

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
sBLA 125057/110

STATISTICAL REVIEW(S)



US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION SUPPLEMENTAL BLA (sBLA)

ADDENDUM

sBLA/Serial Number: 125057/110
Drug Name: Humira[®] (Adalimumab)
Indication(s): Psoriasis
Applicant: Abbott Laboratories

Dates: Submitted: March 23, 2007
PDUFA: January 21, 2008

Review Priority: Standard Review

Biometrics Division: Division of Biometrics III

Statistics Reviewer: Clara Y. Kim, Ph.D.

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Project Manager: Tamika White

Keywords: Psoriasis

This addendum includes additional analyses of Study M04-716 and to correct Table 5 (p.12) of the Statistical Review and Evaluation. The efficacy and safety of adalimumab were evaluated in two phase 3 studies (M03-656 and M04-716) in the treatment of moderate to severe psoriasis. Both studies included male and female subjects, 18 years of age or older with $\geq 10\%$ body surface area (%BSA), and a baseline PGA scores of at least moderate. Subjects in Study M03-656 had a baseline PASI greater than 12. However, in Study M04-716 subjects with baseline PASI greater or equal to 10 were included in the study. Per the request of the clinical review team, in this addendum we present results of the baseline disease severity and primary efficacy analyses excluding the subjects who had a baseline PASI score of less than 12 in Study M04-716.

Table 1 presents the baseline disease severity of subjects who had a baseline PASI score greater or equal to 12. The balance between the two arms in baseline disease severity does not change much from that of the ITT population after excluding subjects with baseline PASI score less than 12.

Table 1: Baseline Severity by Treatment Arm (Baseline PASI ≥ 12)

	Study M04-716	
	Adalimumab n=99 [†]	Placebo n=48
PGA		
Moderate	43 (43.4%)	17 (35.4%)
Severe	46 (43.0%)	29 (60.4%)
Very Severe	10 (10.1%)	2 (4.2%)
PASI		
Mean (std)	21.4 (7.8)	20.1 (6.5)
Median	20.6	18.6
Min, Max	(12.0,52.9)	(12.3,38.1)
%BSA		
Mean (std)	35.6 (19.8)	30.0 (16.1)
Median	30.6	28.0
Min, Max	(10.4,90.0)	(10.0,90.0)

[†] Subject ID # 15601 and 16530's baseline %BSA was not provided. Therefore, the baseline %BSA calculations for adalimumab were based on n=97 subjects.

Reviewer analysis

Table 2 presents the primary efficacy results for Study M04-716. As shown in the table, the efficacy results of baseline PASI ≥ 12 subjects was very similar to that prior to excluding subjects with baseline PASI score from 10 to 12.

Table 2: Number (%) of successes on PASI75 and PGA score at Week 16 (Study M04-716)

	Baseline PASI \geq 10		Baseline PASI \geq 12	
	Adalimumab n=108	Placebo n=53	Adalimumab n=99	Placebo n=48
PASI75				
Number of successes (%)	86 (79.6%)	10 (18.9%)	77 (77.8%)	9 (18.8%)
p-value		<0.0001 [†]		<0.0001 [†]
PGA				
Number of successes (%)	78 (72.2%)	6 (11.3%)	70 (70.7%)	5 (10.4%)
p-value		<0.0001 [†]		<0.0001 [†]

[†] P-value is calculated using CMH test, stratified by country.

All missing values were imputed as failures.

Source: Reviewer analysis

Table 5 (p.12) of the statistical review did not include the baseline disease severity of Subject ID # 16530. The sponsor's baseline disease severity data set (\crt\analysis ready\m04-716\vas716.xpt) did not have Subject ID # 16530's baseline severity information and the study report stated that this subject withdrew after randomization, but prior to administration of drug. However, after further examination of the data sets, this subject's baseline disease severity information was found in the efficacy data sets (\crt\analysis ready\m04-716\pga716.xpt and \crt\analysis ready\m04-716\pasi716.xpt). Table 3, which should replace Table 5 (p.12) of the statistical review, presents the results of the baseline severity by treatment arm including Subject ID # 16530's information.

Appears This Way
On Original

Table 3: Baseline Severity by Treatment Arm (ITT)

	Study M03-656		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=108 [†]	Placebo n=53
PGA				
Moderate	417 (51.2%)	220 (55.3%)	52 (48.6%)	20 (37.7%)
Severe	346 (42.5%)	155 (38.9%)	46 (43.0%)	31 (58.5%)
Very Severe	51 (6.2%)	23 (5.8%)	10 (9.3%)	2 (3.8%)
PASI				
Mean (std)	19.0 (7.1)	18.8 (7.1)	20.6 (7.5)	19.2 (6.9)
Median	16.8	16.5	18.7	18.2
Min, Max	(10.8,56.9)	(12.0,55.5)	(10.4,52.9)	(6.5,38.1)
%BSA				
Mean (std)	25.8 (15.5)	25.6 (14.8)	33.7 (19.9)	28.4 (16.1)
Median	20.0	21.0	28.3	25.0
Min, Max	(10.0,92.0)	(10.0,87.7)	(10.0,90.0)	(10.0,90.0)

[†] Subject ID # 15601 and 16530's baseline %BSA was not provided.

Therefore, the baseline %BSA calculations for adalimumab were based on n=106 subjects.

Source: M03-656 Clinical Study Report, p. 239; M04-716 Clinical Study Report, p. 140 and reviewer analysis

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Clara Y. Kim, Ph.D.

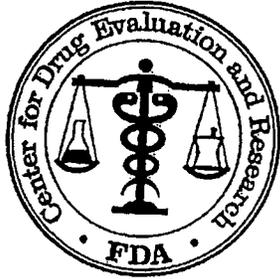
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December 13, 2007



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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The short term efficacy of adalimumab has been demonstrated to be statistically superior to placebo in two studies (Studies M03-656, Period A and M04-716) in the treatment of moderate to severe psoriasis. The long term efficacy of adalimumab has also been demonstrated to be statistically superior to placebo in one year study (Study M03-656, Period C) for the same indication. Efficacy was evaluated on (i) PASI75 response rate at Week 16 and (ii) success rate based on the Physician Global Assessment (PGA) at Week 16. Long term efficacy was assessed by comparing the proportion of subjects who experience loss of adequate response before Week 52. Table 1 presents the summary of the co-primary endpoints for the short term and long term efficacy.

Table 1: Efficacy Results Summary - Number (%) of Success and Number (%) of Losses of Adequate Responses Based on PASI75 and PGA Scores

	Study M03-656a		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
PASI75				
Number of successes (%)	578 (71.1%)	26 (6.5%)	86 (79.6%)	10 (18.9%)
p-value		<0.0001 [†]		<0.0001 [‡]
PGA				
Number of successes (%)	506 (62.2%)	17 (4.3%)	78 (72.2%)	6 (11.3%)
p-value		<0.0001 [†]		<0.0001 [‡]

	Study M03-656c	
	Adalimumab N=250	Placebo N=240
PASI75		
Number of losses (%)	52 (20.8%)	138 (57.5%)
p-value		<0.0001 [†]
PGA		
Number of losses (%)	80 (32.0%)	173 (72.1%)
p-value		<0.0001 [†]

[†] P-value is calculated using CMH test, stratified by pooled sites.

[‡] P-value is calculated using CMH test, stratified by country

All missing values were imputed as failures

Source: M03-656 Clinical Study Report, p. 252, M04-716 Clinical Study Report, p. 147 and reviewer analysis.

The adverse events rate was higher in adalimumab arm subjects than in the placebo arm

subjects. The most common adverse event was infections followed by injection site reactions.

1.2 Brief Overview of Clinical Studies

The sponsor conducted two phase 3 studies (Studies M03-656 and M0-416) to evaluate the safety and efficacy of adalimumab versus its placebo in the treatment of moderate to severe psoriasis. In Study M03-656, a total of 1212 were randomized in a 2:1 ratio to either adalimumab or placebo, and Study M04-716 enrolled a total of 271 subjects who were randomized in a 2:2:1 ratio to either adalimumab, MTX or placebo. ☐

☐ Short term efficacy was evaluated at Week 16 for the following co-primary endpoints: (i) PASI75 response rate; and (ii) success rate based on the Physician Global Assessment (PGA). Long term efficacy (loss of adequate response) was evaluated in treatment arm subjects who responded at Week 16 (end of M03-656, Period A), and continued to respond at Week 33 (end of M03-656, Period B). Assessment of loss of adequate response was based on the PASI75 and PGA scores. Investigative sites of Study M03-656 were all located in the United States and Canada, whereas that of Study M04-716 were located in Europe and Canada.

b(4)

1.3 Statistical Issues and Findings

The sponsor conducted two studies (Studies M03-656 and M04-716) under the protocols that were evaluated by the Agency in terms of study design and endpoints. Short term efficacy was evaluated at Week 16 using PASI75 and PGA scores. The differences in the success rates based on PASI75 were statistically significant in both studies (p-values < 0.0001). This was also true for the success rates based on PGA. Long term efficacy was assessed by the proportion of subjects who experienced a loss of adequate response before Week 52. The difference in the two arms' proportions was statistically significant with a p-value of less than 0.0001. Within each study, the efficacy results were relatively consistent across subgroups and investigative sites. The protocol ranked 61 secondary endpoints in the order of importance according to the sponsor, where the first one (success rate based on PGA score at Week 16) was considered as one of the co-primary endpoints by the Division. After discussing with the clinical review team, the remaining 60 secondary endpoints ☐

b(4)

2 INTRODUCTION

2.1 Overview

Humira[®] (adalimumab) was approved on December 31, 2002 in the U.S. for the treatment of moderate to severe rheumatoid arthritis (RA). Adalimumab was also approved for indications

such as psoriatic arthritis (PsA), ankylosing spondylitis (AS), and moderate to severe Crohn's Disease (CD). In the current application of adalimumab, the sponsor is seeking an indication of moderate to severe psoriasis.

