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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

STN/BLA 125075/0

Statistical Review(s)

Biostatistical Review

BLA: **STN# 125075 / 0**

Efalizumab (Anti-CD11a) for the treatment of moderate to severe plaque psoriasis

Submission received 12/27/02

Genentech, Inc.

Date: **September 3, 2003**

Reviewer: ***Clare Gnecco, Ph.D.***

Through: ***Aloka Chakravarty, PhD***
Acting Staff Director
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9/3/03

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STATISTICAL REVIEW ISSUES / SUMMARY: The sponsor's major efficacy analyses were investigated and statistical findings confirmed for the three pivotal studies, #ACD2058g, #ACD2059g, #ACD2390g as well as for safety study, #ACD2600.

BACKGROUND: Two sponsors, XOMA, Ltd. And Genentech, Inc., participated in the development of this product. In September of 2001, the Agency expressed concerns about the comparability of these products and recommended that a PK comparability study be performed in healthy volunteers. This study showed that XOMA- and Genentech-produced efalizumab was not equivalent pharmacokinetically. The Genetech-manufactured product appeared to have higher bioavailability and/or slower clearance. Consequently the FDA requested additional Phase III studies to assess the safety and efficacy of the Genentech-manufactured product. Genentech sponsored the Phase III studies and is the current manufacturer of the to-be-marketed efalizumab product. It is to be noted that Study ACD2058g used the XOMA manufactured product exclusively. Most patients on Study ACD2059g received the XOMA product. The two subsequent Phase III studies, ACD2390g and ACD 2600g, used the Genentech manufactured product exclusively.

SUMMARY OF STUDY #ACD2058g: This study was entitled ***"A Phase III, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Mult-icenter, Multi-dose Study to Evaluate the Efficacy and Safety of subcutaneously administered Anti-CD11a in adults with Moderate to Severe Plaque Psoriasis."*** It was initiated on January 4, 2000 and completed on October 15, 2001. There were 29 study centers in the United States and Canada and the Xoma-manufactured product was used exclusively.

Study Design: The study consisted of 5 periods: FT (First Treatment), Observation (OB), RT (retreatment), ET (Extended Treatment), and Follow-up (FU), and an optional Extended FU (EFU). During the FT period, approximately 450 subjects were to be randomly assigned to low-dose efalizumab (1.0 mg/kg), high dose efalizumab (2.0 mg/kg), low dose placebo or high dose placebo in a 2:2:1:1 ratio. During the FT period, subjects received a conditioning dose of 0.7 mg/kg followed by 11 weekly SC injections of 1.0 or 2.0 mg/kg study drug (efalizumab or equivalent placebo). **Primary efficacy determinations** were made on FT Day 84 (end of FT period). Subjects defined as responders at the end of the FT period entered the OB (observation) period and were followed either for 24 weeks or until relapse, whichever occurred first. At the time of relapse, subjects who received active drug during the FT period entered the RT period and were re-randomized in a 2:1 ratio to efalizumab or placebo, respectively. If there were any subjects who received placebo during the FT period and qualified as responders, they received efalizumab during the RT period. During the RT period subjects received a second course of treatment consisting of 12 weekly SC injections. Subjects not responding to this second course of treatment (i.e., < 50% improvement in PASI at RT Day 56 compared to FT Day 0) were eligible to transfer to the open-label study, #ACD2062g. Following completion of the RT period, subjects entered the FU period. Subjects in the OB period who did not relapse by OB Day 168 entered the FU period. Subjects defined as partial responders or non-responders at the end of the FT period were assigned to the ET period. Subjects remained within the dose levels assigned during the FT period. Subjects who received efalizumab during the FT period were re-randomized 2:1 to efalizumab or placebo. All subjects who received placebo during FT were assigned to efalizumab within their dose level. ET Day 0 occurred on the same day

as FT Day 84; hence the two courses of study drug treatment were continuous over a 24-week period. Subjects who did not experience a ≥ 50% PASI improvement by ET Day 56 (compared to FT Day 0) could transfer to open-label treatment in Study ACD2062g. Subjects not responding to this second course of treatment were eligible to transfer to the open-label study. Following completion of the ET period, subjects entered the FU period. The FU period consisted of three monthly safety visits after the last dose of the study drug. EFU was offered to interested subjects who were responders or partial responders during the RT and ET periods and who had not relapsed by the end of the FU period.

Randomization: Randomization to study treatment was carried out centrally via a centralized telephone system. For the FT period, subjects were randomized to low-dose (1.0 mg/kg) anti-CD11a, high dose (2.0 mg/kg) anti-CD11A, low-dose placebo, or high dose placebo in a 2:2:1:1 ratio. Randomization was balanced within the categories defined by the FT Day 0 PASI (≤ 16.0 vs. ≥ 16.1), by history of prior treatment for psoriasis (naïve to systemic treatment vs. prior systemic treatment), and by study site. The random treatment assignments were blinded to subjects, investigators, and the sponsor. At the start of the RT period, subjects who previously received anti-CD11a were re-randomized within the low- or high-dose groups to active therapy or placebo in a 2:1 ratio. At the start of the ET period, subjects who previously received anti-CD11a were re-randomized within the low- or high-dose groups to active therapy or placebo in a 2:1 ratio. Randomization was to be balanced for subjects who were partial responders (PASI change of ≥ 50% and < 75% between FT Day 0 and FT Day 84) and non-responders (PASI change of < 50% between FT Day 0 and FT Day 84). All subjects who received placebo during the FT period were to be assigned to receive anti-CD11a, whether or not they participated in the RT or ET periods.

Primary Efficacy Outcome Measure: The primary efficacy outcome measure was the proportion of subjects with a ≥ 75% improvement in PASI score at FT Day 84 (end of the FT period) relative to FT Day 0.

Secondary Outcome Measures: These are listed in order of clinical importance for the FT period of the study as follows: (1) proportion of subjects achieving an OLS (Overall Lesion Severity) rating of Minimal or Cleared at FT Day 84 (2) proportion attaining a rating of Excellent or Cleared on the PGA (Physician's Global Assessment) at FT Day 84 (3) time to relapse after FT Day 84 for subjects who achieved a ≥ 75% improvement in PASI score at FT Day 84 relative to FT Day 0 (4) change in the thickness component of the PASI at FT Day 84 relative to FT Day 0 (5) change in the itching scale at Day 84 relative to FT Day 0 (6) % of BSA affected by psoriasis at FT Day 84.

Other Outcome Measures: Additional outcome measures are listed in **order of clinical importance for the FT period** as follows: (1) time to first occurrence of a PASI score consistent with a ≥ 75% improvement relative to FT Day 0 through FT Day 84 (2) change in the Dermatology Quality of Life Index (DLQI) at FT Day 84 relative to FT Day 0 (3) change in the Psoriasis Symptom Assessment (PSA) at FT Day 84 relative to FT Day 0. Although all of the measures used for efficacy assessment during the FT period were also collected during the RT and ET periods, analyses of response to treatment for the RT and ET periods were based principally on the PASI, PGA, and OLS.

Outcome measures for the RT period include: (1) proportion achieving a ≥ 75% decrease in PASI score at RT Day 84 relative to FT Day 0 PASI (2) proportion achieving

an OLS rating of Minimal or Clear at RT Day 84 (3) proportion attaining a PGA rating of Excellent or Cleared at RT Day 84 (4) time to relapse after RT Day 84 for subjects who achieved a ≥ 75% improvement in PASI through Day 84 relative to FT Day 0 PASI (5) time to occurrence of a PASI score consistent with a ≥ 75% improvement through RT Day 84 relative to FT Day 0 PASI. **Outcome measures for the ET period** included the following: (1) proportion achieving a ≥ 75% decrease in ET Day 84 PASI score relative to FT Day 0 PASI (2) proportion achieving an OLS rating of Minimal or Clear at ET Day 84 (3) proportion attaining a PGA rating of Excellent or Cleared at ET Day 84 (4) time to relapse after ET Day 84 for subjects who achieved a ≥ 75% improvement in PASI score at ET Day 84 relative to FT Day 0.

Safety Outcome Measures: In addition to all of the usual AE's, the incidence of clinically significant changes in hearing were compared to baseline as measured by audiograms and the incidence of anti-human antibody (HAHA) responses were examined. The safety outcome measures were summarized by treatment period, i.e., FT, OB, RT, ET, and FU.

Sample Size: 450 subjects were planned; 498 subjects were randomized and treated. The sample size was based on safety and regulatory considerations. The planned accrual was 150 subjects in each of three treatment groups. The probability of observing one or more instances of an AE with a background rate of 1% or 2% in a treatment group containing 150 subjects over the time frame of this study was 0.779 and 0.952, respectively. The estimation of power for efficacy assumed a response rate of 20% in the 1.0 mg/kg and 2.0 mg/kg efalizumab treatment groups versus a placebo response rate of 5%. Given these rates and 150 subjects/group, this study had more than 90% power to detect a difference in the primary endpoint at the 0.025 level by Fisher's exact test.

