7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The evaluation of the safety of adalimumab in patients with moderate to severe chronic plaque psoriasis was obtained from 3 placebo controlled trials and 3 continuation studies. The "Placebo Controlled Study Set" consists of 1469 patients, 966 treated with adalimumab and 503 on placebo. Except for 45 patients in the phase 2 dose ranging study who were treated for 12 weeks, all patients in the adalimumab arms were treated with an initial dose of 80 mg sq followed by 40 mg eow subcutaneously for 16 weeks.

The second study set is the "All Adalimumab Study Set" which consists of 1696 subjects. These are subjects that were treated with adalimumab in any of the studies, placebo controlled and continuation, and received adalimumab for up to 3 years. These 1696 subjects consist of 142 from the phase 2 trial and its extension (M02-528/M02-529), 247 subjects from pivotal trial M04-716, 1159 subjects from pivotal trial M030-656, and 148 subjects from safety trial, M02-538. See section 4.1 and 4.2.

7.2.1.2 Demographics

Baseline demographics are described for two study sets: the placebo-controlled study set, which includes the two phase 3 pivotal trials and one phase 2 dose ranging trial, and the all adalimumab study set, which includes subjects that continued in the extension studies from the placebo controlled trials and other open-label long term trials. This encompasses all the subjects in the trials. Table 23 presents the demographic data.

Table 23
Baseline Demographics
ITT Population

	Placebo Controlled Study Set		**All Adalimumab Treatment Set**	
Baseline Characteristics[a]	Placebo N=503 n (%)	ADA N=966 n(%)	ADA N=1696 n(%)	p-value*
Age (years)				0.451[b]
N	503	966	1691	
Mean (SD)	44.6 (13.2)	44.1 (13.1)	44 (12.84)	

Range	45.0 (18.0 – 82.0)	44 (18.0-81.0)	44 (18.0-86.0)	
Age categories, n (%)				
< 40 years	183 (36.4)	368 (38.1)	640 (37.7)	
40-64 years	284 (56.5)	536 (55.5)	954 (56.3)	
65-74 years	33 (6.6)	53 (5.5)	91 (5.4)	
≥ 75 years	3 (0.6)	9 (0.9)	11 (0.6)	
Sex, n (%)				0.416[c]
Male	326 (64.8)	647 (67.0)	1130 (66.6)	
Female	177 (35.2)	319 (33.0)	566 (33.4)	
Race[d], n (%)				0.627[c]
White	456 (90.7)	884 (91.5)	1557 (91.8)	
Black	22 (4.4)	31 (3.2)	56 (3.3)	
Asian/Pacific Islander	11 (2.2)	25 (2.6)	46 (2.7)	
American Indian /Alaskan Native	2 (0.4)	3 (0.3)	5 (0.3)	
Other	12 (0.4)	23 (2.4)	32 (1.9)	
Ethnicity, n (%)				
Hispanic	41 (8.2)	70 (7.2)	114 (6.7)	
Not Hispanic	462 (91.8)	896 (92.8)	1582 (93.3)	
Weight (kg)				0.178[b]
N	503	966	1691	
Mean (SD)	92.8 (23.0)	91.1 (22.7)	91.6 (22.53)	
Median (range)	91.0 (44.5-176.0)	88.0 (40.4-203.6)	89 (40.4-203.6)	
Height (cm)				0.991[b]
N	502	964	1693	
Mean (SD)	172.5 (10.4)	172.6 (9.9)	172.6 (9.98)	
Median (range)	172.7 (142.0-197.0)	173.0 (141.0-203.0)	173.0 (141.0-203.0)	
Nicotine[e], n (%)				0.419[c]
User	180 (35.8)	325 (33.7)	583 (34.4)	
Ex-user	151 (30.0)	309 (32.0)	530 (31.3)	
Non-user	172 (34.2)	331 (34.3)	582 (34.3)	
Unknown	0	1	1	
Alcohol[f]				0.368[c]
Drinker	344 (68.4)	683 (70.8)	1175 (69.4)	
Ex-drinker	22 (4.4)	58 (6.0)	91 (5.4)	
Non-drinker	137 (27.2)	224 (23.2)	428 (25.3)	
Unknown	0	1	2	

ADA = adalimumab
Note: Percentages calculated on non-missing values
a. Baseline was defined as the last value before the first study drug injection
c. fisher's Exact test
e. Ex-smokers and non-smokers were combined for analysis of nicotine
f. Ex-drinkers and non-drinkers were combined for analysis of alcohol
* p-value for the placebo controlled study set
b. One-way ANOVA
d. Non-white races were combined for analysis of race
Cross Reference: Table 2.1_1.3.1, Table 2.1_1.3.2, and Table 2.1_1.3.3 & Table 2.1_2.3.1, Table 2.1_2.3.2, and Table 2.1_2.3.3
Source: BLA 125057, ISS tables 9 and 11, pages 37 and 45, respectively

7.2.1.3 Extent of exposure (dose/duration)

The placebo controlled study set comprises subjects from the two phase 3 pivotal trials, M03-656, Period A and M04-716 and the phase 2 dose-ranging trial, M02-528. In the former, subjects received either 80 mg sq initially, followed by 40 mg sq eow for 16 weeks or placebo, and in the

latter, subjects received 80 mg sq initially, followed by 40 mg sq either eow or weekly for 12 weeks or placebo. In study M03–656 and M04–716, most adalimumab treated subjects (92.2%) and placebo treated subjects (86.0%) received all ten study drug injections. In Study M02–528, most adalimumab treated subjects (88.9%) and placebo treated subjects (90.4%) received all fourteen study drug injections. Subjects from the 12-week Study M02–528 received a greater number of mean injections as a result of weekly dosing compared with eow dosing in the 16-week Studies M03–656 (Period A) and M04-716. Table 24 describes the extent and duration of exposure for the placebo controlled study set.

Table 24
Duration and Extent of Treatment
Placebo Controlled Study Set

Treatment	Patient–Years of Exposure	N	Mean Days ± SD	Median (Range)
PBO	147.7	503	107.3 ± 24.01	119.0 (14.0 – 133.0)
ADA	294.0	966	111.2 ± 13.78	112.0 (14.0 – 129.0)
Total	441.7	1469	109.8 ± 18.03	114.0 (14.0 – 133.0)

ADA = adalimumab; PBO = placebo
Source: BLA 125057, ISS, table 2, page 24

For the all adalimumab treatment set (1696 subjects), the median and mean durations of treatment were 542.9 days and 553.0 days, respectively, representing an average treatment duration of approximately one and one-half years. The maximal treatment duration was more than three years. Almost three-fourths of subjects [1270 subjects (74.9%)] had greater than 48 weeks of exposure. More than half of the subjects [980 (57.8%)] had greater than 72 weeks of exposure and a little more than a quarter of subjects [453 (26.7%)] had greater than 96 weeks of exposure. Table 25 describes the duration and extent of exposure for the all adalimumab treatment set.

Table 25
Duration and Extent of Treatment
All Adalimumab Treatment Set

Treatment	PY	N	Mean Days (SD)	Median (Range)
ADA	2520.7	1696	542.9 (299.37)	553.0 (14.0-1505.0)

Duration Interval (Weeks)*	ADA N = 1696 n (%)
> 4	1680 (99.1)
> 12	1643 (96.6)
> 24	1542 (90.9)
> 36	1377 (81.2)
> 48	1270 (74.9)
> 60	1146 (67.6)
> 72	980 (57.8)
> 84	735 (43.3)
> 96	453 (26.7)
> 108	227 (13.4)
> 120	152 (9.0)
> 132	143 (8.4)
> 144	131 (7.7)
> 156	112 (6.6)
> 168	86 (5.1)
> 180	77 (4.5)
> 192	64 (3.8)
> 204	31 (1.8)

*Methodology for calculating treatment exposure: the first day of the exposure period is the date of the first adalimumab injection. The last day of the exposure period is the date of the last adalimumab injection + 14 days.
Source: BLA 125057, 120 day safety update, table 2.1-2.12, page 25

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary clinical data sources used to evaluate safety. All safety evaluations came from the clinical trials submitted to support an approval of the BLA.

7.2.2.2 Postmarketing experience

According to a consult prepared by DDRE on May 11, 2006, as of April 1, 2006, the AERS database contained 14,438 adverse event reports for adalimumab (both serious and non-serious). Of these, 628 reports were associated with fatal outcomes. Adalimumab was also used for the treatment of psoriasis and/psoriatic arthritis in 255 of the adverse event reports. The fatalities in

the psoriasis/psoriatic arthritis population were 3, two patients died from sepsis and one patient died from a myocardial infarction. They were all male, ages 32, 46, and 65 years. Causality, according to the consult, was difficult to establish given pre-existing medical history and/or co-morbidities.

