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, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Study Comparing the Safety and Efficacy of Adalimumab to Methotrexate and Placebo in Subjects with Moderate to Severe Chronic Plaque Psoriasis

Investigator:

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Study Site(s): Multicenter (23 centers across eight European countries and five centers in Canada)

Publications: There was one poster presentation based on the study: Saurat J, Stingl G, Dubertret L, Papp K, Ortonne J, Unnebrink K, *et al*. CHAMPION Phase III Study Results: Adalimumab Efficacy and Safety Compared With Methotrexate and Placebo in Patients with Moderate to Severe Psoriasis. 15th Congress of the European Academy of Dermatology and Venereology. Oct 4-8, 2006; Rhodes, Greece. P305.165.

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 12 Jul 2005 Last Subject Last Visit: 17 May 2006	

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

Methodology: This 16-week, multi-center, double-blind, double-dummy study was designed to evaluate the safety, tolerability, and clinical efficacy of adalimumab *vs.* placebo and adalimumab *vs.* MTX in the treatment of adult subjects with moderate to severe chronic plaque Ps. The maximum duration of enrollment for any subject was 30 weeks. The study consisted of a Screening period; a 16-week, double-blind, double-dummy treatment period; and 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.

Subjects were to be randomized in a 2:2:1 ratio to one of three treatment regimens (regimen A: adalimumab, Regimen B: MTX, or Regimen C: placebo):

Regimen A: Adalimumab:	80 mg adalimumab (two 40 mg injections) subcutaneously (SC) at Baseline (Week 0), followed by 40 mg adalimumab SC every other week (eow) from Week 1 to Week 15. Placebo capsule(s) Per Os (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.

The dose of MTX was to be 7.5 mg at Week 0 and Week 1, 10 mg at Week 2 and Week 3, and 15 mg from Week 4 until Week 15. It was to be adjusted to aspartate transaminase (AST), alanine transaminase (ALT), white blood cell count, platelet count, and serum creatinine from Week 2 until Week 15. The dose of MTX was to be increased to 20 mg at Week 8 and 25 mg at Week 12 if PASI 50 response (50% reduction in Baseline Ps Area and Severity Index [PASI] score) was not achieved and if there was no safety concern.
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 study drug was to be self-administered, or by designee (SC adalimumab or placebo for adalimumab eow, and PO MTX or placebo for MTX).

An Interactive Voice Response system was to be utilized to maintain the blind and dispense the appropriate medication to subjects. Approximately 250 adult subjects with moderate to severe chronic plaque Ps were to be enrolled from approximately 25 investigative sites in Europe and Canada.

Efficacy and safety measurements were performed throughout the study.

Number of Subjects (Planned and Analyzed):
Planned: 250

Randomized: 271
Analyzed: 271 (Intent-to-Treat [ITT] Analysis Set); 270 (Safety Analysis Set); 240 (Per-protocol [PP] Analysis Set)

Diagnosis and Main Criteria for Inclusion: Eligible subjects included males and females ≥ 18 years of age with moderate to severe chronic plaque Ps who were candidates for systemic therapy or phototherapy. Subjects had to have a clinical diagnosis of Ps for at least one year as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by the Investigator. In addition, subjects had to have stable plaque Ps for at least two months before Screening and at Baseline visits as determined by subject interview of his/her medical history, and moderate to severe plaque psoriasis defined by ≥ 10% body surface area (BSA) involvement and a PASI score of ≥ 10 at the Baseline visit.

Female subjects had to either not be of childbearing potential, defined as postmenopausal for at least one year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or of childbearing potential and practicing one of the protocol-defined methods of birth control throughout the

study and for 150 days after study completion. In addition, female subjects of childbearing potential had to have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at Baseline. Male subjects had to be either vasectomized or practicing one of the protocol-defined forms of birth control throughout the study and for 90 days after study completion.

