Table 25 Duration (days) of PASI-75 Response during Washout from the First 12 Weeks of Treatment in PASI 75 Responders

Characteristic	Efalizumab 1.0 mg/kg/wk	Efalizumab 2.0 mg/kg/wk	All Efalizumab
Subjects With PASI-75 at FT Day 84	60	41	101
Events	58	39	97
Censored Observations	2	2	4
Median	55.5	54.0	55.0
95% C.I. for Median	(29.0, 56.0)	(28.0, 56.0)	(31.0, 56.0)
25-75 %ile	15.0 - 57.5	26.0 - 69.0	17.0 - 59.0
Minimum - Maximum	11.0 - 427.0+	0.0 - 225.0	0.0 - 427.0+

The median time to loss of PASI 75 was 55.5 days for the efalizumab 1 mg/kg weekly group, 54 days for the 2 mg/kg/ weekly group and 55 days for the combined dose groups.

Time to loss of PASI 50 among the PASI 75 responders is shown below.

Table 26 Duration (days) of PASI-50 Response during Washout from the First 12 Weeks of Treatment in PASI 75 Responders

Characteristic	Efalizumab 1.0 mg/kg/wk	Efalizumab 2.0 mg/kg/wk	All Efalizumab
PASI 75 Responders	60	41	101
Events	56	38	94
Censored Observations	4	3	7
Median	56.0	56.0	56.0
95% C.I. for Median	(55.0, 61.0)	(54.0, 76.0)	(56.0, 60.0)
25-75 %ile	28.0 - 83.0	35.0 - 84.0	34.0 - 84.0
Minimum - Maximum	11.0 - 427.0+	0.0 - 255.0	0.0 - 427.0+

The median time to loss of PASI 75 was 56 days for both of the efalizumab dose groups. The similarity between duration of response as measured by PASI-75 and PASI-50 was likely attributable to frequency of assessment of PASI during the Washout period, biweekly for the first 4 weeks and monthly thereafter. It is likely that the frequency of the ascertainment schedule has led to an overestimation of the duration of PASI 75.

Estimates for median duration of response (PASI 50 and PASI 75) among PASI 75 responders using the four assumptions discussed are summarized in Table 27 below.

Table 27 Duration of Response for PASI-75 Responders following 12 Weeks of Efalizumab Treatment (1 mg/kg/wk)

Response Criterion Definition for Loss of Response	Median Duration in Days (95% CI for the Median)
PASI-75	
Linear interpolation	30.5 (28,36)
Midpoint	41.5 (24,42)
Last visit with a response	28 (17,28)
First visit without response	55.5 (29,56)
PASI-50	
Linear interpolation	48 (39,54)
Midpoint	42 (41,48)
Last visit with a response	28 (28,33)
First visit without response	56 (55,61)

Duration of PASI-75 [PASI-50] response was measured from date of last dose to date PASI-75 [PASI-50] response was lost as determined by one of three approaches.

From these results, the median duration of treatment response (by both PASI 50 and PASI 75) was between one and two months after the 12-week dosing period.

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 168-day observation period.

Table 29 below shows the disposition of subjects during the OB period.

Table 28 Disposition of Subjects and Reasons for Discontinuation during the OB Period

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

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 29 below shows the psoriasis-related concomitant medications started during the observation period among first treatment period PASI 75 responders.

Table 29 Psoriasis-Related Concomitant Medications Initiated during the OB Period among FT Period Responders

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

Overall, 24% of patients entering the observation period initiated at least one psoriasis-related medication (See Table 29). 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 concomitant medications during the observation period may affect the estimate of the duration of response. For this reason, analyses in which patients were assumed to have lost response at the time such medications were initiated were considered relevant for estimation of duration of response.

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 ≥ 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 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 43, the majority of both placebo- and efalizumab-treated patients discontinued the observation period due to relapse of their psoriasis.

Table 30 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 for retreatment.

Table 30 Disposition of RT-A Subjects and Reasons for Discontinuation

		Efalizumab	
	Placebo	**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 retreatment. Of these, 82 were rerandomized to retreatment. 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 31 below shows the psoriasis characteristics of the subset of responders who entered retreatment upon relapse.