Since that postmarketing consult, a more recent look at the AERS data base as of November 2007, the AERS database contains 17,450 adverse event reports for adalimumab, of which 1024 had an outcome of death. Those adverse events associated with psoriasis/psoriatic arthritis are 487. The total number of fatalities is 14 for the psoriatic arthritis population. This includes the 3 fatalities described above. Seven of the deaths are US, six are foreign, and one is definitely not related to adalimumab, as the patient died from a subdural hematoma as the result of a fall. Six of the 14 deaths were due to infection, 3 to a cardiovascular event (MI x 2 and CVA), and one to promyelocytic leukemia. One patient died of peritonitis as the result of a perforated diverticulum and in another case the cause of death is unknown. Finally, in the last death reported, the subject complained of epigastric pain, chest pain, and lethargy after 1 dose of adalimumab and was found dead 1 month later.

For the infection-related deaths, HUMIRA may have been a contributing factor. The label has a black-box warning that states that infection can result in fatality. For the other non-infection-related deaths, causality cannot be definitively established, as there did not appear to be a particular trend that could be discerned and some cases did not provide enough information and/or had co-morbidities. A phase 4 long-term trial will try to elucidate some of these issues. Finally, a review of all the adverse events reported does not raise any new safety issues with HUMIRA.

7.2.2.3 Literature

No literature sources were reviewed to support this application.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience in the development program for patients with psoriasis is adequate for the indication sought by the applicant, with a caveat. A total of 1696 subjects with moderate to severe psoriasis were exposed to adalimumab in the phase 2 and 3 portions of the program. The median and mean durations of treatment were 329.5 days and 362.7 days, respectively, representing an average treatment duration of approximately 1 year. The maximal treatment duration was more than three years. This was an adequate time to assess the safety of the drug for use in psoriasis patients up to the time studied. There were enough patients in the trials to do subset analysis on various demographic groups.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.6 Assessment of Quality and Completeness of Data

The data provided for the safety review was complete and the quality was good. Study M03-658, a long-term safety study in which subjects are treated for an additional 2 years, is still ongoing for some subjects.

7.2.7 Additional Submissions, Including Safety Update

The 120-day safety update was submitted on July 20, 2007 and includes data for the All Adalimumab Treatment Set (cut-off date of June 25, 2007), which is approximately another year's worth of safety data, as in the original submission, the safety data in the long-term study had a cut-off date of June 29, 2006. This includes data that were not fully cleaned and reconciled. The Agency in the pre-BLA meeting preferred this approach over fully cleaned data from an earlier cut-off date.

As compared with earlier data, discontinuations increased by 8.7% over this subsequent year. Thirty percent (30%) of subjects discontinued from the All Adalimumab Treatment Set. The primary reason for discontinuations was "unsatisfactory therapeutic effect" which had an incidence of 10.8%, up 3.3% from the original data. The other three highest reasons for discontinuations were withdrew consent, 8.8%, adverse event, 6.4%, and lost to follow-up, 4.4% (table 2.1_2.2, page 24, safety update).

Table 26 describes an overview of adverse events in totality from the 120 day safety update. The data from the original submission is included here for ease of review (see also section 7.1.6).

Table 26
Treatment Emergent AEs and Treatment Emergent AEs
Per 100 Patient-Years of Exposure
AEs of Interest – All Adalimumab Study Set

Adverse Event Preferred Term	**ADA N=1696 n(%)**	**ADA N=1696 PY = 1684.2 E (E/100 PY)**	**ADA N=1696 120 day safety update**	**ADA* N=1696 (PY=2520.7) E(E/100 PY)**
Any Adverse Event	1300 (76.7)	5351 (317.7)	1457 (85.9)	7306 (289.8)
AE at least possibly related	509 (30.0)	1200 (71.3)	593 (35.0)	1434 (56.9)
Severe AE	102 (6.0)	138 (8.2)	168 (9.9)	232 (9.2)
SAE	88 (5.2)	111 (6.6)	139 (8.2)	184 (7.3)
AE Leading to Discontinuation of Study Drug	86 (5.1)	115 (6.8)	118 (7.0)	157 (6.2)
Fatal AE	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.1)
Infections	813 (47.9)	1541 (91.5)	1000 (59.0)	2169 (86.0)
Serious Infections	21 (1.2)	24 (1.4)	34 (2.0)	38 (1.5)
Malignancies	22 (1.3)	26 (1.5)	36 (2.1)	40 (1.6)
Lymphoma	0	0	0	0
Non-melanoma skin cancers	12 (0.7)	15 (0.9)	18 (1.1)	21 (0.8)
Other malignancies (excluding non-melanoma skin cancers and lymphoma	11 (0.6)	11 (0.7)	19 (1.1)	19 (0.8)

Demyelinating Disorders	0	0	1 (0.1)	1 (0.0)
Congestive Heart Failure	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.0)
Allergic Reactions	3 (0.2)	3 (0.2)	6 (0.4)	6 (0.2)
Injection Site Reaction	159 (9.4)	306 (18.2)	170 (10.0)	330 (13.1)
Opportunistic Infection (excluding TB)	4 (0.2)	4 (0.2)	7 (0.4)	7 (0.3)
TB@	3 (0.2)	3 (0.2)	1 (0.06)	1 (0.04)
Lupus-like Syndrome	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.0)
Hematologic Event	3 (0.2)	3 (0.2)	3 (0.2)	3 (0.1)
Hepatic Events	58 (3.4)	83 (4.9)	75 (4.4)	114 (4.5)

*120 day safety update
@The sponsor only reported 1 case of TB in the 120 day safety update, but there were 3 cases in the original submission in the extension trials.
Source: BLA 125057, ISS, adapted from table 16, page 61
120 day safety update, table 2.2_2.1.1.1.1, page 26

Reviewer's Comment: *Overall, the 120-day safety update does not reveal any new safety concerns. The most common adverse events remained the most common adverse events, e.g infections. Interestingly, the rate of infections, in terms of exposure, actually decreased. The difference in rate of serious infections was 0.1% in terms of events/100 PY. Other adverse events that increased by a rate of 0.1% in terms of events/100 PY were malignancies, excluding non-melanoma skin cancer, and opportunistic infections, excluding TB; but the overall rate (1.6E/100 PY) is not higher than the rate in the adalimumab arm of the placebo controlled study set (2.4E/110 PY). Interestingly, the rate for non-melanoma skin cancer decreased by 0.1%, and although the event rate was higher, by 0.1%, than placebo in the placebo controlled trials, it is lower than the rate in the adalimumab arm of the placebo controlled trials (1.7E/100 PY). Thus, given adjustments for exposure rates, the rate of nonmelanoma skin cancer does not appear to increase for a given subject over time. A phase 4 long-term trial may help elucidate this issue.*

Laboratory Investigations

Long term evaluation of laboratories in the 120 day safety update did not reveal any new concerns. Between 1% and 3% of subjects had elevations in ALT, AST, CPK, serum triglycerides, serum cholesterol, and blood glucose.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Infections

This was the highest occurring adverse event in the trials, occurring in 30.3% of subjects on adalimumab. It was also statistically significantly higher than in placebo subjects. In terms of exposure, it is 1.3 infections per patient year. HUMIRA is labeled for this at 1 per patient year (see sections 7.1.5.3, 7.1.5.4) .

Upper Respiratory Tract Infection
This AE occurred in 6.4% of subjects on adalimumab and was statistically significantly higher than in placebo subjects. HUMIRA is labeled for this at a rate of 17% (see sections 7.1.5.3, 7.1.5.4).

Serious Infections
The AEs that occurred in more than one subject were cellulitis (3/966, 0.3%) and pneumonia (2/966, 0.2%) in the placebo controlled study set. HUMIRA is labeled for both of these serious infections (see section 7.1.2 & 7.1.6). No patient discontinued because of these events (see section 7.1.3.2)

Tuberculosis
No subject contracted TB during the placebo controlled portions of the trials. There were 3 cases during the open-label trials. In terms of exposure, the rate is 0.17 per 100 patient years. HUMIRA is labeled for tuberculosis and the overall rate of exposure for subjects on HUMIRA is approximately 0.26 per 100-patient years.

Malignancies (other than non-melanoma skin cancer and lymphoma)
The rate in the controlled portions of the psoriasis trials was 0.68/100 PY for adalimumab subjects vs. 0.67/100 PY for placebo. The rate across all indications for HUMIRA as labeled is 0.6/100 PY for adalimumab subjects vs. 0.4/100 PY for controls. Although no difference was shown in this trial, the data across all indications is more appropriate for labeling.

Non-Melanoma Skin Cancer
The rate in the controlled portions of the psoriasis trials was 1.7/100 PY for adalimumab subjects vs. 0.7/100 PY for placebo subjects. The rate across all indications for HUMIRA as labeled is 0.9/100 PY for adalimumab subjects vs. 0.3/100 PY for controls. The difference between adalimumab subjects overall is 3 times that of control vs. only approximately 1 times control for the psoriasis population (see sections 7.1.2, 7.1.3.3).

Injection Site Reactions
The proportion of subjects on adalimumab with injection site reactions (irritation, pain, erythema) in the placebo controlled study set was 10.6%. In the placebo controlled trials across all indications, it was 20% (see section7.1.5.3).