Note: Because of an error in the IVRS (central randomization), 13 subjects (10003, 11510, 11515, 11517, 12017, 12023, 12031, 13006, 14501, 15014, 16514, 17502, and 18012) who received placebo during the FT period were inadvertently assigned to receive placebo during the ET period. Based on the DMC recommendation, the treatment assignments for these subjects were unblinded early to give them the opportunity to enter the open-label study, #ACD2062. Because all subjects had completed the ET period at the time of notification and because no inferential statistical tests were dependent on data from these subjects, this unblinding did not affect the data collected for ET objectives.

Analysis Populations: Adults with plaque psoriasis covering ≥ 10% of the BSA and a PASI score of ≥ 12.0 who were candidates for systemic therapy were enrolled.

The primary analysis population comprised all subjects who were randomized, whether or not they received any study drug or completed the first course of treatment (ITT). All treated subjects were included in the safety analysis. The analysis population for the RT period consists of all subjects who were randomized into the RT period regardless of whether they received any study drug or completed the full treatment course during this period. These subjects are limited to those responders from the FT period who received anti-CD11a during FT and who relapsed prior to OB Day 168. Subjects who received placebo are not included in this analysis population. For the ET period the analysis population comprises all subjects who were randomized into the ET regardless of whether they received any study drug or completed the full treatment course during this period. These subjects are limited to partial responders and non-responders from the FT

who received anti-CD11a during FT. Subjects who received placebo during FT are not included in this analysis population.

Statistical Methods: All statistical tests are two-sided. The two treatment comparisons of interest during the FT period are: 1.0 mg/kg anti-CD11a versus placebo and 2.0 mg/kg anti-CD11a versus placebo. The placebo groups for each of the two dose levels will be combined for all statistical comparisons. For the primary efficacy endpoint at the end of the FT period, response status is determined as follows: (1) **Responder:** any subject whose PASI score has decreased $\geq$ 75% from FT Day 0 to FT Day 84 (2) **Partial responder:** any subject whose PASI score has decreased $\geq$ 50% but < 75% from FT Day 0 to FT Day 84 and (3) **Non-responder:** any subject whose PASI score has decreased < 50% from FT Day 0 to FT Day 84. The **evaluation for the primary endpoint** will consist of pair-wise comparisons of the proportion of responders in each anti-CD11a dose group versus placebo using Fisher's exact test for the ITT population. Partial responder and non-responder categories will be combined for the primary analysis. To maintain the type I error rate for the primary analysis at $\alpha = 0.049$ (two-sided) given the two pair-wise comparisons, the Hochberg-Bonferroni multiple comparisons procedure (MCP) will be used for adjustment (Hochberg 1988). If both comparisons yield a p-value of < 0.049 in favor of anti-CD11a over placebo, both active treatment groups are considered to be significantly different from placebo. If one comparison yields a p-value of > 0.049, the other active treatment will be considered to be statistically significantly different from placebo only if its associated p-value is < 0.0245 in favor of anti-CD11a over placebo.
Note: A formal interim analysis of the primary efficacy endpoint was performed by an independent DMC once approximately half (~ 225) of the subjects had completed the FT period. The stopping rules established prior to review of the results by the DMC allowed the trial to be stopped for futility only; stopping for efficacy was not allowed.
Supportive Analyses for the Primary Endpoint: Additional analyses were to be performed as follows: (1) The primary endpoint results were to be assessed for generalizability by examining summaries by sex, age group (18 – 40, 41 – 64, $\geq$ 65), baseline PASI ($\leq$ 16.0, 16.1 – 30.0, > 30.0), history of prior systemic therapy (yes, no), and by study site (2)The robustness of primary endpoint results were to be examined by analyses that included pertinent covariates in an analytical model using logistic regression. Covariates to be examined include baseline PASI, geographic region, season of the year, and history of prior systemic therapy (yes, no) (3) The robustness of primary endpoint results were also to be examined using other methods for the imputation of missing data and (4) The primary endpoint analysis were to be performed for those subjects classified as "evaluable."
Secondary Efficacy Endpoints:

A. **Principal Secondary Endpoint:** The evaluation of OLS for the FT period, the principal secondary endpoint, was to consist of the pair-wise comparisons of the proportion of responders (Minimal or Clear) in each anti-CD11a dose group versus placebo using Fisher's exact test. The remaining OLS categories were to be combined for this analysis. The Hochberg-Bonferroni MCP was to be used for adjustment as for the primary endpoint.
B. **Other Secondary Endpoints:** The evaluation of the remaining secondary efficacy endpoints from the FT period was to consist of the pair-wise comparison of each anti-CD11a dose group to the placebo group. No adjustments for multiplicity (of

endpoints or treatment comparisons) was to be incorporated into these analyses. The Statistical Analysis Plan (SAP) rightly states that the p-values from these analyses should be interpreted accordingly. The SAP states the remaining secondary endpoints along with appropriate analytic methodology as follows: (1) Proportion achieving a PGA rating of Excellent or better at FT Day 84 to be compared using Fisher's exact test (2) Time to relapse after FT Day 84 was to be estimated across and within the two active treatment groups for subjects entering the OB period after achieving a $\geq$ 75% improvement in PASI at FT Day 84 relative to FT Day 0 using the Kaplan-Meier product-limit method. Time to relapse is defined as the number of days from FT Day 84 to the visit day at which the first PASI consistent with relapse is obtained. Relapse is defined as loss during the OB period of $\geq$ 50% of the improvement in PASI score achieved at FT Day 84 relative to FT Day 0. Because this analysis is conditional upon response at FT Day 84, no formal statistical comparisons were planned (3) Mean change from baseline in the PASI thickness component at FT Day 84 to be compared via two-sample t-tests using the pooled error term from an ANOVA of all three treatment groups (4) Mean change from baseline to FT Day 84 on the Itching Scale to be compared by two sample tests as above (5) Mean change from baseline to FT Day 84 in % of BSA involved in psoriasis to be compared by two sample t-tests as above

C. **Tertiary Endpoints:** (1) Time to first occurrence of a PASI score consistent with a $\geq$ 75% improvement through FT Day 84 to be compared between anti-CD11a treatment groups and placebo in a pair-wise fashion using the logrank test. Kaplan-Meier estimates of the distribution of the time to first occurrence of a change in PASI consistent with a $\geq$ 75% improvement to be presented graphically (2) Data from the Dermatology Life Quality Index (DLQI) to be analyzed as change from baseline in score at FT Day 84 compared between each anti-CD11a dose group versus placebo in a pair-wise manner by the Wilcoxon rank sum test.

Efficacy analyses for the RT and ET periods comprise essentially the same efficacy endpoints and associated methods. These endpoints are also listed in the SAP in order of clinical importance. The reference point for computing change is FT Day 0. **Note:** Subjects who received placebo during the FT period will be automatically treated with anti-CD11a during the RT and ET periods. The psoriatic disease activity in these subjects after 12 weeks of treatment with anti-CD11a will be summarized by dose group for the PASI, OLS, PGA, and time to relapse endpoints after ET Day 84.

Missing data: For all study endpoints, if a subject discontinues prior to Day 84 but after receiving the final scheduled dose of study drug on Day 77, data from the early termination visit will be used for analysis, i.e., the Day 84 data will not be considered missing in such a case. For the PASI primary endpoint, if any of the individual components are missing, the PASI score will be set to missing for that observation. If the baseline (FT Day 0) value for the PASI is missing for a subject, it will be replaced by that subject's screening PASI value. **Subjects with a missing PASI score at FT Day 84 will be classified as non-responders for analysis of the primary endpoint (worst outcome imputation). This same method will be used to categorize subject response in the RT and ET periods for subjects missing the PASI score at RT Day 84 or at ET Day 84.** For the OLS endpoint, subjects missing the FT Day 84 score will be classified as non-responders (Mild or Worse) for the analysis of this principal secondary endpoint

(worst outcome imputation). The same approach will be taken for RT and ET periods. Subjects missing the FT Day 84 PGA score will be classified as non-responders (Good or Worse) for analysis (worst outcome imputation). The same approach will be taken for RT and ET periods. For the PASI thickness component, if the Day 84 value is missing, the last available value will be used for analysis (LOCF). The LOCF approach will also be used for the itching scale, % BSA affected by psoriasis, DLQI, and PSA endpoints. The SAP states that exploratory analyses will be performed to examine the pattern of missing data for the primary and secondary endpoints. For each of the endpoints, the sensitivity of results to the choice of the missing data handling rules will be examined using alternative imputation methods. Alternative imputation methods include the following: worst outcome, no change (i.e., using zero for change from baseline endpoints), LOCF, overall mean, overall median, and complete cases.

Safety Analyses: Safety will be assessed through the summary of AE's, laboratory test results, vital signs, antibodies to anti-CD11a, and audiologic assessments. These summaries will be produced separately for the FT, RT, ET, and FU periods.

SPONSOR's EFFICACY RESULTS FOR STUDY #ACD2058g:

Demographic and Baseline Characteristics: More male (approximately 73%) than female patients participated in this study. The clinical review notes that in the general psoriasis population, men and women are equally affected. Other then the gender distribution, characteristics are reflective of the general psoriasis population of the U.S. A higher proportion of patients were 65 or older in the active treatment arms versus placebo. The other baseline characteristics (race, weight, and BMI) were well balanced across the three treatment arms.