Table 31 Psoriasis Characteristics of RT-A Subjects

Characteristic, n	Placebo (n=27)	Efalizumab 1.0 mg/kg/wk (n=32)	Efalizumab 2.0 mg/kg/wk (n=23)
Duration of psoriasis (yr)			
Mean	20.6	20.0	18.9
Median	21	20	18
Range	3–46	3–43	2–43
Prior systemic therapy			
Yes	15 (55.6%)	19 (59.4%)	13 (56.5%)
No	12 (44.4%)	13 (40.6%)	10 (43.5%)
Baseline PASI (FT Day 0)			
Mean	18.7	17.7	19.2
Median	17.5	15.4	17.1
Range	11.9–29.7	12.0–35.3	12.1–36.0
RT Day 0 PASI			
Mean	14.8	13.2	13.7
Median	12.4	11.9	11.6
Range	7.5–39.0	7.4–29.2	8.5–28.7
Baseline (FTDay 0) PASI category			
≤16.0	12 (44.4%)	19 (59.4%)	11 (47.8%)
16.1–30.0	15 (55.6%)	10 (31.3%)	8 (34.8%)
>30	0	3 (9.4%)	4 (17.4%)
Baseline (FT Day 0) OLS			
Moderate	18 (66.7%)	21 (65.6%)	12 (52.2%)
Severe	9 (33.3%)	10 (31.3%)	11 (47.8%)
Very severe	0	1 (3.1%)	0
RT Day 0 OLS			
Mild	0	1 (3.2%)	4 (17.4%)
Moderate	23 (85.2%)	25 (80.6%)	15 (65.2%)
Severe	4 (14.8%)	4 (12.9%)	4 (17.4%)
Very severe	0	1 (3.2%)	0
% BSA of psoriasis			
Mean	31.7	29.1	31.5
Median	32.0	24.6	28.0
Range	13.0–63.0	11.0–59.0	11.0–81.0
RT Day 0 % BSA of psoriasis			
Mean	24.0	17.1	21.8
Median	20.0	14.0	15.5
Range	5.0–74.0	6.2–43.0	7.0–54.0
FT Day 84 dPGA			
Cleared	1 (3.7%)	2 (6.3%)	0
Excellent	23 (85.2%)	27 (84.4%)	20 (87.0%)
Good	2 (7.4%)	2 (6.3%)	3 (13.0%)
Fair	1 (3.7%)	0	0
Missing	0	1 (3.1%)	0
RT Day 0 dPGA			
Good	1 (3.7%)	2 (6.3%)	0
Fair	12 (44.4%)	17 (53.1%)	7 (30.4%)
Slight	4 (14.8%)	5 (15.6%)	12 (52.2%)
Unchanged	2 (7.4%)	2 (6.3%)	1 (4.3%)
Worse	8 (29.6%)	6 (18.8%)	3 (13.0%)

Unless otherwise stated baseline was FT Day 0.

The rerandomized patients were reasonably well balanced in terms of the baseline disease severity. The baseline characteristics were comparable to the ITT population as a whole. 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 (11.6-12.4) was lower than that at Day 0 of the first treatment period. The patients' retreatment baseline BSA affected by psoriasis was also better than their original baseline.

Treatment compliance in the patients randomized to retreatment is shown in

Table 32 below.

Table 32 Treatment Compliance for RT-A Subjects

No. of Doses Received	Placebo (n=27)	Efalizumab 1.0 mg/kg/wk (n=32)	Efalizumab 2.0 mg/kg/wk (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.

A distribution of response to retreatment is shown 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 33 PASI Response to Retreatment (% Improvement from FT Day 0)

Response Category	Placebo (n=27)	Efalizumab 1.0 mg/kg/wk (n=32)	Efalizumab 2.0 mg/kg/wk (n=23)
≥90%	0	5 (15.6%)	1 (4.3%)
≥75% to <90%	0	6 (18.8%)	5 (21.7%)
≥50% to <75%	5 (18.5%)	12 (37.5%)	8 (34.8%)
≥25% to <50%	2 (7.4%)	2 (6.3%)	0
<25%	1 (3.7%)	1 (3.1%)	2 (8.7%)
Missing [a]	19 (70.4%)	6 (18.8%)	7 (30.4%)