Arthralgia
The incidence of arthralgia in the adalimumab treated subjects in the placebo controlled study set was 2.9% vs. 1.4 in the placebo controls. This adverse event is not labeled for HUMIRA. As such, it should be added to the psoriasis section of the label.

Discontinuations due to Adverse Events
In the placebo controlled study set in the psoriasis trials, 1.8% of subjects on adalimumab discontinued due to an adverse event. This compares favorably to the 7% of subjects who

discontinued in the rheumatoid arthritis trials (see section 7.1.5.3 and HUMIRA label, Appendix 10.3)

Lipid Alterations
In the placebo-controlled study set, 0.9% of subjects reported hypercholesterolemia as an adverse event compared to 0 in the placebo arm. This is listed as an AE in the RA trials, where hypercholesterolemia was reported as an AE in 6.0% of subjects on adalimumab compared to 4.0% in the placebo arm.

While hypertriglyceridemia was not reported as an AE in the placebo controlled study set, shifts to high that were potentially clinically significant occurred at a higher rate in the adalimumab arm (5.4%) than in the placebo arm (4.0%). In the RA trials, in the label, the rate is 7.0% vs. 5.0%, for adalimumab subjects vs. placebo subjects, respectively. No subjects discontinued because of lipid alterations.

Alterations in Liver Enzymes
In the controlled portions of the trials, shifts to high of hepatic enzymes occurred in a greater proportion of subjects on adalimumab than placebo. Shift to high for ALT was 7.8 in the adalimumab arm vs. 6.3 in the placebo arm. Shift to high for AST was 4.9 in the adalimumab arm vs. 3.9 for the placebo arms. In terms of hepatic events per 100PY of exposure, adalimumab subjects had a slightly higher incidence, 10.2 vs. 9.5. The shifts to high should be noted in the label, as it is not labeled for the RA (prototype) population in the label but is labeled separately for the psoriatic arthritis and ankylosing spondylitits subjects.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The pooled data for safety in the psoriasis development program is representative of the data for the individual study data of the pivotal trials. The most common AEs in the adalimumab treatment group for trial M03-656, Period A were URI, nasopharyngitis, and headache. The incidence of URI, hypercholesterolemia, and muscle spasms were statistically significantly higher in the adalimumab treatment group compared with placebo (p=0.010, 0.035, and 0.035, respectively).

The most common adverse events in the adalimumab treatment group for trial M04-716 remained nasopharyngitis, headache, and arthralgia. These events, except for URI, in the pooled data still occurred at a higher rate in the adalimumab treatment group compared to placebo.

7.4.1.2 Combining data

Pooling of the data was done across the two pivotal trials and the phase 2 dose ranging trial simply by combining the total number of patients exposed to the drug product. The number of patients who experienced the adverse event was the numerator and the total number of patients exposed in the intent-to-treat population was the denominator. The intent-to-treat population included all patients who were dispensed study drug. The same was done for the vehicle arm in the pivotal trials.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

There was a small subset of subjects, 188, that had their dose of adalimumab increased from 40 mg eow to 40 mg weekly. These were subjects from study M02-529 or Study M03-658 who failed to achieve at least a 50% improvement in PASI scores relative to baseline. Overall, the incidence of AEs did not increase during dose escalation as compared to before dose escalation. However, in two categories, there was a slight increase, in malignancies and opportunistic infections (excluding TB). In malignancies, the incidence rose from 0.5% before dose escalation to 1.6% during dose escalation, with an exposure adjustment rate of 0.7 before dose escalation to 5.4 events/100 PY during dose escalation. For opportunistic infections (excluding TB), the incidence rose from 0% before dose escalation to 0.5% during dose escalation, with an exposure adjustment rate of 0.0 before dose escalation to 1.8 events/100 PY during dose escalation.

The number of subjects in this subset is small and thus meaningful conclusions cannot be drawn but the suggestion of a higher incidence of malignancy and opportunistic infection portends against using adalimumab any more frequently than every other week.

7.4.2.2 Explorations for time dependency for adverse findings

Data from Period C of pivotal trial M03-656 is illustrative of the overall findings that continued use of adalimumab, at least for 1 year, does not appear to increase one's risk for serious adverse events. Subjects who entered Period C of the trial had received adalimumab 40 mg eow for 33 weeks. Half of these subjects were re-randomized to placebo vs. adalimumab. Table 27 below is an overview of treatment emergent adverse events during the 19 weeks of Period C. There was a slight increase in the incidence of infection for the adalimumab group than for the placebo group, 34.0% and 32.1%, respectively. However, for development of serious infection, malignancy, and TB, the converse was true.

Table 27
Overview of Treatment-Emergent AEs
Period C – Study M03-656

AE Category Subjects with any:	ADA/ADA/PBO N = 240	ADA/ADA/ADA N = 250
	n (%)	
AE	143 (59.6)	146 (58.4)
AE at least possibly drug related	25 (10.4)	23 (9.2)
Severe AE	10 (4.2)	8 (3.2)
SAE	7 (2.9)	5 (2.0)
AE leading to discontinuation of study drug	2 (0.8)	4 (1.6)
Fatal AE	0	0
Infection	77 (32.1)	85 (34.0)
Serious infection	2 (0.8)	1 (0.4)
Malignancy	1 (0.4)	0
Lymphoma	0	0
Non-melanoma skin cancer	1 (0.4)	0
Other malignancy (excluding non-melanoma skin cancers and lymphomas)	0	0
Demyelinating disorder	0	0
Congestive heart failure	0	0
Allergic reaction	0	0
Injection site reactions	4 (1.7)	2 (0.8)
Opportunistic infections (excluding TB)	0	0
TB	1 (0.4)	0
Lupus-like syndrome	0	0
Hematologic event	0	0
Hepatic event	0	1 (0.4)

ADA = adalimumab; PBO = placebo

Cross Reference: Table 14.3__1.3.1.1, 14.3__1.3.2, and 14.3__1.3.9.
Source: BLA 125057, Study report – M03-656, table 116, page 579

However, it may be that beyond one year of treatment, the risk for serious adverse events, such as opportunistic infection excluding TB, malignancies excluding non-melanoma skin cancer, and serious infection may rise (see section 7.2.9 Safety Update).

7.4.2.3 Explorations for drug-demographic interactions

See section 7.5.1.6

7.4.2.4 Explorations for drug-disease interactions

Subjects with a history of psoriatic arthritis (PsA) had higher incidences than subjects without a history of PsA for AEs overall (83.5% vs. 74.2%) and AEs at least possibly drug–related (36.1% vs. 27.8%). However, only approximately 25% of the subjects in the All Adalimumab Treatment Set (454 of 1696 subjects) had a history of PsA at Baseline.

7.4.2.5 Explorations for drug-drug interactions

There were no notable differences in any of the AE categories in the All Adalimumab Treatment Set based on whether or not subjects had systemic biologic or non–biologic therapy within 12 months of the start of the initial study. Similar results across these two extrinsic factors were observed in the remaining subgroup analyses in the All Adalimumab Treatment Set and in all subgroup analyses in the Placebo–Controlled Study Set and EOW Treatment Set.

7.4.3 Causality Determination

Cancer Incidence in Adalimumab-Treated Subjects in Psoriasis Clinical Program Relative to the General US Population

A separate investigation was performed by an independent epidemiology organization, the [redacted], to compare the incidence of malignancies in the adalimumab Psoriasis clinical program with those of age and sexmatched men and women in the general US population. Standardized incidence ratios (SIR) were calculated for the controlled trial period only as well as for the combined controlled and open-label period. b(4)

The incidence of malignancies in the Psoriasis studies with adalimumab was compared to the NCI SEER registry. For this comparison, one melanoma in situ was excluded, because in situ cancers are not captured in the SEER database. The observed number of malignancies excluding non-melanoma skin cancers and cancer in situ, but including lymphoma was 10, which is very similar to the expected incidence of malignancies in an age-matched population of the SEER database, which was 10.77, resulting in a point estimate of the SIR of 0.93 (95% CI: 0.44-1.71) and not indicating an increased risk for the adalimumab-treated subjects to develop malignancies excluding non-melanoma skin cancer.

Age specific incidence rates for non-melanoma skin cancers are not captured in the SEER database but were taken from an NCI survey of 8 locations in the US in the years 1977 and 1978 and were compared to the incidence of non-melanoma skin cancer in the adalimumab Psoriasis program. One case of unclear malignant diagnosis (endophytic epidermoid proliferation) was excluded from that analysis. For the All Adalimumab group, 14 non-melanoma skin cancers occurring during adalimumab treatment were compared to an expected incidence of 6.39, resulting in a point estimate of the SIR of 2.19 (95% C.I.: 1.20 – 3.68). These consisted of 9 basal cell tumors (BCCs) and 5 squamous cell tumors (SCCs). The 5 reported SCCs compared with an expected incidence of 1.10, resulting in a point estimate of the SIR of 4.54 and a lower limit of the 95% C.I. (1.46 – 10.6) above unity. The 9 reported BCCs compared with and

expected incidence of 5.29, resulting in a point estimate of the SIR of 1.70 and a lower limit of the 95% C.I. (0.78 – 3.23) below unity. These data are consistent with the increased risk of nonmelanoma skin cancer seen in the entire adalimumab clinical trial dataset that includes the rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease populations.