The sponsor met with the Agency on February 24, 2004 for an End of Phase (EoP) 2 meeting. At this meeting, the Agency stated that two adequate and well controlled studies would be required to establish short-term efficacy in addition to the sponsor's phase 2 study (M02-529). Also stated was the requirement of rigorous evidence of long-term (at least 1 year) efficacy due to the expected chronic use of this product. The Agency stressed the importance of using the proportion of patients who achieve a rating of "clear" or "nearly clear" based on the Physician Global Assessment (PGA) score as an co-primary efficacy endpoint.

The sponsor submitted two phase 3 study protocols M03-656 and M04-716, and the corresponding statistical analysis plans (SAP) in SN 120 (stamp date 5/18/06), 126 (stamp date: 8/01/06), and 132 (stamp date 9/18/06). The statistical comments regarding these submissions were faxed to the sponsor on 9/07/06 (SN120) and 1/18/07 (SN126 and SN132). The key statistical comments were (i) to limit the number of secondary endpoints to a small number of clinically relevant endpoints; (ii) that the Division considers achieving 'clear' or 'minimal' on the PGA as the primary efficacy endpoint; (iii) that the supportive imputation method (LOCF) proposed in the SAP is likely to lead to very similar results to the primary analysis (treating missing data as non-responders). The sponsor met with the Division again on February 7, 2007 for a pre-BLA meeting. At this meeting, the Division conveyed that both PASI75 (the primary endpoint in the protocol) and success on the PGA score (the endpoint generally recommended by the Division of Dermatology and Dental Products) will be considered as co-primary endpoints.

Through the above communications, the sponsor and Division came to an agreement on endpoints and most aspects of the study design. Table 2 lists the phase 3 clinical study programs and the enrollment of each study by treatment arm. This review evaluated the efficacy and safety of the phase 3 clinical study programs. The short term efficacy results were based on both phase 3 studies, whereas long term efficacy results were based on Study M03-656 (Period C).

Table 2: Overview of Pivotal Studies

Study	Duration (Weeks)	Enrollment			
		Adalimumab	Placebo	MTX	Total
M03-656					
Period A	16	814	398	0	1212
Period B	17	606	0	0	606
Period C	19	250	240	0	490
M04-716					
	16	108	53	110	271

2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in CTD format and was entirely electronic. The data sets used in this review are archived at

\\Cbsap58\m\EDR Submissions\2007 BLA\DCC60004544\125057\crt\datasets\m03-656 and
\\Cbsap58\m\EDR Submissions\2007 BLA\DCC60004544\125057\crt\datasets\m04-716.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

To evaluate the efficacy and safety of adalimumab in the treatment of moderate to severe psoriasis, the sponsor submitted results from five clinical studies:

- two phase 2 studies:
 - M02-528: placebo-controlled study
 - M02-529: continuation of M02-528
- three phase 3 studies:
 - M03-656: placebo-controlled study
 - M04-716: placebo-controlled study
 - M03-658: continuation of the phase 2 and phase 3 psoriasis studies.

Protocols M03-656 and M04-716 were evaluated by the Division in September 2006 and January 2007. Both studies were designed as multicenter, randomized, double-blind, placebo-controlled studies. Study M03-656 consisted of three treatment periods: A, B, and C. (Each period's treatment regimen is described below.) This study planned to enroll approximately 1200 subjects. The actual enrollment was 1212 subjects from 82 sites. The inclusion criteria of Study M03-656 was male and female subjects, 18 years of age or older with moderate to severe plaque psoriasis, defined as $\geq 10\%$ body surface area (%BSA), PASI ≥ 12 , and a PGA score of at least moderate at baseline. The enrolled subjects were randomly assigned to receive either adalimumab or placebo in a 2:1 ratio in Period A. The randomization resulted in 814 and 398 subjects in adalimumab and placebo arms, respectively. The treatment regimen and randomization for each period are the following.

- Period A (16 weeks): Subjects were randomized to receive either

- 80 mg adalimumab (two 40 mg injections) subcutaneously (SC) at baseline (Week 0), followed by 40 mg adalimumab SC every other week (eow) from Week 1 to Week 15 (Subjects with at least a PASI 75 response at Week 16 received two placebo injections at Week 16 in a blinded fashion.); or
- two placebo injections SC at baseline, followed by one placebo injection SC eow from Week 1 to Week 15. (Subjects with at least a PASI 75 response at Week 16 will receive 80 mg adalimumab at Week 16 in blinded fashion).
- Period B (17 weeks): Subjects who achieved at least a PASI 75 response at Week 16 (end of Period A) received open-label 40 mg adalimumab SC eow from Week 17 to Week 31.
- Period C (19 weeks): Subjects who maintained at least a PASI 75 response at Week 33 (end of Period B) entered a double-blind, placebo-controlled treatment period as follows
 - subjects who were randomized to adalimumab in Period A were re-randomized in a 1:1 ratio to receive 40 mg adalimumab SC eow or placebo from Week 33 to an ‘event’ (i.e., loss of an adequate response), early termination, or the Week 52 visit, whichever came first; or
 - subjects who were originally randomized to placebo in Period A continued to receive 40 mg adalimumab eow in a blinded fashion from Week 33 to an ‘event’ (i.e., loss of an adequate response), early termination, or the Week 52 visit, whichever came first.

Period A was designed to evaluate the short-term efficacy and safety. The purpose of Period C was to evaluate adalimumab withdrawal in subjects who previously responded well to adalimumab. Clinical evaluations were conducted at baseline, Weeks 4, 8, 12, and 16 in Period A. In Period C, these were done at Weeks 33, 36, 40, 44, 48, and 52.

Study M04-716 planned to randomize approximately 250 subjects to one of three treatment regimens in a 2:2:1 ratio from approximately 25 investigative sites in Europe (the three regimens are described below). The actual enrollment was 271 subjects from 29 centers in Europe and Canada. The inclusion criteria of M04-716 were male and female subjects, 18 years of age or older with moderate to severe plaque psoriasis, defined as $\geq 10\%$ body surface area (%BSA), PASI ≥ 10 , and a PGA score of at least moderate at baseline. The three treatment regimens were

- Regimen A (Adalimumab):
 - 80 mg adalimumab (two 40 mg injections) SC at baseline, followed by 40 mg adalimumab SC eow from Week 1 to Week 15.
 - Placebo capsule(s) once weekly from baseline (Week 0) to Week 15.
- Regimen B (Methotrexate (MTX)):

- Two placebo injections SC at baseline, followed by 1 placebo injection SC eow from Week 1 to Week 15.
- MTX (7.5-25.0 mg) capsule(s) once weekly from baseline to Week 15.
- Regimen C (Placebo):
 - Two placebo injections SC at baseline, followed by 1 placebo injection SC eow from Week 1 to Week 15.
 - Placebo capsule(s) once weekly from baseline to Week 15.

Clinical evaluations were conducted at baseline, Weeks 4, 8, 12, and 16. Note that the efficacy of adalimumab was evaluated based on the comparisons of adalimumab and placebo arms and not the MTX arm. b(4)

The protocols of the two phase 3 studies defined the response rate at Week 15 based on the PASI75 as the primary efficacy endpoint and that based on the 6-grade PGA score as secondary. Success rate based on PASI75 was defined as the proportion of subjects with a 75% reduction in PASI score from baseline. Subjects who achieve a PGA score of “Clear”, or “Minimal” were defined as successes based on the PGA. (All randomized subjects were to have a baseline PGA score of “Moderate” or worse. Therefore, achieving a PGA score of “Clear” or “Minimal” implies an improvement of at least 2 units.) As mentioned in Section 2.1, the Division conveyed to the sponsor that both PASI75 and success rates based on the PGA will be considered as co-primary endpoints. PGA score was defined as the following.

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

Study M03-656, Period C included an additional primary efficacy endpoint, the proportion of subjects who experience a loss of adequate response after Week 33 and on or before Week 52. The protocol defined “loss of adequate response” as a PASI score after Week 33 that resulted in

a <PASI50 response relative to the baseline PASI score and at least a 6-point increase in PASI score relative to the PASI score at Week 33. In this review, "Loss of adequate response" was evaluated using a different definition. After discussing with the clinical review team, a subject who did not maintain what was considered as a response (i.e., PASI75, PGA score of "clear" or "minimal") from Week 33 to Week 52, was considered to have experienced a loss of adequate response.

The protocols listed a total of 61 secondary endpoints that were highly correlated. These secondary endpoints were ranked in the order of what the sponsor considered as important, and were to be tested sequentially. The first five secondary endpoints listed in the protocol were the following. (Note that the Division considered the first secondary endpoint as a co-primary endpoint.)

1. Proportion of subjects achieving a PGA of "Clear" or "Minimal" at Week 16
2. Proportion of subjects achieving a clinical response defined as \geq PASI50 at Week 16
3. Proportion of subjects achieving a clinical response defined as \geq PASI90 at Week 16
4. Proportion of subjects achieving a clinical response defined as a PASI100 at Week 16
5. Proportion of subjects achieving a clinical response defined as \geq PASI75 at Week 12

The protocol and submission defined the intent-to-treat (ITT) population as all randomized subjects. The per protocol (PP) population included all subjects in the ITT population who had no major protocol violations (i.e., criteria that, if violated, would influence the analysis of efficacy). The sponsor stated that the PP population criteria was defined before unblinding the data. The detailed list can be found on pages 346 and 211 of M03-656 Clinical Study Report and M04-716 Clinical Study Report, respectively.