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

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

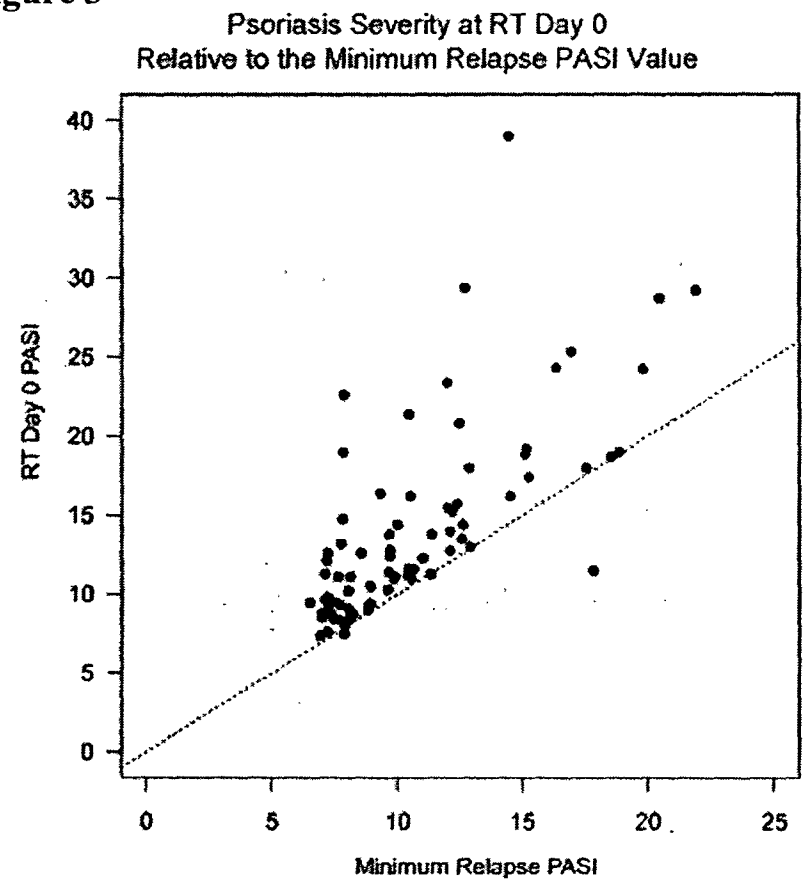
was in contrast to patients rerandomized to placebo who had no PASI 75 responders to retreatment. The majority of the patients receiving efalizumab upon retreatment, 72% and 61% the 1 mg/kg group and 2 mg/kg group, respectively, responded at the PASI 50 level.

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.

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 without completing the retreatment period, due to non-response.

Figure 3 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 3



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.

The responses to retreatment when compared to the new baseline are shown in Table 34 below.

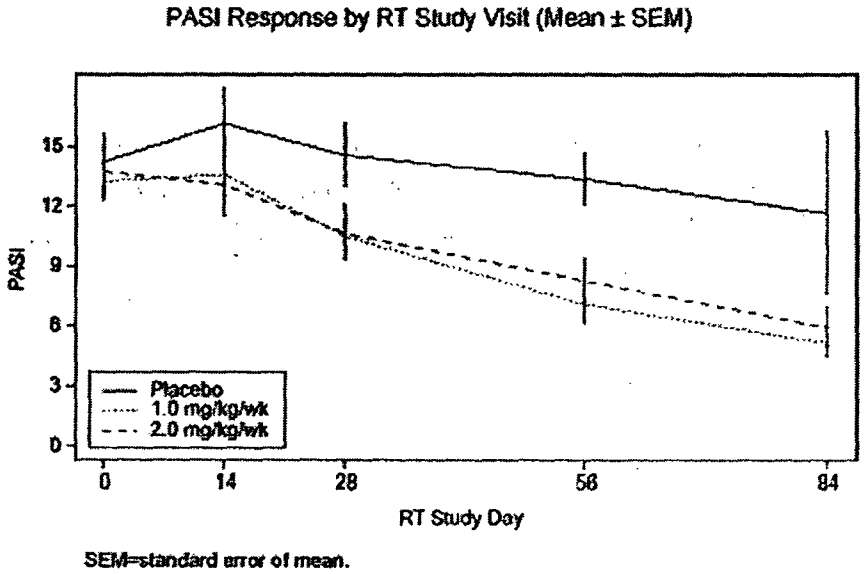
Table 34 PASI Response to Retreatment (% Improvement from RT Day 0)

Response Category	Placebo (N=27)	Efalizumab (1 and 2 mg/kg/wk dose groups) (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 4 below. Separation of the efalizumab curves from that of placebo took place by 28 days of retreatment.

Figure 4



SEM=standard error of mean.

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 35 below.

Table 35 OLS Response to Treatment for RT-A Subjects

RT Day 84 Characteristic	Placebo (n=27)	Efalizumab 1.0 mg/kg/wk (n=32)	Efalizumab 2.0 mg/kg/wk (n=23)	All Efalizumab-Treated Subjects (n=55)	All Efalizumab vs. Placebo
Minimal or Clear	1 (3.7%)	9 (28%)	6 (26%)	15 (27%)	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 who received efalizumab during the first treatment period and were re-randomized to extended treatment with efalizumab or placebo was also analyzed.

The patient disposition of this group is shown below.

Table 36 Disposition of ET-A Subjects and Reasons for Discontinuation

Subject Status	Withdrawal/ Placebo (n=60) [a]	Efalizumab 1.0 mg/kg/wk (n=57)	Efalizumab 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 37).

Table 37 Baseline Psoriasis Characteristics of ET-A Subjects

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

[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 38).

