2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Adalimumab	**Volume:**	
Name of Active Ingredient: Adalimumab	**Page:**	

Title of Study: A Phase 3, Multicenter Study of the Efficacy and Safety of Long-term Adalimumab Treatment in Subjects with Moderate to Severe Chronic Plaque Psoriasis

Investigator:

M. Alan Menter, MD
Texas Dermatology Research Institute
5310 Harvest Hill Road
Dallas, TX 75230

Study Site(s): Multicenter (81 centers: 67 centers in the US, 14 centers in Canada)

Publications: None

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 13 Dec 2004 Last Subject Last Visit: 29 June 2006	

Objective(s): The objective of this study was to confirm the short- and long-term clinical efficacy and safety of subcutaneously administered adalimumab, as well as to determine the proportion of subjects losing an adequate response (*i.e.*, achieving an event) after Week 33 and on or before Week 52 after withdrawal of long-term continuous adalimumab therapy (re-randomization to placebo) in the treatment of adult subjects with moderate to severe chronic plaque psoriasis (Ps). Losing an adequate response was defined as a PASI score after Week 33 that resulted 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 was higher. The pharmacokinetics and immunogenicity of adalimumab following subcutaneous (SC) injection was also to be assessed.

Methodology: This multicenter study was designed to evaluate the short- and long-term safety and efficacy of adalimumab in the treatment of subjects with moderate to severe plaque Ps. The maximum duration of enrollment for any subject was 52 weeks. The study consisted of a 28-day screening period and three treatment periods (A, B, and C).

Period A (2:1 randomization, adalimumab: placebo): Adalimumab versus placebo was evaluated for efficacy and safety in a 16-week, double-blind, placebo-controlled treatment period in which subjects were randomized to receive either:

(1) 40 mg adalimumab SC eow following an 80 mg adalimumab SC loading dose at Baseline (Week 0). Subjects with at least a PASI 75 response at Week 16 received two placebo injections at Week 16; or,

(2) one placebo injection SC eow following two placebo injections SC at Baseline. Placebo subjects with at least a PASI 75 response at Week 16 received 80 mg adalimumab SC at Week 16, administered as two 40 mg SC injections.

Period B: Long-term response to adalimumab was evaluated in a 17-week, open-label treatment period in which all subjects who achieved at least a PASI 75 response at Week 16 (the end of Period A) received open-label 40 mg adalimumab SC eow.

Period C: Subjects who achieved at least a PASI 75 response at Week 33 (the end of Period B) entered a 19-week, double-blind, placebo-controlled treatment period (Period C) for the evaluation of maintenance of response:

(1) Subjects randomized to adalimumab in Period A were re-randomized in a 1:1 ratio to 40 mg adalimumab SC eow or matching placebo injections from Week 33 to loss of an adequate response, early termination, or the Week 52 visit, whichever came first.

(2) Subjects who were originally randomized in Period A to receive placebo and were eligible for Period C continued to receive 40 mg adalimumab eow from Week 33 to loss of an adequate response, early termination, or the Week 52 visit, whichever came first.

Number of Subjects (Planned and Analyzed):

Period A: Planned: 1200; Analyzed: 1212 (Intent-to-Treat [ITT] Analysis Set and Safety Analysis Set); 1172 (Per-protocol [PP] Analysis Set)

Period B: Analyzed: 606 (ITT Analysis Set and Safety Analysis Set); 586 (PP Analysis Set)

Period C: Analyzed: 512 (ITT Analysis Set and Safety Analysis Set [re-randomized, 490; not re-randomized, 22]); 482 (PP Analysis Set [re-randomized, 461; not re-randomized 21])

Across All Periods: All Adalimumab Treatment Set: 840

Diagnosis and Main Criteria for Inclusion: Eligible subjects included male and female subjects ≥ 18 years of age with moderate to severe plaque Ps (defined as ≥ 10% BSA, PASI score ≥ 12, and PGA of at least moderate disease) at Baseline. Subjects had to have a confirmed clinical diagnosis of Ps for at least six months and stable plaque Ps for at least two months. Subjects who demonstrated evidence of latent tuberculosis (TB) infection (either PPD ≥ 5 mm of induration, irrespective of Bacille Calmette-Guérin (BCG) vaccination status, and negative CXR findings for active TB, and/or suspicious CXR findings) were allowed to participate in the study provided that prophylactic treatment was initiated and completed, according to local guidelines for recommended preventive therapy for TB, prior to administration of study drug. Repeat treatment was not required for subjects with documented prophylactic treatment for TB.

