



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 Multi-center Open-label Continuation Study in Moderate to Severe Chronic Plaque Psoriasis Subjects Who Completed a Preceding Psoriasis Clinical Study with Adalimumab		
Coordinating Investigator: Kim Papp, MD, PhD; Waterloo, Ontario, Canada		
Study Sites: Total of 104 sites; 85 sites in the United States/Canada/Puerto Rico and 19 sites in Europe		
Publications: 3 posters, 1 abstracts		
Studied Period (Years): First Subject First Visit: 25 May 2004 Last Subject Last Visit: 30 Jun 2009	Phase of Development: 2/3	
Objectives: The objectives of this study were to evaluate the long-term safety, tolerability, and clinical efficacy of adalimumab in subjects with moderate to severe chronic plaque psoriasis (Ps) who entered from prior adalimumab Ps studies as well as to examine the effectiveness of adalimumab retreatment following withdrawal from therapy and subsequent relapse (defined as a Physician's Global Assessment [PGA] \geq 3) of Ps (implemented via Amendment 6 to fulfill a FDA postmarketing commitment). In the open-label (OL) period of the study, an investigation into the effectiveness of dose escalation and de-escalation was also conducted.		



Methodology: Multicenter study in 3 periods (OL, withdrawal, retreatment).

Subjects (adults with moderate to severe plaque Ps) who had participated in all prior Phase 2 and Phase 3 Ps studies in North America and the EU and satisfied the inclusion/exclusion criteria were eligible to enroll into this multicenter OL continuation study. Enrolled Ps subjects had either prematurely terminated from one of those studies due to relapse/loss of adequate response (Study M02-538, M03-596, or M03-656) or had completed the study (Study M02-529, M03-596, M03-656, or M04-716). The study consisted of the following 3 periods:

Period O (OL): Period O was an OL period of a minimum of 104 weeks and a maximum of 252 weeks. This was initially the only study period.

Period W (withdrawal): Period W was at maximum a 52-week period of withdrawal from adalimumab therapy until relapse ($\text{PGA} \geq 3$). The withdrawal period was specifically added via Amendment 6 to fulfill the FDA post-marketing commitment and pre-specified the evaluable subjects (mITT-W population) in Period W: subjects who had entered Period W with a PGA of 0 or 1 at the last 2 visits in Period O, at least 12 weeks apart, and had been on adalimumab 40 mg every other week (eow) for at least 12 weeks prior to entering Period W.

Period R (retreatment): Period R was a 16-week period of adalimumab retreatment. This period was also added via Amendment 6 to fulfill the FDA post-marketing commitment.

At the end of Period O, all subjects with a PGA of ≤ 2 were eligible to continue in Period W. All subjects who relapsed ($\text{PGA} \geq 3$) in the withdrawal period prior to 52 weeks were eligible to enter Period R and receive adalimumab retreatment. Subjects who completed Period W without experiencing relapse were to be discontinued from the study; however, when approximately 150 evaluable subjects entered Period R, all remaining subjects in Period W had the opportunity to enter Period R and begin 16 weeks of adalimumab treatment. Efficacy and safety measurements were performed throughout all 3 periods of the study.

Number of Subjects (Planned and Analyzed):

Total planned: 1500 subjects; Total enrolled: 1469 subjects; Total Analyzed: 1468 subjects (All Adalimumab Treatment Population)

Planned for Period W and Period R: 150 evaluable subjects to be enrolled in Period O (at least 120 evaluable subjects were required to fulfill the FDA postmarketing commitment).

Analyzed in Period O: 1468 subjects who received at least 1 dose of adalimumab in Period O

Analyzed in Period W and Period R: 347 evaluable subjects in Period W (modified intent-to-treat [mITT-W] population); 285 subjects of the mITT-W set who received at least 1 dose of adalimumab in Period R (mITT-R population); of these, 178 who entered Period R with relapse and 107 who entered without relapse.