Table 38 Proportion of ET-A Subjects Who Achieved PASI 75 Response

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

These results suggest that additional patients may achieve 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 may result in an additional response in those patients who failed to respond to the first course.

In a separate tertiary analysis, the response rates of the first treatment period partial responders and non-responders were determined separately at the end of the extended treatment period. This analysis is shown in tables 39 and 40 below.

Table 39 Proportion of ET-A Subjects Who Were Partial Responders (PASI ≥ 50 and <75) and Achieved PASI 75 Response with Extended Treatment

		Efalizumab		All Efalizumab-Treated Subjects (n=52)
	Placebo (n=24)	1.0 mg/kg/wk (n=26)	2.0 mg/kg/wk (n=26)	
ET Day 84 Responders	1 (4.2%)	10 (38.5%)	7 (26.9%)	17 (32.7%)
95% CI for the response rate	[0.001,0.211]	[0.202,0.594]	[0.116,0.478]	[0.203,0.471]

Trends towards higher response rates among partial responders receiving an extended treatment with efalizumab compared with those receiving placebo during the subsequent 12-week dosing period. However, this is a non-randomized subgroup analysis and the difference from placebo did not reach statistical significance.

Table 40 Proportion of ET-A Subjects Who Were Non Responders (PASI<50) and Achieved PASI 75 Response with Extended Treatment

		Efalizumab		All Efalizumab-Treated Subjects (n=71)
	Placebo (n=36)	1.0 mg/kg/wk (n=31)	2.0 mg/kg/wk (n=40)	
ET Day 84 Responders	3 (8.3%)	2 (6.5%)	6 (15.0%)	8 (11.3%)
95% CI for the response rate	[0.018, 0.225]	[0.008, 0.214]	[0.057, 0.298]	[0.050, 0.210]

The response of the combined efalizumab-treated patients was only 11% compared with 8% of placebo-treated patients with overlapping 95% confidence intervals. Therefore, the data suggest that a patient who does not achieve at least a partial response during the first 12 weeks of treatment will not likely respond to extended treatment with efalizumab.

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 OLS, the 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 and the time to PASI50 response was 6 weeks.
- Among PASI 75 responders, the median time to relapse (loss of 50% of the improvement obtained during the first treatment period) after treatment discontinuation was variable, but estimated as a median of 67 days. The estimated median duration of PASI 75 response and PASI 50 response were both between one and two months after the first 12-week treatment period. The timing of PASI assessments did not allow for a more precise estimate of duration of response.
- Only one-third of patients who responded to the first treatment period and were followed until relapse responded to retreatment with efalizumab.
- Among the non-responders and partial responders 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 ≥ 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 where relapse was defined as loss of at least 50% of the improvement achieved in PASI score between FT Day 0 and FT Day 84.

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

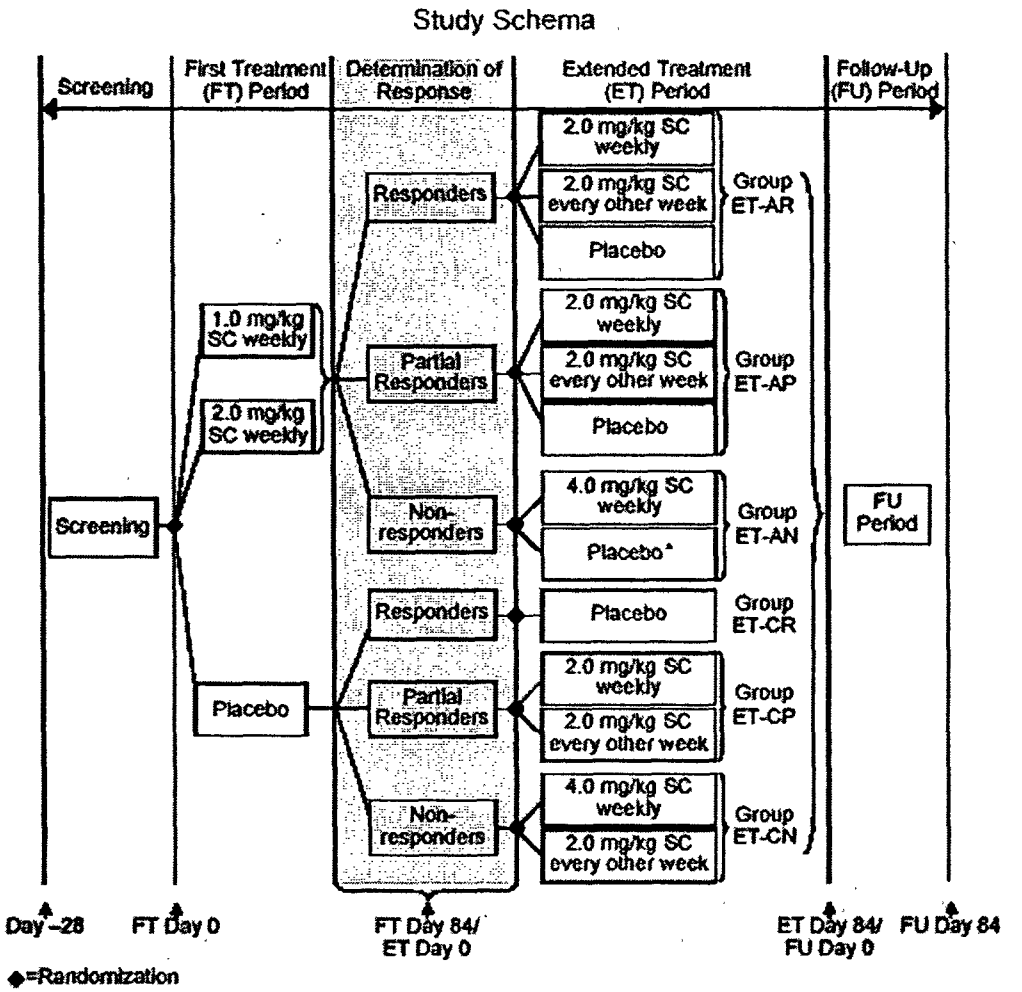
- To investigate the efficacy of SC efalizumab administered for 24 weeks compared with 12 weeks followed by placebo for 12 weeks as measured by PASI, Overall Lesion Severity (OLS), and Physician's Global Assessment, with particular attention to the proportion of subjects who became "cleared" or "almost 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 5).