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 subjects could not have had a previous exposure to MTX. 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 Number: 21244HK

Duration of Treatment: 16 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 Number: 90-014HK

Redacted information - 08Jun2012

Placebo (over-encapsulated placebo tablets) for PO administration
Bulk Lot Number for Placebo Tablets: [redacted] (92016HB)
Bulk Lot Numbers for Capsules: [redacted] (23090HB [2, 5 mg]; 23093HB [5 mg]; 23094HB [10 mg]; 29101HB [2, 5 mg]; 29102HB [5 mg]; 29103HB [10 mg])

MTX (over-encapsulated placebo tablets) for PO administration
Bulk Lot Numbers for MTX Tablets: [redacted] (231419S and 300119S)
Bulk Lot Numbers for Capsules: [redacted] (23089HB [2, 5 mg]; 23091HB [5 mg]; 23092HB [10 mg]; 29098HB [2, 5 mg]; 29099HB [5 mg]; 29100 [HB])

Criteria for Evaluation

Efficacy: The efficacy of adalimumab in reducing the signs and symptoms of Ps was evaluated *via* both physician-reported outcomes (*i.e.*, PASI and the Physician Global Assessment [PGA] of disease severity) and patient-reported outcomes (*i.e.*, the Patient Global Assessment of disease severity, pain associated with psoriatic plaques and PsA [if applicable], and the degree of pruritus related to Ps). In addition, the efficacy of adalimumab in improving overall quality of life was assessed by two patient-reported outcomes (the Dermatology Life Quality Index [DLQI] and the EQ-5D Health Questionnaire).

The primary efficacy variable was the proportion of subjects achieving 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.

Secondary efficacy variables included the proportion of subjects with a PGA of clear or minimal at and before Week 16, PASI 75 response rates at and before Week 12, PASI 50/90/100 response rates at and before Week 16, the time to a PASI 50/75/90/100 response, the time to PGA of clear or minimal, change from Baseline DLQI at or before Week 16, the proportion of patients with DLQI=0 (best possible quality of life) at or before Week 16, the proportion of subjects achieving a Patient Global Assessment of "0" or "1" (complete or good disease control) at or before Week 16, change from Baseline in Ps/psoriatic arthritis (PsA) at or before Week 16, change from Baseline in Ps related pruritus at or before Week 16,

change from Baseline in EQ-5D Index Score at or before Week 16.

Subgroup analyses were conducted on the ITT Analysis Set to explore the effect of age, sex, history of Ps/PsA, receipt of systemic therapy and/or phototherapy, strict adherence to the oral dosing scheme, decrease of oral dose prescribed over the study period, and severity of disease at Baseline on: (1) PASI 50/75/90/100 response rates at Week 16; (2) the time to a PASI 50/75/90/100 response; and (3) the proportion of subjects with a PGA of clear or minimal at Week 16.

Safety: Safety was determined by the evaluation of treatment-emergent adverse events (AEs), (incidence, relationship to study drug, severity), serious AEs (SAEs), AEs leading to discontinuation from the study, AEs of special interest, laboratory data, and vital signs.

Statistical Methods

Efficacy: The primary efficacy analyses compared the proportions of subjects with a clinical response, defined as at least a 75% reduction in the PASI score (≥ PASI 75) at Week 16 relative to the Baseline (Week 0) PASI score, in the adalimumab 40 mg eow treatment group with the proportions in the placebo and MTX treatment groups. The tests were to be performed in the following sequence: (1) the superiority of adalimumab *vs.* placebo was to be established by Cochran Mantel Haenszel (CMH) test stratified by country at an alpha level of 0.05 (changed *via* Protocol Amendment 01); and (2) the comparison of adalimumab and MTX was to be performed if the superiority of adalimumab *vs.* placebo was established. The 95% confidence interval for the difference in the clinical response rate between the adalimumab treatment group and the MTX treatment group was to be calculated based on the CMH statistic stratified by country (changed *via* Protocol Amendment 01). Non-inferiority of adalimumab *vs.* MTX was to be established if the lower limit of the confidence interval for the difference (adalimumab – MTX) was between –0.2 and 0.0 and the upper limit was positive. If the lower limit of the confidence interval was positive, the adalimumab treatment group was to be considered superior to the MTX treatment group. Subjects who did not have PASI assessments at Week 16 were to be imputed as non−responders in the primary analyses. Added *via* Protocol Amendment 01: For the above CMH analyses, centers were to be pooled by country. For countries with only few subjects and small centers, the following pooling according to the geographic region was to be done: Netherlands + Belgium, Switzerland + France.

