, 0.5%, or 7/1387 patients who received 1.0 mg/kg/wk of efalizumab in the first exposure of the clinical trials, experienced a shift in absolute neutrophil counts to low from a normal baseline level. In addition, a listing of all patients with grade 3 or greater NCI toxicity criteria was

evaluated for decreases in absolute neutrophil counts and failed to show decreases that were sustained or confirmed by repeat testing (data not shown).

Reviewer's comment: Most of the grade 3 or 4 abnormalities in absolute neutrophil counts in efalizumab-treated patients were not sustained and some of these events were also noted in placebo-treated patients. However, follow-up is not available on one patient with a grade 4 decrease in absolute neutrophil counts (45223) and one patient with a grade 3 decrease in neutrophil counts (45207). The clinical significance of the transient decreases in absolute neutrophils is not known.

Eosinophils

Mean values of eosinophils were increased in efalizumab-treated patients by 50% and there was an increase in high-value abnormalities. Approximately 10% of efalizumab-treated patients had treatment emergent elevations in eosinophil count compared to 3% of placebo-treated patients. While the mean absolute eosinophils increased, the percent eosinophils decreased because the increase in lymphocytes was relatively greater.

Chemistry

Consistently observed in the chemistry panel, was an increase in mean alkaline phosphatase in efalizumab-treated patients compared with placebo-treated patients (See Table 89).

Table 89 Change in Alkaline Phosphatase (U/L) from Baseline to Day 84 of Each Period for Subjects Treated with Genentech Efalizumab

Type of Study/Period	Placebo	Genentech Efalizumab, Mean			
		2.0 mg/kg/qow	1.0 mg/kg/wk	2.0 mg/kg/wk	3.0–4.0 mg/kg/wk
FE/Controlled	–0.08 (11.69)	NA	6.87	9.57	NA
FE	NA	–1.27	6.71	11.09	23.17
EE-1	NA	9.27	7.78	33.40	0.87
EE-2	NA	NA	7.97	13.54	9.25
EE-3	NA	NA	7.03	11.90	12.00
EE-4	NA	NA	10.49	9.98	15.50
RE-1	NA	NA	14.43	8.63	NA
WO	NA	0.95	0.46	5.21	–1.42

The degree of elevation was higher in the 2.0 mg/kg/wk group than in the 1.0 mg/kg/wk group suggesting a dose effect. Both the liver and intestinal isoenzymes have demonstrated shifts to the upper limit of normal.

Liver function tests have been examined for concordant elevations in multiple tests for the first treatment period in the four phase 3 placebo-controlled studies: ACD2058g, ACD2059g, ACD2390g, and ACD2600g. See Table 90 below.

Table 90 Summary of High Shift in One or More Liver Function Tests during the First 12 Weeks in Studies ACD2058g, ACD2059g, ACD2390g, and ACD2600g

	Placebo	Efalizumab
No shift	562/604 (93.0%)	1203/1374 (87.6%)
Shift on one liver function test	31/604 (5.1%)	120/1374 (8.7%)
Shift on two liver function tests	9/604 (1.5%)	43/1374 (3.1%)
Shift on three liver function tests	2/604 (0.3%)	8/1374 (0.6%)
Shift on four liver function tests	0/604 (0.0%)	0/1374 (0.0%)
Shift on five liver function tests	0/604 (0.0%)	0/1374 (0.0%)

The summary represents the proportion of subjects with a shift from low or normal baseline values to values above the upper limit of normal at Day 84 on one or more liver function tests. The number of subjects with shifts on one or more liver function tests was higher in the efalizumab group than in the placebo group. No subjects had a shift above upper limit of normal on four or five liver function tests.

Transaminase elevations accounted for other shifts in liver function tests. Adverse events consisting of increases in SGPT occurred in 1.1% (n=29) of patients and SGOT occurred in 0.7% (n=19) patients. Bilirubinemia occurred as an adverse event in 0.1% of patients (n=3).

7.6.2.1 Inflammation-associated laboratory changes

Adverse events of thrombocythemia were observed in a small number of patients and appear to be reactive in etiology. In one patient (17512) thrombocythemia was associated with increases in peripheral white blood cell count, increases in serum CRP and peripheral edema. The clinical significance is unknown. Overall the frequency of high platelet counts was 4.0% (n=35) in efalizumab-treated patients vs. 2.7% (n=11) in placebo-treated patients.

Examination of changes in representative acute phase reactants and in complement activation products demonstrated some increases in efalizumab-treated subjects. In Study ACD2600g, mean levels of C-reactive protein and fibrinogen increased more in the efalizumab group (0.4 mg/dL and 46.8 mg/dL, respectively) than in the placebo group (0.1 mg/dL and 13.6 mg/dL, respectively) (See Table 91). Mean levels of both C3a and C5a decreased during the study. The decrease was greater in the placebo group for both analytes (data not shown). Shifts to elevated levels of CRP, fibrinogen, C3a, and C5a were all observed at rates approximately 10% higher in subjects receiving efalizumab compared with those receiving placebo. All of these markers show mean changes consistent with higher inflammation in the efalizumab-treatment group. The clinical significance of these changes in markers of inflammation is not known.

Table 91 C- Reactive Protein (mg/dL) Mean Changes from Baseline

Treatment Group	Baseline (min-max)	Day 84 (min-max)	Change (max)
Placebo (N=216)	0.6 (0.4-8.9)	0.7 (0.4-7.0)	0.09 (6.6)
Efalizumab (1.0mg/kg/wk) (N=425)	0.6 (0.4-5.4)	1.0 (0.4-22)	0.40 (22)

8 SUMMARY OF SAFETY

- Serious adverse events occurred at a comparable incidence in the two treatment groups, 2.2% in efalizumab-treated patients vs. 1.7% in placebo-treated patients.
- Serious infections
 - There has been a safety signal for serious infections in the controlled portion of clinical trials with efalizumab. The incidence of serious infection in the first exposure of the controlled studies was 0.4% for efalizumab (sepsis, pneumonia, cellulitis, gastroenteritis) and 0.1% for placebo (gastroenteritis).
 - Some of these infections have had atypical and life-threatening courses (vertebral Staphylococcal osteomyelitis with sepsis) and have required prolonged courses of antimicrobial therapy.
 - One opportunistic infection, *Legionella* pneumonia, has been reported in an efalizumab-treated patient.
- Malignancies
 - There is no clear evidence of increased risk of malignancy, but the numbers are small. Based upon the immunosuppressive action of efalizumab, further study is needed.
 - There have been two cases of lymphoproliferative malignancies in clinical trials of efalizumab.
 - The incidence of non-melanoma skin cancer was similar in efalizumab-treated patients vs. placebo (1.12% and 1.08% per 100 subject years, respectively). The incidence of non-melanoma skin cancer was higher in efalizumab-treated subjects than in the external reference cohort. The difference may represent ascertainment bias.
 - The point estimates for malignant melanomas and solid tumors in efalizumab-treated subjects are within the range expected based on external cohorts.
- Psoriasis-related adverse events
 - An increased incidence of psoriasis-related adverse events in placebo-controlled portions of clinical trials was seen in efalizumab-treated patients.

