4.5.4.2 Study Conduct

Table 64 below shows protocol deviations noted in Study ACD2390g.

Table 64 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 65 below.

Table 65 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 66 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 67 below.

Table 67 PASI Response by Percent Improvement from Baseline

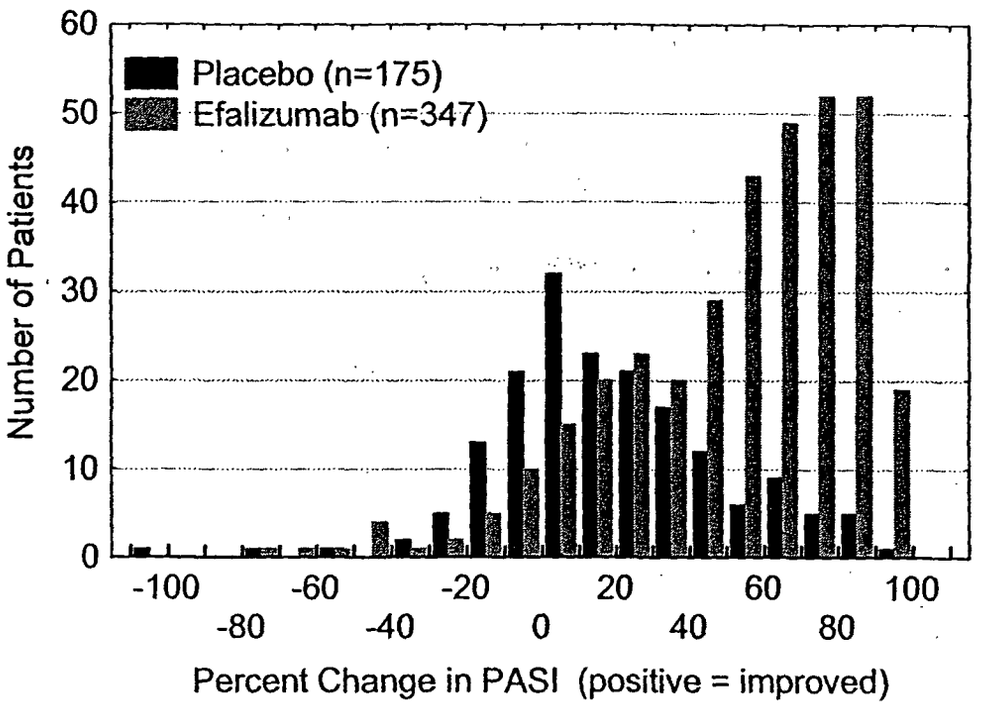
Percent Improvement from Baseline at Day 84	Placebo (n=187)	Efalizumab (n=369)
≥90%	1 (0.5%)	19 (5.1%)
≥75% to <90%	7 (3.7%)	79 (21.4%)
≥50% to <75%	18 (9.6%)	118 (32.0%)
≥25% to <50%	39 (20.9%)	59 (16.0%)
≥0% to <25%	70 (37.4%)	48 (13.0%)
≥ –25% to <0%	32 (17.1%)	15 (4.1%)
≥ –50% to < –25%	5 (2.7%)	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 7 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 7 Percent Change in PASI Score at Day 84 by Treatment Group



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

Table 68 depicts the percentage changes in PASI score by quantiles.

Table 68 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

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.

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 69).

Table 69 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.

PASI response was also analyzed by site. The findings are summarized in Table 70 below.

Table 70 PASI Response to Treatment by Site

Site	Placebo (N=187)	Efalizumab 1.0 mg/kg/wk (N=369)
S01909	0/4	1/7
S01981	1/8	2/11
S02101	0/6	3/12
S06312	2/21	16/43
S06319	0/7	4/15
S06324	1/6	5/16
S06336	1/10	7/21
S06338	0/12	3/25
S06346	0/6	3/10
S06349	0/6	3/11
S06396	5/5	7/7
S06481	0/10	2/17
S06556	1/17	5/38
S06559	0/6	4/12
S07640	0/9	4/20
S07789	0/8	3/9
S07816	0/5	4/12
S07911	0/19	14/37
Combined*	2/22	15/46

* Sites that enrolled fewer than 10 subjects were combined

In general treatment effect was seen within the various sites.

Responses in the components of the PASI score are shown in Table 71 below.