Diagnosis and Main Criteria for Inclusion and Exclusion:

Main inclusion criteria were: male and female subjects who were ≥ 18 years of age with moderate to severe chronic plaque Ps who had previously participated in a Ps study with adalimumab, including Phase 3 (Study M04-716 and Study M03-656) Ps subjects, Study M02-529 or Study M03-596 Ps subjects with a \geq PASI 50 (50% reduction from Baseline in PASI score) at the Final Visit, and subjects who had relapsed after Week 24 in Study M02-538.

Excluded were subjects who had prematurely discontinued from Study M02-538 for reasons other than relapse; had other active skin diseases that might interfere with the evaluation of Ps; had to use topical therapies for the treatment of Ps such as corticosteroids, vitamin D analogs, or retinoids during the study; had a history of cancer or lymphoproliferative disease or neurologic symptoms suggestive of a demyelinating disease; had active tuberculosis (TB); had a known immune deficiency or were immunocompromised; had erythrodermic Ps or generalized pustular Ps; or were pregnant.

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

Adalimumab; sterile, preservative-free solution for injection containing 40 mg/0.8 mL; SC injection using prefilled syringe. Vials containing 40 mg/0.8 mL were allowed by protocol but were never used during the study.

Lot numbers [REDACTED]: 1319HK, 90018HK, 15207HK, 24264HK/05-000159, 25272HK/05-000756, 25274HK/05-001593, 05-002379, 05-003453, 06-007920

Lot numbers [REDACTED]: 05-000384, 05-002187, 06-007039, 06-007924

Duration of Treatment: Duration of treatment with adalimumab in Study M03-658 was a total maximum of 268 weeks (Period O, maximum of 252 weeks; Period R, 16 weeks). Subjects had prior exposure in feeder Phase 3 Ps studies: 16 weeks in Study M04-716 and up to a maximum of 52 weeks in Study M03-656.

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

None

Redacted information - 08Jun2012



Criteria for Evaluation

Efficacy:

Primary and secondary efficacy variables were not designated. The efficacy variables in the 3 periods were as follows:

Period O	Proportion of subjects achieving PGA of "Clear or Minimal" at each visit
	Proportion of subjects achieving PASI 50/75/90/100 at each visit
Period W	Proportion of subject experiencing relapse ($PGA \geq 3$)
	Time to relapse
	Time to loss of PGA "Clear or Minimal"
	Proportion of subjects achieving PGA of "Clear or Minimal" at each visit
	Proportion of subjects achieving PASI 50/75/90/100 at each visit
	Change and percent change from Week 0 _W in FACIT-Fatigue Scale at each visit
	Change from baseline Week 0 _W in DLQI at each visit
	Proportion of subjects with DLQI = 0 at each visit
Period R	Proportion of subjects regaining PGA of "Clear or Minimal" at each visit
	Change and percent change from Week 0 _R in FACIT-Fatigue Scale at each visit
	Change from Week 0 _R in DLQI at each visit
	Proportion of subjects with DLQI = 0 at each visit

Pharmacokinetic:

Blood samples were collected to analyze blood serum concentrations in Period W at the beginning of the period (Week 0) and in Period R just prior to dosing (Week 0) and at Weeks 4, 12, and 16/Early Termination. Blood samples for anti-adalimumab antibody (AAA) serum concentrations were obtained in Period W (Week 0) and in Period R just prior to dosing (Week 0) and at Weeks 12 and 16/Early Termination.

Safety:

Adverse events (AEs), clinical laboratory test values (hematology, chemistry, and urinalysis), and vital signs were collected during all 3 periods.



Statistical Methods

Efficacy:

Demographic and baseline disease characteristics (Psoriasis Area and Severity Index [PASI], PGA, Dermatology Quality of Life [DLQI], and the Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue scale) were described by summary statistics: number of observations, mean, standard deviation, and median for continuous variables; frequencies for categorical data.