- Serious and life-threatening psoriasis-related adverse events including psoriasis variants have occurred with a frequency that is greater than placebo.
- Such adverse events have occurred during treatment as well as following discontinuation of efalizumab.
- Further study is needed to assess how to identify patients at risk of psoriatic flare and manage these patients appropriately.
- Thrombocytopenia
 - There have been eight cases of clinically significant thrombocytopenia, (serious and/or with platelet counts of less than 50,000 cells per ul) among efalizumab-treated patients.
 - Thrombocytopenia associated with efalizumab appears to be immune-mediated. Treatment with systemic corticosteroids results in improvement in platelet counts. In some cases, where systemic corticosteroids were withdrawn, the thrombocytopenia recurred. Where performed, bone marrow biopsies have shown normal maturation indicating a peripheral consumption or sequestration of platelets.
- Arthritis-related adverse events
 - Arthritis-related adverse events have occurred during treatment with efalizumab and have occasionally been serious.
- Inflammatory/ Autoimmune-related adverse events
 - Other rare, unexpected cases of potentially autoimmune adverse events- e.g. transverse myelitis, pneumonitis, and arthritis-have occurred in association with efalizumab-treatment.
 - One case of a serum sickness-like illness has occurred in an efalizumab-treated patient.
- Severe adverse events occurred at a rate of 10% in efalizumab-treated patients, nearly twice that seen in the placebo-treated group.
- Dose-related acute adverse events (e.g. fever, headache, nausea, vomiting, meningismus) occur after the first administration of therapeutic doses of efalizumab. The incidence of these events is lessened by the use of a subtherapeutic “conditioning dose” (0.7 mg/kg) as first dose. In some cases patients have had serious adverse events, e.g. aseptic meningitis, that have shown a temporal relationship to initiation of dosing despite the use of a conditioning dose.
- Laboratory abnormalities

- Inflammation-associated laboratory analytes were higher in efalizumab-treated patients as compared to placebo. These included C reactive protein, fibrinogen and C3a and C5a.
- Hematologic changes included increases in mean total white blood cell counts, approximate doubling of mean lymphocyte counts and smaller degrees of elevations in absolute eosinophil and neutrophil counts.
- Elevations in alkaline phosphatase levels which are mostly unassociated with elevations in other hepatic tests. Both the intestinal and hepatic fractions are shown to be elevated. Other liver function tests (e.g.transaminases) have been also elevated in efalizumab-treated patients compared to placebo.
- Efalizumab has been associated with anti-efalizumab antibody (HAHA) in 6.3% of patients. Injection site reactions may be associated with HAHA in some patients. The clinical association of HAHA with other adverse events is under investigation.

9 USE OF EFALIZUMAB IN SPECIAL POPULATIONS

See Appendix 2 for the use of efalizumab in special populations.

10 CONCLUSIONS: EFFICACY AND SAFETY OF EFALIZUMAB FOR THE TREATMENT OF PATIENTS WITH MODERATE TO SEVERE PSORIASIS

Patient population and efficacy outcomes:

Efalizumab has been studied in four efficacy trials in patients with moderate-to-severe stable, plaque psoriasis. Patients studied have had long-standing psoriasis (median 19 years), and 66% of patients have had a history of systemic therapy for psoriasis. The median PASI score was 19 and median body surface area involvement was 30%.

The treatment effect (proportion of PASI 75% responders) for efalizumab (1mg/kg/wk for 12 weeks SC) ranges from 18% to 37% depending on the study. Responses according to physician's static global assessment (19%-26%) and PASI 50 criteria (36%-46%) support the primary efficacy endpoint.

Efalizumab remains active during an extended treatment period. In patients who responded to 12 weeks of therapy with efalizumab, 77% maintain full clinical response during an additional 12-week treatment period.

When used to retreat responders who relapse off-treatment (loss of 50% of efalizumab treatment effect) efalizumab has shown limited ability to recapture response. Only about one third of patients respond upon retreatment.

With continuous treatment for an additional contiguous 12-week treatment period, an additional proportion of responders were captured (11-14%) who were non-responders to the first treatment period.

Safety Assessments:

- No deaths in psoriasis trials have been linked causally to the use of efalizumab.
- Malignancies in the first exposure, placebo controlled portion of trials were few (n=4) and were not higher in efalizumab-treated patients relative to control or to external cohorts. However, the numbers of cases are too small to make any definitive conclusions with regard to cancer risk.
- There is no apparent increase in the incidence of NMSC in efalizumab-treated patients compared to placebo. However, the numbers are too small to assess the potential for increased risk due to efalizumab.
- Serious infections have been reported in the first exposure of controlled clinical trials in a higher proportion of efalizumab-treated patients than placebo (0.4% vs.

- 0.1%). One opportunistic infection was observed, *Legionella* pneumonia. Other serious infections have consisted of severe local infections complicated by sepsis and seeding of distal sites.
- Of the 2589 subjects treated with SC efalizumab, 19 (0.7%) had a serious adverse event of psoriasis (including psoriatic erythroderma and pustular psoriasis). In the first exposure of controlled clinical trials of efalizumab, adverse events of psoriasis occurred in more subjects receiving efalizumab (2.4%, n=22) than placebo (1.1%, n=5).
 - Thrombocytopenia consisting of platelets < 50,000 cells/cmm occurred in a total of 8 efalizumab-treated patients. Clinical response to treatment with systemic corticosteroids suggests an immune-mediated thrombocytopenia. One patient had clinically significant bleeding requiring hospitalization.
 - Rare cases of serious inflammatory and/or potentially autoimmune events (e.g. transverse myelitis, pneumonitis, idiopathic hepatitis, serum sickness) have occurred in efalizumab-treated patients.
 - Laboratory abnormalities
 - Inflammation-associated laboratory analytes were higher in efalizumab-treated patients as compared to placebo. These included C reactive protein, fibrinogen and C3a and C5a.
 - Hematologic changes included increases in mean total white blood cell counts, approximate doubling of mean lymphocyte counts and smaller degrees of elevations in absolute eosinophil and neutrophil counts.
 - Elevations in alkaline phosphatase levels which are mostly unassociated with elevations in other hepatic tests. Both the intestinal and hepatic fractions are shown to be elevated.
 - Efalizumab has been associated with anti-human antibody (HAHA) in 6.3% of patients. There is no apparent decrease in clinical efficacy associated with HAHA positivity. The clinical significance with regard to safety is under investigation.