Reviewer's Comment: *This analysis was done on the study sets of the original submission. For other malignancies (excluding nonmelanoma skin cancer), the risk does not seem to be increased in this population. The 120 day safety update, however, did reveal another 8 malignancies that occurred over another year of therapy. The 120 day safety update did not address an age-matched control. As stated in section 7.2.9, for use of adalimumab up to 2 years, there doesn't appear to be an increased risk. Phase 4 studies will help to elucidate the risk.*

While the analysis does show an increase in non-melanoma skin cancer (BCC and SCC) for this population, and while the sponsor points out confounding risk factors (previous PUVA treatment, other immunosuppressive therapies) for this population, the finding is not inconsistent with that which has been found across all indications. It is of interest, that given the additional risk factors, the incidence in the psoriasis population on adalimumab, is not higher than for the entire population across all indications, which is 3x the incidence of the placebo controlled population across all indications.

Deaths in the Adalimumab Population in the Psoriasis Trials

It is difficult to unequivocally attribute these deaths solely to adalimumab, as all had confounding factors. In the cases of the treatment-emergent deaths, both the subject who died from a CVA and the subject who committed suicide had co-mobidities that could easily explain their deaths. In the case of the death from gastric cancer, the subject's symptoms began in < 3 months after the start of adalimumab, and he was dead around the 4.7 month mark. Thus, it is unlikely that adalimumab was the initiator of the cancer. However, this subject did receive adalimumab weekly for 107 days, thus adalimumab, being an immunosuppressant, may have contributed to the progression of the disease. The subject who died from the CVA also received adalimumab weekly. It should be noted that adalimumab will not be approved for weekly dosing in psoriatic patients.

In the cases of the non-treatment emergent deaths, those that occurred beyond the 70 day post adalimumab treatment, again there are confounding factors. The subject who died of an MI, had many co-morbidities associated with cardiovascular disease. The subject who died 35 days post cholecystectomy may well have died from surgical complications, as this is well within the perioperative period. The actual cause of death of the 81 y/o subject is not known, but he was found to have metastatic melanoma. It may be that adalimumab contributed to the development of the melanoma, as it is labeled for an increased risk for development of malignancy. In summary, from the available data, adalimumab may have contributed to two of the deaths, the gastric cancer and the melanoma.

A consult from Dr. Carolyn McCloskey in the Division of Drug Risk Evaluation was obtained to compare these deaths that occurred in the trials to the standard mortality rate in the United

States and in psoriasis populations. She calculated the death rate for these 6 deaths out of 1696 subjects exposed to adalimumab to be 358.8 deaths per 100,000 psoriasis patients on adalimumab. She found this to be below all other death rates found in the US total population, US males, US females, US deaths in 45-62 year olds, US deaths in over 65 year olds, the University of Toronto psoriatic arthritis clinic, and the US multi-center psoriasis patients (see Appendix 10.1).

According to a consult prepared by DDRE, there have been 14 deaths reported in the psoriatic arthritis population on HUMIRA. Except for the infection-related deaths, causality cannot be definitively established, as there did not appear to be a particular trend that could be discerned and some cases did not provide enough information and/or had co-morbidities. A phase 4 long-term trial will try to elucidate some of these issues.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen of 80 mg sq initially, followed by 40 mg sq eow starting one week after the initial dose, has been adequately explored in these trials. It has been found to be efficacious by 16 weeks of treatment and efficacy has been studied up to 1 year of treatment. As discussed under section 5, there will be a subset of subjects who will develop autoantibodies to adalimumab and thus, efficacy will decrease. This dosing regimen is similar to ones that have been approved for other indications (see section 2.1).

The adalimumab trials were conducted with patients using the prefilled syringe. The rheumatoid arthritis trials were also conducted with the prefilled syringe. Since the approval of HUMIRA for the indication of RA, a use study was submitted to DAARP using one population for the HUMIRA pen. This supplement was approved with the intent that it would apply across all indications. A use study was not submitted for the indication of Crohn's Disease. Therefore, it is appropriate that psoriasis patient can also choose to use the HUMIRA pen, if preferred over the prefilled syringe.

8.2 Drug-Drug Interactions

No formal drug- drug interactions studies were performed.

8.3 Special Populations

There are not any outstanding issues with any special populations. See section 7.1.5.6.

8.4 Pediatrics

Partial Waiver Request

The sponsor has requested a partial waiver of pediatric studies for ages 0 months up to 4 years old. The reasons sited for this waiver request is that the studies are impossible or highly impractical because the number of patients is so small, geographically dispersed, and the disease may be difficult to accurately diagnose.

The sponsor sites the following justification for this waiver with literature references:

- The incidence of psoriasis increases until the age of 69 for both sexes. The lowest average annual incidence rate per 100,000 is seen in patients less than 20 years of age with a rate of 30.9 in comparison to 130.6 in adults at the age of 70 or above.3 In the Stanford Psoriasis Life History Survey, the percentages for onset of psoriasis decreased with age: 27% of patients reported the onset before the age of 16, 10% before the age of 10, 6.5% before the age of 5 and 2% before the age of 2.
- Psoriasis in childhood and adolescents manifests in many forms, most commonly as plaque and guttate psoriasis. The most common type of psoriasis seen among very young children (less than two years of age) is napkin psoriasis/psoriatic diaper rash. This type can be present in the first days of life. However, there is controversy regarding whether or not psoriatic diaper rash represents true psoriasis as the diagnosis is clinical and may be confused with other dermatologic conditions.
- It is anticipated that some physicians may be hesitant to administer an immune response modifier to patients under the age of 4, since there is some evidence to suggest that the immune system in this youngest age bracket is not yet mature.

Reviewer's Comment: *Agree with the request for partial waiver of pediatric studies in ages 0-4 for the reasons stated by the sponsor.*

Deferral Request of Pediatric Studies

The sponsor requests a deferral of pediatric studies in ages 4-17 years as the adult studies are completed and waiting to conduct pediatric studies, pending approval, would delay the availability to adults.

In this deferral, Abbott references the efficacy supplement, which is currently under review for juvenile rheumatoid arthritis (JRA). Safety and efficacy is being evaluated in study DE038. Abbott had the following to say about the study currently under review,

[redacted] b(4)

[redacted]

b(4)

Reviewer's Comment: *The sponsor was advised in March 07 to not submit a pediatric protocol or initiate any pediatric studies until an action had been taken in the adult population. Please refer to the Pediatric page concerning this BLA for the Division's decision on the waiver/deferral.*

8.5 Postmarketing Risk Management Plan

The post-marketing risk management plan for the psoriasis population involves a phase 4 registry to further ascertain the safety of Humira in the psoriasis population, and particularly to capture safety as it pertains to long-term safety risks. A draft protocol for the registry was submitted with the BLA entitled: [redacted]

b(4)

[redacted] b(4)

9 OVERALL ASSESSMENT

9.1 Conclusions

The two pivotal trials in this BLA demonstrated that HUMIRA® (adalimumab) is efficacious in the treatment of moderate to severe plaque psoriasis. The data demonstrate that by 16 weeks, in trials M03-656a and M04-716, 62.2% and 70.7% of subjects, respectively, have clearing or almost clearing of their disease. This was highly statistically significant, with a p value less than 0.0001. This efficacy was maintained even in a subgroup analysis of subjects with at least severe disease. This is not unexpected, as subjects with at least severe disease at baseline represented 48.7% of subjects in trial M03-656a and 53.1% in trial M04-716. Long term efficacy was also demonstrated, as only 32.0% of subjects re-randomized to adalimumab compared to 72.1% of subjects re-randomized to placebo had a loss of efficacy (adequate response) at 52 weeks ($p<0.0001$). Conversely, 68% vs. 28% of subjects were able to maintain efficacy at 52 weeks. The fact that 28% of subjects re-randomized to placebo, after 33 weeks of treatment with adalimumab, were able to maintain efficacy, has implications for drug free periods until a subject has a relapse. There was no clinically significant difference in the response rate for gender, race, or age. There were no instances of rebound flare or transformation to more life-threatening forms of psoriasis.

The risk/benefit calculus of HUMIRA (adalimumab) is acceptable for patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy where other medical therapies are less medically appropriate. Discontinuations in the psoriasis trials were low, both in the placebo controlled portions, 1.8% and in subjects on adalimumab up to three years, 4.6%. In the long-term portions of the trials, the primary reasons for discontinuations were "unsatisfactory therapeutic effect", "withdrew consent", followed by "adverse events". I suspect that some subjects may have lost efficacy because of the development of AAA. Long term data in terms of exposure rates, in an adequate number of subjects, >300, for at least 96 weeks, suggests that risks of adverse events with adalimumab for a given subject does not increase over time.