Summary statistics were provided for efficacy variables: counts and percentages for categorical variables; Baseline mean, visit mean, and mean, standard deviation, and median for change (percent change) from Baseline for continuous variables.

Efficacy analyses of PASI and PGA were performed for populations in the periods of the study as follows:

The analysis of each efficacy variable was performed using Observed Cases (OC) for Period O and Period W. In addition, summary of efficacy data was presented using Last-Observation-Carried-Forward (LOCF) for the Period O EOW Treatment, Continuous Treatment (Subjects from Study M04-716), Continuous Treatment (Subjects from Study M03-656), and the Retreatment (Subjects from Study M03-656) Populations, with subsets within the Retreatment Population (subjects who lost and who did not lose adequate response in Period C of Study M03-656) analyzed using Non-Responder Imputation (NRI). NRI and LOCF for discrete variables, and OC and LOCF for continuous variables were employed in Period R, and only assessments after the start of each period were carried forward for the analysis in that particular period. NRI was also used for subsets in Period R (subjects who did and who did not relapse in Period W).

Patient-reported quality of life (QoL) outcomes (added as part of Amendment 6) were evaluated in Period W and Period R using the DLQI and the FACIT-Fatigue scale.

Pharmacokinetic and Immunogenicity:

Adalimumab concentrations were summarized at each timepoint using descriptive statistics, including number of subjects (N), number of non-missing observations (N_{miss}), mean, median, standard deviation (SD), coefficient of variation (CV), minimum, and maximum. Individual subject concentration versus time plots and mean concentration versus time plots were provided.

For immunogenicity, a subject was considered to be AAA+ if the subject had at least 1 AAA+ sample. The number and percent of subjects who were AAA+ were calculated, and efficacy and safety for AAA+ subjects were listed.

Safety:

AEs (All Adalimumab Treatment Population) included AEs from the first dose of adalimumab, either in the feeder studies or in Study M03-658, to 70 days after the last dose of adalimumab except AEs that occurred during the protocol-designed gaps (the placebo treatment period and off-treatment period in Study M02-538, the placebo treatment period in Period C of Study M03-656, and the Period W in Study M03-658) that were more than 70 days from the last dose in the preceding treatment period and prior to the first dose in the subsequent treatment period. For subjects who dose escalated, AEs after the first escalated dose were not included in the summaries for the EOW Treatment Population. For subjects who dose de-escalated, AEs after the first de-escalated dose were not included in the summaries for Dose Escalation Population. The same approach was taken in the summaries for Dose Re-escalation Population.



Safety (Continued):

AEs with an onset date the same date as the start of Period W were counted toward Period O and attributed to adalimumab treatment.

Summary/Conclusions**Efficacy Results:**

Across all subjects who received at least 1 adalimumab injection in Study M03-658 and who, in an earlier adalimumab Ps study had either started with adalimumab 40 mg administered eow or had started with placebo treatment and continued on with adalimumab 40 mg eow treatment in the feeder study or in Study M03-658 (EOW Treatment Population, N = 1256), the mean Baseline PASI score was 18.8 and the Baseline PGA score ranged from moderate (52.1%) to severe (41.7%) to very severe (6.2%). At Week 120 relative to the first adalimumab injection, PGA of "Clear or Minimal" response was shown by 46.3% (LOCF) of subjects. At Week 120, PASI 75 response was achieved by 57.3% (LOCF) of subjects in this population.

For subjects who had been randomized to adalimumab in Study M04-716 and received at least 1 adalimumab injection in Study M03-658 (Continuous Treatment Population [Subjects from Study M04-716], N = 94), 46.2% (LOCF) had a PGA of "Clear or Minimal" and 58.1% (LOCF) had a PASI 75 response after a further 108 weeks of therapy (cumulative 124 weeks of continuous therapy).