11 APPENDIX 1: AUDIOLOGIC ASSESSMENTS

11.1 Audiology

Audiologic testing was performed in three studies (HUPS254, HUPS256, ACD2058g) after 1 subject in the Phase 2 study (HUPS252) experienced a serious adverse event of transient unilateral hearing loss. All audiologic testing was performed in studies using XOMA efalizumab.

The criteria for meaningful threshold change in one ear relative to a pretreatment, baseline assessment were the same in all studies as follows:

- ≥ 20 -dB Change at any one frequency
- ≥ 15 -dB Change at any two frequencies
- ≥ 10 -dB Change at any three frequencies

These criteria were used in the 1997 Anti-Infectives Drugs Advisory Committee Meeting review of tobramycin. An increase in decibels (dB) indicated worsening, and a decrease in decibels indicated improvement in hearing threshold.

Audiologic testing by air and bone conduction was performed by a certified audiologist prior to study drug administration and at the end of the FT, RT, and ET periods. Frequencies from 500 Hz to 8000 Hz were routinely assessed. If the audiologist had equipment and training for performance of high-frequency testing up to 16,000 Hz, this assessment was also conducted. The baseline audiogram was obtained up to 14 days prior to FT Day 0 and prior to study drug administration. A second audiogram was obtained within ± 7 days of FT Day 84. Subjects who were responders at FT Day 84 entered the OB period, and when relapse occurred, began the RT period. These subjects were scheduled to have a third audiogram obtained ± 7 days of RT Day 84. Subjects who were partial responders or non-responders at FT Day 84 were followed during the ET period when a third audiogram was obtained within ± 7 days of ET Day 84. Retests were to be conducted after 2 weeks for any subject with a significant threshold shift, as defined in the Audiology Manual for Study ACD2058g. Determination of a significant threshold shift was made at the FT Day 84, the ET Day 84, and the RT Day 84 visits.

At screening, subjects were asked about their hearing history. Questions included whether they had experienced a hearing loss in the previous year, had experienced tinnitus, had been diagnosed with hearing problems, had previous surgery or trauma to the ear, had frequent exposure to loud noises, and whether their employer required periodic hearing tests. If hearing problems were diagnosed, six conditions were ascertained, including noise exposure.

A decrease in threshold (dB) at a frequency in either ear represented a potential improvement in hearing at that frequency; an increase in threshold (dB) at a frequency in either ear represented a potential worsening in hearing. For any of the criteria listed above, a worsening in one ear took precedence over an improvement in the same or in the

other ear. Changes in values by bone conduction were not considered part of the “significant threshold shift” determination.

Based on the criteria above, a subject was classified as:

- “Worsened” if the subject’s hearing was worse by any one individual criterion
- “Improved” if the subject’s hearing was improved by any one individual criterion and had not been classified as “worsened”
- “Unchanged” otherwise

The tables below summarize the changes measured by audiologic tests.

Table 92 Study HUPS254: Treatment-Emergent Changes in Audiogram Testing

Dose Group	Hearing Test Result	
	Improved	Worsened
Group C (n=15) 1.0 mg/kg/wk SC	1 (6.7%)	1 (6.7%)
Group E ^a (n=15) 2.0 mg/kg/wk SC	5 (33.3%)	4 (26.7%)
Total (n=30)	6 (20.0%)	5 (16.7%)

^a One of the 16 subjects enrolled did not have audiograms performed.

Table 93 Treatment-Emergent Changes in Audiogram Testing: Study HUPS256

XOMA Efalizumab Dose Group	Hearing Test Result	
	Improved	Worsened
0.3 mg/kg/wk IV (n=5)	1 (20.0%)	0 (0)
1.0 mg/kg/wk IV (n=10)	4 (40.0%)	1 (10.0%)
All IV subjects (n=15)	5 (33.3%)	1 (6.7%)
1.0 mg/kg/wk SC (n=20)	3 (15.5)	7 (35.0%)
2.0 mg/kg/wk SC (n=19)	6 (31.6%)	6 (31.6%)
4.0 mg/kg/wk SC (n=21)	6 (28.6%)	6 (28.6%)
All SC efalizumab (n=60)	15 (25.0%)	19 (31.7%)
Total (n=75)	20 (26.7%)	20 (26.7%)

Note: The numbers of subjects who improved or worsened differs slightly between the SCS and final report because of differences in analysis.

Table 94 Treatment-Emergent Changes in Audiogram Testing: Study ACD2058g

Dose Group	Hearing Test Result	
	Improved	Worsened
Placebo (n=156)	8 (5.1%)	6 (3.8%)
XOMA efalizumab 1.0 mg/kg/wk (n=148)	14 (9.5%)	11 (7.4%)
XOMA efalizumab 2.0 mg/kg/wk (n=152)	13 (8.6%)	16 (10.5%)
Total All XOMA efalizumab (n=300)	27 (9.0%)	27 (9.0%)

The audiology testing in studies HUPS254, HUPS256 and ACD2058g showed no evidence of efalizumab-induced hearing loss. Audiology testing was not performed in the clinical studies that followed.

12 APPENDIX 2 Use of Efalizumab in Special Populations

12.1 Pediatric Studies

Genentech, Inc. asked for and received a deferral of its obligation to carry out pediatric studies in the phase 3 program.

12.2 Pregnancy

Pregnant/ lactating women were excluded from the clinical trials. Female patients were monitored monthly with pregnancy testing and were instructed to use contraception during and 3 months after the study. Nine subjects became pregnant during clinical trial program. Study dosing was immediately discontinued in these patients. Patients were followed during pregnancy and for 6 months following birth.