Disease Characteristics at Baseline: The treatment groups were well balanced on all measures of baseline disease activity. These include duration of psoriasis (years), prior systemic therapy (yes/no), PASI total score, thickness component, itching component, erythema component, scaling component, and % BSA of psoriasis.

Reviewer's Comment: *This reviewer examined the distributions of these baseline disease characteristics and found that each of them had a skewed distribution. The long tail was toward the higher end of the scale for baseline %BSA, PASI total score and its scaling, erythema, and thickness components. The baseline distribution of the PASI itching component was slightly skewed with a longer tail toward the lower end of the scale. In all cases the median, twenty fifth and seventy fifth percentiles were comparable across treatment arms. The number of outlying observations was comparable and not excessive looking across treatment arms. The highest number occurred in the Efalizumab 2.0 mg arm and amounted to only about 6%.*

Primary Efficacy Outcome:

Sponsor's Table: PASI Response to Treatment during the FT Period: All Randomized Subjects (Table 11.4.1-1)

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

* Included subjects who discontinued.

Reviewer's Comment: *The proportion of responders was statistically significantly higher in both treatment groups versus the placebo group by the pre-specified Fisher's exact test and taking into account the Hochberg multiplicity adjustment. Since this study was stratified by balancing factors at randomization (baseline PASI, history of prior treatment, and study site), this reviewer performed a stratified Cochran Mantel-Haenszel test, stratifying by baseline PASI and prior treatment, and found that the results were still highly statistically significant ($p < 0.0001$). For analysis of this primary endpoint, the sponsor used worst case imputation for missing data, i.e., assigning non-response. LOCF missing data imputation and other sensitivity analyses did not change these findings.*

In addition, it is informative to look at the finer descriptive breakdown of responders, partial responders, and non-responders by treatment group. These are presented in Reviewer's Table 1 below.

Reviewer's Table 1: Three PASI Response Categories by Treatment Group During FT Period (all randomized subjects)

	Placebo	Efalizumab 1.0 mg	Efalizumab 2.0 mg
Responder	**4 (2%)**	**63 (39%)**	**44 (26%)**
Partial Responder	**21 (12%)**	**36 (22%)**	**41 (25%)**
Non-Responder	**145 (85%)**	**63 (39%)**	**81 (49%)**
Total	**170**	**162**	**166**

The partial response rate in the two treatment arms is approximately double that of the placebo arm. No further statistical analysis was performed since the statistical analysis plan indicated combining partial responders with non-responders for the primary analysis.

Sponsor's Table 11.4.1-9: Percent Improvement in PASI Thickness, Erythema, and Scaling Components during the FT Period

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

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

Reviewer's Comment: *This reviewer confirmed the sponsor's descriptive analysis for individual components of the PASI. All three components of the PASI score - thickness, erythema, scaling- reveal higher estimated percentage improvement in the efalizumab-treated patients as compared to placebo-treated patients. Given the large number of efficacy endpoints in this study, individual PASI components did not receive formal statistical testing. Rather, this analysis serves to provide context via a detailed breakdown for the statistically significant primary analysis of PASI-75 response.*

Sponsor's Table 11.4.1-11: Mean Improvement in Percent BSA of Psoriasis during the FT Period

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

[a] Improvement was reflected by a decrease in the percent BSA score.
[b] Using the pooled error term from an ANOVA of all three treatment groups.

The mean percentage body surface area affected at the end of the 84-day treatment period improved by 13.8% in the 1.0 mg/kg/wk group and 10.0% in the 2.0 mg/kg/wk group vs. 1.8% in the placebo-treated patients.

Reviewer's comment: *This reviewer confirmed the sponsor's analysis. Both active treatment groups were statistically significantly better than placebo by the two-sample t-test ($p < 0.001$).*

The PASI-75 response for several subsets of the studied population is show in Sponsor's Table 11.4.1-3, which follows:

Sponsor's Table 11.4.1-3: PASI Responders by Subsets of Randomized Subjects: FT Period

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

Reviewer's Comment: *This reviewer confirmed the above analysis. As the clinical reviewer points out in her review, the results of the primary efficacy analysis are generalizable across gender, age, baseline PASI and history of prior systemic therapy subgroups. There was a trend towards higher response rates for patients in the low dose group compared to the high dose group.*

The sponsor performed adjusted analyses via multivariate logistic regression to assess whether important prognostic factors had an effect on treatment effect as estimated by the adjusted odds ratio. The sponsor's adjusted analytical findings appear in the following table.

Sponsor's Table: Covariates Potentially Predictive of PASI Response: FT Period

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

Reviewer's Comment: *This reviewer confirmed the sponsor's adjusted analysis. The following covariates, examined in the logistic regression model, were found not to have any relationship to PASI-75 treatment response: baseline PASI score, age, history of*

prior systemic therapy, and season of the year (spring vs. summer). There was a suggestion of higher responses in women (lower confidence limit for the estimated odds ratio is slightly larger than 1.0), but this was not supported in subsequent studies. Also, one of the odds ratio confidence intervals for specific geographic region suggests a higher response in the Western United States vs. that seen in the Northeastern United States.

Secondary Efficacy Endpoints:

The principal secondary efficacy endpoint was OLS (Overall Lesion Severity) response, based on a score of 'Minimal' or 'Clear,' at FT Day 84. The sponsor's analysis of this endpoint appears in the following table:

Sponsor's Table 11.4.1-6: Principal Secondary Efficacy Endpoint: FT Period

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

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

Reviewer's Comment: *This reviewer confirmed the sponsor's analysis. This analysis of the principal secondary efficacy outcome measure indicated that efalizumab was statistically significantly superior to placebo. The sponsor also performed reviewer-requested additional analyses of the following endpoints, excluding subjects whose baseline OLS scores were 'Mild' or better on study entry: PASI-75, PASI-50, PASI –90, OLS 'Minimal' or 'Clear,' and OLS 'Clear.' The same analytic approach as was used in the clinical study report was applied to these subsets. The response rate was very similar with and without subjects whose baseline OLS values were 'Mild' or better for this study as well as for the other Phase III efficacy studies and for all five endpoints: PASI-75, PASI-50, PASI-90, OLS 'Minimal' or 'Clear,' and OLS 'Clear.'*

Finally, the sponsor provided a more refined descriptive breakdown of PASI-75 response by % improvement from baseline within 25%-tile categories.

Sponsor's Table 11.4.1-2: PASI Response by Percent Improvement from Baseline for Subjects during the FT Period (% of total)

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

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

Reviewer's Comment: *This analysis indicates a shift toward improvement in the efalizumab groups compared to the placebo group. Also, there appears to be a more pronounced trend toward improvement in PAS-75 response in the low dose group than in the high dose group.*

The **Physician's Global Assessment (PGA)** was used to measure patients' dynamic response to treatment compared to baseline. Sponsor's Table 11.4.1-7 below presents the analytic findings.

Sponsor's Table 11.4.1-7: PGA Response for Subjects during the FT Period

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

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

Reviewer's Comment: *This reviewer confirmed the sponsor's analysis. A much larger proportion of patients achieved 'Excellent' or 'Cleared' scores in both of the efalizumab treatment arms compared to the placebo group based on the PGA assessment. The differences were highly statistically significant.*

Time-to-onset of PASI-75 response was analyzed and the results are shown in Sponsor's Table 14.2/37a below.

Sponsor's Table 14.2/37a: Time (days) to PASI-75 Response, Using Kaplan Meier Estimates Study ACD2058g (FT Period): Subjects Who Achieved a PASI-75 Response at Any Time (Table 14.2/37a)

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

Reviewer's Comment: *Thus, the median time to achieve a PASI-75 response in patients who achieved a PASI-75 at any time was approximately 2 months for the efalizumab treatment arms compared to 6 weeks for placebo. However, the responder sample size is quite small for the placebo group.*

For **duration of PASI-75 response**, time to relapse was defined as a loss of ≥ 50% improvement in PASI score between baseline and Day 84. The sponsor's summary of findings by treatment group are presented in Sponsor's Table 11.4.1-14 below.