Table 71 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 72 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 73 below.

Table 73 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 74 below.

Table 74 OLS Response to Treatment at Day 84

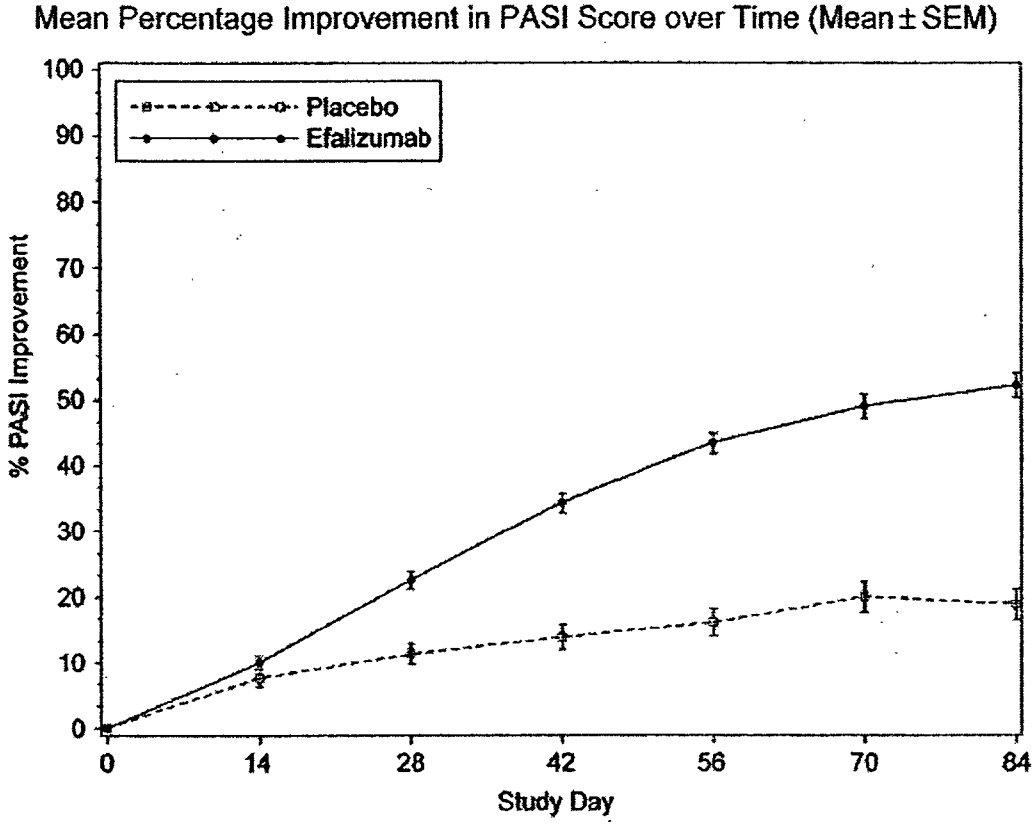
OLS Response at Day 84	Placebo (n=187)	Efalizumab (n=369)
Clear	0	7 (1.9%)
Minimal	6 (3.2%)	88 (23.8%)
Mild	32 (17.1%)	125 (33.9%)
Moderate	92 (49.2%)	99 (26.8%)
Severe	40 (21.4%)	25 (6.8%)
Very Severe	6 (3.2%)	7 (1.9%)
Missing	11 (5.9%)	18 (4.9%)

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 8 below shows the mean percentage improvement in PASI score over time. Assessment of PASI was performed biweekly during the first treatment period.

Figure 8



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

An exploratory analysis of time to onset of PASI 50 response among PASI 75 responders is shown in Table 75 below.

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

	Placebo N=8	Efalizumab 1.0 mg/kg/wk N=98
Median (days)	56	43
95% CI	31, 71	43, 44
25th–75th Percentile	37–64	30–57

Among 98 efalizumab-treated patients classified as PASI 75 responders, the median onset to PASI 50 in this study was 43 days. These results are consistent with those obtained in studies ACD2058g and ACD2059g.