Subjects who had previously participated in Study M03-656 and had a PASI 75 response at Week 33 had been re-randomized to placebo or adalimumab treatment at Week 33. Of those subjects who had been re-randomized to receive adalimumab and entered this continuation Study M03-658 (Continuous Treatment Population [Subjects from Study M03-656], N = 233), 59.0% (LOCF) had a PGA of "Clear or Minimal" and 74.7% (LOCF) had a PASI 75 response after a further 108 weeks of therapy (cumulative 160 weeks of continuous therapy). Of those subjects who had been re-randomized to receive placebo and entered Study M03-658 (Retreatment Population [Subjects from Study M03-656], N = 227), 55.9% (LOCF) had a PGA of "Clear or Minimal" and 72.5% (LOCF) had a PASI 75 response after a further 108 weeks of therapy. In the subset of subjects who lost adequate response during Period C of Study M03-656, 34.8% had a PGA of "Clear or Minimal" and 54.5% had a PASI 75 response by Week 24 compared to 69.6% and 83.8% (nonresponder imputation [NRI]), respectively, in the subset of subjects who did not lose adequate response during Period C of Study M03-656.

For subjects who were in the Dose Escalation Population (dose escalated from 40 mg eow to 40 mg weekly (ew) due to a < PASI 50 response), 26.6% (93/349) either achieved a PASI 75 response or resumed eow dosing upon achieving a PASI 75 response by 12 weeks after dose escalation. Subjects with missing responses were counted as nonresponders in this analysis.

Adalimumab withdrawal and retreatment upon loss of response was evaluated in Period W and Period R of this OL continuation study. A total of 347 subjects with a stable PGA of "Clear or Minimal" response (Period W mITT Population) discontinued adalimumab. Of these, 55.5% (188/339) experienced relapse (decline to PGA moderate or worse) during the withdrawal period. Median time to this relapse was 141 days. Upon relapse, adalimumab treatment was re-initiated (80 mg at Week 0 followed by 40 mg eow starting at Week 1). Among subjects who relapsed and subsequently reinitiated therapy, a total of 69.1% (123/178) (NRI; Period R mITT Population [subjects who entered Period R after relapse]) had a PGA of "Clear or Minimal" after 16 weeks of adalimumab retreatment.



Efficacy Results (Continued):

The withdrawal period was terminated when approximately 150 evaluable subjects had entered Period R; at that time, all subjects in Period W who had not yet relapsed had the opportunity to enter Period R and begin 16 weeks of adalimumab retreatment. Among subjects who did not relapse and re-initiated therapy, a total of 88.8% (95/107) (NRI; Period R mITT Population with no relapse) had a PGA of "Clear or Minimal" after 16 weeks of adalimumab retreatment.

Rebound was defined as experiencing a PASI score of $\geq 125\%$ of the Baseline score or developing new generalized erythrodermic or pustular Ps within 3 months after withdrawal of adalimumab treatment. Upon examining the PASI scores and TEAEs, no subject experienced rebound in Period W.

Pharmacokinetic Results:

For subjects in the Period R mITT Population, the mean serum adalimumab concentration at Week 0 of Period W (8.19 $\mu\text{g/mL}$) was very similar to the mean serum adalimumab concentration at Week 16 of Period R (8.23 $\mu\text{g/mL}$).

Subjects in the Retreatment Population (Subjects from Study M03-656) had a mean serum adalimumab concentration at Week 0 of Period W (9.24 $\mu\text{g/mL}$) that was very similar to the mean serum adalimumab concentration at Week 16 of Period R (8.51 $\mu\text{g/mL}$). Subjects in the Continuous Treatment Population (Subjects from Study M03-656) had a mean serum adalimumab concentration at Week 0 of Period W (7.32 $\mu\text{g/mL}$) that was very similar to the mean serum adalimumab concentration at Week 16 of Period R (6.87 $\mu\text{g/mL}$).

