



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: N/A	(For National Authority Use Only): N/A
Name of Study Drug: Adalimumab	Volume: N/A	
Name of Active Ingredient: Adalimumab	Page: N/A	
Title of Study: A Canadian Open-label Study to Evaluate the Safety and Effectiveness of Adalimumab When Added to Inadequate Therapy for the Treatment of Psoriatic Arthritis (PsA) (ACCLAIM)		
Investigator: [REDACTED] MD, FRCPC redacted information 01Oct2014		
Study Site(s): Multicenter with a total of 24 sites in Canada		
Publications: None		
Studied Period (Years): First Subject First Visit: 26 Apr 2006 Last Subject Last Visit: 12 Apr 2007	Phase of Development: 3b	
Objective(s): The primary objective of this study was to evaluate the safety profile of adalimumab when used for the treatment of subjects with active PsA who have not adequately responded to prior PsA therapy. The secondary study objective was to evaluate the effectiveness of adalimumab when used for the treatment of subjects with active PsA who have not adequately responded to prior PsA therapy.		
Methodology: This was a Canadian open-label, multicenter, Phase 3b, noncomparative access study designed to further assess the safety and effectiveness of adalimumab in the treatment of subjects with active PsA who had failed prior PsA treatment. The study was to have enrolled up to 400 subjects, having a diagnosis of active PsA, who fulfilled the study eligibility criteria at approximately 40 sites in Canada. A total of 127 subjects who had a diagnosis of active PsA were enrolled at 24 sites in Canada. Safety and efficacy measurements were performed throughout the study. The study consisted of a screening period of up to two weeks (14 days) followed by a minimum 12-week treatment period. Subjects who completed the 12-week treatment before adalimumab became commercially available for PsA entered a continuation phase with visits occurring every 12 weeks. The continuation phase ended when adalimumab became commercially available for PsA. The continuation phase therefore had a different duration for individual subjects, depending on when they entered the 12-week treatment period relative to the date of commercial availability. Subjects who entered the		



continuation phase returned to the clinic for a Completion Visit, similar to the Week 12 visit, when adalimumab became commercially available. Subjects who withdrew from the study before the Week 12 visit returned to the clinic for an Early Termination (ET) visit at which time they underwent the same procedures prescribed for the Week 12 and Completion visits. A window of ± 7 days was permitted for each study visit.

The study was to be completed when marketing approval was granted in Canada. However, marketing approval was received earlier than expected. As a result, enrollment was continued until 30 Nov 2006. At that time, subjects who had been in the study for longer than 12 weeks were discontinued upon reaching the Week 24 visit, and subjects who had not reached the 12-week visit were continued in the study until they reached that time point.

All subjects received adalimumab 40 mg by subcutaneous (SC) self-injection every other week (eow). Subjects were to receive their first dose of study drug from site personnel and were to be trained to self-inject for the remaining doses. Subjects were to return every 12 weeks thereafter for the duration of the study. However, although the design included a continuation period, just four subjects completed the 12-week treatment period before adalimumab became commercially available in Canada for the treatment of PsA, and remained in the study.

Number of Subjects (Planned and Analyzed):

Planned: Up to 400 subjects

Analyzed: 127 subjects were enrolled and analyzed for both efficacy and safety

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were males and females aged ≥ 18 years with active PsA defined by ≥ 3 swollen joints despite standard PsA therapy. Eligible subjects must also have had an unsatisfactory response or intolerance to therapy for the treatment of PsA as defined by the individual provincial requirements for the reimbursement of biologic tumor necrosis factor (TNF) inhibitors (the applicable conditions are dependent upon the availability of individual provincial requirements for the reimbursement of biologic TNF inhibitors for the treatment of PsA); or, had unsatisfactory response or intolerance to therapy for the treatment of PsA as defined by the subject's private insurance requirements for the reimbursement of biologic TNF inhibitors; or, if the former was not applicable, had to have had an unsatisfactory response or intolerance to at least two prior ongoing disease-modifying antirheumatic drugs (DMARDs). If female, the subject was either not of childbearing potential, defined as postmenopausal for at least one year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or was of childbearing potential and practiced one of the following methods of birth control: condoms, sponge, foams, jellies, diaphragm, or intrauterine device; contraceptives (oral or parenteral) for three months (90 days) prior to study drug administration; a vasectomized partner; or total abstinence from sexual intercourse. If female and was of childbearing potential, the result of a serum pregnancy test performed at Screening was negative. The subject must have been able and willing to self-administer SC injections or had to have available qualified person(s) to administer SC injections. The subjects also had to have been able and willing to give written informed consent and comply with the requirements of the study protocol.