The following analysis methods were proposed in the protocols and were used in the current submission.

- The primary endpoint, proportion of subjects achieving PASI75, was analyzed with the Cochran-Mantel-Haenszel (CMH) test stratified by pooled investigative sites (M03-656) or country (M04-716).
- The protocol proposed to analyze the Division defined co-primary endpoint, success rate based on the PGA score, using Fisher's exact test. However, this reviewer used CMH test to include the stratification factors, pooled investigative sites (M03-656) and country (M04-716), in the analysis.
- Investigative sites were pooled according to their rank (based on the number subjects): the largest site was combined with the smallest site, and the second largest site was combined

with the second smallest site and so on. The sponsor stated that this method was discussed and agreed upon during a telephone contact on December 21, 2004 with the FDA medical reviewer of the protocol at that time.

- Secondary efficacy endpoints were analyzed with Fisher's exact test if the outcome was proportions, one-way Analysis of Variance (ANOVA) if it was continuous, and log-rank test if it was time to event.
- Missing PASI or PGA scores at Week 16 were imputed as non-responders in the primary analysis.

3.1.2 Subject Disposition

A total of 1212 and 271 subjects were enrolled in Studies M03-656 and M04-716, respectively. M03-656 randomized the enrolled subjects in a 2:1 ratio to either adalimumab or placebo, while M04-716 randomized subjects in a 2.2:1 ratio to either adalimumab, MTX or placebo. Thus, in Study M03-656, 814 subjects were randomized to adalimumab and 398 to the placebo arm, and in Study M04-716, 108 subjects were randomized to adalimumab and 53 subjects to placebo. Table 3 presents the reasons for study discontinuation.

Table 3: Number (%) of Subjects Who Discontinued the Study - Classified by the Reason for Discontinuation

	Study M03-656a		Study M03-656c		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab† n=250	Placebo† n=240	Adalimumab n=108	Placebo n=53
Subjects who discontinued	31 (4%)	43 (10.8%)	23 (9.2%)	56 (23.3%)	4 (3.7%)	5 (9.4%)
<i>Reason</i>						
Adverse Event	10 (1.2%)	4 (1.0%)	3 (1.2%)	1 (0.4%)	1 (0.9%)	1 (1.9%)
Lost to Follow-up	6 (0.7%)	8 (2.0%)	4 (1.6%)	5 (2.1%)	0 (0%)	0 (0%)
Unsatisfactory Therapeutic Effect	2 (0.2%)	17 (4.3%)	0 (0%)	5 (2.1%)	0 (0%)	4 (7.5%)
Withdrawal of Consent	6 (0.7%)	9 (2.3%)	2 (0.8%)	2 (0.8%)	2 (1.9%)	0 (0%)
Protocol Violation	2 (0.2%)	2 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Administrative Problems	0 (0%)	1 (0.3%)	2 (0.8%)	1 (0.4%)	0 (0%)	0 (0%)
IVRS Required‡	NA	NA	10 (4.0%)	41 (17.1%)	NA	NA
Other	5 (0.6%)	2 (0.5%)	2 (0.8%)	1 (0.4%)	1 (0.9%)	0 (0%)

† Adalimumab arm subjects received adalimumab in all periods whereas placebo arm subjects received adalimumab in Periods A and B, and received placebo in Period C.

‡ When an event was reached, the Interactive Voice Response (IVRS) was to instruct the site to discontinue the subject from the study.

Source: M03-656 Clinical Study Report, p. 212-213 and 216, M04-716 Clinical Study Report, p. 127 and reviewer analysis

The proportion of subjects who discontinued the study in the placebo arm was more than twice of that in the adalimumab arm in both studies. In the two short-term effect studies (M03-656, Period A (M03-656a) and M04-716), the most common reasons for discontinuation

in the adalimumab arm were 'Adverse Events' (M03-656a: 1.2%) and 'Withdrawal of Consent' (M04-716: 1.2%), whereas that of the placebo arm was 'Unsatisfactory Therapeutic Effect', 4.3% and 7.5% in Studies M03-656a and M04-716, respectively. Study M03-656, Period C was designed to discontinue subjects who experienced an 'event', loss of adequate response. This type of discontinuation was denoted as 'IVRS required', and was the most common reason for study discontinuation in this period in both arms. Four percent of the adalimumab arm subjects and 17.1% of the placebo arm subjects dropped out for this reason.

3.1.3 Baseline and Demographic Data

Table 4 presents the baseline demographic data. Baseline demographic variables were generally balanced across treatment arms. The mean age of all subjects were 44.5 and 41.7 years in Studies M03-656 and M04-716, respectively. More male subjects than female subjects were enrolled in both studies. Adalimumab arm had a marginally higher proportion of males than the placebo arm in Study M03-656, whereas the opposite was true in Study M04-716. In both studies, more than 90% of the study participants were white.

Table 4: Baseline Demographics

	Study M03-656		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
Age (in years)				
mean (std)	44.1 (13.2)	45.4 (13.4)	42.4 (12.5)	40.2 (11.4)
median	44	46	42	41
min, max	(18,79)	(18,82)	(18,81)	(20,69)
Gender				
Male	546 (67.1%)	257 (64.6%)	79 (64.8%)	35 (66.0%)
Female	268 (32.9%)	141 (35.4%)	38 (35.2%)	18 (34.0%)
Race				
White	742 (91.2%)	359 (90.2%)	103 (95.4%)	49 (92.5%)
Black	28 (3.4%)	20 (5.0%)	2 (1.9%)	1 (1.9%)
Asian	21 (2.6%)	7 (1.8%)	3 (2.8%)	2 (3.8%)
American Indian/Alaska Native	3 (0.4%)	1 (0.3%)	0 (0%)	0 (0%)
Other	20 (2.5%)	11 (2.8%)	0 (0%)	0 (0%)

Source: M03-656 Clinical Study Report, p. 225, M04-716 Clinical Study Report, p. 134, and reviewer analysis

Table 5 presents the baseline PGA, PASI scores and body surface area (%BSA) by treatment arm. The baseline PGA scores were fairly balanced between the two arms in both studies.

Adalimumab arm had a larger proportion of subjects that had a PGA score of ‘Very Severe’ at baseline than the placebo arm in both studies. There were more ‘Moderate’ subjects in the adalimumab arm than the placebo arm in Study M03-656, whereas the opposite was true in Study M04-716. The mean baseline PASI score was also generally balanced between the two arms in both studies. Adalimumab arm mean baseline PASI scores were slightly larger than that of the placebo arm in both studies. The mean baseline %BSA was marginally larger in the adalimumab arm than the placebo arm in Study M04-716. However, in general, the baseline %BSA balanced between the two arms in both studies.

Table 5: Baseline Severity by Treatment Arm

	Study M03-656		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=107 ^{††}	Placebo n=53
PGA				
Moderate	417 (51.2%)	220 (55.3%)	52 (48.6%)	20 (37.7%)
Severe	346 (42.5%)	155 (38.9%)	46 (43.0%)	31 (58.5%)
Very Severe	51 (6.2%)	23 (5.8%)	9 (8.4%)	2 (3.8%)
PASI				
Mean (std)	19.0 (7.1)	18.8 (7.1)	20.3 (7.5)	19.2 (6.9)
Median	16.8	16.5	18.7	18.2
Min, Max	(10.8,56.9)	(12.0,55.5)	(10.4,52.9)	(6.5,38.1)
%BSA				
Mean (std)	25.8 (15.5)	25.6 (14.8)	33.7 (19.9)	28.4 (16.1)
Median	20.0	21.0	28.3	25.0
Min, Max	(10.0,92.0)	(10.0,87.7)	(10,90)	(10,90)

[†] Subject ID # 16530 withdrew because of a late positive purified protein derivative (PPD) result after randomization, but prior to administration of drug. Therefore, baseline information was not provided for this subject.

^{††} Subject ID # 15601’s baseline %BSA was not provided. Therefore, the baseline %BSA calculations for adalimumab were based on n=106 subjects.

Source: M03-656 Clinical Study Report, p. 239, M04-716 Clinical Study Report, p. 140 and reviewer analysis

3.1.4 Primary Efficacy Endpoints

3.1.4.1 ITT Analyses

The co-primary efficacy endpoints of the short-term studies were

- the proportion of subjects with a 75% reduction in PASI at Week 16 from baseline (PASI75 response rate); and
- the proportion of subjects achieving a PGA score of “Clear” or “Minimal” at Week 16.

Table 6 presents the primary efficacy results in the intent-to-treat (ITT) population. At Week 16, the primary time point, 71.1% and 79.6% of the adalimumab arm subjects had a 75% reduction in their PASI score compared to baseline in Studies M03-656 and M04-716, respectively. Whereas, the proportions of subjects in the placebo arms who had a PASI75 response rate were 6.5% and 18.9% in Studies M03-656 and M04-716, respectively. The differences of the success rates based on PASI75 in the two arms were highly statistically significant in both studies with p-values of <0.0001. At Week 16, 62.2% and 72.2% of the subjects in the adalimumab arm reached success status based on the PGA score, while 4.3% and 11.3% of the placebo arm subjects were successes in Studies M03-656 and M04-716, respectively. The differences of the success rates based on the PGA scores in the two arms were also highly statistically significant in both studies with p-values of <0.0001. Therefore, the short-term efficacy of adalimumab was established based on the results from these analyses.