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 76 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

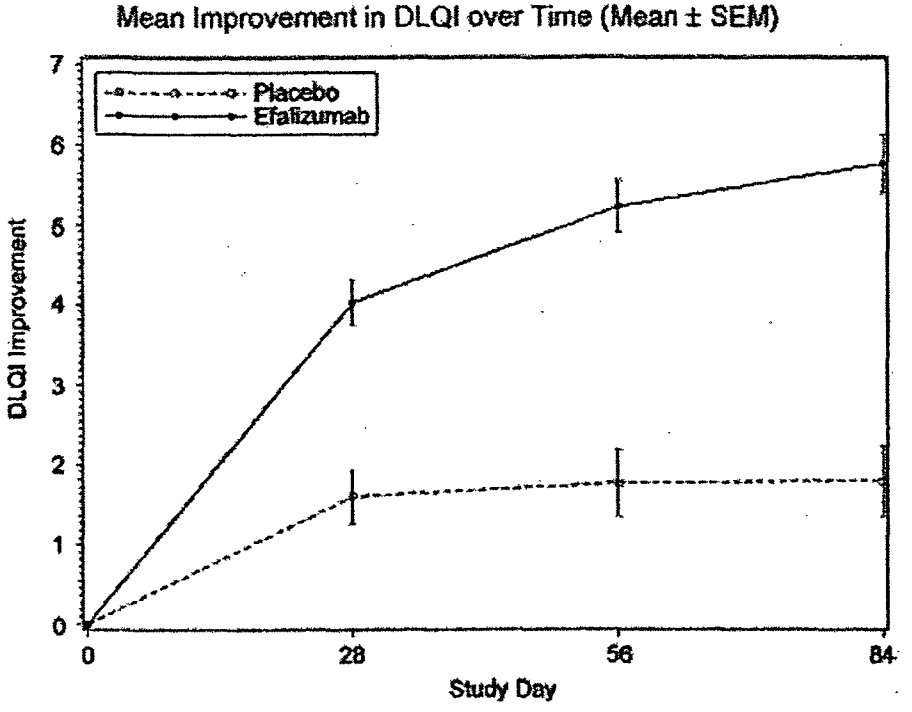
[a] The last observation carried forward was used to impute missing Day 84 DLQI values.
[b] Improvement was reflected by a decrease in DLQI overall score.

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.

Mean Improvement from Baseline in DLQI over Time. Subjects in the efalizumab group showed a clear improvement in mean DLQI scores versus the placebo group as early as 28 days following initial treatment ($p<0.001$). The mean improvement in DLQI score over time is shown for each treatment group in Figure 9.

Figure 9



SEM=standard error of mean.

Reviewer's comment: The sponsor has not provided references or analyses to support the clinical significance of this degree of change.

PASI ≥ 50% Improvement

The majority of subjects receiving efalizumab (58.5%) experienced ≥ 50% improvement in PASI score from baseline compared with 13.9% of subjects receiving placebo .

Table 77 PASI Response to Treatment for Randomized Subjects

PASI Response at Day 84	Placebo (n=187)	Efalizumab (n=369)
≥ PASI 50	26 (13.9%)	216 (58.5%)
Non-responders [a]	161 (86.1%)	153 (41.5%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001

[a] Included subjects whose Day 84 PASI score was missing.

The Itching Scale was a modified visual analog scale that has been used in previous Genentech studies (ACD2058g and ACD2059g).

Table 78 Mean Improvement from Baseline in Scores in the Itching Scale

Change in Itching Score	Placebo (n=187)	Efalizumab (n=369)
Day 0	6.2	6.4
Day 84 [a]	5.6	3.6
Improvement [b]	0.7	2.8
Percent improvement [c]	n=184	n=360
	–0.2	37.7
Two-sample t-test p-value efalizumab vs. placebo	—	<0.001

[a] The last observation carried forward was used to impute missing Day 84 Itching Scale values.
[b] Improvement was reflected by a decrease in the 10-point score in Itching Scale.
[c] Subjects with a baseline Itching Scale score of zero were not included.

The mean baseline severity was comparable in each treatment group- 6.2 for placebo and 6.4 for efalizumab. The percentage improvement was 38% in the efalizumab vs. negligible change in placebo. The difference was statistically significant ($p<0.001$).

Reviewer's comment: It is not clear whether these data contribute additional information of clinical relevance to the data already proposed for the primary and principal secondary endpoints.

PSA. A comparison of improvement from baseline in the frequency and severity of the psoriasis-specific symptom scores at Day 84 for the efalizumab group versus the placebo group was performed using the Wilcoxon rank-sum test. A decrease in PSA score represents improvement.