Sponsor's Table 11.4.1-14: Time (days) to Relapse during the OB Period, Using Kaplan-Meier Estimates: Subjects Treated with Efalizumab during the FT Period

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

Reviewer's Comment: *The median time to relapse during the observation period (OB) was 60 days for the 1.0- mg/kg/wk group and 59 days for the 2-mg/kg/wk group. There were only four responders in the placebo group.*

DLQI (Dermatology Life Quality Index: A pair-wise comparison of change from baseline in the DLQI overall score at FT Day 84 for each of the efalizumab groups versus placebo was performed on the ITT population via the Wilcoxon rank sum test. All three treatment groups were found to have had comparable scores at baseline. A decrease in score represents improvement. The decrease in overall DLQI scores, on the order of twice as good, was statistically significant ($p < 0.001$) for each of the efalizumab

treatment arms versus placebo. Patients missing a Day 84 value received an imputed value of zero for change in DLQI.
Reviewer's Comment: *The amount of missing data, however, was minimal, 2.6% in the efalizumab 1.0 mg arm, 5.0% in the efalizumab 2.0 mg arm, and 4.6% in the placebo arm.*

Observation (OB) and Retreatment (RT) Periods: Patients who achieved a PASI –75 response at the end of the first treatment period(FT) could enter the observation period (OB). 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 met the endpoint of relapse during the observation period and entered the retreatment (RT) period. Overall, 9.9% of patients did not experience relapse during the 84-day observation period. A protocol amendment enabled patients experiencing severe psoriasis on relapse to enter Study #ACD2062g. Of the 100 patients who discontinued OB, 86 experienced a relapse. Out of this group, 83 patients re-entered the RT period and 3 patients went on Study #ACD2062g.

NOTE: Please refer to the Clinical Review for discussion of findings for the OB and RT periods. The sample sizes are too small to make definitive statistical inferences.

SUMMARY OF STUDY #ACD2059g: This study was entitled ***"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."*** It was initiated on May 4, 2000 and completed on June 6, 2001. There were 51 study centers in the U.S. and Canada who participated. Some subjects on this study received the Genentech-manufactured product. Theses were in the minority. The majority of subjects received the Xoma-manufactured product.

Study Design: The study consisted of three periods: FT, ET, and FU. The FT and ET periods were of 12 weeks duration. During the FT period approximately 150 subjects per group were to be randomized in a 4:4:1:1 ratio to high dose (2.0 mg/kg) efalizumab, low dose (1.0mg/kg) efalizumab, high dose placebo or low dose placebo. During the FT period, subjects received a conditioning dose of 0.7 mg/kg followed by 11 weekly SC injections of 1.0 or 2.0 mg/kg study drug (efalizumab or placebo). Primary efficacy determinations were made on FT Day 84. Subjects received a different treatment regimen during the ET period, depending on their response at the end of FT. Responders and partial responders received an additional 12 weeks of treatment with 2.0 mg/kg weekly or every other week (qow) efalizumab or placebo during the ET period. Non-responders received an additional 12 weeks of treatment with 4.0 mg/kg/week efalizumab, 2.0 mg/kg/qow efalizumab or placebo during ET. Following completion of the ET period (ET Day 84 / FU Day 0), subjects entered the FU period. Subjects who discontinued treatment early during either the FT or ET period also began the FU period. All subjects completed 3 monthly safety visits after the last dose of study drug. The

landmark efficacy outcomes were collected at the end of the FT period. The **primary efficacy endpoint** was the proportion of subjects achieving a ≥ 75% decrease in PASI on FT Day 84 compared to baseline. Response at the end of the FT period was defined as follows: (1) **Responder**: Any subject whose PASI score decreased ≥ 75% between baseline (FT Day 0) and the end of the FT period (FT Day 84) (2) **Partial Responder**: Any subject whose PASI score decreased ≥ 50% but < 75% between FT Day 0 and FT Day 84 and (3) **Non-responder:** Any subject whose PASI score decreased < 50% between FT Day 0 and FT Day 84. The **principal secondary endpoint** was the proportion of subjects achieving an OLS rating of 'Minimal' or better at FT Day 84. Other secondary endpoints were the PGA of change, plaque thickness, itching, and body surface area (BSA) affected by psoriasis. Patient reported outcomes (PRO's) were examined as **exploratory endpoints** using the Dermatology Life Quality Index (DLQI) and Psoriasis Symptom Assessment (PSA). The primary objectives were addressed in the FT period. Secondary efficacy objectives and other exploratory outcomes were investigated in all three study periods.

Protocol Amendments: The protocol was amended on March 14, 2001 to allow the use of topical psoriasis therapies and/or UVB phototherapy for subjects who relapsed during the extended treatment (ET) period.

Randomization: During the FT and ET periods, randomization was employed. The initial randomization and subsequent re-randomizations were performed through an IVRS, the use of which was to prevent unblinding of the clinical teams at the site, the CRO, and the sponsor. During FT, subjects were randomized to low dose efalizumab, high dose efalizumab, low dose placebo, or high dose placebo in a 4:4:1:1 ratio. Randomization was balanced within categories defined by the FT Day 0 PASI score (≤ 16.0, ≥ 16.1), prior treatment for psoriasis (naïve to systemic treatment vs. prior systemic treatment), and study site. A dynamic approach was used through the IVRS. Re-randomization on ET Day 0 was dependent upon response status at FT Day 84 and whether a subject received active drug or placebo in the FT period. For subjects who received active drug, randomization was balanced within categories defined by the FT dose (i.e., 1.0 mg/kg or 2.0 mg/kg SC weekly) using static randomization tables. For the **ET-AN group** (i.e., subjects who received efalizumab and who were non-responders during the FT), randomization was stratified by degree of PASI improvement (≥ 25% and < 50% between FT Day 0 and FT Day 84 or < 25% between FT Day 0 and FT Day 84) and FT dose level. To maintain blinding of FT and ET treatments received by all non-responders (**ET-AN and ET-CN**, where ET-CN denotes control non-responders), subjects randomized to ET placebo received regimens to match the active treatments.

Definitions of ET Groups: In addition to the definitions above, the remaining ET groups are denoted as follows:

ET-AR (active responders): those subjects who received efalizumab and were responders in the FT period. At the beginning of ET, these subjects were re-randomized in a 1:1:1 ratio to receive 2.0 mg/kg/week SC efalizumab, 2.0 mg/kg/qow SC efalizumab or placebo. The objectives were to assess the safety and impact of maintenance dosing on relapse rate and continued therapy on clearing rate.

ET-AP (active partial responder): those subjects who received efalizumab and who were partial responders during the FT. At the beginning of the ET period these subjects were re-randomized in a 1:1:1 ratio to receive 2.0 mg/kg/week SC efalizumab, 2.0 mg/kg/qow

SC efalizumab or placebo. The objectives were to assess the safety and impact of continued therapy on response rate and relapse rate.

ET-AN (active non-responder): those subjects who received efalizumab and who were non-responders during FT. At the beginning of ET, these subjects were re-randomized in a 2:1 ratio to receive 4.0 mg/kg/week SC efalizumab or placebo. The objective was to assess safety and to determine whether extended treatment at a higher dose improved response rate.

ET-CR (control responders): those subjects who received placebo and were responders during FT. At the beginning of ET, these subjects were assigned to receive placebo. No formal efficacy objectives were addressed for this group.

Primary Efficacy Outcome Measure: The primary efficacy outcome measure was the proportion of subjects with a $\geq$ 75% improvement in PASI score between FT Day 0 and FT Day 84.

Secondary Outcome Measures: The **primary secondary outcome measure** was the proportion of subjects achieving an OLS rating of 'Minimal' or better at FT Day 84. The PGA (Physician's Global Assessment) of change, plaque thickness, itching, and psoriatic BSA were additional secondary endpoints.

Other Efficacy Outcome Measures: These included time to response, DLQI (Dermatology Life Quality Index), PSA, Patient's Global Assessment of Arthritis, and NPF Psoriasis Scale.

Safety Assessment: The following were performed: physical examinations (including vital signs and body weight); monitoring for adverse events; blood chemistry, hematology (CBC, platelet, differential); urinalysis; antibodies to efalizumab and urine pregnancy test (females of childbearing potential), RPR at baseline. PPD and/or chest X-ray were done at screening for high risk subjects only. Adverse events and concomitant medications were recorded. Adverse events were defined as any sign, symptom, data or medical diagnosis, regardless of relationship to study drug that began or worsened after the start of study drug treatment and were recorded in the subject's adverse event CRF. Definitions of seriousness, severity and causality were included in the protocol. Provisions were made for reporting serious adverse events to sponsor, to IRB, and to FDA.

Protocol Amendments: This protocol was first amended on May 12, 2000. It specified the use of efalizumab manufactured for Genentech by XOMA. A multiple testing adjustment for the analysis of OLS was added to the Statistical Methods. The protocol was amended again on March 14, 2001, to allow for the use of topical psoriasis therapies and/or UVB phototherapy for subjects who relapsed during the ET period.

Product Source: Efalizumab manufactured by Genetech was introduced at a subset of study sites beginning July 22, 2000. The study was in progress at the time, and rapid enrollment resulted in 145 of the 597 subjects receiving the Genentech product or placebo. The remaining subjects received efalizumab or placebo manufactured by XOMA.

Sample Size: 500 subjects were planned; 597 subjects were randomized and treated. The sample size for this study was based primarily on safety and regulatory considerations. The planned accrual was 200 subjects in each of the two active treatment groups (1.0 mg/kg and 2.0 mg/kg of efalizumab) and 100 subjects in the placebo group for a total of 500 subjects. The probability of observing one or more adverse events with a

background rate of 1% or 2% in a treatment group containing 200 subjects over the time frame of this study was 0.866 and 0.982, respectively. Power estimation for efficacy assumed a response rate of 25% in the 1.0 mg/kg and 2.0 mg/kg efalizumab treatment groups versus a placebo response rate of 2%. Given 200 subjects receiving efalizumab in each dose group and 100 subjects receiving placebo, this study had more than 95% power to detect a difference in the primary efficacy endpoint at the .025 level using Fisher's Exact test.