Subjects were not permitted to have had a previous exposure to any systemic anti-TNF therapy (*e.g.*, thalidomide, infliximab, or etanercept), including adalimumab, and were not permitted to take exclusionary therapies during the study. Subjects were not permitted to have a history of an allergic reaction or significant sensitivity to constituents of study drug, including latex (a component of the pre-filled syringe). Subjects were not permitted to have other active skin diseases or skin infections (bacterial, fungal, or viral) that might interfere with evaluation of Ps.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Adalimumab (40 mg adalimumab in 0.8 mL) in pre-filled syringes for SC injection
Bulk Lot Numbers: 1319HK/171024227,21244HK/17102427,15207HK/17102427, and 25272HK/17102427

Duration of Treatment: 52 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Placebo (0.8 mL) in pre-filled syringes for SC injection.
Bulk Lot Numbers: 08137HK/17102415 and 08138HK/17102415

Criteria for Evaluation

Efficacy: The efficacy of adalimumab in reducing the signs and symptoms of Ps was evaluated *via* both physician-reported outcomes (the Ps Area and Severity Index [PASI] and the Physician's Global Assessment [PGA] of disease severity) and patient-reported outcomes (PROs) (the Patient's Global Assessment of disease severity (PtGA), pain associated with psoriatic plaques and PsA (VAS), and the degree of pruritus related to Ps). In addition, the efficacy of adalimumab in improving overall quality of life was assessed by three additional PROs (the Dermatology Life Quality Index [DLQI] questionnaire, Short Form-36 Health Survey [SF-36], and the Work Productivity and Activity Impairment Questionnaire - Specific Health Problem [WPAI-SHP]).

The study had two independent primary efficacy variables:

1. The primary efficacy variable in Period A was 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 PASI score.
2. The primary efficacy variable in Period C was the proportion of subjects losing an adequate response after Week 33 and on or before Week 52. A loss of adequate response was defined as a PASI score after Week 33 that resulted 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 was higher.

Secondary efficacy variables were analyzed in rank order in each period and included variables PGA, PASI 75/50/90/100 response, DLQI, Ps/PsA pain (VAS), Ps-related pruritus, PtGA, SF-36, and WPAI−SHP. Other efficacy variables were also analyzed, and subgroup analyses were performed for the key efficacy variables.

Safety: Safety was determined by the evaluation of adverse events (AEs), including AEs of special interest, laboratory data, and vital signs.

Statistical Methods

Efficacy: The proportion of subjects with at least PASI 75 response at Week 16 (the first primary efficacy variable) was analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for center. Subjects who did not have a Week 16 PASI score were counted as nonresponders in the primary analysis (non-responder imputation).

The proportion of subjects losing an adequate response after Week 33 and on or before Week 52 (the second primary efficacy variable) was analyzed using the CMH test adjusting for center. In the primary analysis, a missing Week 52 PASI assessment was imputed as a loss of adequate response if it was a result of premature discontinuation due to lack of efficacy or study drug toxicity. The complete imputation results were finalized prior to breaking the blind.

The secondary variables for Periods A and C were analyzed in the corresponding ITT population according to the rank order as outlined in the study protocol. The Fisher's Exact test, one-way ANOVA, and Log-rank test were used to assess potential treatment differences for discrete variables, continuous variables, and time to loss of adequate response variables, respectively. The Breslow-Day test was used to examine homogeneity across centers in ≥ PASI 75 response rate at Week 16. Counts and percentages of subjects with a ≥ PASI 75 response at Week 16 were presented for each center as well.

Summary statistics were provided for the secondary variables in Period B.

Analyses based on non-responder imputation, observed cases, and last observation carried forward (LOCF) were provided as appropriate. The primary approach for each variable in Periods A and C used the ITT analysis set with non-responder imputation for discrete variables, and LOCF for continuous variables.