Figure 5 Study ACD 2059 Schema



Group ET-AR = active responder; Group ET-CR = control responder;
Group ET-AP = active partial responder; Group ET-CP = control partial responder;
Group ET-AN = active non-responder; Group ET-CN = control non-responder.
[a] Placebo to match 4.0 mg/kg weekly and 2 mg/kg every other week.

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).

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 page23).

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.)

4.4.3.9 Study Assessments
Assessments of Efficacy
PASI and OLS were assessed at biweekly intervals during the first treatment period and at Days 14, 28, 56 and 84 of the extended treatment period. During the follow-up period, PASI and OLS were assessed at days 28, 56, and 84. Psoriatic BSA, dPGA and patient's assessment of itch were assessed at baseline and Days 56 and 84 during the first treatment period and the extended treatment period. Patient photography, target lesion assessment, DLQI, and PSA were assessed at baseline and at day 84 of both the first treatment period and the extended treatment period. Patient photography was performed at baseline and Day 84 of the first treatment period.

Safety Assessments
Physical examination was done at screening and at Day 84 of the first treatment period. Monitoring for adverse events and concomitant medications was done weekly during the first treatment period. The following laboratories were obtained at baseline and at Days 56 and 84 of both the first treatment period and the extended treatment period: blood chemistry, hematology (CBC, platelet, differential), and urinalysis. Serum antibodies to efalizumab were obtained at predose and at day 84 of the first treatment period. During the follow-up period serum antibodies were assessed at Days 28 and 84. Urine pregnancy test for females of childbearing potential was obtained at monthly intervals. RPR was obtained 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. Chemistries, hematology and UA were not assessed during the follow-up period.

4.4.3.10 Efficacy Outcomes and Statistical Considerations
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 Fisher's exact test for the ITT population was performed comparing each efalizumab group to placebo. To maintain a type I error rate for the primary analysis of α=0.05 (two sided), the Hochberg-Bonferroni multiple comparisons procedure was used to adjust for the two comparisons (Hochberg 1988). If both comparisons attained a p-value of <0.05 in favor of efalizumab, both active treatment groups were considered significantly different from placebo. If the p-value for one comparison exceeded 0.05, the other active treatment was considered statistically significantly different from placebo only if its associated p-value was <0.025 in favor of efalizumab.

The principal secondary efficacy outcome measure was the proportion of subjects achieving an OLS rating of Minimal or better at FT Day 84. No adjustments for multiplicity (of endpoints or treatment comparisons) were incorporated into the analyses of secondary endpoints, except for

the OLS in the FT period, the principal secondary endpoint. Comparisons were made as described above for the primary endpoint.