For all subjects who entered the withdrawal period (Period W ITT Population), the prevalence of AAA was 1.9% (11/590) at Week 0 of Period W. After the withdrawal period and prior to the subject's first retreatment dose, the AAA rate was 10.1% (52/513) at Week 0 of Period R; 44 of these 52 AAA+ subjects were newly positive at Week 0 in Period R. However, after 16 weeks of retreatment, the AAA rate decreased such that there were only 4 new subjects who became AAA+ during the remainder of Period R, and AAA rates returned to similar levels at Week 16 of Period R (2.3% [11/482]) as prior to withdrawal.

Among subjects in the Period R mITT Population who relapsed in Period W, those who were AAA- had a higher mean serum adalimumab concentration at Week 0 of Period W (8.26 $\mu\text{g/mL}$) compared with those who were AAA+ (3.17 $\mu\text{g/mL}$). At Week 16 in Period R, AAA+ subjects had a lower PGA 0/1 response rate than AAA- subjects, but the difference was not significant (60% versus 78%, respectively [$P = 0.097$]). The proportion of Period R mITT Population AAA+ subjects who relapsed in Period W and regained PGA "Clear or Minimal" response at Week 16 in Period R was 38% (5/13), compared with the proportion of Period R mITT Population AAA- subjects who relapsed in Period W and regained PGA "Clear or Minimal" response at Week 16 in Period R (71%, or 114/161).

For the ITT populations in both Periods W and R, there was little difference between the overall AEs between the AAA+ groups. The overall percentage of subjects with any AE was lower in AAA+ subjects than in AAA- subjects.

Safety Results:

- Adalimumab was generally safe and well-tolerated as evaluated by the incidence of deaths, other SAEs, and premature discontinuations due to AEs, by TNF inhibitor related AEs of interest, and by assessments of hematologic values, serum chemistries, and urinalyses in subjects with moderate to severe Ps in the All Adalimumab Treatment Population, as shown by the following:



Safety Results (Continued):

- Approximately 93% of subjects reported at least one treatment-emergent AE (TEAE). The most frequently reported TEAEs were nasopharyngitis, upper respiratory tract infection, headache, and hypertension. These AEs are consistent with the current safety profile of adalimumab.
- Five treatment-emergent deaths were reported; 4 of the 5 deaths occurred more than 30 days after the last dose of adalimumab. All treatment-emergent deaths were considered by the Investigator to be not related or probably not related to study drug.
- One-hundred eighty-nine subjects (12.9%) reported treatment-emergent SAEs. Of these 189 subjects, 47 subjects had SAEs that were considered possibly or probably related to study drug. The incidences of all individual SAEs were low ($\leq 0.7\%$ of subjects).
- One-hundred twelve subjects (7.6%) reported TEAEs leading to discontinuation. Over half of the subjects experienced events considered by the Investigator to be not related or probably not related to the study drug.
- Approximately 71% of subjects reported treatment-emergent infections, with the most frequently reported infectious AEs ($\geq 10\%$ of subjects) being nasopharyngitis, upper respiratory tract infection, and sinusitis.
- Forty-one subjects (2.8%) reported treatment-emergent serious infections including TB. In about half (22/41) of the subjects, the serious infections were considered by the Investigator to be possibly or probably related to study drug, including: 4 subjects with cellulitis; 4 subjects with serious tuberculosis [TB]/pulmonary TB/disseminated TB; 5 subjects with a type of abscess; and 4 subjects with pneumonia/pneumonia legionella/lobar pneumonia.
- No lymphoma was reported during the study. Forty-six subjects reported malignancies (non-melanoma skin cancers [NMSCs], 1.6%; other malignancies [excluding NMSCs and lymphoma], 1.6%).
- Eighty-one subjects (5.5%) reported treatment-emergent hepatic events. The majority of these subjects had hepatic events that were not serious, and the events resolved with continued adalimumab treatment. Two subjects permanently discontinued due to a hepatic event (hepatic enzyme increased due to hepatitis C infection and hepatic enzyme increased, respectively).
- Mean changes from Baseline in hematology values suggest that treatment with adalimumab is associated with small fluctuations in WBCs and small decreases in platelets. The mean changes for these hematology parameters were similar to those reported for adalimumab-exposed subjects in approved adalimumab indications.
- Review of the number of subjects with changes of potential clinical significance in hematology parameters and of reported hematologic AEs showed that clinically important changes are uncommon following treatment with adalimumab.