HUMIRA is a drug that has significant risks and as such the population of psoriasis subjects should be restricted. HUMIRA is associated with serious infections, which in some cases has led to fatalities. Although serious infections did occur in the psoriasis trials, including infection with

tuberculosis, there were no fatalities due to infection. Other adverse events both serious and non-serious occurred at a lower incidence in this population as compared to all populations for which HUMIRA is indicated. However, in the psoriasis population and other populations, HUMIRA is associated with an increased risk of non-melanoma skin cancer, primarily basal cell carcinoma. Although no lymphomas occurred in the psoriasis trials over 3 years, lymphoma has been observed at a rate 3 times the general population in HUMIRA-treated subjects. This cannot be ignored when assessing the risk for psoriasis patients. It may be that the trials were not long enough or large enough to discern this adverse rare adverse event. Finally, although there were no deaths from infections, which would clearly have been associated with HUMIRA use, there were 6 fatalities in the overall clinical program. None of them can be unequivocally linked to HUMIRA but it is of concern that all had been treated with HUMIRA. Further long-term studies with HUMIRA may help to elucidate the association of HUMIRA with serious disease and fatalities.
The clinical trials found that HUMIRA is very efficacious in the treatment of moderate to severe chronic plaque psoriasis. Although HUMIRA is not a drug to be used in every patient with moderate to severe psoriasis, the benefits for the subset of subjects, as noted in the indication, justifies its risks. It should be labeled that efficacy and safety has been studied for 1 year in controlled clinical trials.

9.2 Recommendation on Regulatory Action

It is recommended from a clinical perspective that HUMIRA (adalimumab) for subcutaneous injection be approved for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy *and* when other systemic therapies are medically less appropriate.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

1) HUMIRA will have a Medication Guide as part of risk management for patients. A consult was sent to DSRCS and DDMAC to comment on the content of the Medication Guide. This section will only highlight the differences in the suggestions made by DSRCS and this reviewer. Agreed with the comments made by DDMAC. The line-by-line review of the medication guide can be found in Appendix 10.3 at the end of the line-by-line review of the label.

b(4)

b(4)

2) As this drug product is an immunosuppressive, a post marketing registry, with at least 5,000 patients, will be conducted over a longer time period. to better ascertain the occurrence of rare but serious adverse events. b(4)

9.3.2 Required Phase 4 Commitments

The sponsor will conduct a phase 4 registry.

b(4)

The final study report for trial M03-658 should be submitted.

9.4 Labeling Review

Label – see line-by-line review in Appendix 10.3

• The indication for which the drug product will be approved has been changed from the sponsor's proposed indication:

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.

to the following indication:

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy *and* when other systemic therapies are medically less appropriate.

[ ] b(4)

- Expansion of the Psoriasis safety section to include increases in LFTs and increased incidence of arthralgias

[

b(4)

]

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 7

10 APPENDICES

10.1

Deaths in HUMIRA Trials Compared to SMR

Deaths: Psoriasis Patients Exposed to Adalimumab With Comparison Populations & Standardized Mortality Ratios	Deaths	Population	Death Rate per 100,000 persons per year	Expected	Carolyn's Calculated or Reported (literature) SMR	References
Adalimumab in Ps, 44 and over, 5M:1F, 2 over 65	6	1,696	353.77			
US Population, 2004, all deaths	2397615	299402472	800.80	13.58	0.44	cdc.gov/nchs
US Population over 20 years old	2344008	212103606	1105.12	18.74	0.32	wonder.cdc.gov
Adalimumab in Ps, male	5	1131	442.09			
US Population, 2004, male deaths	1181668		955.70	10.81	0.46	cdc.gov/nchs
US Population, 2004, male deaths over 20 years old	1149350	102778737	1118.28	12.65	0.40	wonder.cdc.gov
Adalimumb in PS, female	1	565	176.99			
US Population, 2004, female deaths	1215947		679.20	3.84	0.26	cdc.gov/nchs
US Population, 2004, female deaths over 20 years old	1194658	109324869	1092.76	6.17	0.16	wonder.cdc.gov
Adalimumab in Ps, 44-64 years	4	955	418.85			
US Deaths, Age 45-64, 1996			708.00	6.76	0.59	diastercenter.com/cdc
US Deaths, Age 45-64, 2004 over 20 years old	442394	70697728	625.75	5.98	0.67	wonder.cdc.gov
Adalimumab in Ps, over 65 years	2	102	1960.78			
US Deaths, Age over 65, 1996			5071.40	5.17	0.39	diastercenter.com/cdc
US Deaths, Age over 65, 2004 over 20 years old	1755669	36,293,986	4837.36	4.93	0.41	wonder.cdc.gov
Literature						
Adalimumab in Ps, 44 and over, 5M:1F, 2 over 65	6	1,696	353.77			
US **hospitalized** psoriasis pts, 1988-2001 (1.5% died in 3 yrs)	7	471	495.40	8.40	0.71	Pearce 2006
US psoriasis pts, 1999 - 2001, NCHS data, over 3 yrs	29-33/yr		0.64	0.01	552.77	
Literature						
Adalimumab in Ps, 44 and over, 5M:1F, 2 over 65	6	1,696	353.77	10.17	0.59	
U Toronto **PsA Clinic**, 1978-2004, death rate 15,600 over 26 yrs	106	680	599.55		Lit: 1.36 (1.12, 1.64)	Ali 2007

U Toronto PsA, male	51					compared to Ontario pop
U Toronto PsA, female	55					
Literature						
Adalimumab in Ps, 44 and over, 5M:1F, 2 over 65	6	1,696	353.77	22.00	0.27	
US Multi-ctr, **Ps pts**, 1976-1986, over 10 yrs (13224 PY)	179	1380	1297.10		Lit: 0.94 (0.8, 1.1)	Stern 1998 compared to matched pop
US Multi-ctr, Ps pts, 1976-1986, males	127					
US Multi-ctr, Ps pts, 1976-1986, females	52					

10.2 Review of Individual Study Reports

Key Parts of Protocol for Pivotal Study – M03-656

Study Objective

The objective of this study is to confirm the short and long term clinical efficacy and safety of subcutaneously administered adalimumab, as well as determine the time to loss of an adequate response (*i.e.* event) after withdrawal of long-term continuous adalimumab therapy in the treatment of adult subjects with moderate to severe chronic plaque psoriasis. The pharmacokinetics and immunogenicity of adalimumab following subcutaneous injection will also be assessed.

Definition of Event Criteria for Period C

An event, or loss of adequate response, is defined as:

- a PASI score after Week 33 that results in less than a 50% reduction relative to the Week 0 PASI score (<PASI 50 response), or
- a 6-point increase in PASI score relative to the Week 33 PASI score, whichever is the more stringent criteria for the subject (*i.e.* the higher PASI score).

Investigational Plan

Overall Study Design and Plan: Description

This is a short and long-term, multi-center, efficacy and safety study using adalimumab in the treatment of subjects with moderate to severe plaque psoriasis. This study consists of three treatment periods:

- Period A, a 16-week, double-blind, placebo-controlled treatment period where subjects are randomized in a 2:1 ratio to receive adalimumab or placebo for an evaluation of efficacy and safety,
- Period B, a 17-week, open-label treatment period where all subjects who achieved at least a PASI 75 response at Week 16 (the end of Period A), defined as a PASI score improvement of at least 75% relative to Baseline (Week 0), receive open label adalimumab for an evaluation of long term response, and
- Period C, a double-blind, placebo-controlled treatment period where subjects who maintain at least a PASI 75 response at Week 33 (the end of Period B), and were originally randomized to active therapy in Period A, are rerandomized in a 1:1 ratio to receive adalimumab or placebo for an evaluation of time to event (*i.e.* loss of an adequate response). Period C will continue until approximately 140 events have occurred or the last Week 33 responder's projected Week 52 date is reached, whichever comes first.

Subjects who were originally randomized in Period A to receive placebo and are eligible for Period C, will continue to receive adalimumab in a blinded fashion.

To maintain the blind during all periods, an Interactive Voice Response/Interactive Web

Response (IVR/IWR) system will be used to dispense the appropriate medication to subjects.

Table 1 Treatment Regimens

Period A (2:1 randomization, adalimumab: placebo)	(1) 80 mg adalimumab (two 40 mg injections) sc at Baseline (Week 0), followed by 40 mg adalimumab sc eow from Week 1 to Week 15. Subjects with at least a PASI 75 response at Week 16 will receive 2 placebo injections at Week 16 in a blinded fashion; or, (2) two placebo injections sc at Baseline (Week 0), followed by 1 placebo injection sc eow from Week 1 to Week 15. Placebo subjects with at least a PASI 75 response at Week 16 will receive 80 mg adalimumab (two 40 mg injections) at Week 16 in a blinded fashion.
Period B	Open-label 40 mg adalimumab sc eow from Week 17 to Week 31 for all subjects who achieved at least a PASI 75 response at Week 16.
Period C (1:1 randomization, adalimumab: placebo)	For subjects with at least a PASI 75 response at Week 33: Subjects randomized to adalimumab in Period A are re-randomized to 40 mg adalimumab sc eow or matching placebo injections from Week 33 to event or the end of the study, whichever comes first. Subjects originally randomized to placebo in Period A continue to receive 40 mg eow in a blinded fashion from Week 33 to event or the end of the study, whichever comes first.