Safety: Safety analyses were carried out using the Safety Analysis Set for each period and the All Adalimumab Treatment Set (subjects who received at least one dose of adalimumab during the study). The number and percent of subjects experiencing treatment-emergent AEs was tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA) Version 9.0, system organ class (SOC), and preferred term (PT). In addition, a summary of AEs by severity and relationship to study drug was presented. Treatment-emergent AEs that were judged by the Investigator to be probably or possibly related to study drug also were tabulated. Comparisons of the percentages of subjects experiencing an adverse event (AE) between the adalimumab and placebo groups were performed using Fisher's Exact tests for data collected in Periods A and C, respectively. Summaries of serious AEs (SAEs), deaths, AEs leading to discontinuation of study drug, and AEs of special interest also were provided. Mean changes in laboratory parameters and vital signs at each visit were summarized for all treated subjects in each period, as well as in the All Adalimumab Treatment Set, and compared between treatment groups using a one-way ANOVA in Periods A and C. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 2 or higher was provided. Shift tables for changes from Baseline according to the normal range also were provided.

Summary/Conclusions

Efficacy Results:

Primary Endpoints:

The primary efficacy endpoint in Period A, the PASI 75 response rate at Week 16, was statistically significantly higher in the adalimumab treatment group compared with the placebo treatment group [adalimumab *vs.* placebo (center-adjusted rate): 70.9% *vs.* 6.5%; Difference 64.4% (95% CI for difference: 58.4%, 70.4%); $p < 0.001$ from CMH adjusting for center].

The primary efficacy endpoint in Period C, the proportion of subjects losing an adequate response after re-randomization (Week 33) and on or before Week 52, was statistically significantly lower for subjects who were re-randomized to adalimumab compared with subjects who were re-randomized to placebo [adalimumab *vs.* placebo (center-adjusted rate): 4.9% *vs.* 28.4%; Difference –23.5%; (95% CI for difference: -30.2%, -16.9%); $p < 0.001$ from CMH adjusting for center].

Secondary Endpoints:

The results of the primary analyses were supported by a variety of secondary and other efficacy analyses.

In Period A, the proportions of subjects with a PGA rating of clear or minimal were greater in the adalimumab treatment group compared with the placebo treatment group from Weeks 4 through 16 ($p < 0.001$ at each visit). Also, the PASI 50/75/90 response rates in the adalimumab treatment group were statistically significantly higher compared with the placebo treatment group from Weeks 4 through 16 ($p < 0.001$at each visit). For PASI 100, the statistically significantly higher responses were seen at Weeks 12 and 16 ($p < 0.001$ at each visit) in the adalimumab treatment group.

Summary of PGA (Clear/Minimal) and PASI 75 Response, Period A

	Proportion of Subjects with PGA Clear or Minimal		Proportion of Subjects with PASI 75	
	PBO N=398	ADA N=814	PBO N=398	ADA N=814
Visit	**n (%)**			
Week 4	5 (1.3)	139 (17.1)	5 (1.3)	154 (18.9)
Week 8	9 (2.3)	389 (47.8)	12 (3.0)	440 (54.1)
Week 12	15 (3.8)	490 (60.2)	19 (4.8)	551 (67.7)
Week 16	17 (4.3)	506 (62.2)	26 (6.5)	578 (71.0)

Note: $p < 0.001$ at each visit, Fisher's Exact test (without adjusting for center).

In addition, the times from Baseline to a PASI 50, PASI 75, PASI 90, and PASI 100 response in the adalimumab treatment group were statistically significantly shorter compared with placebo ($p < 0.001$).

Adalimumab-treated subjects, as compared with placebo, demonstrated:

- statistically significantly greater proportions of PtGA scores 0 or 1 (score of 0 corresponds to "complete disease control" and score of 3 corresponds to "uncontrolled disease") at Weeks 4 through 16 ($p < 0.001$ at each visit).
- statistically significantly greater improvements in mean changes from Baseline in both Ps/PsA pain scores (VAS) ($p < 0.001$ at each visit), and Ps-related pruritus scores at Weeks 4 through 16 ($p < 0.001$ at each visit).
- statistically significantly greater proportions of DLQI total scores = 0 (best possible quality of life) at Week 16 ($p = 0.001$).
- statistically significantly greater improvements in mean changes from Baseline in DLQI scores at Weeks 4 and 16 ($p < 0.001$ at each visit).
- statistically significantly greater improvements in mean changes from Baseline in the SF-36 Physical Component Summary (PCS) score at Week 16 ($p < 0.001$).

Across all endpoints in Period B (PASI response, PGA, DLQI, PtGA, Ps/PsA pain [VAS], and SF-36), the majority of subjects who were originally randomized to adalimumab in Period A maintained their response to treatment, while subjects who were originally randomized to placebo showed an improvement in their responses with adalimumab treatment.