Analysis Populations: The primary analysis population for the assessment of efficacy consisted of all subjects who were randomized, whether or not they received any study drug or completed the full course of treatment (ITT). All treated subjects were included in the safety analysis.

Statistical Methods: For the primary endpoint, response status at the end of FT was determined as follows: (a) **Responder:** any subject whose PASI score decreased by ≥ 75% from FT Day 0 to FT Day 84 (b) **Partial Responder:** any subject whose PASI s

core decreased ≥ 50% but < 75% from FT Day 0 to FT Day 84 and (c) **Non-responder:** any subject whose PASI score decreased < 50% from FT Day0 to FT Day 84. The primary analysis consisted of pairwise comparisons of the proportion of responders in each efalizumab dose group versus placebo using Fisher's exact test. To maintain a type I error rate of 0.05 (two-sided) for the primary analysis, the Hochberg-Bonferroni multiple comparisons procedure was used to adjust for the two comparisons. If both comparisons to placebo attained a p-value < .05, the other active treatment was considered statistically significantly different from placebo only if its associated p-value was < .025 in favor of efalizumab.

Missing Data: For the primary efficacy endpoint, if the baseline (FT Day 0) value for the PASI was missing for a subject, it was replaced by that subject's screening PASI value. A PASI value missing at Day 84 was not replaced. The subject was considered a treatment failure (worst outcome imputation).

SPONSOR's EFFICACY RESULTS FOR STUDY #ACD2059g:

Patient Disposition: 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.

Sponsor's Table 10.1.1-1: Subject Disposition and Reasons for Discontinuation during the FT Period

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

A total of 597 subjects were enrolled and randomized, 122 in the placebo group and 232 in the 1.0 mg/kg/wk group and 243 in the 2.0 mg/kg/wk group. A total of 48 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. There were 65% males. The median age was 46 with 8% of subjects over 65. Per the clinical reviewer's comment, this study's population demographic characteristics are reflective of the general population of patients with psoriasis, with the exception that more males than females were enrolled.

Baseline Disease Severity:

Sponsor's Table 11.2.1-3: 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)	n=117	n=226	n=233
Mean (SD)	19.6 (12.3)	19.3 (12.3)	18.2 (11.6)
Range	0–62	1–60	1–70
Prior systemic therapy, n			
Yes	86 (70.5%)	160 (69.0%)	152 (62.6%)
No	36 (29.5%)	72 (31.0%)	91 (37.4%)
PASI category, n			
≤16.0	52 (42.6%)	95 (40.9%)	100 (41.2%)
16.1–30.0	54 (44.3%)	107 (46.1%)	120 (49.4%)
>30.0	16 (13.1%)	30 (12.9%)	23 (9.5%)
PASI score			
Mean (SD)	20.43 (8.72)	19.98 (8.25)	19.83 (8.28)
Range	11.7–49.6	11.7–53.4	5.6–53.4
OLS, n			
Minimal	0	4 (1.7%)	0
Mild	5 (4.1%)	12 (5.2%)	23 (9.5%)
Moderate	59 (48.4%)	128 (55.2%)	127 (52.3%)
Severe	52 (42.6%)	76 (32.8%)	81 (33.3%)
Very severe	6 (4.9%)	12 (5.2%)	12 (4.9%)
Percent BSA of psoriasis			
Mean (SD)	31.11 (18.87)	31.97 (18.12)	30.44 (17.75)
Range	10.0–90.0	10.0–98.0	7.0–94.0
Patient's Assessment of Itch			
Mean (SD)	3.1 (1.5)	3.0 (1.4)	3.1 (1.4)
Range	0–5	0–5	0–5

The overall baseline disease severity was moderate to severe plaque psoriasis with a large percentage of subjects (66.7%) having a history of prior systemic therapy. The mean duration of psoriasis was 19 years. The mean PASI score upon entry was 20 and ranged from 5.6 to 53. The proportion of placebo patients classified as moderate or higher by the OLS score was 95.9% vs. 91.8% of the combined active treatment arm. Overall baseline disease severity was comparable between treatment groups.

Protocol Deviations: Thirty-three subjects were treated with excluded psoriasis medications during FT. Four of these were in the placebo group (3.3%), 19 were in the 1.0 mg/kg group (8.2%), and 10 were in the 2.0 mg/kg group (4.1%). When looking across treatment groups, comparable numbers of subjects were found to have protocol deviations, 24% - 30%. The most common protocol violation noted was missing baseline

laboratory data. The clinical reviewer states that these deviations were unlikely to have affected the study's outcome.

Primary Efficacy Outcome:

Sponsor's Table 11.4.1-1 below presents statistical analytical results for the primary efficacy endpoint for Study #ACD2059g.

Sponsor's Table 11.4.1-1: 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.

Reviewer's Comment: *The proportion of responders was statistically significantly higher in both treatment groups versus the placebo group by the pre-specified Fisher's exact test and taking into account the Hochberg multiplicity adjustment. A stratified analysis, based on the randomization balancing factors, still yielded a similar result. The sensitivity of the analysis to the choice of missing data handling rules was also examined by using alternative data imputation methods, including worst outcome, no change, LOCF, overall mean, overall median, and complete cases analysis. The results of these sensitivity analyses were consistent with the reported result. For Study #ACD2058g the 2mg/kg/wk group had a numerically lower response rate than the 1.0 mg/kg/wk group. In this study, however, the response rate was numerically higher in the 2mg/kg/wk group.*

The following Sponsor's Table 11.4.1-9 presents the mean improvement in the components of the PASI score during the FT period. Greater improvements (i.e., decreases) were observed in the erythema and scaling components of the PASI at FT Day 84 compared to FT Day 0 for the efalizumab treatment groups versus placebo. The mean % improvement in erythema and scaling corresponded closely to the mean % improvement in thickness. See the sponsor's table below.

Sponsor's Table 11.4.1-9: 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.

Mean changes in percentage of body surface area during the first treatment period are shown below in Sponsor's Table 11.4.1-1.1.

Sponsor's Table 11.4.1-1.1: 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.

Reviewer's Comment: *Each efalizumab treatment group achieved a statistically significant improvement (i.e., a decrease) in %BSA affected by psoriasis compared to the placebo group. The distributions by treatment arm of change in BSA did not deviate from normality in a major way. In each of the three groups there was a slight skew (longer tail) towards the upper end of the scale. The t-test is robust to this type of departure from normality. Alternative methods of missing data imputation, as previously described, were used to examine the sensitivity of this result. Sensitivity analyses yielded comparable findings.*

Sponsor's Table 11.4.1-2 below presents a more detailed examination of the distribution of % improvement in PASI achieved at FT Day 84. There is a general shift toward improvement in the efalizumab groups compared to a minimal change in placebo. The majority of subjects receiving efalizumab experienced a ≥ 50% improvement in PASI score from baseline (51.7% in the 1.0 mg/kg/wk group and 56.8% in the 2.0 mg/kg/wk group) compared to 15.6% of placebo subjects.

Sponsor's Table 11.4.1-2: 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 sponsor explored the generalizability of the primary efficacy endpoint results for subsets of randomized subjects. These were groups by sex, age group (18-40, 41 – 64, ≥ 65), baseline PASI score (≤ 16.0, 16.1 – 30.0, > 30.0), prior systemic therapy (yes/no), and study site. Results indicated that subsets defined by sex, age group, baseline PASI scores, and prior systemic therapy were generally consistent with results for the randomized population as a whole. Response rates by study site demonstrated some site-to-site variability in the % of responders but showed an overall consistent trend for greater response rates in the two efalizumab treatment groups versus placebo. Sponsor's Table 11.4.1-3 appears in the clinical review.

The **median time to onset of PASI -75 response** is shown below in Sponsor's Table 14.2/39a.

Sponsor's Table 14.2/39a: Time (days) to PASI-75 Response, Using Kaplan Meier Estimates Study ACD2059g (FT Period)

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

Reviewer's Comment: *As in Study #ACD2058g, the median time to onset of PASI-75 in patients who responded at any time was approximately 2 months.*

Robustness of Primary Efficacy Endpoint Results: The sponsor examined robustness via a logistic regression model that included a number of covariates potentially predictive of outcome. These included: baseline PASI score, age, sex, prior systemic therapy, geographic region, and season of the year. This analysis supports the primary analysis of the primary efficacy endpoint. The estimated odds ratios from this model indicate that the odds efalizumab-treated subjects would be classified as responders are more than 5 times greater than the odds for placebo-treated subjects. With the exception of geographic region, no other factor was predictive of response. The predictive power of geographic region was modest ($p = 0.0075$).

First Treatment Course / Secondary Outcomes:

The results of the analysis for the **principal secondary endpoint**, the static physician's global assessment or **OLS (Overall Lesion Severity),** is shown below in Sponsor's Table 11.4.1-6 below.