Table 95 Pregnancies that Occurred during the Efalizumab Psoriasis Program

Subject ID/ Study	Treatment Group	Outcome and Comments
15065/ ACD2058g	1.0 mg/kg/wk XOMA efalizumab	Vaginal delivery of healthy infant. Eleven doses of efalizumab were administered before discovery of pregnancy, 5 weeks from last dose.
16004/ ACD2058g	2.0 mg/kg/wk XOMA efalizumab	Delivery of healthy infant. Twelve doses of efalizumab were administered before discovery of pregnancy, 10 weeks from last dose.
81216/ ACD2059g	2.0 mg/kg/wk XOMA efalizumab	Vaginal delivery of healthy infant. Twelve doses of efalizumab were administered before discovery of pregnancy, 5 days from last dose.
19505/ ACD2062g	1.0 mg/kg/wk Genentech efalizumab	Partner of male subject became pregnant. Pregnancy ended in spontaneous miscarriage. Thirty-one doses of efalizumab were administered before discovery of pregnancy, 9 weeks from last dose
21406/ ACD2062g	1.0 mg/kg/wk XOMA efalizumab	Vaginal delivery of healthy infant. Twelve doses were administered in Study ACD2062g before discovery of pregnancy, 3 months from last dose

27106/ ACD2243g	2.0 mg/kg/wk Genentech efalizumab followed by 1.0 mg/kg/wk efalizumab	Estimated date of delivery was 28 January 2002. Fourteen doses of efalizumab were administered before discovery of pregnancy, 7 days from last dose. Subject was lost to follow-up.
27130/ ACD2243g	2.0 mg/kg/wk Genentech efalizumab followed by 1.0 mg/kg/wk efalizumab	Estimated date of delivery was 8 August 2002. Thirty-eight doses of efalizumab were administered before discovery of pregnancy, 1 day from last dose.
27706/ ACD2243g	2.0 mg/kg/wk Genentech efalizumab followed by 1.0 mg/kg/wk efalizumab	Subject voluntarily terminated pregnancy.
29208/ ACD2243g	2.0 mg/kg/wk Genentech efalizumab followed by 1.0 mg/kg/wk efalizumab	Partner of male subject became pregnant and voluntarily terminated pregnancy.
547/ ACD2389g	1.0 mg/kg/wk XOMA efalizumab	Estimated date of delivery as 28 September 2002. One dose of efalizumab was administered before the discovery of pregnancy, 4 weeks from last dose. Subject was lost to follow-up.
2564130607/ HUPS256	4.0 mg/kg/wk XOMA	Subject delivered healthy infant.

The data of use during pregnancy are limited. Thus far, there is no evidence for fetal harm. Prospective studies are needed to further evaluate the risks of use during pregnancy if the product is licensed.

12.3 Safety and Efficacy in the Geriatric Population

The numbers of patients over the age of 65 are limited. However, efficacy was not decreased among patients over the age of 65.

With regard to adverse events, of the two cases of hypothyroidism, both were in patients older than 65. Skin related adverse events that were more commonly seen in patients older than age 65 were psoriasis, pruritus and rash. For example, 4.8% of patients over 65 had psoriasis-related adverse events vs. 2.9% of patients 41-64 and 1.9% of patients 18-40. Otherwise, no clear safety signals were identified in patients over the age of 65.

The table below shows the incidence rate for infections that required hospitalization for patients by age group.

Table 96 Incidence Rate for Infections that Required Hospitalization by Age Group Total Exposure All Subjects Treated with Efalizumab in Psoriasis Studies

COSTART Preferred Term	Age Group	Number of Events	Subject-Years	95% CI for Observed Number of Events	Incidence Rate Per 100 Subject-Years	95% CI for Incidence Rate Per 100 Subject-Years
- TOTAL -	18 - 40 yr	7	634.60	[2.81, 14.42]	1.10%	[0.44, 2.27]
	41 - 64 yr	18	942.06	[10.67, 28.45]	1.91%	[1.13, 3.02]
	>= 65 yr	2	104.02	[0.24, 7.22]	1.92%	[0.23, 6.95]

Although the numbers are small, there is not an indication of an increased incidence of hospitalization for infections among patients over the age of 65.

Overall, no clear safety concerns arose with the use of efalizumab in the geriatric population.

13 APPENDIX 3: Phase 1 study protocols

13.1 Selected Phase 1 Studies of Efalizumab in Patients with Psoriasis

The Phase 1 clinical studies were conducted in patients with psoriasis. These studies are reviewed primarily from the perspective of clinical safety and activity of efalizumab.

13.1.1 Protocol HU9602

Xoma completed the first Phase 1 study of efalizumab, HU9602, in 1998. This study investigated single intravenous (IV) doses (0.03, 0.1, 0.3, 0.6, 1.0, 2.0, 3.0 or 10.0 mg/kg) of efalizumab administered in a dose-escalation manner to 31 subjects moderate to severe plaque psoriasis. The subjects were enrolled at seven study centers. Of the 31 subjects, 4 subjects each were enrolled in the 0.03 and 0.1 mg/kg groups, 8 were enrolled in the 0.3 mg/kg group, 1 was enrolled in the 0.6 mg/kg group, 8 were enrolled in the 1.0 mg/kg group, 1 was enrolled in the 2.0 mg/kg group, 4 were enrolled in the 3.0 mg/kg group and 1 was enrolled in the 10.0 mg/kg group.

The subjects were to be followed for a minimum of 72 days after dosing.

**Table 97 Summary of Most Frequently^a Reported Adverse Events
Subjects Evaluable for Safety**

Body System and Preferred term	≤ 0.3 mg/kg N	≥ 0.6 mg/kg N	Combined N (%)
Total Number of Subjects	16	15	31
Body as a Whole	12	14	26 (84)
Headache	4	8	12 (39)
Chills	2	8	10 (32)
Infection ^b	4	4	8 (26)
Fever	1	6	7 (23)
Pain	4	1	5 (16)
Skin and Appendages	6	9	15 (48)
Psoriasis ^c	5	6	11 (36)
Pruritus	4	1	5 (16)
Digestive System	6	6	12 (39)
Nausea	0	5	5 (16)

^a Defined as any adverse event reported by ≥ 5 subjects.

^b Infections included cold symptoms (four subjects), infection at biopsy site (three subjects), and infection at left buttock suture site (one subject).

^c Indicated worsening of psoriasis post treatment.

Table 98 Summary of Serious Adverse Events

Dose	Subject	Gender	Age	Adverse Event	Onset	Severity	Relation: Study
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group(mg/kg)				(Day)		Drug	
0.6	031	F	35	Meningismus	0	Severe	Probable
1.0	028	F	59	Carcinoma skin	36	Mild	Possible
1.0	029 ^a	M	55	Ataxia	11	Moderate	Possible
				Vertigo	11	Severe	Possible
				Nausea	11	Moderate	Possible
				Vomiting	11	Severe	Possible
				Nystagmus	12	Mild	Possible
1.0	007	M	51	Aseptic meningitis	0	Moderate	Probable
3.0	010	M	56	Chills	0	Moderate	Probable
				Hypertension	0	Moderate	Probable
				Fever	0	Moderate	Probable
10.0	013	M	28	Vomiting	0	Severe	Probable

There were no deaths in the study. Fever was commonly reported within 24 hours after completion of infusion. A dose-related incidence and severity of headache, chills, fever and nausea was observed.