Safety Results (Continued):

- Mean changes from Baseline in clinical chemistry values suggest that treatment with adalimumab is associated with small increases in liver function tests (ALT, AST and total bilirubin), creatine phosphokinase, creatinine, and serum triglycerides and decreases in alkaline phosphatase. The mean changes from Baseline for these parameters were generally small. Cholesterol fluctuations were small throughout. Changes in values for triglycerides and cholesterol were similar to those reported for adalimumab-exposed subjects in approved adalimumab indications.
- Review of the number of subjects with changes of potential clinical significance in clinical chemistry parameters indicate that the majority of elevations in ALT, AST and total bilirubin resolve during continued treatment with adalimumab.

The safety results in the EOW Treatment Population in Period O were similar to those observed for the All Adalimumab Treatment Population. The Continuous Treatment Population (Subjects from Study M04-716) in Period O, Continuous Treatment (Subjects from Study M03-656) in Period O, Retreatment (Subjects from Study M03-656) in Period O, Dose Escalation in Period O, Dose De-escalation in Period O, and Dose Re-escalation in Period O Populations are subsets of the All Adalimumab Treatment Population; the overall safety results for and conclusions for these populations were consistent with the All Adalimumab Treatment Population. No new safety findings were observed in these subpopulations in Period O.

In addition, safety results for the Period W ITT and Period R ITT Populations were consistent with the All Adalimumab Treatment Population. Although the incidence of AEs in these 2 populations was generally similar or smaller than in the All Adalimumab Treatment Population, the types of AEs reported were similar. No subject in the Period R ITT Population had a fatal AE, and none reported an opportunistic infection, lymphoma, NMSC, lupus-like syndrome, allergic reaction, demyelinating disorder, congestive heart failure, myocardial infarction, intestinal perforation, or hematologic event. Changes in laboratory values and vital signs were consistent with those observed in the All Adalimumab Treatment Population. Overall, no new safety findings were observed in the Period W ITT and Period R ITT Populations.



Conclusions:

In summary, long-term OL adalimumab treatment, 40 mg eow and dose escalation to 40 mg ew (including dose de-escalation), in subjects with moderate to severe chronic Ps was effective in reducing the signs and symptoms of Ps as evaluated via physician-reported outcomes (i.e., PASI and PGA of disease severity). Withdrawal of therapy in subjects with stable Ps control led to relapse (PGA ≥ 3) at a median time of 141 days, with 69% of subjects regaining clinical response (PGA of "Clear or Minimal") after 16 weeks of retreatment.

With regards to PK after withdrawal and retreatment, serum adalimumab concentrations returned to similar levels as prior to withdrawal regardless of relapse or responder status. For subjects who participated from Study M03-656, 1 or 2 treatment interruptions did not affect the ability to return to similar concentrations as prior to withdrawal. Higher AAA rates were detected after withdrawal of adalimumab therapy, but returned to pre-withdrawal rates upon retreatment after 16 weeks. Furthermore, AAA status did not impact safety and efficacy.

Adalimumab retreatment following withdrawal of therapy was effective in reducing the signs and symptoms of Ps that appeared during adalimumab withdrawal as evaluated via the patient-reported QoL outcomes DLQI and FACIT-Fatigue score.

Finally, the safety results in this OL continuation Study M03-658 of adalimumab for the treatment of subjects with moderate to severe chronic Ps are consistent with the known safety profile of adalimumab.

Date of Report: 14Apr2010