Study Subject Definitions:

Responder: a subject who achieves at least a PASI 75 response. Week 16 responders and Week 33 responders are eligible for continued treatment in Periods B and C, respectively. Responders who complete Period C will be eligible for treatment with open-label adalimumab in extension study M03-658.

Partial responder: a subject who achieves a PASI response $\geq 50\%$ and $< 75\%$. Week 16 and Week 33 partial responders will be discontinued from the study, but will be eligible for treatment with open-label adalimumab in extension study M03-658. Partial responders who complete Period C will be eligible for treatment with open-label adalimumab in extension study M03-658.

Non-responder: a subject who achieves a PASI response less than 50%. Week 16 nonresponders will be discontinued from this study, but will be eligible for treatment with open-label adalimumab in extension study M03-658. Week 33 non-responders will be discontinued from this study and are not eligible for participation in extension study M03-658.

Rebounder: a subject who achieves a PASI score $\geq 125\%$ of the PASI score at Baseline (Week 0) or develops new generalized pustular or erythrodermic psoriasis within three months after Week 33 will be discontinued from the study and is not eligible for participation in extension study M03-658.

Subjects who prematurely discontinue the study for any reason other than IVR/IWR required during period A or period B, or for any reason other than an event during Period C, are not eligible for the extension study M03-658.

A total of 1200 subjects with a diagnosis of psoriasis for at least 6 months and stable moderate to severe chronic plaque psoriasis for two months, defined as an affected body surface area (BSA) of ≥ 10%, PASI score ≥ 12 and Physician's Global Assessment (PGA) of at least moderate disease at study entry will be enrolled at approximately 90 sites in the United States and Canada. Additional sites may be added if necessary.

Efficacy and safety measurements will be performed throughout the study.

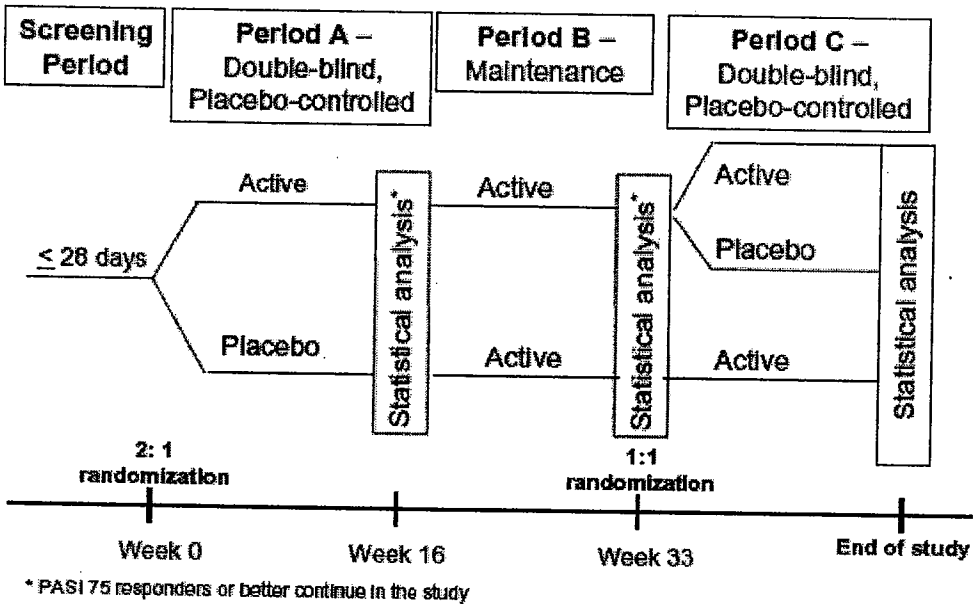
Blood samples for the evaluation of serum adalimumab and anti-adalimumab antibodies (AAAs) will be obtained at Baseline, Week 16, Week 33, and either the Week 52 or Early Termination A, B, or C (before Week 52) visit, whichever comes first.

The maximum duration of enrollment for any subject in this study is projected to be 52 weeks plus the length of the enrollment period. A subject will be enrolled in the study until they either have an event, the last event (approximately 140) occurs, or until the last Week 33 responder's projected Week 52 visit date is reached, whichever comes first.

Complete participation will consist of:
- a maximum 28 day screening period,
- Period A: a 16 week, double-blind treatment period,
- Period B: a 17 week, open label treatment period,
- Period C: when approximately 140 events have occurred or when the last Week 33 responder's projected Week 52 date is reached, whichever comes first,
- a 70-day post last dose telephone call for subjects who discontinue/complete this study and do not enroll into the extension study, M03-658.

A table of the study design is shown in Figure 1.

Figure 1. Study Design



Note: Subjects who were originally randomized in Period A to receive placebo and are eligible for Period C will receive adalimumab in a blinded fashion.

Selection of Study Population

Subjects will be adult men and women who meet all of the inclusion criteria and none of the exclusion criteria specified in the protocol.

Inclusion Criteria

1. Subject is ≥ 18 years of age.
2. Female subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or is of childbearing potential and practicing one of the following methods of birth control throughout the study and for 150 days after study completion:
   - condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD)
   - contraceptives (oral or parenteral) for three months prior to study drug administration)
   - a vasectomized partner
3. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening visit.
4. Subject is judged to be in good general health as determined by the principal investigator based upon the results of medical history, laboratory profile, physical examination, chest X-ray (CXR), and 12-lead ECG performed at Screening.
5. Subjects will be evaluated for latent TB infection with a purified protein derivative

(PPD) test and chest X-ray. Subjects who demonstrate evidence of latent TB infection (either PPD $\geq$ 5 mm of induration, irrespective of Bacille Calmette- Guerin (BCG) vaccination status, and negative CXR findings for active TB, and/or suspicious CXR findings) will be allowed to participate in the study provided that the following are met:

- Prophylactic treatment is initiated prior to administration of study drug; however the course of prophylaxis need not be completed prior to the onset of study drug. Prophylactic treatment will be according to local guidelines.
- Subject has documented prophylactic treatment for TB and so need not repeat this treatment

6. Subjects must be able and willing to provide written informed consent and comply with the requirements of this study protocol.
7. Subject has a clinical diagnosis of psoriasis for at least 6 months as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the investigator.
8. Subject must have stable plaque psoriasis for at least 2 months before Screening and at Baseline visits as determined by subject interview of his/her medical history.
9. Subject has moderate to severe plaque psoriasis defined by $\geq$ 10% BSA involvement at the Baseline visit.
10. Subject must have a PASI score of $\geq$ 12 at the Baseline visit.
11. Subject must have a PGA of at least moderate disease at the Baseline visit.
12. Subjects must be able and willing to self-administer sc injections or have a qualified person available to administer sc injections.

Exclusion Criteria

1. Subject has previous exposure to systemic (*e.g.* thalidomide) or biologic (*e.g.* infliximab or etanercept) anti-TNF therapy, including adalimumab.
2. Subject has other active skin diseases or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of psoriasis.
3. Subject has a history of an allergic reaction or significant sensitivity to constituents of study drug.
4. Subject cannot discontinue topical therapies for the treatment of psoriasis such as corticosteroids, vitamin D analogs, or retinoids at least 2 weeks prior to the Baseline visit and during the study. Subjects are allowed to use:

- Shampoos that contain no corticosteroid,
- bland (without beta or alpha hydroxy acids) emollients,
- low potency (Class VI or Class VII) topical corticosteroids on the palms, soles, face, inframammary area, and groin only..

5. Subject cannot avoid UVB phototherapy for at least 2 weeks prior to the Baseline visit and during the study.
6. Subject cannot avoid PUVA phototherapy for at least 4 weeks prior to the Baseline visit and during the study.
7. Subject cannot avoid excessive sun exposure or the use of tanning booths for at least 2 weeks prior to the Baseline visit and during the study.
8. Subject cannot discontinue systemic therapies for the treatment of psoriasis or systemic therapies known to improve psoriasis during the study:

- Systemic therapies must be discontinued at least 4 weeks prior to the Baseline visit.
- Alefacept must be discontinued at least 12 weeks prior to the Baseline visit.
- Efalizumab must be discontinued at least 6 weeks prior to the Baseline visit.
- Biologic agents not mentioned must be discontinued for at least 12 weeks prior to the Baseline visit.
- Investigational chemical agents must be discontinued at least 30 days or 5 half-lives prior to the Baseline visit (whichever is longer).