Summary statistics were to be provided for all secondary variables. Proportions were to be analyzed using Fisher's Exact test to assess the potential treatment differences; the 95% confidence interval for the difference between the adalimumab treatment group and the MTX treatment group was to be calculated based on the normal approximation to the binomial distribution. Continuous variables were to be analyzed using a one-way analysis of variance (ANOVA). Time to event variables were to be analyzed using the Log-rank test. Analyses based on non-responder imputation, observed cases, and last observation carried forward were to be provided as appropriate. To adjust for multiplicity, secondary variables were analyzed according to the rank order as outlined in the Statistical Analysis Plan.

Safety: Safety analyses were to be carried out using the Safety Analysis Set. The number and percent of subjects experiencing treatment-emergent AEs was to tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA) Version 9.0, system organ class and preferred term. In addition, a summary of AEs by severity and relationship to study drug was to be presented. Treatment-emergent AEs that were judged by the Investigator to be probably or possibly related to study drug also were to be tabulated. Pairwise comparisons of the percentages of subjects experiencing an AE among the adalimumab, MTX, and placebo treatment groups were to be performed using Fisher's Exact tests. Summaries of SAEs, deaths, AEs leading to discontinuation from the study, and AEs of special interest

also were to be provided. Mean changes in laboratory variables and vital sign values at each visit were to be summarized for all treated subjects. Pairwise comparisons were to be performed using a one-way ANOVA. The last evaluation prior to the first dose of study drug was to be used as the Baseline for all analyses. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 2 or higher was to be provided. Shift tables for changes from Baseline according to the normal range also were to be provided.

Summary/Conclusions

Efficacy Results: A total of 271 subjects were enrolled. The majority were male (64.8% to 66.4%) and White (92.5% to 95.5%). Mean subject age ranged from 41 to 43 years. The majority of subjects assessed their disease state as 'uncontrolled' (63.3% to 71.7%), and the majority of subjects had severe disease activity, defined as PASI > 20 and/or BSA > 20 at Baseline (60.4% to 70.1%). Between 82.2% and 90.4% of the subjects had previously received phototherapy and/or systemic therapy (*e.g.*, cyclosporine, retinoids).

The primary efficacy endpoint in Study M04-716, the PASI 75 response rate at Week 16, was statistically significantly higher in the adalimumab treatment group than in the placebo (79.6% *vs.* 18.9%; p<0.001) and MTX treatment groups (79.6% *vs.* 35.5%; 95% CI: 0.308, 0.567; p<0.001).

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

With regard to physician-reported outcomes, beginning at Week 2 for PASI 50, Week 4 for PASI 75, Week 8 for PASI 90, and Week 12 for PASI 100, the response rates in the adalimumab treatment group were higher than the response rates in the placebo group through Week 16. Beginning at Week 2 for PASI 50 and PASI 75, Week 4 for PASI 90, and Week 8 for PASI 100, the response rates in the adalimumab treatment group were higher than the response rates in the MTX treatment group through Week 16. PASI responses from Week 2 to 16 are shown below:

PASI Response	Timepoint	Placebo N = 53	MTX N = 110	Adalimumab N = 108
>= PASI 50	Week 2	2 (3.8)	3 (2.7)	21 (19.4)
	Week 4	5 (9.4)	17 (15.5)	73 (67.6)
	Week 8	13 (24.5)	42 (38.2)	88 (81.5)
	Week 12	14 (26.4)	60 (54.5)	98 (90.7)*
	Week 16	16 (30.2)	68 (61.8)	95 (88.0)*
>= PASI 75	Week 2	0 (0)	0 (0)	5 (4.6)
	Week 4	2 (3.8)	3 (2.7)	25 (23.1)
	Week 8	7 (13.2)	10 (9.1)	67 (62.0)
	Week 12	8 (15.1)	27 (24.5)	83 (76.9)*
	Week 16	10 (18.9)	39 (35.5)	86 (79.6)*
>= PASI 90	Week 2	0 (0)	0 (0)	0 (0)
	Week 4	0 (0)	1 (0.9)	7 (6.5)
	Week 8	2 (3.8)	3 (2.7)	29 (26.9)
	Week 12	4 (7.5)	10 (9.1)	52 (48.1)*
	Week 16	6 (11.3)	15 (13.6)	56 (51.9)*