Table 6: Pivotal Studies Primary Efficacy Results - Number (%) of successes on PASI75 and PGA score at Week 16 (ITT)

	Study M03-656a		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
PASI75				
Number of successes (%)	578 (71.1%)	26 (6.5%)	86 (79.6%)	10 (18.9%)
p-value		<0.0001 [†]		<0.0001 [‡]
PGA				
Number of successes (%)	506 (62.2%)	17 (4.3%)	78 (72.2%)	6 (11.3%)
p-value		<0.0001 [†]		<0.0001 [‡]

[†] P-value is calculated using CMH test, stratified by pooled sites.

[‡] P-value is calculated using CMH test, stratified by country

All missing values were imputed as failures

Source: M03-656 Clinical Study Report, p. 252, M04-716 Clinical Study Report, p. 147 and reviewer analysis.

The protocol of Study M03-656 included an additional primary efficacy endpoint that evaluated the proportion of subjects, who responded to adalimumab at the end of Period A and Period B, that experience a loss of adequate response after Week 33 and before Week 52. In this review, as described in Section 3.1.1, ‘loss of adequate response’ was evaluated using three

definitions: (i) subjects who did not maintain a PASI75 response; (ii) subjects who did not maintain a PGA score of 'Clear' or 'Minimal'; and (iii) subjects who did not maintain either a PASI75 response or a PGA score of 'Clear' or 'Minimal' (composite). Table 7 presents the analyses of loss of adequate response based on the three definitions:

Table 7: Number of Subjects with Loss of Efficacy Based on PASI75 and PGA Score (M03-656c)

	Adalimumab n=250	Placebo n=240
PASI75		
Number of loss of efficacy (%)	52 (20.8%)	138 (57.5%)
p-value		<0.0001 [†]
PGA		
Number of loss of efficacy (%)	80 (32.0%)	173 (72.1%)
p-value		<0.0001 [†]
PASI75 & PGA[‡]		
Number of loss of efficacy (%)	82 (32.8%)	178 (74.2%)
p-value		<0.0001 [†]

[†] P-value is calculated using CMH test, stratified by pooled sites.

[‡] Loss of efficacy was defined as subjects who did not maintain a PASI75 response or did not maintain a PGA score of clear or minimal (composite).

All missing values were imputed as failures

Source: Reviewer Analysis.

Subjects considered in the analyses were those who were randomized to adalimumab in Period A and had a PASI75 response at the end of Period A and Period B. Among the subjects who were randomized to adalimumab at the beginning of Period C, approximately 21% and 32% lost adequate response of efficacy after Week 33 and before Week 52, based on PASI75 and PGA scores, respectively. Among the placebo arm subjects, approximately 58% and 72% experienced loss of efficacy, based on PASI75 and PGA scores, respectively. The difference between the two arms were strongly statistically significant with p-values of less than 0.0001, based on both definitions. The proportion of subjects who experience a loss of efficacy was larger when the definition was based on the PGA score than the PASI75 response in both arms. Similar results were obtained when 'loss of adequate response' was defined as the composite of PASI75 and PGA scores, in other words, when defined as (iii) above. The results show that among subjects who responded well to adalimumab previously, the proportion of subject who experience a loss of adequate response is statistically significantly different between subjects who withdrew from

adalimumab and those who continued.

3.1.4.2 Sensitivity Analysis of the Primary Efficacy Endpoint

Per protocol, missing observations were imputed as non-responders in the primary analyses in the previous section. The detailed numbers and proportions of missing observations in each treatment arm and study over time is provided in Appendix A.1. The sponsor conducted a sensitivity analysis to ensure that the efficacy results were not driven by the imputation method, using last observation carried forward (LOCF). Table 8 presents the primary efficacy results using LOCF as the missing data imputation method.

Table 8: Pivotal Studies Primary Efficacy Results-Number (%) of Successes on PASI75 and PGA Scores at Week 16 (LOCF)

	Study M03-656a		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
PASI 75				
Number of successes (%)	594 (73.0%)	27 (6.8%)	86 (79.6%)	10 (18.9%)
p-value		<0.0001 [†]		<0.0001 [‡]
PGA				
Number of successes (%)	521 (64.0%)	18 (4.5%)	78 (72.2%)	6 (11.3%)
p-value		<0.0001 [†]		<0.0001 [‡]

[†] P-value is calculated using CMH test, stratified by pooled sites.

[‡] P-value is calculated using CMH test, stratified by country

All missing values were imputed using last observation carried forward.

Source: Reviewer analysis.

This imputation method is similar to the primary analysis method, imputing missing observations as non-responders. In study M04-716, the results from using LOCF as the imputation method were the same as that when missing data were imputed as non-responders. However, in Study M03-656, the number of successes in the adalimumab arm increased by 14 and 15 subjects in endpoints PASI75 and PGA, respectively, while that of the placebo arm increased by one subject in both endpoints. Nonetheless, the sensitivity analysis ensures that the statistically significant results were not driven by the imputation method. Sensitivity of M03-656c was not done because 43% (10 subjects) and 73% (41 subjects) of the missing observations in the adalimumab and placebo arms, respectively, were due to the subject experiencing loss of adequate response and consequently being removed from the study. Per the request of the clinical review team, primary efficacy analyses was done in subjects who had a PGA score of “Severe” or “Very Severe” at baseline. The results from these analyses are presented in Appendix A.2

3.1.4.3 Per Protocol Analysis

The per protocol (PP) population included all subjects in the ITT population who had no major protocol violations. Among other criteria, subjects had to have at least 75% compliance with study treatment (*i.e.*, at least 75% compliance with SC injections and with oral medication.) Compliance with SC injections [%] was calculated as (number of injections received/number of injections planned during the subject's participation in the study)*100 and compliance with oral medication [%] was calculated as total dose taken [mg]/ total dose instructed to take [mg]*100. A total of 60 (4.4%) subjects were excluded from the per protocol (PP) population in the short term efficacy evaluation studies: 37 (4.0%) subjects from the adalimumab arm and 23 (5.1%) subjects from the placebo arm. Table 9 presents the results of the co-primary endpoint analyses at Week 16 on the per protocol population.

Table 9: Per Protocol Population Primary Efficacy Results - Number (%) of Successes Based on PASI75 and PGA score at Week 16.

	Study M03-656a		Study M04-716	
	Adalimumab n=792	Placebo n=380	Adalimumab n=93	Placebo n=48
PASI75				
Number of successes (%)	570 (72.0%)	24 (6.3%)	75 (80.1%)	9 (18.8%)
p-value		<0.0001 [†]		<0.0001 [‡]
PGA				
Number of successes (%)	497 (62.8%)	16 (4.2%)	68 (73.1%)	5 (10.4%)
p-value		<0.0001 [†]		<0.0001 [‡]

[†] P-value is calculated using CMH test, stratified by pooled sites.

[‡] P-value is calculated using CMH test, stratified by country

All missing values were imputed as failures

Source: Reviewer analysis.

The PP population's proportion of successes based on PASI75 and PGA in the adalimumab arm were very similar to, but slightly higher than that of the ITT population in both studies. The PP population's proportion of successes in the placebo arm were also similar to, but slightly lower than that of the ITT population. In the short term efficacy trials, the difference in the two arms' success rates were strongly statistically significant with p-values less than 0.0001 in both studies and for both endpoints, PASI75 and PGA. The similarity of the ITT and PP population results further supports the superiority of adalimumab over placebo in the short term efficacy trials.

Table 10 presents the results of the additional primary efficacy endpoint - the proportion of subjects, who responded to adalimumab at the end of Period A and Period B, that experience

loss of adequate response after Week 33 and before Week 52 in the PP population. As in the ITT population analyses, 'loss of adequate response' was evaluated using all three definitions. In the long term study, the proportion of subjects who experience loss of adequate response in the PP population is similar, but slightly lower than that of the ITT population in both arms and in all three definitions. Once again, the difference between the two arms regarding this endpoint was statistically significant with a p-value less than 0.0001, and the results from the PP population further supports the superiority of adalimumab over placebo in the long-term maintenance study in subjects who previously responded well to adalimumab.

Table 10: Per Protocol Population-Number of Subjects with Loss of Efficacy Based on PASI75 and PGA Score

	Adalimumab n=236	Placebo n=225
PASI75		
Number of loss of efficacy (%)	42 (17.8%)	127 (56.4%)
p-value		<0.0001 [†]
PGA		
Number of loss of efficacy (%)	69 (29.3%)	162 (72.0%)
p-value		<0.0001 [†]
PASI75 & PGA[‡]		
Number of loss of efficacy (%)	71 (30.1%)	166 (73.8%)
p-value		<0.0001 [†]

[†] P-value is calculated using CMH test, stratified by pooled sites.

[‡] Loss of efficacy was defined as subjects who did not maintain a PASI75 response or did not maintain PGA score of clear or minimal (composite).

All missing values were imputed as failures

Source: Reviewer Analysis.

3.1.5 Secondary Efficacy Endpoints

The protocol listed a total of 61 secondary endpoints that were highly correlated and which the Division had strongly recommended to limit to a small number of clinically relevant endpoints. The first few secondary endpoints that were ranked in the order of importance to the sponsor are the following:

1. Proportion of subjects achieving a PGA of "Clear" or "Minimal" at Week 16
2. Proportion of subjects achieving a clinical response defined as \geq PASI50 at Week 16

3. Proportion of subjects achieving a clinical response defined as \geq PASI90 at Week 16
4. Proportion of subjects achieving a clinical response defined as a PASI100 at Week 16
5. Proportion of subjects achieving a clinical response defined as \geq PASI75 at Week 12
6. Proportion of subjects achieving a PGA of "Clear" or "Minimal" at Week 12
7. Proportion of subjects achieving a clinical response defined as \geq PASI50 at Week 12.