Sponsor's Table 11.4.1-6: Principal Secondary Efficacy Endpoint for the FT Period

		FT Efalizumab	
	FT Placebo	1.0 mg/kg/wk	2.0 mg/kg/wk
OLS Response at FT Day 84	(n=122)	(n=232)	(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.

Reviewer's Comment: *This analysis was confirmed. The proportion of OLS responders, those achieving 'Minimal' or 'Clear,' was statistically significantly higher in each of the active treatment arms compared to placebo. Thus, the principal secondary outcome supports the primary efficacy outcome. The percentages of responders by OLS are comparable to those by the PASI-75 criteria.*

An **additional secondary efficacy outcome** was the proportion of patients achieving 'Excellent' or 'Cleared' on the **PGA (Physician's Global Assessment),** the physician's dynamic scale. Analytic results are presented in Sponsor's Table 11.4.1-7.

Sponsor's Table 11.4.1-7: PGA Response of Subjects during the FT Period

PGA Response at FT Day 84	FT Placebo (n=122)	FT Efalizumab 1.0 mg/kg/wk (n=232)	FT Efalizumab 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.

Reviewer's Comment: *This analysis was confirmed. The proportions of responders, those achieving 'Excellent' or 'Cleared' on the PGA scale, was statistically significantly higher in each of the active treatment arms compared to placebo. Thus, the response by PGA also supports the primary analysis.*

DLQI (Dermatology Life Quality Index): DLQI was prospectively identified as an **exploratory endpoint** for Study #ACD2059g. The sponsor performed a pair-wise comparison of change from baseline in the DLQI overall scores at FT Day 84 for each efalizumab dose group versus the placebo group via the Wilcoxon rank sum test. A decrease in DLQI overall scores denotes improvement. The mean decrease in mean DLQI overall scores was statistically significant ($p < 0.001$). Mean improvements were 1.7 in the placebo group and 5.5 and 6.0 in the 1.0 mg/kg/wk and 2.0 mg/kg/wk efalizumab groups, respectively. Mean decreases in DLQI for the efalizumab dose groups were at least three times those observed for the placebo group. The sponsor notes that the greatest improvement in absolute score at FT Day 84 between placebo and efalizumab groups was observed for the "symptoms and feelings" domain (with a mean change of 0.6 for the placebo group and 1.9 for each efalizumab dose group). For subjects with missing Day 84 values, a value of zero was imputed for the change from baseline.

Reviewer's Comment: *The amount of missing data was small, 1.2% in the efalizumab 1.0 mg arm, 1.8% in the efalizumab 2.0 mg arm, and 1.3% in the placebo arm.*

Response to Second Treatment Course: The outcome of those subjects who responded during the FT period to subsequent contiguous treatment was evaluated. This issue is discussed in the clinical review.

SUMMARY OF STUDY #ACD2390g: This study was entitled ***"A Phase IIIb, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multcenter Study to Evaluate the Efficacy and Safety of 1.0 mg/kg Subcutaneously Administered Efalizumab in Adults with Moderate to Severe Plaque Psoriasis."*** The study period was from January 25, 2002 to July 30, 2002. There were thirty study sites in the U.S. and Canada. The Genentech to-be-marketed product was used exclusively.

Study Design: This is a phase IIIb, randomized, double-blind, parallel-group, placebo-controlled, multi-center study to evaluate the efficacy and safety of 1.0 mg/kg sub-cutaneously (SC) administered efalizumab in adults with moderate to severe plaque psoriasis. Duration of treatment was 12 weeks. It had the following **primary objectives**: (1) to evaluate the efficacy of a 12-week course of 1.0 mg/kg/wk SC efalizumab relative to placebo as measured by the proportion of subjects achieving a **≥ 75% improvement in PASI on Day 84** relative to Day 0 and (2) to evaluate the safety and tolerability of a 12-week course of 1.0 mg/kg/wk SC efalizumab relative to placebo. The **secondary objective** was to characterize efficacy relative to placebo as measured by the following secondary endpoints: OLS, the primary secondary endpoint, proportion with ≥ 50% PASI improvement, mean % of PASI improvement over time, DLQI, Itching Scale, Psoriasis Symptom Assessment (PSA), Physician's Global Assessment (PGA) of change, Thickness component of the PASI, % BSA affected by psoriasis. **Other efficacy objectives** include assessment of: Patient's Global Psoriasis Assessment (PGPA), mean improvement in the Itching Scale over time, mean improvement in PSA over time, and pharmacokinetics/pharmacodynamics of efalizumab.

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

Sample Size: 556 subjects were enrolled and randomized, 187 subjects in the placebo group and 369 subjects in the efalizumab group. With this sample size, the probability of observing one or more instances of an AE with a background rate of 1% or 2% over the period of observation was 0.965 and 0.999, respectively.

Analysis Populations: The ITT population was the primary population for the primary and secondary efficacy endpoints. The ITT group consisted of all subjects who were randomized, whether or not they received any study drug or completed the full course of treatment. The ITT population was the primary population for the safety endpoints. An efficacy-evaluable population was also used in secondary analyses of the primary efficacy endpoint and the principal secondary outcome measure (OLS scale).

Statistical Methods: For the primary endpoint, response status at the end of study was determined as follows: (1) a **responder** was defined as any subject whose PASI score decreased by ≥ 75% on Day 84 relative to Day 0 (2) a **partial responder** was defined as any subject whose PASI score decreased by ≥ 50% but < 75% on Day 84 relative to Day 0 and (3) a **non-responder** was defined as any subject whose PASI score decreased by < 50% on Day 84 relative to Day 0. The treatment effect was defined as the difference in the proportion of responders between the active efalizumab group and the placebo group. The primary endpoint was evaluated by comparing the proportion of responders between the active and placebo groups using Fisher's exact test for the ITT population. The exact 95% CI for response rate within each treatment group and the difference in response rates between groups were calculated. For the principal secondary endpoint of OLS, the proportion of subjects who achieved an OLS rating of 'Minimal' or 'Clear' at Day 84 was compared between the two arms via Fisher's Exact test. Other endpoints were analyzed using statistical methodology previously described for such endpoints in the

other pivotal studies. All statistical tests were two-sided and were performed at the .05 level of significance.

Missing Data: For 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. For the primary and principal secondary efficacy endpoints (PASI-75, OLS, and PASI-50), subjects with missing data at Day 84 were classified as non-responders (worst outcome imputation).

SPONSOR's EFFICACY RESULTS FOR STUDY #ACD2390g:

Demographics and Baseline Characteristics: Demographic characteristics were balanced among the treatment groups.

Disease Characteristics at Baseline: The two treatment groups were well-balanced with respect to baseline disease characteristics, including PASI, OLS, and BSA.

Primary Efficacy Outcome:

The proportion of PASI-75 responders was higher in the treatment group than in placebo. The absolute difference was 22.3%. These results were statistically significant. Details of the analysis are presented in Sponsor's Table 11.4.1-1 which follows.

Sponsor's Table 11.4.1-1: 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.

Reviewer's Comment: This reviewer confirmed the analysis. A Cochran Mantel-Haenszel stratified analysis, using the randomization balancing factors, was also statistically significant.

A more detailed breakdown by percentiles of the percentage change in PASI-75 at the end of the FT period is shown in Sponsor's Table 11.4.1.2 which follows.

Sponsor's Table 11.4.1.2: 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-75 response from baseline. 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%).

Treatment Response in Patient Subgroups:

Treatment responses were examined by various patient subgroups based on demographic factors, baseline PASI-75 and prior history of systemic therapy. Results are presented in Sponsor's Table 11.4.1-3 below.

Sponsor's Table 11.4.1-3: 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%)

Reviewer's Comment: The results for PASI-75 in subgroups defined by sex, age group, baseline PASI score and history of prior systemic therapy show a consistent pattern when compared to the findings of the whole ITT population.

The sponsor performed a logistic regression analysis that examined baseline PASI score, age, sex, prior systemic therapy, geographic region and season of the year. This analysis did not uncover any statistically significant prognostic factors predictive of response with the exception of geographic region.

Responses for the components of the PASI-75 score are shown in Sponsor's Table 11.4.1-14 below.

Sponsor's Table 11.4.1-14: 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.

Each of the three components of the PASI-75 score appears to contribute about the same amount of improvement. This pattern was also observed in Studies #ACD2058g and #ACD2059g.

Sponsor's Table 11.4.1-15 below presents results for analysis of mean improvement in % of BSA.

Sponsor's Table 11.4.1-15: 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.

Thus, efalizumab-treated patients demonstrated a statistically significant mean improvements in % body surface area affected by psoriasis.

Secondary Efficacy Outcomes:

The principal secondary efficacy endpoint results are shown in Sponsor's Table 11.4.1-6 below.

Sponsor's Table 11.4.1-6: 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 subjects with an OLS rating of 'Minimal' or 'Clear' was statistically significantly higher in the efalizumab arm than in the placebo arm. These findings are supportive of the primary efficacy analysis.

Reviewer's Comment: *This analysis was confirmed.*

A finer breakdown of the distribution of Day 84 OLS categories is presented in Sponsor's Table 11.4.1-7 below.