In Period C, subjects who were re-randomized to adalimumab compared with subjects who were re-randomized to placebo demonstrated:

- statistically significantly longer time from Week 33 to a loss of adequate response on or before Week 52 ($p = 0.001$).
- statistically significantly longer time from Week 33 to a loss of PASI 50, PASI 75, PASI 90 or PASI 100 response on or before Week 52 ($p < 0.001$).
- statistically significantly greater proportion of subjects with a PGA rating of clear or minimal at Week 52 ($p < 0.001$).
- statistically significantly greater proportion of subjects with a PtGA score of 0 or 1 at Week 52 ($p < 0.001$).
- statistically significant mean improvement in the DLQI total score (relative to the first dose of study drug in Period C) at Week 52 ($p < 0.001$).
- statistically significantly greater proportion of subjects achieving a DLQI = 0 (*i.e.,* best possible quality of life) score at Week 52 ($p = 0.001$).
- statistically significant mean improvement in the SF-36 PCS score (relative to the first dose of study drug in Period C) at Week 52 ($p = 0.002$).

Safety Results:

The safety results are presented by treatment period.

In Period A, the overall incidence of AEs reported in the adalimumab treatment group (62.2%) was higher than that in the placebo group (55.5%), and this difference was statistically significant. Among commonly reported AEs (2% of subjects in either treatment group), seven AEs (upper respiratory tract infection, headache, injection site reaction, arthralgia, sinusitis, fatigue, and pruritus) occurred at higher incidences in the adalimumab group than in the placebo group in Period A. All of these AEs, except pruritus, are consistent with the safety profile for approved HUMIRA®. The difference in AE incidence between adalimumab- and placebo-treated subjects for pruritus is not considered to be clinically relevant.

The majority of AEs for both treatment groups were mild to moderate in severity. The overall incidence of AEs at least possibly related to study drug in the adalimumab treatment group (20.8%) was statistically significantly higher than in the placebo group (13.8%). Most of the AEs at least possibly related to study drug are consistent with the current safety profile for approved adalimumab indications.

No subjects died during Period A. The overall incidences of SAEs and AEs leading to discontinuation of study drug were comparable between treatment groups (SAEs: 1.8% each treatment group; discontinuations: adalimumab,1.7% *vs.* placebo, 2.0%).

In the AE categories of special interest of lymphoma, demyelinating disorder, opportunistic infection (excluding TB), TB, and lupus-like syndrome, no AEs were reported by adalimumab-treated subjects. Infections occurred at a higher incidence in the adalimumab treatment group (28.9%) compared with the placebo group (22.4%); however, this difference was regarded as consistent with the current safety profile for approved adalimumab indications. Injection site reactions occurred at a higher incidence in the adalimumab treatment group (6.9%) compared with the placebo group (5.3%); however, this difference was not statistically significant. Malignancies (all), non-melanoma skin cancers, other malignancies (excluding non-melanoma skin cancers and lymphomas), congestive heart failure, allergic reactions, hematologic events, and hepatic events occurred at comparable incidences in the adalimumab and placebo treatment groups.

Evaluation of mean changes in hematology parameters during Period A suggests that treatment with adalimumab is associated with decreases in WBCs, neutrophils, and platelets, and increases in lymphocytes compared to treatment with placebo. The mean changes in these parameters were small, and were similar to those reported for adalimumab-exposed subjects with other primary conditions. Evaluation of hematology values of potential clinical significance (meeting CTC criteria grade 2 or above) showed that a small number of subjects in both treatment groups had clinically relevant values. These hematologic effects are similar to those seen in adalimumab-exposed subjects with other primary conditions, and are not expected to result in an increased risk in this population.

Mean increases in liver function tests (AST, ALT, and bilirubin) were small for adalimumab-treated subjects; statistically significant between-group differences were observed for ALT at Week 4 and for bilirubin at all timepoints. However, the maximal mean difference between the adalimumab and the placebo groups in bilirubin reached only 0.8 μmol/L at Week 16. For alkaline phosphatase, mean decreases were observed at all timepoints in both treatment groups; the mean decreases were statistically significantly larger in the adalimumab group. Values of ALT or AST > 2.5xULN and values of bilirubin > 1.5xULN were reported at a similar incidence in the two treatment groups.