Infusion reactions had not been observed in a safety study conducted in chimpanzees, a species that shares a similar binding affinity for efalizumab as humans, after administration of up to 40 mg/kg efalizumab. However, adverse side effects, including fever, headache and nausea, were seen in the several hours after the first intravenous infusion of efalizumab in psoriasis patients. Body temperature began to increase within 2 hours after the infusion, and returned to the normal range within 24 hrs. In addition, white blood cell counts were elevated within 8 hours of infusion and increased expression of the activation marker CD69 was observed on a subpopulation of circulating T cells. The circulating CD69-positive T cells do not seem to express CD25, suggesting that they are not fully activated. Plasma samples collected after efalizumab administration indicated elevated levels of TNF- α , IL-6 and the acute phase proteins CRP and LBP within the first 48 hours of dosing. Plasma TNF- α was detected in some patients 2 hours after infusion, but showed no correlation with dose level or severity of adverse events. Adverse symptoms and the associated neutrophil counts and CD69 expression usually subsided after the first 48 hours, even when plasma levels of efalizumab remained relatively high. In subsequent studies where efalizumab was administered multiple times on a weekly basis, adverse events were most common after the first dose hence the phenomenon was called a “first-dose” effect. The first dose response may be initiated by activation of cells of the monocytic/macrophage lineage. Activation of macrophages in vitro could be induced by immobilized efalizumab..

Reviewer's comments

It was concluded that efalizumab was poorly tolerated at doses needed to achieve target serum levels of drug. The repeat-dosing studies would be designed to achieve these safety objectives: to find an initial tolerable dose of efalizumab and determine if upon repeated dosing the infusion reactions continued or worsened. The starting dose level for the study

would be conservative to take into account the potential for additive toxicity of repeated dosing. The hypothesis would also be tested that the initial infusion reaction would induce tolerization and would permit ratcheting up to the optimal pharmacologic dose. This led to the dev of an initial low “tolerization dose.” Treatment with acetaminophen or nonsteroidal anti-inflammatory medications was allowed in the clinical trials for management of these acute adverse events.

13.1.2 Protocol HUPS249

Another Phase 1 study (HUPS249) investigated multiple IV doses (0.1-1.0 mg/kg/wk), which were also administered in a dose-escalation manner.

This study was to examine the safety, immunogenicity, and tolerability of multiple doses of efalizumab in subjects with moderate to severe plaque psoriasis; to determine the pharmacokinetics and pharmacodynamics of efalizumab; and to determine the in vitro and in vivo immunosuppression correlates to drug dose levels.

Reviewer's comment:

Following the Phase 2 study (HUPS252), a transition was made to subcutaneous (SC) dosing.

13.1.3 Protocol HUPS254

13.1.3.1 Study Title

“A Single-dose and Multiple-dose, Escalating-dose Study to Evaluate the Safety, Pharmacokinetics, and Biological Activity of Subcutaneously Administered hu1124 (Efalizumab) in Subjects with Moderate to Severe Plaque Psoriasis”

13.1.3.2 Study Objectives

The objectives of this study were as follows:

To evaluate the safety, immunogenicity, and tolerability of a single dose and multiple doses of efalizumab administered by subcutaneous injection to subjects with moderate to severe plaque psoriasis

To determine the pharmacokinetics and pharmacodynamics of efalizumab.

13.1.3.3 Study Design

A Phase I study (HUPS254) evaluated the safety, PK, and PD of multiple SC doses (0.5–2.0 mg/kg/wk) administered for 8 weeks in a dose-escalation manner. For groups C-E, the study employed both an inter-patient dose escalation (escalation between dose groups and an intra-patient dose escalation (higher maintenance doses after an initial “tolerization” dose.

At least 56 subjects were to receive subcutaneous injections of efalizumab administered as a single dose of 0.3 mg/kg or as escalating multiple doses of 0.5-2.0 mg/kg.

The dose groups evaluated in this study were:

0.3 mg/kg administered as a single dose (Group A),

0.5 mg/kg administered weekly for 8 weeks (Group B),

0.5 mg/kg escalated to 1.0 mg/kg (Group C and C.1),

0.7 mg/kg escalated to 1.5 mg/kg (Group D),

1.0 mg/kg escalated to 2.0 mg/kg (Group E and E.1) administered weekly for 8 weeks.

Subjects in the single-dose group were followed for a minimum of 28 days and subjects in the multiple-dose groups were followed for a minimum of 91 days.

Subjects in Groups C.1 and E.1 had extra target lesion and hearing assessments.

Reviewer's comment:

In the phase 1 studies, the adverse events included facial, vestibular and auditory nerve impairment and meningeal irritation. In addition to careful neurologic assessments, auditory testing was added to assess the potential for development of subclinical ototoxicity.

13.1.3.4 Results and Discussion

Safety:

The total proportion of patients experiencing a drug-related adverse event was 58%. The most frequently reported adverse events were headache (19/57 [33%]), pain (14/57 [25%]), rhinitis (11/57 [19%]), leukocytosis (10/57 [18%]), pharyngitis (10/57 [18%]), increased cough (9/57 [16%]), nausea (7/57 [12%]), chills (6/57 [11%]), and myalgia (6/57 [11%]). There was only one adverse event (peripheral edema) in the single-dose group. Acute adverse events of fever, headache, nausea, chills, and myalgia within 48 hours after study drug administration were reported by 21/57 (37%) of the subjects.

One (2%) subject in the study (Subject 22 in the 1.0-2.0 mg/kg group) experienced a serious adverse event. The serious adverse event of kidney calculus was severe in nature and considered to be unrelated to the study drug.

Audiology tests were performed for the 31 subjects in Groups C.1 (0.5-1.0 mg/kg) and E.1 (1.0-2.0 mg/kg). The hearing abnormalities observed during this study were not consistent with a pattern of ototoxicity because improvements in hearing were observed in some subjects at the same time as deteriorations in hearing, and because deteriorations in hearing were not consistently evident in the higher sound frequencies. One (2%) subject experienced a hearing-related adverse event (decreased hearing secondary to impacted cerumen), which was considered to be unrelated to the study drug.

The proportion of subjects who experienced an infection-related adverse event was 75% in the 0.5 mg/kg group, 24% in the 0.5-1.0 mg/kg group, 17% in the 0.7-1.5 mg/kg group,

and 58% in the 1.0-2.0 mg/kg group. The most frequently reported infection-related adverse events were rhinitis, pharyngitis, and increased cough. Additionally, two subjects (4%) in the 0.5-1.0 mg/kg group experienced *Herpes simplex* infections.

The incidence of CMV disease and evidence of CMV reactivation was evaluated in this study because CMV disease is known to increase in subjects who receive immunosuppressive medications. One subject developed a new positive CMV IgM response at Day 91, having had a negative CMV IgM response at screening. This subject had a positive IgG titer at baseline and did not experience any clinical signs or symptoms of CMV disease.