As mentioned in Section 3.1.1, the Division considered the first secondary endpoint as one of the co-primary endpoints. \llcorner \lrcorner

\llcorner \lrcorner and most of the higher ranked endpoints were proportions of successes based on PGA, PASI50, PASI90, PASI100, and PASI75 at various time points. Therefore, this reviewer explored PASI50, PASI90 and PASI100 at Weeks 4, 8, 12, and 16 without conducting statistical tests. PGA and PASI75 will be evaluated at these time points in the following section, titled "Efficacy Results Over Time". b(4)

Table 11 presents the proportions of success based on PASI50, PASI90, and PASI100 responses over time. Also, Figure 1 presents these success rates using a plot, which also includes PASI75 over time.

The plots from the two studies are similar when comparing the same endpoints. The efficacy increases over time in all four endpoints, however it tends to level out after Week 12. In both studies, the treatment effect was greatest when using PASI50 as the endpoint and least when using PASI100. In study M03-656, approximately 45% of the adalimumab arm subjects reached a PASI90 response at Week 16, whereas only roughly 2% of the placebo arm subjects responded. In study M04-716, the response rates for PASI90 were approximately 52% and 11% in adalimumab and placebo arms, respectively. PASI100 may be of the clinician's interest, since this response is reached when subjects are completely cleared. Only approximately 1% and 2% of the placebo subjects reach that response, whereas 20% and 17% of the adalimumab arm subjects reach PASI100 in Studies M03-656 and M04-716, respectively.

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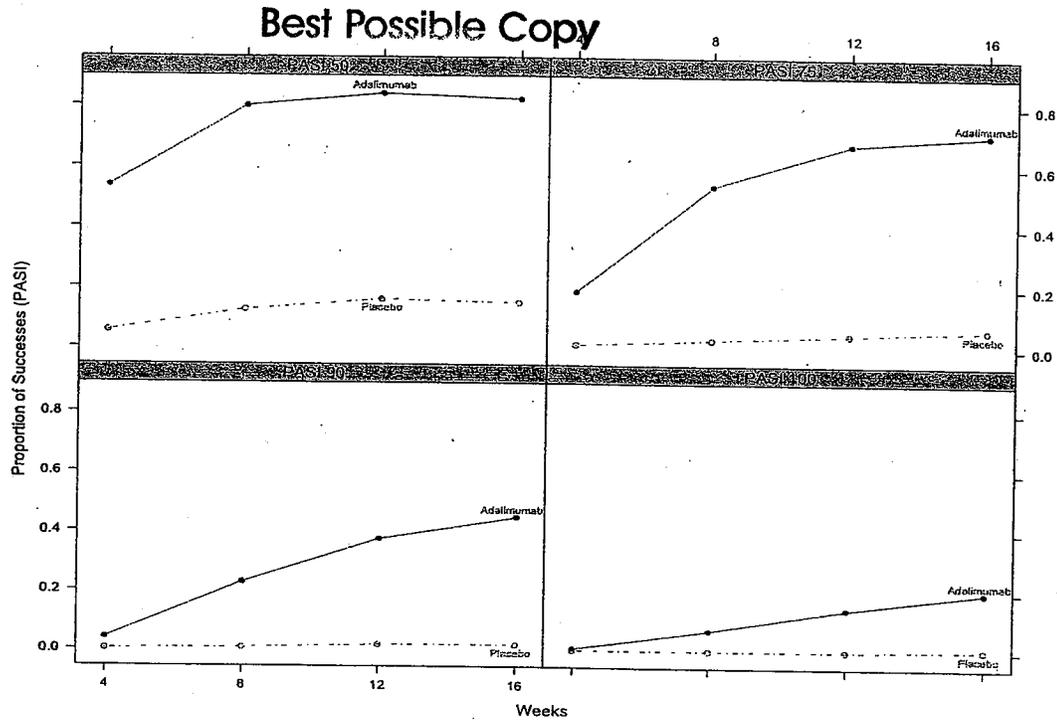
Table 11: Number of Subjects (%) that Achieve Success in PASI 50/90/100 at Weeks of Visits

Endpoint	Week	Study M03-656a		Study M04-716	
		Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
PASI50	4	437 (53.7%)	22 (5.5%)	73 (67.6%)	5 (9.4%)
	8	651 (80.0%)	50 (12.6%)	88 (81.5%)	13 (24.5%)
	12	684 (84.0%)	64 (16.1%)	98 (90.7%)	14 (26.4%)
	16	671 (82.4%)	60 (15.1%)	95 (88.0%)	16 (30.2%)
PASI90	4	33 (4.1%)	1 (0.3%)	7 (6.5%)	0 (0%)
	8	186 (22.9%)	3 (0.8%)	29 (26.9%)	2 (3.8%)
	12	305 (37.5%)	7 (1.8%)	52 (48.1%)	4 (7.5%)
	16	365 (44.8%)	7 (1.8%)	56 (51.9%)	6 (11.3%)
PASI100	4	7 (0.9%)	1 (0.3%)	1 (1%)	0 (0%)
	8	58 (7.1%)	1 (0.3%)	9 (8.3%)	1 (1.9%)
	12	117 (14.4%)	1 (0.3%)	12 (11.1%)	0 (0%)
	16	163 (20.0%)	3 (0.8%)	18 (16.7%)	1 (1.9%)

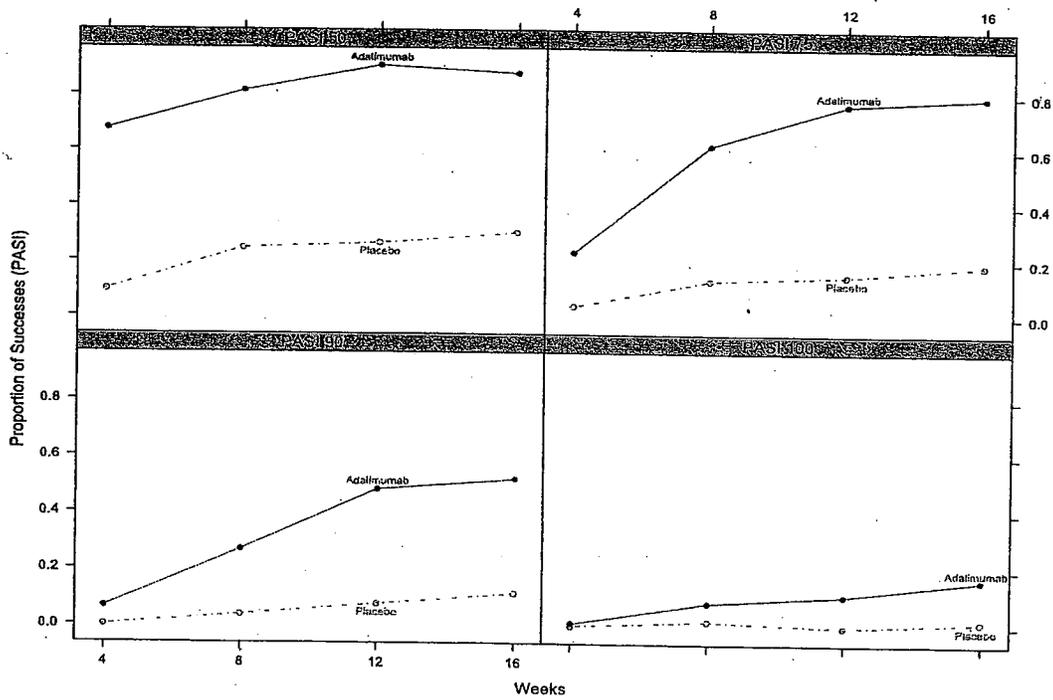
All missing values were imputed as failures

Source: M03-656 Clinical Study Report, p. 272, 275, 278, M04-716 Clinical Study Report, p. 172, 177, 182, and reviewer analysis

Figure 1: PASI 50/75/90/100 over Time



(a) Study M03-656a



(b) Study M04-716

3.1.6 Efficacy Results Over Time

Subjects were followed for a total 16 weeks in the short term efficacy trials (Studies M03-656a and M04-716). The subjects' PASI and PGA scores were evaluated at baseline, Weeks 4, 8, 12, and 16. Table 12 presents the success rates based on both co-primary endpoints over time and Figure 2 plots the proportion of successes based on the PGA score graphically. Note that success rates based on the other co-primary endpoint, PASI75 were presented in Figure 1. The difference in the PGA success rates between to the two arms increased over time.