9. Subject is taking or requires oral or injectable corticosteroids during the study. Inhaled corticosteroids for stable medical conditions are allowed.
10. Subject has a poorly controlled medical condition, such as uncontrolled diabetes with documented history of recurrent infections, unstable ischemic heart disease, congestive heart failure, recent cerebrovascular accidents and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the study.
11. Subject has history of neurologic symptoms suggestive of central nervous system (CNS) demyelinating disease.
12. Subject has history of cancer or lymphoproliferative disease other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix.
13. Subject has a history of listeriosis, untreated TB, persistent chronic infections, or recent active infections requiring hospitalization or treatment with intravenous (iv) anti-infectives within 30 days or oral anti-infectives within 14 days prior to the Baseline visit.
14. Subject currently uses or plans to use anti-retroviral therapy at any time during the study.
15. Subject is known to have immune deficiency or is immunocompromised.
16. Female subject who is pregnant or breast-feeding or considering becoming pregnant during the study or for 150 days after the last dose of study medication.
17. Subject has a history of clinically significant drug or alcohol abuse in the last year.
18. Subject is considered by the investigator, for any reason, to be an unsuitable candidate for the study.
19. Subject has erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis.

Key Study Procedures

Medical History

A complete medical history (which includes psoriasis related and non-psoriasis related medical and surgical history), including history of tobacco and alcohol use, will be obtained from each subject during the Screening visit. Medical history will be reviewed and updated at the Baseline visit to ensure that the subject remains qualified for the study.

Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse (counted for at least 30 seconds) after 5 minutes in the sitting position, respiratory rate, body weight, and body temperature will be obtained at each visit. Blood pressure and pulse should be performed before blood draws are performed. Height will be measured at the Screening visit only.

Physical Examination
A full physical examination will be performed at Screening, Baseline, Week 16, Week 33, Week 52 and every 20 weeks after Week 52 during Period C, and at the appropriate Early Termination or Final Visit. A symptom-directed physical examination should be performed at other visits if, in the opinion of the investigator, it is warranted by the subject's adverse event status. The percent BSA affected by psoriasis will be recorded at the Screening visit and the Baseline visit.

Chest X-Ray
All subjects will undergo a standard chest X-ray (PA and lateral views) at the Screening visit to rule out the presence of TB or other clinically relevant findings. The chest X-ray report must comment on the presence or absence of calcified granulomas and pleural scarring. A qualified radiologist will interpret, sign, and date the chest X-ray. The principal investigator will indicate the clinical significance of any findings and will sign and date the report. If the CXR demonstrates changes suggestive of previous TB (*e.g.* calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the principal investigator is to contact the Abbott Medical Monitor before randomizing the subject at Week 0.

The chest X-ray will be repeated at the Week 24, Week 52 or the appropriate Early Termination or Final visit, only if in the opinion of the investigator, clinically significant adverse events develop during the study that warrant a repeat.

12-Lead Electrocardiogram
A 12-lead resting ECG will be obtained at the Screening Visit. Any findings that are clinically significant should be discussed with the Abbott Medical Monitor before randomizing the subject at Week 0.

A qualified physician (with recent experience reading ECGs) will interpret, document the clinical significance of any findings, and sign and date the ECGs. The ECG will be repeated at the Week 24, Week 52 or the appropriate Early Termination or Final visit only if, in the opinion of the investigator, clinically significant adverse events develop during the study that warrant a repeat.

Purified Protein Derivative (PPD) Skin Test
All subjects will undergo PPD placement at the Screening visit including those with a prior history of BCG administration. The test is administered with a tuberculin syringe by injecting 0.1 mL of 5-TU PPD intradermally (Mantoux method) into the volar skin of the forearm in an area not affected by psoriasis. If the PPD is positive ($\geq$ 5 mm of induration, irrespective of BCG vaccination status), the principal investigator will contact the Abbott Medical Monitor and fax the PPD positive form containing all appropriate information. The subject will then begin prophylactic TB therapy according to local guidelines if appropriate.

The PPD test should be repeated at anytime during the study if it is suspected that the subject has been exposed to TB. If the subject converts to PPD positive status, the principle investigator should contact the Abbott Medical Monitor.

Laboratory Tests

Blood and urine samples will be obtained for the clinical laboratory tests (hematology, clinical chemistry, urinalysis). Blood draws should be performed after vital sign assessments have been completed during a visit. Blood specimens for hematology and chemistry will be obtained at Screening, Baseline, Week 4, Week 8, Week 16, Week 24, Week 33, Week 52, and every 20 weeks after Week 52 during Period C or the appropriate Early Termination or Final visit. Blood specimens for triglycerides during Period A should be obtained after fasting for 8-12 hours. Blood samples for antinuclear antibody (ANA) and anti-double stranded DNA (dsDNA) antibody test, as well as Rheumatoid Factor (RF), will be obtained at Baseline only.

Urine specimens will be obtained at Screening, Baseline, Week 16, Week 33, Week 52 and every 20 weeks after Week 52 during Period C or at the appropriate Early Termination or Final visit. The central laboratory will perform a macroscopic urinalysis on these specimens. All abnormal macroscopic urinalyses will be followed up with a microscopic analysis at the central laboratory.

Blood for pk parameters and anti-adalimumab antibodies (AAA) will occur at baseline (week 0), week 16, week 33, week 52, or early termination before any of those time points.

Table 2 lists the clinical laboratory tests:

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides (fasting in Period A) Albumin Chloride LDH CPK CRP (Baseline, Wk 16, or Early Termination A) ANA/reflex dsDNA (Baseline only) RF (Baseline only)	Specific gravity Ketones pH Protein Blood Glucose

Pregnancy Test

A serum pregnancy test will be performed at the Screening Visit on all female subjects of childbearing potential. Lactating or pregnant females will not be eligible for participation in this study.

Urine pregnancy tests will be performed at Week 12, Week 24, Week 36, and every 12 weeks after Week 36 during Period C or at the appropriate Early Termination or Final visit.

Key Efficacy Parameters

There are two independent primary efficacy variables in this study: PASI 75 response rate in Period A and the time to event in Period C. The primary efficacy variable in Period A is the proportion of subjects with clinical response, defined as at least a 75% reduction in PASI score (≥PASI 75 response) at Week 16 relative to the Baseline (Week 0) PASI score.

The primary efficacy variable in Period C is the time to event after Week 33 and on or before the Final Visit. An event is defined as a PASI score after Week 33 that results in a less than 50% reduction relative to the Week 0 PASI score (<PASI 50 response) or a 6 point increase in PASI score relative to the Week 33 PASI score, whichever is more stringent (*i.e.* the higher PASI score of the two).

Reviewer's Comment: *As stated under PreSubmission Regulatory Activity, success would be determined by both the PASI and the PGA. Therefore, not only would a subject have to have at least a 75% reduction in PASI score at Week 16 relative to Baseline PASI score but also had to have a PGA score of 0 or 1, clear or almost clear at week 16.*

Psoriasis Area and Severity Index (PASI)
A qualified investigator who has been trained by the sponsor/designee will perform the PASI assessment at all study visits including any unscheduled visit and the Early Termination or Final visit. The site will make every attempt to have the same investigator perform this assessment throughout the study for each subject. All raw data used to determine the PASI score will be documented on a worksheet and transcribed onto the CRF at each visit.

The site will calculate and document the PASI score on the CRF at Screening, Baseline, Week 16, Week 33, each visit during Period C, any unscheduled visit and the Early Termination or Final visit. All PASI scores documented on the CRF beginning at Baseline will be entered into the IVR/IWR systems. The IVR/IWR will calculate the subject's PASI response and will determine if the subject is eligible to continue in the study. To increase the accuracy of the score being entered, sites will need to confirm by two methods that the PASI score has been calculated correctly, either by having two site personnel independently calculate the score or by using a PASI calculator (computer based or on the IWR) and a manual calculation. Documentation for both calculations should be maintained in the source documents with the initials of the persons performing the calculation.

Physician's Global Assessment (PGA)
A PGA of disease severity will be performed by the investigator at all study visits (see Table 3) including any Unscheduled and Early Termination or Final Visit. The site should make every attempt to have the same investigator conduct these assessments throughout the study for each subject. The PGA is static and refers to the subject's disease state at the time of the assessment and is not a comparison with the subject's previous disease state, whether at Screening, Baseline, or any previous visits.

Table 3. Physician's Global Assessment (PGA) Scale

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 elevation with rough or sloped edges) Scaling = coarser (coarse scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (coarse, non tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)
5	Very severe	Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)

Note: Presented by Hon-Sum Ko, M.D., Medical Officer, Division of Dermatologic and Dental Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration. Bethesda (MD): Dermatologic and Ophthalmic Advisory Committee 49th Meeting; 20 March 1998.

Key secondary efficacy variables for those subjects who are randomized at week 33 (Period C) include:

1. Time to loss of PASI 75 response after Week 33
2. Proportion of subjects achieving a clinical response defined as ≥PASI 75 at Week 52.
3. Proportion of subjects achieving a PGA of "clear" or "minimal" at Week 52.

Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 70 days, following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent.

2 Page(s) Withheld

2 Trade Secret / Confidential (b4)

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_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 2

Key Parts of Protocol for Pivotal Study – M04-716

Study Objective

The objectives of this study were to compare the safety, tolerability, and clinical efficacy of adalimumab with placebo and with MTX in the treatment of moderate to severe chronic plaque Ps over a 16-week period.