Reviewer's comment:

The report does not state whether the patient had a symptomatic illness.

Lymphocyte counts approximately doubled within 2–7 days after the first dose of study drug in the multiple-dose groups. No increase was observed in the single-dose group. The mean proportion of B and T lymphocytes remained consistent throughout the study; however, a significant decrease in the proportion of NK cells was noted from a pretreatment level of 10% to approximately 6% after Day 14. The average CD11a expression on circulating T lymphocytes decreased by 70-80% within 2-3 days after treatment in all dose groups, and a small increase in CD69 expression was observed. Efalizumab binding sites were not saturated in the single-dose group, but were generally more than 95% saturated in the multiple-dose groups during treatment. Lymphocyte counts, CD11a and CD69 expression, and available binding sites returned to pretreatment levels by Day 91 in all treatment groups; however, the mean percentage of NK cells had not returned to pretreatment levels.

Antibody response to the study drug was assessed in 53/57 patients in the study. A positive response (4.7 ng/mL equivalents/mL) was detected in 1/53 of the subjects (1.0–2.0 mg/kg dose group). Competition studies indicated the response was anti-idiotypic in nature. The positive response was not associated with any adverse events that would be expected during immune complex formation and deposition.

PK results:

In the multiple-dose groups, the average peak levels after the last dose were 4.7 µg/mL for the 0.5 mg/kg group, 7.4 µg/mL for the 0.5-1.0 mg/kg group, 20 µg/mL for the 0.7-1.5 mg/kg group, and 22 µg/mL for the 1.0-2.0 mg/kg group. Average bioavailability (compared to IV administration) varied between 39.0% and 76.0% among the multiple-dose groups, with an overall average bioavailability of 51% ± 32% (mean ± sd, n = 41). In the single-dose group, the peak level was below the level of detection and bioavailability was not applicable for a single dose.

13.1.4 Protocol HUPS256

Study Title

An Open-Label, Extended-Duration, Multiple-Dose Study to Evaluate the Safety, Pharmacokinetics, and Biological Activity of Intravenously and Subcutaneously Administered hu1124 in Subjects with Moderate to Severe Plaque Psoriasis

13.1.4.1 Study Objectives

This Phase 1 study evaluated the safety, efficacy, PK, and PD of multiple IV or SC doses (0.3–1.0 mg/kg/wk IV and 1.0–4.0 mg/kg/wk SC) administered for 12 weeks.

In addition, it evaluated the safety, pharmacokinetics, immunogenicity, and tolerability of 12 multiple doses of efalizumab administered weekly by subcutaneous injection.

13.1.4.2 Protocol

Eligible patients were required to have a minimum PASI score of 12 and a minimum BSA of 15%.

For the intravenous phase, 16 patients were assigned to a dose group. The dose groups evaluated in this phase of the study were 0.3 mg/kg or 0.3–1.0 mg/kg administered weekly for 12 weeks.

For the subcutaneous phase, a total of 61 subjects were assigned to a dose group. The doses evaluated were: 0.7-1.0 mg/kg, 0.7-2.0 mg/kg, and 0.7-4.0 mg/kg weekly for 12 weeks.

All subjects were to be followed for up to Day 180.

13.1.4.3 Outcome Measures

- PGA and PASI scores at Day 84 were compared with baseline.
- Additionally, arthritis symptoms and psoriatic itching evaluations were performed.

13.1.4.4 Clinical and Laboratory Assessments

- Safety assessments included: adverse events, hearing assessments, clinical laboratory assessments, physical and neurological examinations, and pre- and post-treatment vital signs.
- Immunologic activity was assessed by analyzing lymphocyte subpopulations by flow cytometry and testing for human anti-humanized antibody (HAHA) response. Immunologic recovery assessments for the reconstitution of CD11a on T lymphocytes compared with baseline measurement were performed; patients were to be monitored every 20 to 30 days up to 90 days after the final visit until recovery of $\geq 75\%$ expression of CD11a.

- The pharmacodynamic assessments were also performed.

13.1.4.5 Results and Discussion

13.1.4.6 Intravenous Phase

A total of 16 subjects with moderate to severe plaque psoriasis were enrolled at six study centers. Of these 16 subjects, 6/16 received 12 weekly doses of 0.3 mg/kg and 10/16 received 12 weekly doses of 0.3-1.0 mg/kg. The majority of subjects were male 9/16 and Caucasian 14/16. Subjects ranged in age from 21 to 70 years of age and from 63 to 119 kg in weight. Median baseline BSA affected by psoriasis ranged were 27.1 and 37.5, and the median baseline PASI scores were 16.8 and 20.6. Five of 16 patients had previous exposure to efalizumab. All subjects were evaluated for safety and efficacy.

13.1.4.7 Subcutaneous Phase

A total of 61 subjects with moderate to severe plaque psoriasis were enrolled at 11 study centers. Of these subjects, 20/61 received a single conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 1.0 mg/kg, received 12 weekly doses of 0.7–2.0 mg/kg, 20/61 (33%) received a single conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 2.0 mg/kg, and 21/61 (34%) received a single conditioning dose of 0.7 mg/kg followed by 11 weekly doses of 4.0 mg/kg. The majority of subjects were male 41/61 and Caucasian 51/61. Subjects ranged in age from 21 to 71 years of age and from 65 to 123 kg in weight. Median BSA affected by psoriasis ranged from 25.3 to 28.5, and the median baseline PASI scores ranged from 17.6 to 20.6.

The most frequently reported adverse events (reported by at least 10% of subjects) are tabulated below.

Table 99 Summary of Most Frequently Reported Drug-related Adverse Events in IV Groups (HUPS256)

Body System	0.3 mg/kg (N = 6) n (%)	0.3-1.0 mg/kg (N = 10) n (%)	Total Combined (N = 16) n (%)
Subjects Reporting at Least One Drug –Related AE	6 (100)	10 (100)	16 (100)
Body as a Whole	5 (83)	5 (50)	10 (63)
Headache	2 (33)	3 (30)	5 (31)
Pain	2 (33)	1 (10)	3 (19)
Asthenia	2 (33)	0	2 (13)
Chills	0	2 (20)	2 (13)
Skin and Appendages	2 (33)	6 (60)	8 (50)
Psoriasis	1 (17)	2 (20)	3 (19)
Pruritus	1 (17)	1 (10)	2 (13)
Urticaria	0	2 (20)	2 (13)
Hemic and Lymphatic	0	3 (30)	3 (19)
Lymphadenopathy	0	2 (20)	2 (13)
Respiratory	2 (33)	1 (10)	3 (19)
Rhinitis	1 (17)	1 (10)	2 (13)
Digestive	1 (17)	1 (10)	2 (13)
Nausea	1 (17)	1 (10)	2 (13)

Acute events of headache, nausea, and chills within one day after study drug administration were reported for 7/16 (44%) of the subjects. Two of the sixteen subjects (13%) experienced at least one hearing-related adverse event. One of these subjects, with decreased hearing as a result of impacted cerumen, was considered to have hearing loss unrelated to the study drug. The other subject experienced two incidences of vertigo which were possibly related to the study drug, but resolved within 5 hours.