PASI Response	Timepoint	Placebo N = 53	MTX N = 110	Adalimumab N = 108
>= PASI 100	Week 2	0 (0)	0 (0)	0 (0)
	Week 4	0 (0)	1 (0.9)	1 (0.9)
	Week 8	1 (1.9)	0 (0)	9 (8.3)
	Week 12	0 (0)	1 (0.9)	12 (11.1)
	Week 16	1 (1.9)	8 (7.3)	18 (16.7)*

* Based on the rank ordering of the secondary efficacy endpoints, the statistically significant treatment differences between adalimumab *vs*. placebo and MTX can be interpreted as confirmatory

Note: Response rates calculated following imputation of missing values as non-responders.

In addition, the times from Baseline to a ≥ PASI 50, ≥ PASI 75, ≥ PASI 90 and PASI 100 response in the adalimumab treatment group were also statistically significantly shorter compared with placebo and MTX.

The proportions of subjects with a PGA rating of clear or minimal were higher in the adalimumab treatment group than in the placebo and MTX treatment groups from Week 4 through Week 16. The proportions of subjects with PGA clear or minimal are presented below:

PGA of Clear or Minimal	Placebo N = 53	MTX N = 110	Adalimumab N = 108
Week 4	1 (1.9)	4 (3.6)	17 (15.7)
Week 8	5 (9.4)	10 (9.1)	52 (48.1)
Week 12	5 (9.4)	24 (21.8)	72 (66.7)*
Week 16	6 (11.3)	33 (30.0)	79 (73.1)*

* Based on the rank ordering of the secondary efficacy endpoints, the statistically significant treatment differences between adalimumab *vs.* placebo and MTX can be interpreted as confirmatory.

Note: Response rates calculated following imputation of missing values as non-responders.

In addition, the times from Baseline to a PGA rating of clear or minimal in the adalimumab treatment group were statistically significantly shorter compared with placebo and MTX.

With regard to the patient-reported outcomes for the treatment of the signs and symptoms of chronic plaque Ps:

- Beginning at Week 4 through Week 16, the proportions of subjects with a Patient Global Assessment of Ps score of 0 or 1 were higher in the adalimumab treatment group than in the placebo and MTX treatment groups.
- Adalimumab-treated subjects demonstrated greater improvements in change from Baseline in Ps/PsA pain scores at each timepoint from Week 1 through Week 16 compared with placebo- and MTX-treated subjects.
- Adalimumab-treated subjects also showed greater improvements in change from Baseline in Ps-related pruritus scores at each timepoint from Week 1 through Week 16 compared with placebo- and MTX-treated subjects.

In addition to treating the signs and symptoms of Ps, results demonstrate that adalimumab improves the quality of life in adults with moderate to severe chronic plaque Ps.

- The proportions of adalimumab-treated subjects with a DLQI total score = 0 were statistically significantly higher compared with placebo-treated subjects at Week 12 and Week 16. In addition, the proportion of adalimumab-treated subjects with a DLQI total score = 0 was superior to MTX treated subjects at Week 12 and non-inferior at Week 16.
- Adalimumab-treated subjects demonstrated greater improvements in change from Baseline in DLQI scores at Week 12 and Week 16 compared with placebo- and MTX-treated subjects.
- Finally, adalimumab-treated subjects demonstrated greater improvements in change from Baseline in EQ-5D Index Scores at Week 12 and Week 16 compared with placebo- and MTX-treated subjects. The treatment differences between adalimumab *vs.* placebo and MTX were statistically significant at Week 16.