Investigational Plan

Overall Study Design and Plan: Description

This 16-week multicenter, double-blind, double-dummy study was designed to evaluate the safety, tolerability, and clinical efficacy of adalimumab *vs.* placebo and *vs.* MTX in the treatment of adult subjects with moderate to severe chronic plaque Ps.

Approximately 250 adult subjects with moderate to severe chronic plaque Ps were to be enrolled from approximately 25 investigative sites in Europe and North America (Canada). Subjects were to be randomized 2:2:1 to one of three treatment regimens as denoted in table 1.

Table 1. Treatment Regimens

Regimen A: Adalimumab	80 mg adalimumab (two 40 mg injections) SC at Baseline (Week 0), followed by 40 mg adalimumab SC eow from Week 1 to Week 15. Placebo capsule(s) PO once weekly from Baseline (Week 0) to Week 15.
Regimen B: MTX	Two placebo injections SC at Baseline (Week 0), followed by one placebo injection SC eow from Week 1 to Week 15. MTX (7.5-25.0 mg) capsule(s) PO once weekly from Baseline (Week 0) to Week 15.
Regimen C: Placebo	Two placebo injections SC at Baseline (Week 0), followed by one placebo injection SC eow from Week 1 to Week 15. Placebo capsule(s) PO once weekly from Baseline (Week 0) to Week 15.

Note: All treatment groups were to receive the last dose of study drug at Week 15. No study drug was to be administered at the Final (Week 16) visit.

All subjects who had successfully completed the study through Week 16 were eligible for treatment with open-label adalimumab in Study M03-658. Study M03-658 is a continuation of the Phase 2 and Phase 3 Ps studies. The maximum duration of enrollment for any subject in Study M04-716 was 30 weeks.
The study consisted of:

- a maximum 28-day Screening period,
- a 16-week, double-blind, double-dummy treatment period,
- a 70-day post last dose telephone call for subjects who prematurely discontinued or completed the study and did not enroll into the extension study, Study M03-658.

Inclusion Criteria

1. Subject was ε 18 years of age.
2. Subject was a candidate for systemic therapy or phototherapy and had active psoriasis despite treatment with topical agents.
3. Female subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or was of childbearing potential and practicing one of the following methods of birth control throughout the study and for 150 days after study completion:

- condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD)
- contraceptives (oral, parenteral, patch) for three months prior to study drug administration
- a vasectomized partner

4. Male subjects who had been vasectomized or practicing one of the above listed forms of birth control throughout the study and for 90 days after study completion.
5. Female subjects of childbearing potential must have had a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Baseline.
6. Subject was judged to be in good general health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, and 12-lead electrocardiogram (ECG) performed at Screening and chest x-ray (CXR) performed during the Screening period.
7. Subjects were evaluated for latent TB infection with a PPD test and CXR. For this protocol, evidence of latent TB infection was determined using PPD ε 5 mm of induration, 48-72 hrs after placement. The Medical Monitor had to provide a waiver to sites where the available testing materials or the US procedures or guidelines were not accepted. Subjects who demonstrated evidence of latent TB infection, irrespective of Bacille Calmette-Guérin (BCG) vaccination status, and negative CXR findings for active TB were allowed to participate in the study provided that one of the following conditions were satisfied:

    - Prophylactic treatment was initiated prior to administration of study drug; however the course of prophylaxis need not be completed prior to the onset of study drug. Prophylactic treatment was according to Appendix D, (United States Centers for Disease Control [CDC] recommended preventive therapy for TB) or per local guidelines as approved by the Abbott Medical Monitor.
    - Subject had documented prophylactic treatment for TB and so did not need to repeat this treatment.

8. Subjects were able and willing to provide written informed consent and comply with the requirements of this study protocol.
9. Subject had a clinical diagnosis of psoriasis for at least 1 year as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the Investigator.
10. Subject had stable plaque psoriasis for at least 2 months before Screening and at Baseline visits as determined by subject interview of his/her medical history.

11. Subject had moderate to severe plaque psoriasis defined by ε 10% BSA involvement and PASI score of ε 10 at the Baseline visit.
12. Subjects were able and willing to self-administer SC injections or had a qualified person available to administer SC injections.

Exclusion Criteria

A subject was excluded from the study if he/she met any of the following criteria:
1. Subject had previous exposure to any systemic anti-TNF therapy (*e.g.*,thalidomide, infliximab, or etanercept), including adalimumab.
2. Subject had previous exposure to MTX.
3. Subject had other active skin diseases or skin infections (bacterial, fungal, or viral) that might interfere with evaluation of psoriasis.
4. Subject had a history of an allergic reaction or significant sensitivity to constituents of study drugs (adalimumab, MTX, or matching placebo (Table 8 and
Table 9, Appendix 16.1__1).
5. Subject could not discontinue topical therapies for the treatment of psoriasis such as corticosteroids, vitamin D analogs, or retinoids at least 2 weeks prior to the Baseline visit and during the study. Subjects were allowed to use:
- Shampoos that contain no corticosteroid,
- bland (without beta or alpha-hydroxy acids) emollients,
- low potency topical corticosteroids on the palms, soles, face, inframammary area, and groin only (Appendix N, Appendix 16.1__1 for a list of low potency topical corticosteroids).

6. Subject could not avoid UVB phototherapy for at least 2 weeks prior to the Baseline visit and during the study.
7. Subject could not avoid PUVA phototherapy for at least 4 weeks prior to the Baseline visit and during the study.
8. Subject could not avoid excessive sun exposure or the use of tanning booths for at least 2 weeks prior to the Baseline visit and during the study.
9. Subject could not discontinue systemic therapies for the treatment of psoriasis or systemic therapies known to improve psoriasis during the study:
- Systemic therapies had to be discontinued at least 4 weeks prior to the Baseline visit.
- Alefacept had to be discontinued at least 12 weeks prior to the Baseline visit.
- Efalizumab had to be discontinued at least 6 weeks prior to the Baseline visit.
- Biologic agents not mentioned had be discontinued for at least 12 weeks prior to the Baseline visit.
- Investigational chemical agents had to be discontinued at least 30 days or 5 half-lives prior to the Baseline visit (whichever was longer).

10. Subject was taking or required oral or injectable corticosteroids during the study. Inhaled corticosteroids for stable medical conditions were allowed.
11. Subject had a poorly controlled medical condition, such as uncontrolled diabetes, unstable heart disease, congestive heart failure, recent cerebrovascular accidents, or any other condition

which, in the opinion of the Investigator, would put the subject at risk by participation in the study.
12. Subject had a history of clinically significant hematologic (*e.g.,* severe anemia, leukopenia, thrombocytopenia), renal, or liver disease (*e.g.,* fibrosis, cirrhosis, hepatitis).
13. Subject had history of neurologic symptoms suggestive of central nervous system (CNS) demyelinating disease.
14. Subject had history of cancer or lymphoproliferative disease other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix.
15. Subject had a history of listeriosis, histoplasmosis, untreated TB, persistent chronic infections, or recent active infections requiring hospitalization or treatment with intravenous (IV) anti-infectives within 30 days or oral anti-infectives within 14 days prior to the Baseline visit.
16. Subject currently used or planned to use anti-retroviral therapy at any time during the study.
17. Subject was known to have immune deficiency, history of HIV, or was immunocompromised.
18. Female subject who was pregnant or breast-feeding or considering becoming pregnant during the study or for 150 days after the last dose of study drug.
19. Male subject whose female partner was considering becoming pregnant during the subject's study participation or 90 days after the subject's last dose of study drug.
20. Subject had a history of clinically significant drug or alcohol usage in the last year or could not maintain an alcohol intake of 30 g a day or less throughout the study.
One standard drink is defined as 180 mL/6 oz (approx. 10 g) of wine, 360 mL/12 oz (approx. 15 g) of regular beer, or 45 mL/1.5 oz (approx. 10 g) of spirits.
21. Subject was considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
22. Screening clinical laboratory analyses showed any of the following abnormal laboratory results:

- Total white cell (WBC) count < 3500/mm3;
- Platelet count <120,000/mm3;
- Hemoglobin: women δ 8.0 g/dL or men δ 8.5 g/dL;
- Aspartate transaminase (AST) or alanine transaminase (ALT) > 1.5x the upper limit of normal (ULN);
- Positive Hepatitis B or C serology indicative of previous infection; or
- Creatinine > 1.5 mg/dL (133 ⌈mol/L) in subjects < 65 years old and > ULN range in subjects ε 65.

23. Subject had erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis.

Key Study Procedures
These were the same as for pivotal trial M03-656. See above.

Key Efficacy Parameters

Primary efficacy parameters were the PASI and PGA. The primary criteria were the same for this trial s for M03-656, Period A.

Key Safety Parameters

The safety parameters and monitoring for this trial were the same as for pivotal trial M03-656.

b(4)

10.3 Line-by-Line Labeling Review

54 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 3