13.1.5 Protocol HUPS252

13.1.5.1 Study Title

A Double-blind, Placebo-controlled, Multi-center Phase 2 Study to Assess the Safety, Biological Activity, and Efficacy of hu1124 (Efalizumab) in Patients with Moderate to Severe Plaque Psoriasis

13.1.5.2 Study Objectives

The study objective were to evaluate

- the safety of multiple dosing with efalizumab when administered to subjects with moderate to severe plaque psoriasis
- the pharmacodynamic effects of 8 weekly intravenous treatments with efalizumab on the expression of CD11a and skin histology, as compared with placebo; and

- the efficacy of 8 weekly treatments with efalizumab on the severity of psoriasis as compared with placebo.

13.1.5.3 Study Design

This was a Phase 2, double-blind, multiple-dose, placebo-controlled, multi-center study to evaluate the effects of two different doses of efalizumab compared with placebo in subjects with moderate to severe plaque psoriasis. A total of 145 subjects with a minimum Psoriasis Area and Severity Index (PASI) of 12 and at least 10% of BSA coverage by psoriasis were randomized to receive 8 weekly intravenous infusions of efalizumab or placebo at a 2:1 ratio within each of the two dose groups. The first 31 subjects were randomized to receive either efalizumab 0.1mg/kg (n = 22) or placebo (n = 9). The remaining subjects were randomized to receive either efalizumab 0.3 mg/kg (n = 75) or placebo (n = 39). Subjects were to be followed for at least 91 days after the last treatment.

13.1.5.4 Results and Discussion

A total of 145 subjects were randomized to receive treatment at 10 study centers. One subject randomized to placebo in the 0.3 mg/kg treatment group did not receive treatment. Of the 144 subjects randomized and dosed, 22/144 (15%) of the subjects received efalizumab 0.1 mg/kg, 75/144 (52%) received efalizumab 0.3 mg/kg, and 47/144 (33%) received placebo.

The majority of treated subjects were Caucasian (93%) and men (66%). The subjects ranged from 21 to 72 years of age. Baseline BSA affected by psoriasis ranged from 10.5 to 73%, with the median BSA affected by psoriasis ranging from 18.2% to 26.5% across treatment groups. Baseline PASI ranged from 11.4 to 57.2, with the median PASI ranging from 14.5 to 17.7 across treatment groups.

A dose-dependent improvement in the severity of psoriasis was noted by primary outcome measures (PGA) and by secondary outcomes (PASI score).

Table 100 Reduction in PASI score at Endpoint (day 56)

	PASI score Mean <u>+SD</u>		% Reduction <u>+SD</u>
	Baseline	Endpoint	
Placebo (n=48)	16.2 <u>+4.4</u>	13.9 <u>+27</u>	16.5 <u>+27</u>
Efalizumab 0.1 mg/kg (n=22)	18.2 <u>+6.7</u>	14.2 <u>+8.9</u>	24.2 <u>+28.9</u>
0.3 mg/kg (n=75)	19.1 <u>+7.3</u>	10.9 <u>+8.4</u>	43.8 <u>+29.4</u>

There were no deaths in the study. A total of 16 subjects discontinued study drug prematurely. Of these, six discontinued treatment because of adverse events. In the efalizumab 0.1 mg/kg group, 2/22 (9%) (headache, worsening psoriasis). In the efalizumab 0.3 mg/kg group, 2/75 (3%) (worsening psoriasis, hearing loss and tinnitus). In the placebo group, 2/47 (4%) (worsening psoriasis, dizziness).

Acute adverse events of headache, fever, chills, nausea, and vomiting within 24 hours after study drug administration were higher in the efalizumab 0.3 mg/kg group (42/75 [56%]) than the efalizumab 0.1 mg/kg (8/22 [36%]) or the placebo (11/47 [23%]) groups.

Antibody response to efalizumab was detected in 1/19 (5%) of the subjects in the efalizumab 0.1 mg/kg group, 10/70 (14%) of the subjects in the efalizumab 0.3 mg/kg group, and none of the subjects in the placebo group. Competition experiments indicated that the response was anti-idiotypic in nature. These were low titer antibodies and were not associated with any adverse events suggestive of immune complex formation and deposition.

13.1.5.5 Safety

Table 101 Patients with Serious Adverse Events

Treatment Group	Patient	Sex	Age	Adverse Event [Preferred Term]	Onset Day	Severity	Relation to Study Drug ^a	Number of Doses Received
0.1 mg/kg	462	F	50	Fractured r hand [bone fractspontan]	36	Severe	Unrelated	8
0.3 mg/kg	422	M	55	Psoriatic Arthritis [arthritis]	61	Severe	Possible	8
				Carpaltunnel syndrome [tenosynovitis]	122	Severe	Possible	
0.3 mg/kg	582	M	49	Synovitis [synovitis]	20	Severe	Unrelated	8
0.3 mg/kg	642	M	54	Hearing loss – lear (sensorineural hearing loss) [deaf]	36	Severe	Possible	6 ^b
0.3 mg/kg	703	M	68	Retrosternalpain [pain chest substern]	134	Moderate	Unrelated	8
Placebo	239	F	34	Gastroenteritis [gastroenteritis]	112	Severe	Unrelated	8
Placebo	419	M	29	Psoriatic arthritis (Hands and Feet) [arthritis]	100	Severe	Unrelated	8
Placebo	464	M	66	Fractured r ribs [bone fract spontan]	38	Moderate	Unrelated	8
Placebo	641	M	42	Chestpain (notyet diagnosed) [pain chest]	58	Severe	Possible	8

^a As judged by the investigator.

^b Patient 642 did not receive thefinal two doses of study drug due to this adverse event.

13.1.6 Protocol ACD2389g

13.1.6.1 Study Title

A Randomized, Open-Label, Single-Center, Two-Period Crossover Study in Healthy, Adult Volunteers to Evaluate the Pharmacokinetic Comparability and Safety of Single 1.0 mg/kg Subcutaneous Doses of XOMA-Manufactured and Genentech-Manufactured Efalizumab (ACD2389g)

13.1.6.2 Study Objectives

The study's primary objective was to determine the pharmacokinetic (PK) comparability of single, subcutaneous (SC) doses of XOMA and Genentech efalizumab as measured by the area under the concentration–time curve from time 0 until infinity (AUCinf). The goal of the study was to obtain a 90% confidence interval on the relative bioavailability of Genentech to XOMA efalizumab and to determine whether the interval was completely within 80%–125%.