Mean increases in cholesterol and triglycerides for the adalimumab group were observed at all timepoints; between-group differences were statistically significant for cholesterol (all timepoints). These results are consistent with those reported for adalimumab-exposed subjects with other primary conditions. Potentially clinically relevant high values for cholesterol and triglycerides were reported with a similar incidence in the two treatment groups.

In Period B, AEs reported were generally consistent with those reported during Period A for subjects treated with adalimumab. In addition, evaluation of the number of subjects with hematology values of potential clinical significance confirmed that clinically relevant changes for these parameters are uncommon. Similar changes in liver function tests (ALT, AST, and bilirubin) and serum cholesterol and triglycerides were observed in Periods A and B.

No subjects died during Period B. No AEs were reported in the following categories of special interest: lymphoma, other malignancy (excluding non melanoma skin cancer and lymphoma), demyelinating disorder, congestive heart failure, allergic reaction, and lupus-like syndrome. One subject, who was originally randomized to receive adalimumab in Period A, reported a serious infection of TB during Period B. This subject had a positive PPD test at study entry, and had initially received INH for latent TB for the first 46 days, but had discontinued INH thereafter. After the diagnosis of active TB, the subject did receive additional treatment for the TB, and the subject's condition improved. The TB was considered resolved.

In Period C, the incidences of AEs overall, severe AEs, and AEs at least possibly related to study drug, were not statistically significantly different between subjects re-randomized to adalimumab treatment and subjects re-randomized to placebo.

Among commonly reported AEs (≥ 2% of subjects in either treatment group), 11 AEs occurred at a higher incidence in subjects re-randomized to adalimumab treatment than in subjects re-randomized to placebo. All but two of these AEs reported in adalimumab-treated subjects are consistent with the safety profile for approved HUMIRA®. The differences in AE incidence between the two treatment groups for pruritus and skin laceration are not considered to be clinically relevant.

No deaths occurred during Period C. The incidences of SAEs and AEs leading to discontinuation of study drug were comparable between subjects re-randomized to adalimumab treatment and subjects re-

randomized to placebo treatment (SAEs: 2.0% *vs.* 2.9%; discontinuations: 1.6% *vs.* 0.8%, respectively)

In the AE categories of special interest of malignancy (all), lymphoma, other malignant (excluding non-melanoma skin cancer and lymphoma), non-melanoma skin cancer, demyelinating disorder, congestive heart failure, allergic reaction, opportunistic infection (excluding TB), TB, lupus-like syndrome, and hematologic event, no AEs were reported by subjects re-randomized to adalimumab treatment. The incidences for subjects re-randomized to adalimumab treatment compared with subjects re-randomized to placebo treatment were comparable for infections (34.0% *vs.* 32.1%), serious infections (0.4% *vs.* 0.8%), injection site reactions (0.8% *vs.* 1.7%) and hepatic events (0.4% *vs.* 0%). One adalimumab-treated subject with a serious infection (genital abscess) discontinued from the study.

Evaluation of mean changes in hematology values from re-randomization (Week 33) showed decreases in WBCs, neutrophils, and platelets, and increases in lymphocytes for both groups; in clinical chemistry values, both groups showed mean decreases in alkaline phosphatase, and mean increases in triglycerides. Small numbers of subjects had hematology or clinical chemistry values of potential clinical significance in either treatment group.

For the All Adalimumab Treatment group, the observed pattern of AEs (overall and for the other AE categories) was consistent with the current safety profile for approved adalimumab indications, and with the general patterns of AEs observed in adalimumab-treated subjects in Periods A, B, and C. SAEs (3.5%) and AEs leading to discontinuation (3.6%) were relatively infrequent, and no deaths were reported. The patterns of mean changes in hematology and clinical chemistry values were similar to those previously observed in each of the three treatment periods.

Conclusions: In this 52 week, pivotal Phase 3 study consisting of 3 treatment periods (A, B and C), adalimumab at a dose of 40 mg eow SC was generally safe and well tolerated, reduced the signs and symptoms of Ps, and improved the quality of life in subjects with moderate to severe chronic plaque Ps. Treatment with adalimumab was demonstrated to require continuous therapy in a dose of 40 mg weekly over 52 weeks (after an initial loading dose of 80 mg) to maintain the high level of clinical response achieved after 16 weeks. Given the strong clinical efficacy of adalimumab with a generally favorable safety profile, the benefit-risk ratio is considered to be very favorable.