Table 79 Improvement in PSA

PSA	Placebo (n=187)	Efalizumab (n=369)
Symptom frequency		
Day 0		
Mean	14.1	14.3
Median	14.0	14.0
Range	2 to 24	2 to 24
Day 84		
Mean	11.5	7.6
Median	11.0	6.0
Range	1 to 24	0 to 24
Improvement from baseline [a]		
n	185	361
Mean	2.6	6.8
Median	2.0	7.0
Range	–10 to 18	–9 to 24
Wilcoxon rank-sum test p-value efalizumab vs. placebo	—	<0.001
Symptom severity		
Day 0		
Mean	15.0	14.8
Median	15.0	16.0
Range	2 to 24	0 to 24
Day 84		
Mean	12.4	7.8
Median	13.0	6.0
Range	0 to 24	0 to 24
Improvement from baseline [a]		
n	185	362
Mean	2.5	7.0
Median	1.0	7.0
Range	–11 to 17	–11 to 24
Wilcoxon rank-sum test p-value efalizumab vs. placebo	—	<0.001

[a] The last observation carried forward was used to impute missing Day 84 PSA Frequency or Severity values.
[b] Improvement was reflected by a decrease in PSA frequency or severity.

Comparisons of the improvement from baseline of the efalizumab group versus the placebo group were statistically significant for both frequency of symptoms ($p<0.001$) and severity of symptoms ($p<0.001$; see Table 79), implying an improvement in psoriasis-specific symptoms for the efalizumab group relative to placebo. The mean improvements in symptom frequency and severity in the efalizumab group were more than two times that observed in the placebo group. The treatment groups were well balanced at baseline for both frequency and severity on each of the eight symptoms assessed by PSA (hurt, burning or stinging, itched, bothered by water, irritated, sensitive, skin condition bled, scaling). There was a trend toward improvement across all symptoms in both frequency and severity.

Reviewer's comment: Because the PSA has not been validated, these results should not be included in the package insert. The sponsor has not provided information regarding what is deemed a clinically significant change using the PSA.

PGA.

Physician's Global Assessment of Change

The Physician's Global Assessment of change (PGA) captures and categorizes the global response to therapy of all clinical signs and symptoms of disease relative to baseline. The physician is instructed to use all available information for this assessment, including subjective information gathered from the subject and photographs taken at baseline. The categories are Worse, Unchanged, Slight, Fair, Good, Excellent, and Cleared (See Table 80). In the Phase III, placebo-controlled studies, a positive response was defined as a PGA rating of Excellent or Cleared. In analyses, subjects who discontinued treatment early or did not have a PGA assessment at Day 84 were classified in the category of Good to Worse to indicate a lack of positive response.

Table 80 PGA Soring System

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

Table 81 PGA Response of Subjects

PGA Response at Day 84	Placebo (n=187)	Efalizumab (n=369)
Excellent or Cleared	10 (5.3%)	122 (33.1%)
Good to Worse [a]	177 (94.7%)	247 (66.9%)
Fisher's exact p-value efalizumab vs. placebo	—	<0.001

[a] Included subjects who were classified as Good, Fair, Slight, Unchanged, or Worse and those whose Day 84 PGA rating was missing.

The proportion of subjects with a PGA rating of Excellent or Cleared at Day 84 was statistically significantly greater in the efalizumab group compared with the placebo group ($p<0.001$; see

Table 81). More than half of the subjects (56.0%) in the efalizumab group had attained PGA ratings of Good to Cleared compared with 12.8% of subjects in the placebo group.

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 ≥75% improvement in Psoriasis Area and Severity Index (PASI)
- The Overall Lesion Severity (OLS) scale
- The proportion of subjects achieving a ≥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 Elegibility 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 ≥ 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 82 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 83 below.

Table 83 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 AlaskanNative, 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 84 below.

Table 84 ACD2600g: Baseline Psoriasis Characteristics of Randomized Subjects

Characteristic	Placebo (N=236)	Efalizumab (N=450)
Prior systemic therapy		
Yes	174 (73.7%)	328 (72.9%)
No	62 (26.3%)	122 (27.1%)
PASI category		
≤ 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%)
OLS		
Mild	15 (6.4%)	20 (4.5%)
Moderate	131 (55.5%)	253 (56.3%)
Severe	82 (34.7%)	156 (34.7%)
Very severe	8 (3.4%)	20 (4.5%)
PASI score		
Mean	18.69	19.14
Median	17	17
Range	10.5 - 49.6	10.2 - 54.6
Percent BSA of psoriasis		
Mean	26.8	27.7
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 85).

