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:

Safety and Efficacy of Adalimumab in Patients with Active Psoriatic Arthritis (PsA) – An Open-label, Multinational Study to Evaluate the Response to Every-Other Week Adalimumab When Added to Insufficient Standard Therapy, Including Patients Who Failed Prior Treatment With Other TNF-Inhibitors (STEREO)

Investigator:

Dr. Filip Van den Bosch; University Hospital Ghent; Department of Rheumatology; De Pintelaan 185; 9000 Ghent; Belgium.

Study Site(s):

Multicenter (85 study sites in 9 countries - Belgium, Germany, Denmark, Finland, France, Great Britain, Ireland, Norway, and Sweden)

Publications:

N/A

Studied Period (Years):	**Phase of Development:** 3b
First Subject First Visit: 26 Jul 2005 Last Subject Last Visit: 21 Aug 2006	

Purpose of Amendment

The original clinical study report, which was finalized on 12 Jul 2007, has been amended with this current version (referred to as M04-724 Amendment 1). The reason for this amendment is that upon further review, the following issues were discovered and are corrected in this document:

- The scale for the PGA at Baseline was reversed from "severe" to "clear" to "clear" to "severe."
- The labels for ALT and AST were changed from SGOT(ALT) to SGPT(ALT) and from SGPT(AST) to SGOT(AST).
- The calculations of events per patient years for AEs by highest severity and by closest relationship were corrected.

However, the overall conclusions about the efficacy and safety of adalimumab in subjects with PsA in this study are unchanged.

Objective(s):

Efficacy

To establish whether subjects with moderate to severely active psoriatic arthritis will show response when adalimumab is added to the pre-existing insufficient standard psoriatic arthritis therapy, the efficacy profile of adalimumab will be compared for subjects with concomitant disease-modifying antirheumatic drugs (DMARDs) vs. adalimumab monotherapy. The efficacy of adalimumab will also be compared in subjects with or without prior exposure to other tumor necrosis factor (TNF)-inhibitors (etanercept, infliximab).

Safety

To demonstrate the safety of adalimumab in PsA subjects in a normal clinical setting, subjects may be on concomitant non-steroidal anti-inflammatory drugs (NSAIDs), steroids, one or more DMARDs, either as single treatment or in combination. Subjects may have been previously treated and failed TNF-inhibitors (etanercept, infliximab).

Safety effects will also be analyzed by:

a) Concomitant DMARD(s): e.g., methotrexate (MTX), leflunomide, sulfasalazine or others with adalimumab vs. adalimumab monotherapy.

b) Prior treatment with etanercept and/or infliximab vs. anti-TNF naïve subjects.

Methodology:

This was an open-label, multinational, multicenter study designed to further assess the safety and efficacy of adalimumab in the treatment of moderate to severely active PsA subjects with insufficient preexisting standard psoriatic arthritis therapy.

A total of approximately 500 subjects having a diagnosis of active PsA fulfilling study eligibility criteria were planned to be enrolled at approximately 80 to 100 sites in Europe. Study drug (40 mg) was to be self-administered by subcutaneous (SC) injection every other week (eow).

The study included a screening period of at least two days, depending on the availability of all screening results including PPD test assessment, T SPOT-TB in vitro blood test, and tuberculosis (TB) prophylaxis if required, followed by a 12-week study treatment period. Thereafter a supply of adalimumab was to be provided for another eight weeks by which time the PsA indication was expected to be approved and adalimumab would be generally available for the country or region. In case adalimumab would not be generally available at the time point of study termination at Week 20, the treating physician was to discuss the appropriate treatment with the subject.

Number of Subjects (Planned and Analyzed):

Planned: 500

Analyzed: 442

Diagnosis and Main Criteria for Inclusion:

Subjects were eligible for enrollment if they had a confirmed diagnosis of PsA and were over the age of 18. Main criteria for inclusion included: Active PsA with ≥ 3 tender and ≥ 3 swollen joints despite standard psoriatic arthritis therapy and unsatisfactory response or intolerance to at least one prior or ongoing DMARD. Subject study enrollment must be in accordance with the current national guidelines for treatment of PsA with TNF inhibitors.

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

Adalimumab, 40 mg/0.8 mL solution for injection in 1 mL pre-filled syringes, subcutaneous injection

Lot number: 05-000203

Duration of Treatment:

Twelve weeks with potential for extension to 20 weeks depending of availability of commercial adalimumab at that time.

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

None

Criteria for Evaluation

Efficacy:

Efficacy assessments included ACR20/50/70 response, TJC78, SJC76, Physician's Global Assessment of disease activity, Patient's Global Assessment of disease activity, Patient's Global Assessment of pain, Patient's Assessment of back pain, the Disability Index of the Heath Assessment Questionnaire, the Disease Activity Score (DAS) 28, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Physician's Global Assessment of Psoriasis (Ps), Total Ps plaque scores, Ps plaque diameters, nail Ps severity index (NAPSI), Psoriatic Arthritis Response Criteria (PSARC), and Dermatology Life Quality Index (DLQI).

Safety:

Safety assessments included adverse event (AE) monitoring and evaluation based on frequency, severity, and relationship to study drug.

Statistical Methods

Efficacy:

All subjects who received at least one injection of adalimumab were to be included in the efficacy analysis. The efficacy analysis was to be done descriptively by presenting summary statistics and confidence intervals. The values at all visits as well as changes from baseline were to be summarized.