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

- Proportion of subjects achieving an OLS rating of Minimal or better at FT Day 84
- Proportion of subjects attaining a dPGA rating of Excellent or better at FT Day 84
- Mean change from baseline (FT Day 0) in the thickness component of the PASI at FT Day 84
- Mean change from baseline (FT Day 0) on the Patient's Assessment of Itch at FT Day 84
- Mean change from baseline (FT Day 0) in the percentage of BSA affected by psoriasis at FT Day 84

Fisher's exact test for the ITT population was performed comparing each efalizumab group to placebo for the OLS and PGA secondary outcomes. The remaining secondary outcomes were to be evaluated by two sample t tests using the pooled error term from an ANOVA of all three treatment groups.

The DLQI was prospectively identified as an exploratory endpoint. It was to be analyzed using the Wilcoxon rank sum test for each treatment group compared with placebo.

4.4.3.11 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 41).

Table 41 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)	FT Efalizumab 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 42 and in Table 43 below.

Table 42 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)	FT Efalizumab 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 43 Baseline Psoriasis Characteristics of Subjects in the FT Period

Characteristic	FT Placebo (n=122)	FT Efalizumab 1.0 mg/kg/wk (n=232)	FT Efalizumab 2.0 mg/kg/wk (n=243)
Duration of psoriasis (yr)			
Mean	19.6	19.3	18.2
Range	0–62	1–60	1–70
Prior systemic therapy			
Yes	86 (70.5%)	160 (69.0%)	152 (62.6%)
No	36 (29.5%)	72 (31.0%)	91 (37.4%)
PASI category			
≤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	20.43	19.98	19.83
Median	17.2	17.1	17.5
Range	11.7–49.6	11.7–53.4	5.6–53.4
OLS			
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	31.11	31.97	30.44
Range	10.0–90.0	10.0–98.0	7.0–94.0
Patient's Assessment of Itch			
Mean	3.1	3.0	3.1
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. The 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 efalizumb 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 acetonide, prednisone, and triamcinolone. No subjects used phototherapy.

Table 44 Protocol Deviations during the FT Period

Protocol Deviation	FT Placebo (n=122)	FT Efalizumab 1.0 mg/kg/wk (n=232)	FT Efalizumab 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]	10 (8.2%)	17 (7.3%)	22 (9.1%)
<82 Days	2 (1.6%)	6 (2.6%)	2 (0.8%)
>86 Days	8 (6.6%)	11 (4.7%)	20 (8.2%)
OLS performed outside of the FT Day 84 window [b]	10 (8.2%)	17 (7.3%)	22 (9.1%)
<82 Days	2 (1.6%)	6 (2.6%)	2 (0.8%)
>86 Days	8 (6.6%)	11 (4.7%)	20 (8.2%)
Use of excluded medication	4 (3.3%)	19 (8.2%)	10 (4.1%)
Incorrect dosing level	2 (1.6%) [c, d]	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 45 below.

Table 45 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)	FT Efalizumab 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 46).

Table 46 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)	FT Efalizumab 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 47).

Table 47 Mean Improvement in Percent BSA of Psoriasis during the FT Period

Percent BSA	FT Placebo (n=122)	FT Efalizumab 1.0 mg/kg (n=232)	FT Efalizumab 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 plaque elevation.

The table below shows the distribution of improvement by treatment group during the first treatment period (Table 48).

Table 48 PASI Response by Percent Improvement from Baseline for Subjects in the FT Period

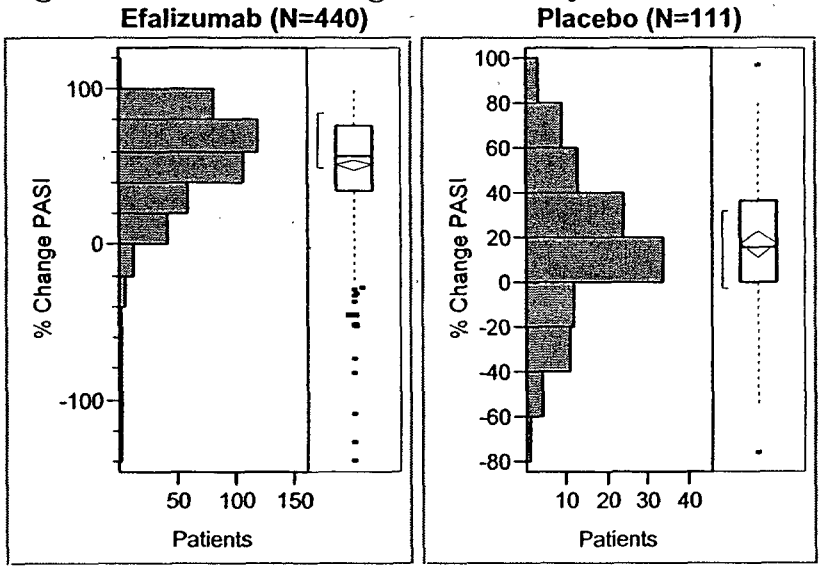
Percent Improvement from Baseline	FT Placebo (n=122)	FT Efalizumab 1.0 mg/kg/wk (n=232)	FT Efalizumab 2.0 mg/kg/wk (n=243)
≥90%	1 (0.8%)	10 (4.3%)	15 (6.2%)
≥75% to <90%	5 (4.1%)	42 (18.1%)	54 (22.2%)
≥50% to <75%	13 (10.7%)	68 (29.3%)	69 (28.4%)
≥25% to <50%	21 (17.2%)	51 (22.0%)	48 (19.8%)
<25%	71 (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 6 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 6 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.