Table 85 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 86).

Table 86 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%.

Reviewer's comment: The purpose of this study was primarily to gain additional safety data with the Genentech-manufactured efalizumab. Efficacy assessments were not performed as frequently as in earlier studies and, therefore, the study is not optimally designed to measure onset and duration of treatment effect.

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 87 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 87 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) and the median time to PASI 50 was approximately 6 weeks. 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 assessments were biweekly; therefore, time to onset could not be estimated more narrowly than a two-week window.
- The median duration of treatment effect based on the time to loss of 50% of improvement was 67 days following discontinuation of treatment.
- Assessments in studies 2058 and 2059 were performed after 2 weeks and subsequently every 4 weeks during the period following the first 12 weeks of dosing. In study 2058, the time to loss of PASI 50 and PASI 75 were both estimated to be between 1 and 2 months after the dosing period. In study 2059, the time to loss of PASI 50 and PASI75 were between 3 and 7 weeks and 4 and 7 weeks, respectively.
- 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 study ACD2059g, in patients who were nonresponders (PASI <50) after the first 12 weeks of efalizumab treatment, extended treatment with a contiguous 3 month treatment course resulted in an additional 11% PASI 75 response.
- Patients who were partial responders in Study 2059g were treated with an additional contiguous 3 months of efalizumabat doses and regimens which were different from the recommended dose for licensure, and different from those that were received during the first 12-weeks of therapy. The data suggest that patients who are partial responders

during the first 12-weeks of treatment may achieve full response with extended treatment. However, more studies with the 1 mg/kg/wk dose are needed to confirm this hypothesis.

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 88 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 pharamcokinetics 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 88 Subjects with Moderate to Severe Plaque Psoriasis Receiving SC Efalizumab Treatment beyond the Initial 12-Week Course (EE)

	Efalizumab Treatment Segment			
Source (Manufacturer)	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 89 below.

Table 89 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	Atherscleroticcardiovascular 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 (Genetech)	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 ≥ age 50 and in whom were known pre-existing cardiovascular risk factors.

Reviewer's note:
For patients28913 and12062 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 90 below.

Table 90 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 91 below.

Table 91 Infections Classified as Serious by the Investigator in the First Exposure Controlled Clinical Experience (Studies 2600, 2058, 2059 and 2390)

Patient/Study	Treatment Group	Age (yr)/ Gender	Event	Resulted in Hospitalization?
45225/ACD2600	Efalizumab (GNE) 1.0	70/ F	Urosepsis associated with possible kidney stone	Yes
45207/ACD2600	Efalizumab (GNE) 1.0	74/ M	Pneumonia associated with decreased neutrophil count	Yes
34229/ACD2390g	Efalizumab (GNE) 1.0	53/ F	cellulitis	Yes
76802/ACD2059g	Efalizumab (GNE) 2.0	54/ M	cellulitis	Yes
16506/ACD2058g	Efalizumab (XOMA)1.0	57/ M	pneumonia	Yes
17501/ACD2058g	Efalizumab (XOMA) 2.0	32/ M	cellulitis (hand),gastroenteritis	No
17512/ACD2058g	Efalizumab (XOMA) 1.0	46/ F	gastroenteritis	No
22006/ACD2058g	Placebo	45/ M	gastroenteritis	Yes

Serious infections were noted with both drug products (Genentech- and XOMA-manufactured efalizumab). In two efalizumab-treated patients classified as having a serious infection, the infection did not result in hospitalization.

The narratives of these patients are given below.