Table 12: Number of Subjects (%) that Achieve Success in PGA and PASI75 at Weeks of Visits

Endpoint	Week	Study M03-656a		Study M04-716	
		Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
PGA	4	139 (17.1%)	5 (1.3%)	17 (15.7%)	1 (1.9%)
	8	389 (47.8%)	9 (2.3%)	52 (48.1%)	5 (9.4%)
	12	490 (60.2%)	15 (3.8%)	72 (66.7%)	5 (9.4%)
	16	506 (62.2%)	17 (4.3%)	78 (72.2%)	6 (1.3%)
PASI 75	4	154 (18.9%)	5 (1.3%)	25 (23.1%)	2 (3.8%)
	8	440 (54.1%)	12 (3.0%)	67 (62.0%)	7 (13.2%)
	12	551 (67.7%)	19 (4.8%)	83 (76.9%)	8 (15.1%)
	16	578 (71.0%)	26 (6.5%)	86 (79.6%)	10 (19.9%)

All missing values were imputed as failures

Source: M03-656 Clinical Study Report, p. 266, 269, M04-716 Clinical Study Report, p.159, 164 and reviewer analysis

Subjects in the long term study were followed-up for 52 Weeks. PGA and PASI scores were evaluated at Weeks 33, 36, 40, 44, 48, and 52 in Study M03-656c. Figure 3 plots the loss of adequate response over time based on the three definitions used in the primary analyses. Table 13 presents the estimates at each visit.

Note that subjects who had had a PASI75 response at the end of Period B were included in Period C, whereas PGA score was not considered as one of the inclusion criteria. For that reason, approximately 18% and 12% of the subjects from adalimumab and placebo arms, respectively were considered to have experienced a loss of adequate response based on the PGA score, at the beginning of Period C (Week 33). The proportion of subjects with 'loss of adequate response' were similar in the two arms up to Week 36, the second visit of Period C. However, after that the proportion in the placebo arm increased at a much higher rate than that of the adalimumab arm.

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Figure 2: Success Rate in PGA over Time

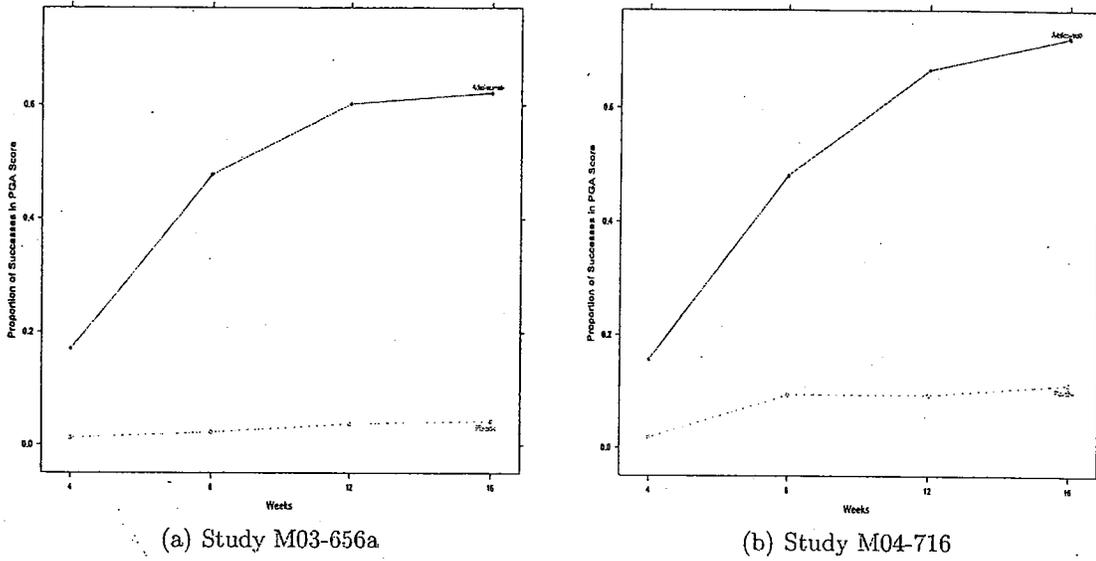
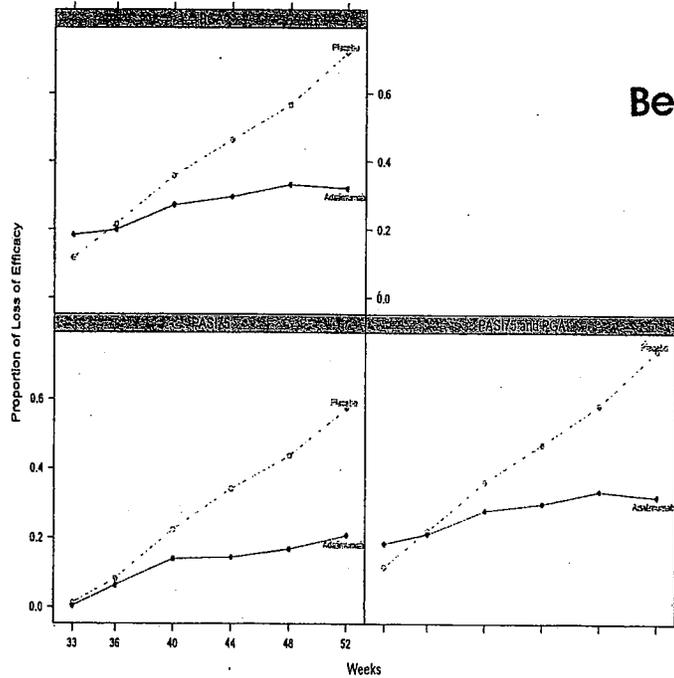


Figure 3: Loss of Adequate Efficacy Over Time



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Table 13: Number of Subjects (%) with Loss of Adequate Response Over Time (M03-656c)

Endpoint	Week	Adalimumab n=250	Placebo n=240
PASI75	33	1 (0%)	3 (1.3%)
	36	16 (6.4%)	20 (8.3%)
	40	35 (14.0%)	54 (22.5%)
	44	36 (14.4%)	82 (34.2%)
	48	42 (16.8%)	105 (43.8%)
	52	52 (20.8%)	138 (57.5%)
PGA	33	46 (18.4%)	28 (11.7%)
	36	50 (20.0%)	52 (21.7%)
	40	68 (27.2%)	86 (35.8%)
	44	74 (29.6%)	111 (46.3%)
	48	83 (33.2%)	136 (56.7%)
	52	80 (32.0%)	173 (72.1%)
PASI75 & PGA [†]	33	46 (18.4%)	28 (11.7%)
	36	53 (21.2%)	53 (22.1%)
	40	70 (28.0%)	87 (36.3%)
	44	75 (30.0%)	113 (47.1%)
	48	84 (33.6%)	140 (58.3%)
	52	82 (32.8%)	178 (74.2%)

[†] Loss of adequate response was defined as subjects who did not maintain a PASI75 response or did not maintain a PGA score of clear or minimal (composite).

All missing values were imputed as failures

Source: Reviewer analysis

3.1.7 Efficacy Results by Center

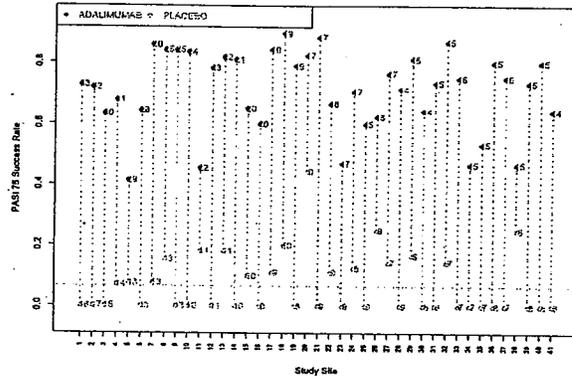
Study M03-656 involved 82 investigators from the United States and Canada and Study M04-716 involved 29 centers in Europe and Canada. The sponsor stated that the method used to pool centers in Study M03-656 was discussed and agreed upon during a telephone contact on December 21, 2004 with the FDA medical reviewer of the protocol at that time. Centers were pooled according to their rank, based on the number of subjects: the largest center was combined with the smallest center, and the second largest center was combined with the second smallest center and so on. There were 41 pooled investigative sites in M03-656. In Study M04-716, centers were pooled by country which resulted in 8 pooled sites. These pooled centers were used in the analyses.

Figure 4 presents the success rates based on the PASI75 and PGA scores and number of subjects enrolled in each pooled site by treatment. Figures 5(a) and 5(c) present the results from Study M03-656a and Figures 5(b) and 5(d) present the results from Study M04-716. The success rates of both arms and the treatment effects appeared to be relatively consistent across the pooled-sites in both endpoints and in both studies. Therefore the results do not seem to be driven by extreme sites. The Breslow-Day test results also support this conclusion for the most part. The p-values from this test are 0.1096 and 0.9852 for PASI75 in Studies M03-656 and M04-716, respectively. The p-values for PGA are 0.0109 and 0.7948 in Studies M03-656 and M04-716, respectively. The p-value of 0.0109 in Study M03-656 (PGA) suggests that the efficacy results based on PGA were not consistent across investigative sites. It should be noted that the Breslow-Day test is not robust to zero cells. The low success rate in the placebo arm and relatively small number of subjects in the pooled-sites caused a large number of sites that had no successes based on the PGA score. Therefore, the Breslow-Day test was sensitive to the zero frequency cells.

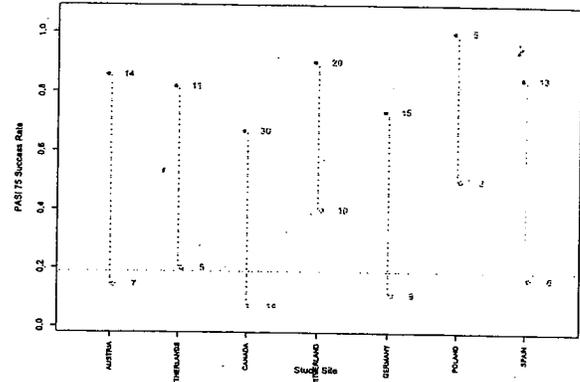
Figure 5 presents the proportion of subjects who experienced a loss of adequate response based on PASI75 and PGA scores, across pooled-sites. The proportions of loss of adequate responses appear to be relatively consistent across the pooled-sites in both definitions, PASI75 and PGA. The Breslow-Day test results also supported this conclusion with p-values of 0.6614 and 0.2944 for definitions based on PASI75 and PGA, respectively. The treatment effect in loss of adequate response does not seem to be driven by extreme sites.