The response rates among subsets defined by gender, age group, baseline PASI score and history of prior systemic therapy are shown in Table 49 below.

Table 49 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)	FT Efalizumab 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.

Efficacy was also analyzed by study site; a total of 597 patients were randomized and treated in 51 study centers. The results are summarized in Table 50 below.

Table 50 PASI 75 Response by Treatment Group and Site

Site	Placebo (N=122)	Efalizumab 1.0 mg/kg/wk (N=232)	Efalizumab 2.0 mg/kg/wk (N=243)
0019	0/2	0/4	2/6
0400	1/4	5/9	3/10
1909	0/ 3	0/ 5	1/ 5
1969	0/2	0/5	2/4
2095	0/4	1/7	2/6
2101	1/3	0/4	2/7
2342	0/4	0/6	2/5
6312	0/4	3/7	5/8
6344	0/4	1/7	2/7
6425	0/10	0/16	1/16
6461	1/4	0/3	1/4
6464	0/4	3/8	4/7
6467	0/2	2/4	1/4
6481	0/3	1/6	2/6
6483	0/6	1/15	1/11
6521	1/7	8/18	5/15
6556	0/7	1/11	1/11
6558	0/5	3/8	1/9
6559	0/17	3/26	4/34
6582	0/2	1/5	2/3
6765	0/2	2/6	3/5
Combined*	2/23 (9%)	17/ 52 (33%)	22/60 (37%)

Among the sites shown in this table, a general trend towards higher response rates in the efalizumab-treated patients was seen The site (6559) with the highest enrollment (n=77) did not have a substantially different treatment effect than was seen in the study as a whole. Many sites (30) were combined for this analysis because they enrolled less than 10 patients per site.

In Study ACD2059g, the evaluations for PASI were done biweely during the first treatment period. The median time to onset of PASI 75 response among patients achieving PASI 75 at any time during the first treatment period using Kaplan Meier Estimates is shown below (Table 51).

Table 51 Time to PASI-75 Response (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 (days)	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

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

Among the PASI 75 responders at Day 84 of the first treatment period, the median time to achieve PASI 50 was analyzed in an exploratory analysis below.

Table 52 Time to a PASI-50 Response for PASI-75 Responders (FT Period)

Study	Placebo	Efalizumab 1.0 mg/kg/wk	Efalizumab 2.0 mg/kg/wk
Subjects who Achieved PASI-75 at FT Day 84	6	52	69
Median (days)	44	43	43
95% CI for Median	(27,58)	(42, 45)	(43, 44)
25th–75th Percentile	27–58	29–57	29–57

For both doses of efalizumab, the median time to a PASI 50 among the patients who were classified as PASI 75 responders was 43 days. These results are consistent with those obtained in Study ACD2058g.

4.4.4.4 First Treatment Course: Secondary Outcomes

The principal secondary endpoint, the static physician's global assessment is shown below (Table 53).

Table 53 Principal Secondary Efficacy Endpoint for the FT Period

		FT Efalizumab	
OLS Response at FT Day 84	FT Placebo (n=122)	1.0 mg/kg/wk (n=232)	2.0 mg/kg/wk (n=243)
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 dPGA, the physician's dynamic scale (See Table 54).

Table 54 dPGA Response of Subjects during the FT Period

		FT Efalizumab	
dPGA Response at FT Day 84	FT Placebo (n=122)	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 proportion of responders, those achieving excellent or cleared on the dPGA 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 55 below.

Table 55 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)	ET-AR Efalizumab 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 ≥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 ≥ 75% improvement in PASI at the end of the extended treatment period is shown in Table 56 below.

Table 56 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)	ET-AR Efalizumab 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 ≥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. 45).

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 (PASI <50) 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 57 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 suggest that treatment with a second contiguous 12 week period of therapy may 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. However, the dose used in this extended treatment group is higher than the one for which the sponsor is seeking approval and there are very little data on the safety of this dose.

4.4.4.7 Response to an additional 12-week treatment course in patients who were partial-responders (PASI ≥ 50, <75) 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 partial responders to active drug in the first treatment period is shown below.