Subject No.: 17501
Events: Cellulitis, gastroenteritis (viral gastroenteritis)
The patient was a 32-year-old man randomized to 2.0 mg/kg/wk efalizumab and received his initial dose of 0.7 mg/kg on 8 May 2000. His medical history was significant for cellulitis of the right arm in 1999 and 2000; his right elbow was incised and drained following the second episode of cellulitis in 2000. He also had a history of bilateral, superficial cuts on his hands since 1990. Concomitant medications consisted of cold and sinus remedies, unscented moisturizing formula, vitamin C, vitamin B complex, ibuprofen, acetaminophen, and bacitracin zinc/polymyxin sulfate for the superficial cuts on his hands. On 13 April 2000 (FT Day 36), 1 day after receiving his last dose of study drug prior to the event, the subject developed moderate cellulitis of the right hand. It was reported that the subject had experienced hand trauma while at work the previous day. He took acetaminophen that night, but awoke the next day with increased pain and erythema in his right hand. He was examined and treated with cephalexin. Event resolution occurred in 11 days.

On 20 April 2000 (FT Day 34), 2 days after receiving his seventh dose of efalizumab, the subject developed moderate viral gastroenteritis. Symptoms included mild fever, nausea, diarrhea, bloating, and right-sided abdominal pain. At the time of the event, the subject was taking antibiotics for cellulitis. A CT scan was performed to rule out appendicitis. All laboratory test results were negative. No treatment was administered, and the event resolved in 3 days. The investigator determined the cellulitis and gastroenteritis to be not related to study drug.

Reviewer's comment: The patients cellulitis was treated as an outpatient with oral antibiotics and resolved in a period of 10 days and the gastroenteritis required no specific treated and resolved in 3 days. The event was classified as serious by the investigator because it may have jeopardized the subject and may have required intervention to prevent hospitalization, a life-threatening illness or disability.

Subject No.: 17512
Event: Gastroenteritis
The patient was a 46-year-old woman and was randomized to 1.0 mg/kg/wk efalizumab and received herinitial dose of 0.7 mg/kg on 2 May 2000. On 7 June 2000 (FT Day 36), 12 hours after receiving her last dose of study drug prior to the event, the subject developed moderate gastroenteritis with mild diffuse abdominal tenderness. After becoming moderately febrile (temperature not reported), the subject presented to the ER and was treated with IV fluids, acetaminophen, and ibuprofen. The subject had experienced mild to moderate dyspepsia lasting 1–2 days during the previous month. She was discharged home after her fever resolved. Additional symptoms included weakness, diarrhea, dizziness, headache, runny nose, and nasal congestion. The subject was noted to have an elevated WBC count with increased neutrophils and decreased lymphocytes. Event resolution occurred in 7 days.

Study drug was held on 13 June 2000 because of the gastroenteritis, but was resumed on 20 June 2000. On 27 June 2000, after receiving seven doses of efalizumab, the investigator decided to discontinue the subject from the FT period. The subject was enrolled in the FU period and

completed the study on 19 September 2000. The results of a CBC count performed on FU Day 84 were within normal range. The investigator determined the gastroenteritis to be not related to study drug.

Reviewer's comment: The patient was treated with IV fluids and observed in the Emergency Department, but was not hospitalized. The event was classified as serious by the investigator because it may have jeopardized the subject and may have required intervention to prevent hospitalization, a life-threatening illness or disability.

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 92.

Table 92 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	169	[0.24, 7.22]	1.18	[0.14, 4.26]

The incidence of serious infections requiring hospitalization per 100 subject years is 1.61 in the efalizumab-treated group and 1.18 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 [redacted] 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 diskectomy 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 streptoccoci. 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 streptoccoci. 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 cellulits. 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.

<u>All infectious adverse events (serious and non-serious):</u>
Serious and non-serious infectious adverse events are shown in Table 93 below.

Table 93 Adverse Events Diagnostic of Infection Reported within the First Exposure Period for Subjects Treated Efalizumab

	FE/Controlled	
Adverse Event n	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%)	6 (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 94.

Table 94 Serious Malignancies Experienced by Subjects Who Received Study Drug in the FE/Controlled Studies

		Efalizumab (XOMA or Genentech)		
Adverse Event	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.

Reviewer's comment:
It is not possible to exclude a meaningful increase in risk of malignancies associated with efalizumab-treatment, however, as the median duration of treatment was approximately 8 months and longer observations are usually necessary to evaluate for malignancy.

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 95).

Table 95 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 96 Observed versus Expected Rate of Solid Tumors and Malignant Melanoma (updated May 2003)

	Efalizumab-Treated Subjects			External Reference Cohorts		
Malignancy Category	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 97 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 98 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 98 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 99).

Table 99 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 100 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), ibuprofin (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),	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	Nefazodone, 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 antiobody	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, normocelluar 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.