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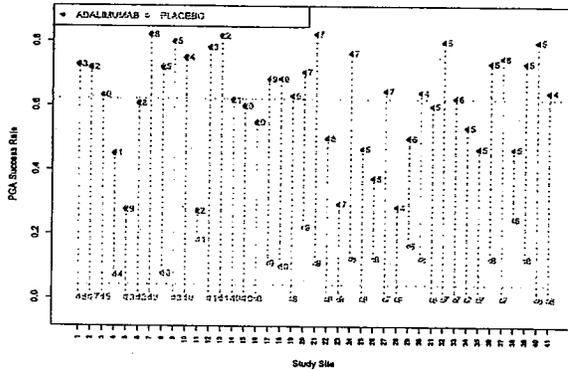
Figure 4: Success Rates Based on PASI75 and PGA Scores by Pooled-Site



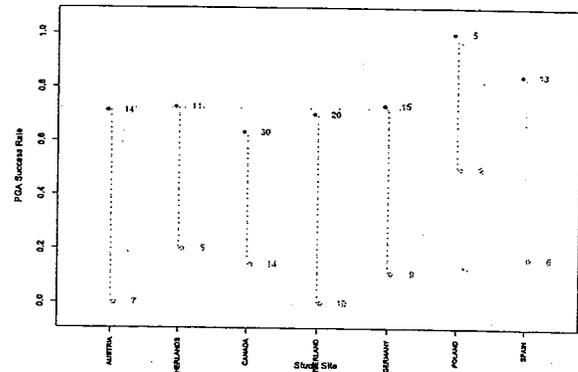
(a) PASI75: Study M03-656a



(b) PASI75: Study M04-716

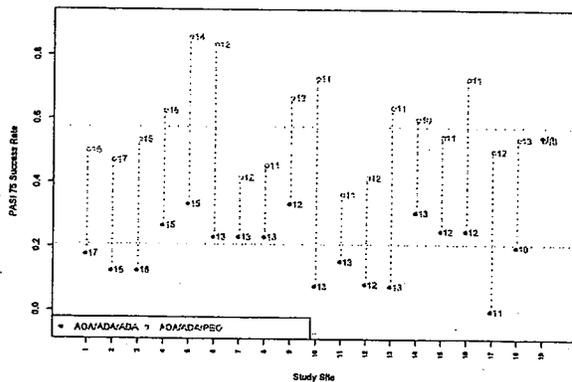


(c) PGA: Study M03-656a

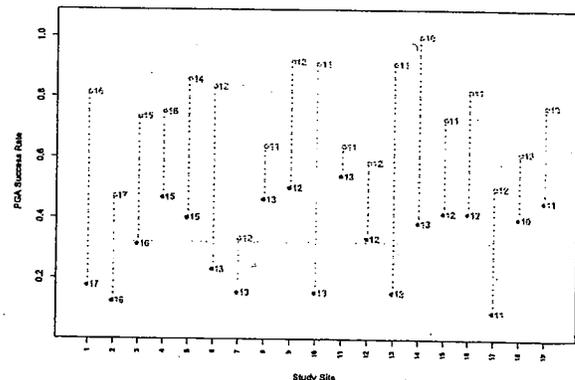


(d) PGA: Study M04-716

Figure 5: Loss of Adequate Response Based on PASI75 and PGA by Pooled-Site- M03-656c



(a) PASI75



(b) PGA

3.2 Evaluation of Safety

The safety evaluation included data from all double-blind and open-label studies (Studies M02-528, M03-7656, M04-716, M02-529 [the extension study for M02-528], M03-596 [the extension for Study M02-538], and M03-658 [an open-label extension study for subjects who participated in Studies M02-529, M02-538, M03-596, M03-656, and M04-716]), on subjects who received at least one dose of adalimumab, through June 2006. The safety population included a total of 1696 subjects. The TNF-inhibitor adverse events (AE) of interest were infections, serious infections, malignancies, opportunistic infections, tuberculosis (TB), demyelinating disorders, lupus-like syndrome, congestive heart failure (CHF), allergic reactions, injection site reactions, hematologic events, and hepatic events.

3.2.1 Extent of Exposure

The mean exposure of adalimumab was approximately one year (362.7 days), where the maximum exposure was 1200 days. Table 14 presents the duration of treatment. Duration of treatment was defined as the date of last adalimumab injection - date of first adalimumab injection + 14 days.

Table 14: Duration of Treatment (All Adalimumab Treatment Set)

Duration Interval (Weeks)	Adalimumab (N=1696)	
	Number	(%) of subjects
> 4	1659	(97.8%)
> 12	1608	(94.8%)
> 24	1417	(83.5%)
> 36	1165	(68.7%)
> 48	810	(47.8%)
> 60	446	(26.3%)
> 72	224	(13.2%)
> 84	163	(9.6%)
> 96	154	(9.1%)
> 108	142	(8.4%)
> 120	117	(6.9%)
> 132	89	(5.2%)
> 144	82	(4.8%)
> 156	60	(3.5%)
> 168	15	(0.9%)

Source: Summary of Clinical Safety, p. 28

3.2.2 Adverse Events

In the placebo-controlled studies, out of a total of 1469 subjects (966 subjects on adalimumab and 503 on placebo), 614 (63.6%) and 297 (59.0%) subjects reported that they have experienced AEs, adalimumab and placebo arms, respectively. According to the investigators' evaluations, the incidence of AEs at least possibly related to study drug (adalimumab 22.9%; and placebo 16.9%) and infections (adalimumab 30.3% and placebo 23.9%) were higher in the adalimumab arm subjects than the placebo arm subjects. There were no subjects who died or experienced AEs in the following category: lymphoma, demyelinating disorder, opportunistic infection (excluding TB), TB, and lupus-like syndrome. The incidence of non-melanoma skin cancer was slightly higher in the adalimumab arm (5 subjects, 0.5%) than the placebo (1 subjects, 0.1%) arm.

In the all adalimumab treatment set, out of a total of 1696 subjects, 1300 (76.7%) subjects reported at least one AE and 509 subjects (30.0%) reported AEs that were determined to be at least possibly related to adalimumab by the investigator. Table 15 presents the AEs, that occurred in more than 1% of the subjects in the all adalimumab treatment set.

Table 15: Overview of Treatment-Emergent AEs (All Adalimumab Treatment Set)

AE Category	Adalimumab (N=1696) Number (%) of subjects
AE	1300 (76.7%)
AE at least possibly related	509 (30.0%)
Severe AE	102 (6.0%)
SAE	88 (5.2%)
AE leading to discontinuation of study drug	86 (5.1%)
Infections	813 (47.9%)
Serious Infections	21 (1.2%)
Injection Site Reactions	159 (9.4%)
Malignancies	22 (1.3%)
Hepatic Events	58 (3.4%)

Source: Summary of Clinical Safety, p. 61

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 16 presents the success rates, based on PASI75 and PGA scores by gender, race, and age groups based on the ITT population. The success rates were relatively consistent across gender, race and age for both PASI75 and PGA. With the exception of one subgroup (Study M04-716,

Asian based on PGA score), the success rates in the adalimumab arm were higher than that of the vehicle arm. It should be noted that the Asian group in M04-716 only had five subjects in total and that the study was not powered to draw statistical conclusions about subgroups.

Table 16: Number (%) of Successes in PASI75 and PGA by Gender Race and Age

		Study M03-656a		Study M04-716	
		Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
Gender					
Male	Total	546	257	70	35
	PASI75	404 (74.0%)	13 (5.1%)	56 (80.0%)	6 (17.1%)
	PGA	346 (63.4%)	6 (2.3%)	49 (70.0%)	31 (11.4%)
Female	Total	268	141	38	18
	PASI75	174 (64.9%)	13 (9.2%)	30 (78.9%)	4 (22.2%)
	PGA	160 (59.7%)	11 (7.8%)	29 (76.3%)	2 (11.1%)
Age (in years)					
- 39	Total	305	137	49	24
	PASI75	225 (73.8%)	8 (5.8%)	38 (77.6%)	7 (29.2%)
	PGA	197 (64.6%)	8 (5.8%)	33 (67.3%)	5 (20.8%)
40 - 64	Total	462	237	53	28
	PASI75	323 (69.9%)	17 (7.2%)	42 (79.2%)	2 (7.1%)
	PGA	285 (61.7%)	8 (3.4%)	39 (73.6%)	0 (0%)
64 -	Total	47	24	6	1
	PASI75	30 (63.8%)	1 (4.2%)	6 (100%)	1 (100%)
	PGA	24 (51.1%)	1 (4.2%)	6 (100%)	1 (100%)
Race					
American Indian †	Total	3	1	0	1
	PASI75	1 (33.3%)	0 (0%)		1 (100%)
	PGA	1 (33.3%)	0 (0%)		1 (100%)
Asian	Total	21	7	3	2
	PASI75	17 (81.0%)	2 (28.6%)	2 (66.7%)	1 (50.0%)
	PGA	12 (57.4%)	2 (28.6%)	1 (33.3%)	2 (100%)
Black	Total	28	20	2	1
	PASI75	15 (53.6%)	1 (5.0%)	2 (100%)	0 (0%)
	PGA	14 (50.0%)	2 (10.0%)	2 (100%)	0 (0%)
White	Total	742	359	103	49
	PASI75	533 (71.8%)	22 (6.1%)	82 (79.6%)	8 (16.3%)
	PGA	471 (63.5%)	11 (3.1%)	75 (72.8%)	3 (6.1%)
Other	Total	20	11	0	0
	PASI75	12 (30.0%)	1 (9.1%)		
	PGA	8 (40.0%)	2 (18.2%)		

† Also includes Alaska Natives.