Table 58 Proportion of ET-AP Subjects Who Achieved PASI 75 Response at ET Day 84

	ET-AP Withdrawal/ Placebo (n=46)	ET-AP Efalizumab 2.0 mg/kg/qow (n=45)	ET-AP Efalizumab 2.0 mg/kg/wk (n=47)
Responders	2 (4.3%)	13 (28.9%)	25 (53.2%)
Partial responders and non-responders a	44 (95.7%)	32 (71.1%)	22 (46.8%)
Fisher's exact p-value efalizumab vs. placebo	—	0.002	<0.001

[a] Included subjects with missing ET Day 84 evaluations.

The proportion of FT partial responders who achieved a ≥ 75 improvement in PASI at with three months of extended treatment was statistically significantly greater for the two efalizumab dose groups compared with the withdrawal/placebo group. Among the partial responders from the first treatment period, 25% to 49% (difference from placebo) went on to achieve PASI 75

response status with the additional three months of efalizumab at 2 mg/kg on alternate weeks or 2 mg/kg weekly, respectively. However, the doses and regimens studied during extended treatment of patients who were partial responders during the first treatment period are different from the dose the recommended dose being considered for licensure. Additionally, not all patients were continued with the same dose from the first treatment period to the extended treatment period. Therefore, some patients may have received a higher dose during the extended treatment period. The effect that this change of dose may have on treatment response during the second twelve-week period is unknown.

4.4.4.8 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 41).

The summary of duration of PASI 75 and PASI 50 responses using exploratory analyses of linear interpolation, midpoint interpolation, assumption of no retained response between observations is shown below.

Table 59 Duration of Response for PASI-75 Responders following 12 Weeks of Efalizumab Treatment (1 mg/kg/wk)

Response Criterion Definition for Loss of Response	Median Duration in Days (95% CI for the Median)
PASI-75	
Linear interpolation	24.9 (16.4,31.5)
Midpoint	35 (21,42)
Last visit with a response	21.5 (14,29)
First visit without response	45.5 (28,56)
PASI-50	
Linear interpolation	40.4 (28.6,61)
Midpoint	41.5 (34,64)
Last visit with a response	28.5 (21,56)
First visit without response	51 (35,64)

Duration of PASI-75 [PASI-50] response was measured from date of last dose to date PASI-75 [PASI-50] response was lost as determined by one of three approaches.

For the 1-mg/kg/wk dose, the duration of PASI 75 was between 3 weeks and 7 weeks and that of PASI 50 was between 4 weeks and 7 weeks.

4.4.4.9 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 60 DLQI, Mean Improvement from Baseline (FT Period)

		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 statistically significant difference in favor of the efalizumab-treated patients vs. placebo and are consistent with the results seen in Study ACD2390g (see page 92).

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 neither the shift in score from 11 to approximately 6 nor the treatment effect of approximately 4 points is known.

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 median time to relapse off treatment (64 days) and time to onset of response (58 days) were similar to those observed in study ACD2058 g.

- For the 1-mg/kg/wk dose, the duration of PASI 75 was between 3 weeks and 7 weeks and that of PASI 50 was between 4 weeks and 7 weeks

- 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.
- There is a suggestion that treatment with a second contiguous 12- week period of therapy may result in additional patients achieving response status, e.g. 11% in this study. This result is consistent with the findings in study ACD2058g
- Time until relapse was similar to that obtained in study ACD2058g (64 days).

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 ≥ 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 and Statistical Considerations

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.

Response Status

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

- Responder: any subject whose PASI score decreased by ≥ 75% on Day 84 relative to Day 0
- Partial responder: any subject whose PASI score decreased by ≥ 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

Primary Efficacy Endpoint

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

Analysis Plan for Primary Endpoint
Treatment effect was defined as the difference in the proportion of responders between treatment groups (active and placebo). 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.

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.

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 ≥ 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 dPGA 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

Analysis Plan for Secondary Endpoints
The treatment groups were compared for the secondary endpoints based on the ITT population. The following were compared between treatment groups using Fisher's exact test:

- The proportion of subjects achieving an OLS rating of Minimal or Clear at Day 84 (the principal secondary endpoint)
- The proportion of subjects achieving a PGA rating of Excellent or Cleared at Day 84

The remaining secondary outcome measures were to be compared between treatment groups using the t-test if the distribution was approximately normal or a non-parametric test if otherwise. The DLQI was to be analyzed by the Wilcoxon rank sum test.

4.5.3.10 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.

4.5.4 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 61 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 62 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

[a]The "Other" group included individuals who described their race/ethnicity as Asian or Pacific Islander, Black, American Indian or Alaskan Native, or Other.
[b]Data 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 63.

Table 63 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
Median	17	17
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.