Sponsor's Table 11.4.1-7: 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%)

Reviewer's Comment: *This distribution of OLS scores shows an overall shift towards better scores in the efalizumab arm compared to the placebo arm. More subjects were classified as severe and very severe in the placebo group. Regarding missing data, the amount was modest and comparable for the two treatment groups.*

DLQI (Dermatology Life Quality Index): The DLQI mean change from baseline at Day 84 was pre-specified as a secondary efficacy endpoint. Decreases in this scale indicates improvement. The mean improvement in the DLQI overall score was analyzed via the Wilcoxon rank sum test, which yielded a statistically significant result in favor of the efalizumab arm ($p < 0.001$). Both treatment groups had comparable scores at baseline. The mean improvement from baseline was 5.6 for the efalizumab treatment arm versus 1.6 for the placebo arm.

Reviewer's Comment: The amount of missing data was modest in the two treatment groups, 5.8% in the efalizumab 1.0 mg arm and 2.7% in the placebo arm.

SUMMARY OF STUDY #ACD2600g: This study was entitled ***"A Phase IIIb, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Multicenter Study to Evaluate the Safety of 1.0 mg/kg SC Administered Efalizumab in Adults with Moderate to Severe Plaque Psoriasis who are Candidates for Systemic Therapy."*** It was initiated on September 6, 2002 and completed on February 19, 2003. This study was conducted at 58 study centers in the U.S. and Canada. The Genentech to-be-marketed product was used exclusively.

Study Design: The duration of treatment was from Day 0 to Day 84 (12 weeks). On Day 0, subjects were randomized in a 2:1 ratio to receive 12 weeks of 1.0 mg/kg SC efalizumab or placebo. At the conclusion of the 12-week treatment period, subjects who completed treatment with study drug (efalizumab or placebo) through Day 84 were given the option of receiving efalizumab in an open-label extension study, Study #ACD2601g. Subjects who discontinued early transferred into Study #ACD2601g for 12 weeks of follow-up observation. The **primary objective** of Study #ACD2600g was to evaluate the **safety and tolerability** of a 12-week course of 1.0 mg/kg SC efalizumab relative to placebo. The **secondary objectives** 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 who achieved a $\geq$ 75% improvement in PASI, the OLS scale, the proportion of subjects who achieved a $\geq$ 50% improvement in PASI, and the Psoriatic Symptom Assessment (PSA).

Randomization and Sample Size: Subjects were centrally randomized 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 ($\leq$ 16.0, $\geq$ 16.1) and by prior treatment for psoriasis (naïve to systemic treatment vs. prior systemic treatment). A randomly permuted block design was used to obtain an approximately 2:1 ratio within categories defined by the stratification variables. 686 subjects were randomized, 236 to the placebo arm and 450 to the efalizumab arm. The sample size for this study was based primarily on safety considerations. The probability of observing one or more instances of an AE with a background rate of 1% or 2% over the observation period in a treatment group with 460 subjects was 0.990 and 1.000, respectively. For a treatment group containing 230 subjects, the corresponding probabilities were 0.901 and 0.990. The estimation of power for the principal secondary efficacy endpoint assumed a response rate of 25% in the 1.0 mg/kg/wk efalizumab treatment group versus a placebo response rate of 5% at the end of the study. Using a two-sided Fisher's exact test at the .05 level of significance, the sample size provides > 99% power to detect a difference between treatment groups.

Analysis Populations: The ITT population consisted of all subjects who were randomized, whether or not they received any study drug or completed the full course of treatment. The ITT population was the primary analysis population for the efficacy endpoints. Safety analyses were based on the number of subjects who received any amount of study drug. In this case, subjects were analyzed according to the actual

treatment they received. One subject, randomized to the efalizumab group, was never dosed and was removed from safety summaries.

Statistical Methods: All statistical tests were two-sided and performed at the.05 level of significance. The principal secondary efficacy endpoint, proportion of subjects whose PASI score decreased by $\geq$ 75% on Day 84 relative to Day 0, was analyzed via Fisher's exact test. For the additional secondary endpoints, statistical methodology was as follows. The following were compared using Fisher's exact test: (a) proportion of subjects who achieved an OLS rating of 'Minimal' or 'Clear' at Day 84 and (b) proportion of subjects who achieved $\geq$ 50% improvement on PASI on Day 84 relative to Day 0 (c) The change from baseline in each of the two scales (frequency and severity) of the PSA at Day 84 were compared between the 1.0 mg/kg/wk efalizumab group and placebo group using the Wilcoxon rank sum test (d) PSA scores were calculated at baseline and at Day 84 in accordance with existing guidelines for the instrument. The change from baseline in each of the PSA itching components (frequency and severity) at Day 84 were compared between the treatment groups using the Wilcoxon rank sum test.

Adjustment for Multiple Comparisons across Secondary Endpoints: To ensure an overall type I error rate of $\alpha = 0.05$ (2-sided) for all the secondary efficacy analyses, the **Hochberg-Bonferroni multiple comparisons procedure** (Hochberg 1988) was used to adjust for multiple comparisons for seven secondary endpoints in the following manner: let $p_{(1)}, \ldots\ldots, p_{(7)}$ be the ordered p-values from the secondary hypothesis tests. If the largest p-value, $p_{(7)}$, was ≤ 0.05, the efalizumab group was considered to be statistically significantly different from placebo for the remaining 6 secondary endpoints. If $p_{(7)}$ exceeded 0.05, the efalizumab group was considered to be statistically significantly different from placebo for the remaining 6 secondary endpoints only if the next to the largest p-value $p_{(6)}$ was ≤ 0.025. If $p_{(7)}$ exceeded 0.05 and $p_{(6)}$ exceeded 0.025, the efalizumab group was considered to be significantly different from placebo for the remaining 5 secondary endpoints only if $p_{(5)}$ was ≤ 0.017, and so on.

Missing Data: If a subject discontinued from the study prior to Day 84 but after receiving the final scheduled dose of study drug on Day 77, then data from the early termination visit were used for analysis for all study endpoints. The missing data imputation approach for secondary endpoints was as follows. If any of the individual PASI components (e.g., severity of erythema for the upper limbs) was missing, the PASI was set to missing for that observation. If the baseline (Day 0) PASI value was missing for a subject, it was replaced by that subject's screening PASI value. If both screening and baseline PASI values were missing, the subject's data were omitted from analysis. Subject's with a missing Day 84 PASI score were classified as non-responders for analysis of the principal secondary endpoint (worst outcome imputation), as well as for the analysis of the proportion of subjects with a $\geq$ 50% improvement in PASI score at Day 84 relative to Day 0. Subjects missing the Day 84 OLS score were classified as non-responders ('Mild' to 'Very Severe') for analysis of this endpoint. If the baseline (Day 0) Psoriasis Symptom Assessment (PSA) was missing for a subject, the subject's data were omitted from the analysis of this endpoint. If the Day 84 value was missing, change from baseline was set to zero (no change imputation). The same approach was applied to the analysis of the PSA itching component.

Safety Analysis: Safety was assess through the summary of AE's, deaths, laboratory test results, vital signs, and anti-efalizumab antibodies. These summaries were produced by

treatment group. Safety analyses were based on the number of subjects who received any amount of study drug. Subjects were analyzed according to actual treatment received.

SPONSOR's EFFICACY RESULTS FOR STUDY #ACD2600g:

Subject Disposition, Demographics, and Baseline Characteristics: The proportions of subjects completing the first treatment course were comparable across treatment groups. The proportion that discontinued the FT for an AE was similar across treatment arms. A total of 47 subjects (6.9%) discontinued treatment. One placebo subject died on study. Overall, 16 patients discontinued due to AE's, which was the most common reason for discontinuation. The proportions discontinuing for AE's were comparable between treatment groups. Overall, the treatment groups were comparable in demographics and baseline psoriasis characteristics. However, there was a higher ratio of male to female patients on the efalizumab arm compared to placebo. The overall baseline disease severity was moderate to severe psoriatic disease and was comparable between treatment arms. A majority of the subjects (73%) had a prior history of systemic therapy use.

Efficacy results at the end of the 12-week (Day 84) treatment period are summarized in the following section.

Principal Secondary Efficacy Endpoints:

Sponsor's Table 11.4.1-1: 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.

Reviewer's Comment: *The proportion of PASI-75 responders was statistically significantly higher in the efalizumab group compared to the placebo group. The proportion of PASI-50 responders was statistically significantly higher in the efalizumab group compared to the placebo group. The efficacy outcome based on the response by physician's static global assessment (OLS) was also statistically significantly better ($p < 0.001$) for the efalizumab arm relative to the placebo arm and, thus, supportive of the PASI response findings. This reviewer confirmed these analyses.*

The sponsor did not perform any covariate adjusted analyses.

Study Centers: For the principal, secondary efficacy endpoint, response rates by study site demonstrated some site-to-site variability, but showed an overall consistent trend for higher response rate in the efalizumab group as compared to the placebo group.