Based on the statistically significant differences observed for most of the secondary efficacy endpoints (excluding the change from Baseline in EQ-5D Index Scores at Week 12), adalimumab, when compared to placebo and MTX at Week 12 and Week 16, was found to be effective in treating subjects with moderate to severe chronic plaque psoriasis.

Safety Results: Adalimumab was generally safe and well-tolerated when administered to subjects with moderate to severe chronic plaque Ps at a dose of 40 mg eow SC for 16 weeks. The overall incidence of treatment-emergent AEs reported in the adalimumab treatment group (73.8%) was lower than the incidences reported in the placebo (79.2%) and MTX (81.8%) treatment groups; however, these differences were not statistically significant. Individual treatment-emergent AEs (nasopharyngitis, arthralgia, and headache) that occurred at a higher incidence in the adalimumab treatment group compared with the placebo and MTX treatment groups are consistent with those included in the current safety profile of adalimumab.

The overall incidences of severe treatment-emergent AEs and SAEs were low and comparable across the three treatment groups. The proportions of subjects who reported treatment-emergent AEs considered possibly or probably related to study drug were comparable across treatment groups and were not statistically significantly different. One adalimumab-treated subject reported an AE that resulted in premature study discontinuation compared to one placebo-treated subject and six MTX-treated subjects. No statistically significant differences were observed across treatment groups. The one AE that occurred in the adalimumab treatment group that resulted in premature study discontinuation (increased transaminases in a 36-year-old male, elevations never exceeded 2X ULN) is an event that is consistent with the current safety profile of adalimumab. No subjects died during the study.

A total of 15 treatment-emergent AEs of special interest categories were specifically assessed as part of the safety evaluation of adalimumab. No adalimumab-treated subjects experienced an AE in 12 of these special interest categories: serious infections; all malignancies; malignancies (excluding non-melanoma skin cancers and lymphomas); non-melanoma skin cancers; lymphomas; opportunistic infections (excluding TB); TB; demyelinating disease; lupus-like reactions; congestive heart failure; allergic reactions; and hematologic events. Of the three remaining special interest categories, overall infectious treatment-emergent AEs occurred at a higher incidence in the adalimumab treatment group (47.7%) than in the MTX (41.8%) and placebo (43.4%) treatment groups, and four individual infections (bronchitis, gastroenteritis, influenza and nasopharyngitis) occurred at a higher incidence in the adalimumab treatment group than in the placebo and MTX treatment groups. These four treatment-emergent AEs are

consistent with those included in the current safety profile of adalimumab. Injection site reactions occurred at a higher incidence in the adalimumab (8.4%) treatment group than in the MTX (3.6%) and placebo (0%) treatment groups; however, none of the injection site reactions resulted in premature study discontinuation, and all but two of the events were reported as a "single episode." The percentage of subjects in the adalimumab treatment group (6.5%) who reported hepatic events was lower than that reported in the MTX and placebo treatment groups (10.9% and 9.4%, respectively).

Evaluation of clinical chemistry and hematology parameters and vital signs did not demonstrate any relevant clinical differences in the adalimumab treatment group compared with placebo or MTX. No adalimumab-treated subjects experienced a CTC Grade 2 or higher elevation in ALT, AST or total bilirubin compared with four, two and four MTX-treated subjects, respectively.

Conclusions: This efficacy results from this study demonstrated that adalimumab reduces the signs and symptoms of Ps and improves the quality of life in adults with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. The safety results demonstrated adalimumab is generally safe and well-tolerated in adults with moderate to severe chronic plaque Ps.

Based on the favorable efficacy results reported in this study as apparent from the various efficacy parameters analyzed and the safety results without any major or difficult to manage findings, it is concluded that this study demonstrates a favorable benefit-risk ratio for adalimumab in the treatment of moderate to severe psoriasis patients, both with respect to the comparison to placebo as well as the comparison to MTX as a conventional systemic therapy option for this condition.

Date of Report: 08Dec2006