Source: Reviewer analysis

Table 17 presents loss of adequate response by gender, race and age. Loss of adequate efficacy was defined as subjects who did not maintain either a PASI75 response or a PGA score of clear or minimal (composite). In all subgroups, the placebo arm subjects had a higher proportion of losing adequate response of efficacy.

Table 17: Loss of Adequate Efficacy (Number (%) of Successes)
by Gender Race and Age

		Study M03-656c		
		adalimumab n=250	Placebo n=240	
Gender	Male	Total	176	179
		Loss of response (%)	47 (26.7%)	133 (74.3%)
	Female	Total	74	61
		Loss of response (%)	35 (47.3%)	45 (73.8%)
Age (in years)	<40	Total	93	95
		Loss of response (%)	34 (36.6%)	72 (75.8%)
	40 ≤ ≤64	Total	142	134
		Loss of response (%)	44 (31.0%)	100 (74.6%)
	≥64	Total	15	11
		Loss of response (%)	4 (26.7%)	6 (54.5%)
Race	American Indian/ Alaska Native	Total	0	2
		Loss of response (%)	0 (0%)	2 (100%)
	Asian	Total	7	8
		Loss of response (%)	1 (14.3%)	5 (62.5%)
	Black	Total	6	5
		Loss of response (%)	2 (33.3%)	2 (40.0%)
	White	Total	234	222
		Loss of response (%)	79 (33.8%)	167 (75.2%)
	Other	Total	3	3
		Loss of response (%)	0 (0%)	2 (66.7%)

Loss of adequate efficacy was defined as subjects who did not maintain either a PASI75 response or a PGA score of clear or minimal (composite).

Source: Reviewer analysis

4.2 Other Special/Subgroup Populations

The proportion of success rates based on PASI75 and PGA scores were explored by baseline disease severity (baseline PGA score). Table 18 and Table 19 present the success rate across baseline PGA scores. The success rates based on PASI75 in the adalimumab arm is very balanced across baseline PGA scores in both studies. The treatment effect is consistent across baseline disease severity in both studies based on both endpoints.

Table 18: Number (%) of Successes based on PASI75 by Baseline Disease Severity

		Study M03-656a		Study M04-716		
		Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53	
Baseline PGA	4	Total	417	220	52	20
		Success (%)	296 (71.0%)	17 (7.7%)	41 (78.8%)	4 (20.0%)
	5	Total	346	155	46	31
		Success (%)	244 (70.5%)	8 (5.2%)	37 (80.4%)	5 (16.1%)
	6	Total	51	23	10	2
		Success (%)	38 (74.5%)	1 (4.3%)	8 (80.0%)	1 (50.0%)

Source: Reviewer analysis

Table 19: Number (%) of Successes Based on PGA by Baseline Disease Severity

		Study M03-656a		Study M04-716		
		Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53	
Baseline PGA	4	Total	417	220	52	20
		Success (%)	268 (64.3%)	14 (6.4%)	40 (76.9%)	3 (15.0%)
	5	Total	346	155	46	31
		Success (%)	205 (59.2%)	3 (1.9%)	33 (71.7%)	3 (9.7%)
	6	Total	51	23	10	2
		Success (%)	33 (64.7%)	0 (0%)	5 (50.0%)	0 (0%)

Source: Reviewer analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor conducted two studies (Studies M03-656 and M04-716) under the protocols that were evaluated by the Agency in terms of study design and endpoints. Short term efficacy was evaluated at Week 16 using PASI75 and PGA scores. The differences in the success rates based on PASI75 were statistically significant in both studies (p-values<0.0001). This was also true for the success rates based on PGA. Long term efficacy was assessed by the proportion of subjects who experienced a loss of adequate response before Week 52. The difference in the two arms' proportions was statistically significant with a p-value of less than 0.0001. Within each study, the efficacy results were relatively consistent across subgroups and investigative sites. The

protocol ranked 61 secondary endpoints in the order of importance according to the sponsor, where the first one (success rate based on PGA score at Week 16) was considered as one of the co-primary endpoints by the Division. After discussing with the clinical review team, the remaining 60 secondary endpoints

b(4)

5.2 Conclusions and Recommendations

The short term efficacy of adalimumab has been demonstrated to be statistically superior to placebo in two studies (Studies M03-656, Period A and M04-716) in the treatment of moderate to severe psoriasis. The long term efficacy of adalimumab has also been demonstrated to be statistically superior to placebo in one year study (Study M03-656, Period C) for the same indication. Efficacy was evaluated on (i) PASI75 response rate at Week 16 and (ii) success rate based on the Physician Global Assessment (PGA) at Week 16. Long term efficacy was assessed by comparing the proportion of subjects who experience loss of adequate response before Week 52. Table 20 presents the summary of the co-primary endpoints for the short term and long term efficacy. The adverse events rate was higher in adalimumab arm subjects than in the placebo arm subjects. The most common adverse event was infections followed by injection site reactions.

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Table 20: Efficacy Results Summary - Number (%) of Success and Number (%) of Losses of Adequate Responses Based on PASI75 and PGA Scores

	Study M03-656a		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
PASI75				
Number of successes (%)	578 (71.1%)	26 (6.5%)	86 (79.6%)	10 (18.9%)
p-value		<0.0001 [†]		<0.0001 [‡]
PGA				
Number of successes (%)	506 (62.2%)	17 (4.3%)	78 (72.2%)	6 (11.3%)
p-value		<0.0001 [†]		<0.0001 [‡]

	Study M03-656c	
	Adalimumab N=250	Placebo N=240
PASI75		
Number of losses (%)	52 (20.8%)	138 (57.5%)
p-value		<0.0001 [†]
PGA		
Number of losses (%)	80 (32.0%)	173 (72.1%)
p-value		<0.0001 [†]

[†] P-value is calculated using CMH test, stratified by pooled sites.

[‡] P-value is calculated using CMH test, stratified by country

All missing values were imputed as failures

Source: M03-656 Clinical Study Report, p. 252, M04-716 Clinical Study Report, p. 147 and reviewer analysis.

APPENDIX

A.1 Proportions of Missing Observations

Table 21 presents the proportion of missing observations in each treatment over time.

Table 21: Number (%) of Missing Subjects at Each Visit

Week	Study M03-656a		Study M04-716	
	Adalimumab n=814	Placebo n=398	Adalimumab n=108	Placebo n=53
4	17 (2.1%)	13 (3.3%)	2 (1.9%)	3 (5.7%)
8	13 (1.6%)	29 (7.3%)	2 (1.9%)	3 (5.7%)
12	23 (2.8%)	36 (9.0%)	3 (2.8%)	4 (7.5%)
16	38 (4.7%)	45 (11.3%)	4 (3.7%)	5 (9.4%)

Source: Reviewer analysis.

The numbers of missing observations at Week 16 were 83 (6.8%) and 9 (5.6%) in Studies M03-656 and M04-716, respectively. The proportion of missing observations in M03-656 was 4.7% in the adalimumab arm at Week 16, whereas that of the placebo arm was 11.3% in the placebo arm. The difference in the proportion of missingness in the two arms were similar in the earlier weeks, however the discrepancy became larger over time.

A.2 Efficacy Results in Subjects with Severe/Very Severe Baseline Assessments

Per the request of the clinical review team, primary efficacy analyses was conducted in subjects who had a baseline PGA score of "Severe" or "Very Severe". Table 22 presents the primary efficacy results in this "Severe" or "Very Severe" population. The results are similar to that of the ITT population. In both studies, the two arms' differences in success rates were strongly statistically significant for both co-primary endpoints.

Table 23 presents the results of loss of adequate response based on the PGA score in subjects who had a baseline PGA score of "Severe" or "Very Severe". The results are similar to that from the ITT population. The difference in the two arms' proportion of subjects who had loss of adequate response was strongly statistically significant.

Table 22: Severe/Very Severe Population Primary Efficacy Results - Number (%) of successes on PASI75 and PGA score at Week 16 (ITT)

	Study M03-656a		Study M04-716	
	Adalimumab n=397	Placebo n=178	Adalimumab n=56	Placebo n=33
PASI75				
Number of successes (%)	282 (71.0%)	9 (5.1%)	45 (80.4%)	6 (18.2%)
p-value		<0.0001 [†]		<0.0001 [†]
PGA				
Number of successes (%)	238 (59.9%)	3 (1.7%)	38 (67.9%)	3 (9.1%)
p-value		<0.0001 [†]		<0.0001 [†]

[†] P-value is calculated using Pearson Chi-Square test.

All missing values were imputed as failures.

Source: Reviewer analysis

Table 23: Severe/Very Severe Population - Number of Subjects with Loss of Adequate Response Based on PGA Score (M03-656c)

	Adalimumab n=121	Placebo n=118
PGA		
Number of loss of efficacy (%)	33 (27.3%)	91 (77.1%)
p-value		<0.0001 [†]

[†] P-value is calculated using Pearson Chi-Square test.

All missing values were imputed as failures.

Source: Reviewer Analysis

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December 4, 2007