Efficacy variables were to be analyzed for the subgroups of subjects with concomitant DMARD(s) and for subjects with adalimumab monotherapy separately, as well as for subjects with or without prior exposure to other biologics. Comparisons between the respective subgroups (such as 1) with concomitant DMARD(s) vs. adalimumab monotherapy; 2) with vs. without prior exposure to other biologics, etc.) were to be done using adequate statistical models that account for relevant confounders. All comparisons were to be descriptive. Further details regarding the statistical analysis, including the identification of confounders, were to be specified in the statistical analysis plan.

Safety:

AEs were to be tabulated by system organ class and preferred term, whereby the most current implemented MedDRA dictionary was to be used. The number and percentage of subjects experiencing AEs was to be presented. Also, summaries by severity and relationship to study drug were to be done. Certain AEs, like serious, severe, or leading to premature withdrawal, were to be listed and described in detail.

Other safety variables, like laboratory data, were to be described by statistical characteristics as mentioned above. In addition, shift tables and listings were to be provided for abnormal values, whereby the normal range of the variables from the analyzing laboratory were to be used.

Safety variables were to be analyzed for the subgroups of subjects with concomitant DMARD(s) and for subjects with adalimumab monotherapy separately, as well as for subjects with or without prior exposure to other biologics. Comparisons between the respective subgroups (with concomitant DMARD(s) vs. adalimumab monotherapy; with vs. without prior exposure to other biologics) were to be done using adequate statistical models that account for relevant confounders. All comparisons were to be descriptive. Further details regarding the statistical analysis, including the identification of confounders, were to be specified in the statistical analysis plan.

Summary/Conclusions

Efficacy Results:

Adalimumab was shown to be efficacious as evidenced by:

1) Arthritic Manifestations
   - ACR20, ACR50, and ACR70 response rates were 73.8% (301/414 subjects), 50.7% (207/414 subjects), and 31.9% (130/414 subjects), respectively at Week 12.
   - There was no difference between groups with and without concomitant DMARDs for ACR20,50,70, DAS 28, PsARC, and most individual ACR core set parameters. Subjects with concomitant DMARDs had a significantly greater mean change from Baseline in ESR than those without concomitant DMARDs ($p = 0.018$) at Week 12. Subjects with concomitant DMARDs reported a significantly greater mean percent change from Baseline in the Patient's Global Assessment of disease activity than those without concomitant DMARDs ($p = 0.046$) at Week 12.
   - The only difference seen between groups with and without prior anti-TNF therapy was that that proportion of subjects achieving ACR 50 response was significantly higher in subjects with no prior anti-TNF therapy ($p = 0.021$) at Week 12.
   - PsARC response rate was 77.7% (314/414 subjects) by Week 12.
2) Disability Measurements
   - The mean change from Baseline in the Disability Index of the HAQ in the ITT population was −0.52 at Week 12. No significant differences were seen in either of the subgroups.
3) Skin Manifestations
   - In the Physician's Global Assessment for Ps, 68.1% (282/414 subjects) of subjects were "clear" or "almost clear" by Week 12. No significant differences were seen in either of the subgroups.
   - At Week 12, the mean change from Baseline of total plaque score was –4.9 for the ITT population. Subjects with concomitant DMARDs had a significantly greater mean change and mean percent change from Baseline in total Ps plaque score than those without concomitant DMARDs ($p = 0.020$ and $p = 0.013$, respectively) at Week 12. Subjects without prior anti-TNF therapy had a significantly greater mean change and mean percent change from Baseline in total Ps plaque score than those with prior anti-TNF therapy ($p = 0.030$ and $p = 0.033$, respectively).
   - At Week 12, the mean change from Baseline for Ps plaque diameter was –39.1 for the ITT population. No significant differences were seen in either of the subgroups.
   - At Week 12, the mean change from Baseline for NAPSI score was –8.9 for the ITT population. No significant differences were seen in either of the subgroups.

4) Quality of Life Evaluations

- At Week 12, the mean change from Baseline was –4.6 for the ITT population. Subjects without prior anti-TNF therapy had a significantly greater mean change from Baseline in DLQI than those with prior anti-TNF therapy (p = 0.025).

Overall, no clinically significant differences were observed.

Safety Results:

There was a low rate of AEs. Only two AEs were reported in more than 5% of subjects: nasopharyngitis (10.4%, 46/442 subjects) and headache (6.1%, 27/442 subjects).

Only 4.1% (18/442 subjects) of subjects reported a SAE during treatment.

The overall rate of serious infection was 0.7% (3/442 subjects; 3.2 events per 100 PY).

On subjects reported tuberculosis (0.2%), and two subjects (0.5%) experiences other opportunistic infections.

No malignancies, lupus-like reactions, congestive heat failures, demyelinating diseases, or deaths were reported in the study.

In comparing the safety profile of adalimumab for subjects with concomitant DMARD(s) vs. adalimumab monotherapy (without concomitant DMARDs), no statistically significant differences were observed. The safety profile of adalimumab is unaffected by concomitant DMARDs.

In comparing the safety profile of adalimumab in subjects with or without prior exposure to other TNF-inhibitors (etanercept, infliximab), subjects with prior anti-TNF therapy were less likely to report a treatment-emergent AE while on adalimumab (Odds Ratio = 0.50; p = 0.021). However, there was no difference in the frequency of SAEs reported based on prior anti-TNF therapy.

Conclusions:

In this open-label study, adalimumab at a dose of 40 mg eow sc was generally safe and well tolerated, and reduced the signs, symptoms, and disability of PsA; ameliorated the associated Ps, and improved the quality of life in patients with active disease who had an inadequate response to prior therapy.

Date of Report: 03Jul2007