Study Design

Subjects were randomized in an equal ratio to one of two treatment sequences: Genentech efalizumab on Day 0 of Period 1 with crossover to XOMA efalizumab on Day 0 of Period 2 (GX Group) or XOMA efalizumab on Day 0 of Period 1 with crossover to Genentech efalizumab on Day 0 of Period 2 (XG Group). A single 1.0 mg/kg dose was administered subcutaneously at Day 0 of each period. Each dose was followed by a 5-week sample collection period, during which serial blood draws were taken for both PK and pharmacodynamic (PD) measurements. The total time from screening to study completion was approximately 13 weeks.

A population of healthy volunteers was chosen to avoid concomitant medications and co-existing disease state interactions. A 6-week washout period was selected based on the expected half-life of approximately 7 days and previous clinical data demonstrating that CD11a expression returns to baseline approximately 4 weeks after a single intravenous (IV) dose of efalizumab.

13.1.6.3 Results and Discussion

Ninety-nine subjects were randomized in this study. A total of 81 subjects completed the study.

Of the 20 subjects who were not PK evaluable, 10 were randomized to the XG group and 10 were randomized to the GX group, leaving 39 PK evaluable subjects from the XG group and 40 subjects from the GX group for a total of 79 PK evaluable subjects.

Overall, the treatment groups were comparable with regard to demographic and baseline characteristics.

Pharmacokinetics:

Table 102 Mean \pm SD Efalizumab Pharmacokinetic Parameters

Parameter	XOMA Efalizumab (n=79)	Genentech Efalizumab (n=79)
C _{max} (μ g/mL)	4.1 \pm 2.0	4.9 \pm 2.0
T _{max} (day) a	3.5 (1.0–7.0)	3.5 (1.4–8.0)
AUC _t (μ g day/mL)	32.6 \pm 18.9	43.6 \pm 24.5
AUC _{inf} (μ g day/mL)	33.4 \pm 19.1	44.9 \pm 24.8
Linear t _{1/2} (day)	5.0 \pm 2.1	5.6 \pm 2.4
Nonlinear t _{1/2} (day)	1.7 \pm 1.6	1.7 \pm 1.7

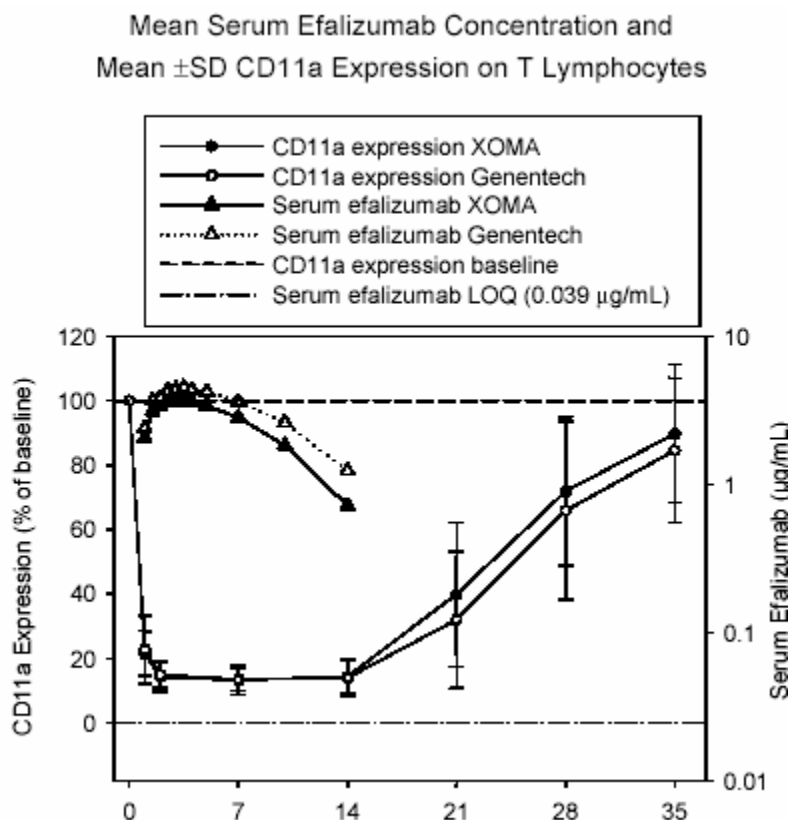
The results of the study demonstrated that single 1.0 mg/kg SC doses of Genentech efalizumab produced an approximately 30% higher exposure (AUC_{inf}) and an approximately 20% higher C_{max} in healthy volunteers compared with an identical dose of XOMA efalizumab. The protocol-specified secondary outcome variables, AUC_t and C_{max}, were also significantly higher after administration of the Genentech efalizumab dose.

	n	Geometric LS mean Xoma GNE		Ratio GNE/Xoma	90% CI	
AUC _{inf} (μ g·day/ml)	79	27.8	36.9	1.32	1.19	1.47

The point estimate and confidence intervals were outside the prespecified 80%–125% interval and therefore did not meet the criterion for comparability.

This difference in exposure did not translate into differences in extent or duration of PD activity (CD11a saturation and CD11a down-modulation on T lymphocytes). XOMA and Genentech efalizumab induced a rapid decrease in CD11a expression and available binding sites with maximal decrease by day 2. This effect was maintained until day 14, when efalizumab serum levels decreased to <1 μ g/mL. These PD effects appeared to be similar for all cell types measured for both XOMA and Genentech (T lymphocytes, NK cells, monocytes, and neutrophils).

Figure 8



No differences in safety including immunogenicity of the two products were detectable in this small study.

Reviewer's comments.

This study was conducted at the request of the Agency. The sponsor hypothesized that the cause of these observed differences in exposure was related to differences in systemic bioavailability of the two products. Differences in the formulation of the two products might account for these differences; in particular the higher concentration of surfactant (polysorbate 20) in the GNE formulation.

The 30% higher serum concentrations of GNE efalizumab did not raise safety concerns strictly on the grounds of exposure given the available clinical safety data that exceeded that exposure. The lack of appreciable difference in the magnitude and duration of CD11a receptor saturation and down-modulation induced by the Xoma and GNE products was also interpreted as suggesting that the GNE product would not manifest higher immunosuppressant clinical activity (including treatment response). The sponsor and the agency agreed that an adequate safety database would be required to demonstrate the safety of GNE efalizumab. Whether or not the clinical safety data using Xoma

efalizumab could be supportive of the safety of GNE efalizumab would become a review issue.