Generalizability: The principal secondary endpoint was examined for generalizability by examining results by stratification categories of gender, age group (18-40, 41-64, and ≥ 65 years old), baseline PASI score (≤ 16.0, 16.1-30.0, and > 30.0), and prior systemic therapy (yes/no). The results in these subgroups were generally consistent with the results for the randomized population as a whole.

Sponsor's Comprehensive Exploratory Efficacy Analyses: At the clinical reviewer's request, the sponsor performed several exploratory analyses of major efficacy endpoints, PASI and OLS. In the first such analysis, subjects having baseline OLS scores of less than moderate were excluded. The hypothesis of interest here was to determine if enrolling patients with less than moderate disease activity at baseline would lead to differences in PASI response rate at Day 84 as compared to the moderate to severe population. The following sponsor's table presents the findings of this analysis for the ITT population.

Sponsor's Table: PASI and OLS Analyses with and without Subjects Whose Baseline OLS Values Were Mild or Better

		Subjects With Baseline OLS of Moderate to Very Severe			All Randomized Subjects		
Study	FT Day 84 Response	Placebo	Efalizumab 1.0 mg/kg/wk	Efalizumab 2.0 mg/kg/wk	Placebo	Efalizumab 1.0 mg/kg/wk	Efalizumab 2.0 mg/kg/wk
ACD2058g	n	164	156	162	170	162	166
	PASI 90	2 (1.2%)	20 (12.8%)	8 (4.9%)	2 (1.2%)	20 (12.3%)	8 (4.8%)
	PASI 75	4 (2.4%)	63 (40.4%)	43 (26.5%)	4 (2.4%)	63 (38.9%)	44 (26.5%)
	PASI 50	25 (15.2%)	96 (61.5%)	82 (50.6%)	25 (14.7%)	99 (61.1%)	85 (51.2%)
	OLS Clear	1 (0.6%)	6 (3.8%)	5 (3.1%)	1 (0.6%)	6 (3.7%)	5 (3.0%)
	OLS C/M	5 (3.0%)	51 (32.7%)	35 (21.6%)	5 (2.9%)	52 (32.1%)	37 (22.3%)
ACD2059g	n	117	216	220	122	232	243
	PASI 90	1 (0.9%)	9 (4.2%)	15 (6.8%)	1 (0.8%)	10 (4.3%)	15 (6.2%)
	PASI 75	5 (4.3%)	48 (22.2%)	61 (27.7%)	6 (4.9%)	52 (22.4%)	69 (28.4%)
	PASI 50	17 (14.5%)	112 (51.9%)	123 (55.9%)	19 (15.6%)	120 (51.7%)	138 (56.8%)
	OLS Clear	1 (0.9%)	4 (1.9%)	5 (2.3%)	1 (0.8%)	5 (2.2%)	5 (2.1%)
	OLS C/M	3 (2.6%)	39 (18.1%)	48 (21.8%)	4 (3.3%)	45 (19.4%)	55 (22.6%)

FT=First Treatment, OLS C/M = OLS Clear or Minimal

Sponsor's Table: PASI and OLS Analyses with and without Subjects Whose Baseline OLS Values Were Mild or Better (Continued)

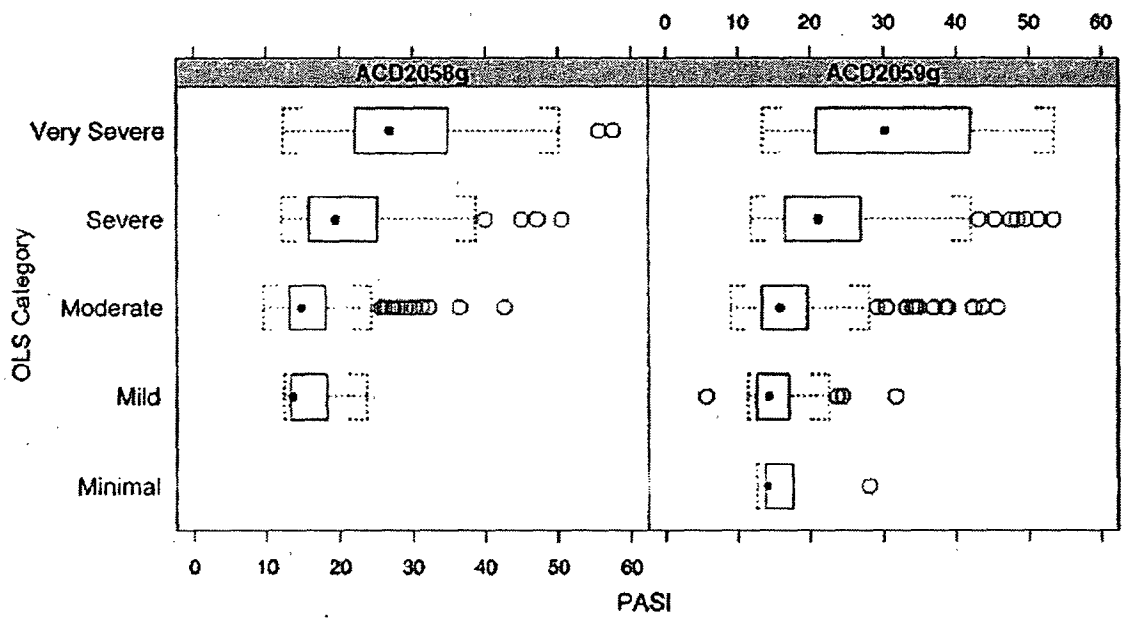
		Subjects with Baseline OLS of Moderate to Very Severe		All Randomized Subjects	
Study	FT Day 84 Response	Placebo	Efalizumab 1.0 mg/kg/wk	Placebo	Efalizumab 1.0 mg/kg/wk
ACD2390g	n	174	345	187	369
	PASI-90	1 (0.6%)	16 (4.6%)	1 (0.5%)	19 (5.1%)
	PASI-75	6 (3.4%)	88 (25.5%)	8 (4.3%)	98 (26.6%)
	PASI-50	24 (13.8%)	196 (56.8%)	26 (13.9%)	216 (58.5%)
	OLS Clear	0	7 (2.0%)	0	7 (1.9%)
	OLS C/M	4 (2.3%)	84 (24.3%)	6 (3.2%)	95 (25.7%)
ACD2600g	n	221	429	236	450
	PASI-90	0	26 (6.1%)	0	29 (6.4%)
	PASI-75	6 (2.7%)	98 (22.8%)	7 (3.0%)	106 (23.6%)
	PASI-50	29 (13.1%)	225 (52.4%)	33 (14.0%)	234 (52.0%)
	OLS Clear	0	11 (2.6%)	0	12 (2.7%)
	OLS C/M	6 (2.7%)	84 (19.6%)	10 (4.2%)	91 (20.2%)

FT=First Treatment OLS C/M = OLS Clear or Minimal

Note that the proportion of subjects with baseline OLS scores of less than moderate ranged from 3% in #ACD2058g to 8% in #ACD2059g. This analysis, excluding subjects who were less than moderate, produced results similar to those for the entire ITT population.

The sponsor also examined the correlation between OLS and PASI scores. Both of these are static scales used to assess disease severity at any one point in time. The next analysis was conducted to assess the degree of correlation between PASI and OLS at baseline (Day 0).

Sponsor's Figure 1: PASI by OLS Category at Baseline



In the sponsor's next analysis, the relationship between PASI response and OLS category was examined at FT Day 84:

Reviewer's Comment: *This reviewer performed a by treatment arm breakdown of PASI-75 response by OLS score category at Day 84 for the three efficacy studies, #ACD2058g, #ACD2059g, and #ACD2390g. These counts (not change score counts) of score categories revealed a consistent pattern across all three studies. The percent of PASI-75 responders having a Day 84 OLS score of 'Clear' or Minimal' on efalizumab treatment arms ranged from 68.2% - 70.4% versus 50% - 66% for placebo responders. For partial responders, the corresponding percentages were 10.1% - 22.2% for efalizumab groups versus 0% - 9.5% for placebo. And, for non-responders, the corresponding percentages were 0.9% - 1.3% for active treatment arms versus 0.6% - 0.7% for placebo. For the remaining OLS score categories, "Mild' to 'Very Severe,' there was again a very consistent pattern by treatment arm across these studies. The percent of efalizumab non-responders with a Day 84 OLS score of 'Mild' ranged from 16.3% - 29.5% versus 9.6% - 10.7% for placebo. Thus, the observed OLS count pattern is remarkably consistent across the three efficacy studies, but as previously discussed, discrimination is much better at the lower end of the OLS scale.*

OVERALL SUMMARY AND CONCLUSIONS:

This reviewer's analyses of the major efficacy endpoints for all four pivotal studies, based on the electronic database provided, confirmed the sponsor major reported statistical findings. There was a statistically significant improvement favoring efalizumab for both the primary and major secondary endpoints during the first twelve weeks of treatment for all four of these studies. Appropriate multiplicity adjustments were applied to control the false positive error rate. The sponsor's analyses of the other secondary endpoints and tertiary/exploratory endpoints also revealed a consistent pattern of improvement for the efalizumab treatment groups versus the placebo group.