<p>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</p> <p>Test Product: adalimumab Test Dose/Strength/Concentration: 40 mg/0.8 mL Mode of Administration: SC injection Lot Number: [REDACTED] redacted information 01Oct2014</p> <p>Duration of Treatment:</p> <p>Subjects were to receive 12 weeks of study treatment.</p>
<p>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</p> <p>None</p>
<p>Criteria for Evaluation</p> <p>Efficacy:</p> <p>The primary efficacy measurement was the ACR20 response rate. A subject was considered to have a response, if he/she showed at least a 20% improvement in both tender joint count (TJC) and swollen joint count (SJC) and at least a 20% improvement in 3 of the 5 remaining ACR core set measures (Patient's Assessment of Pain, Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, erythrocyte sedimentation rate, and the Disability Index of the Health Assessment Questionnaire (HAQ-DI).</p>
<p>The secondary efficacy measurements included the following rheumatic components: ACR50 and ACR70 response; modified Psoriatic Arthritis Response Criteria (PsARC) response; absolute and percent change in DAS28; proportion of subjects with severe, moderate or low disease activity as assessed by the DAS28; absolute and percent change in joint count (swelling and tenderness); absolute and percent change in the Patient's Assessment of Pain; and absolute and percent change in the Patient's Global Assessment of Disease Activity.</p>
<p>The secondary efficacy measurements also included the following psoriatic components: absolute and percent changes in the Psoriasis Target Lesion Assessment in subjects having a target lesion with a plaque score ≥ 6 at Baseline; PASI50/75 in subjects with $\geq 3\%$ BSA Ps involvement at Baseline; and target lesions were assessed for erythema, induration, and scaling. Other secondary efficacy components were: absolute and percent change in the number of fingers or toes with active dactylitis; absolute and percent change in the number of enthesitis (tenderness on Achilles' tendon and plantar fascia upon pressure); physical function and health-related quality of life; and absolute and percent change in HAQ-DI.</p>
<p>As an exploratory tertiary objective, the impact of adalimumab treatment on work-related productivity indices was to be evaluated by comparing absolute and percent changes from Baseline in work limitations questionnaire (WLQ) domains.</p>
<p>Safety:</p> <p>Safety was assessed from adverse events (AEs), laboratory values, and physical examination.</p>



Statistical Methods

All analyses were conducted in the intent-to-treat (ITT) population. Demographic and Baseline variables were described by summary statistics. Descriptive statistics were reported for all efficacy variables. For all outcome measures, the actual values and the changes from Baseline for all visits were described. Stratified descriptive statistics were reported for subgroups of subjects treated concomitantly with different numbers of DMARDs (0, 1, ≥ 2), for subjects with and without prior exposure to other biologics and based on the reasons for discontinuation of prior biologic agents. Comparisons between these subject subgroups were based on the appropriate statistical tests that included Analysis of Variance (ANOVA) for continuous scale variables, and the Chi-Square statistic for categorical variables. AEs were tabulated by system organ class and preferred term, using the most current MedDRA dictionary. The number and percentage of subjects experiencing AEs were calculated and summarized by severity and relationship to study drug. Serious adverse events (SAEs) leading to premature withdrawal of the subject from the study were listed separately and described in detail.

Summary/Conclusions

Efficacy Results:

Rheumatic Components

The primary efficacy endpoint was ACR20 response. A total of 78.0% of subjects exhibited an ACR20 response following treatment with adalimumab 40 mg SC eow for up to 12 weeks. In terms of secondary endpoints of signs of symptoms, a total of 55.9% and 21.3% of subjects achieved ACR50 and ACR70 responses, respectively, while 70.1% subjects achieved a PsARC response. Clinically and statistically significant decreases were observed in TJC (-14.7) and SJC (-9.1) from Baseline to Week 12 ($p < 0.001$). Additionally, clinically significant changes were observed in the change in the proportion of subjects with fingers and toes with active dactylitis. At Baseline, 46.5% subjects exhibited dactylitis in fingers or toes. At 12 weeks, these numbers had decreased to 24.4% of subjects. Clinically significant changes were observed in the change in tenderness of the Achilles tendon (from 29.9% at Baseline to 14.2% at Week 12; $p = 0.004$) and tenderness of the plantar fascia (from 24.4% at Baseline to 11.0% at Week 12; $p = 0.008$).

Disease Activity

Secondary endpoints to assess disease activity demonstrated clinically and statistically significant improvements as measured by DAS28 (-2.0 from Baseline to Week 12). Statistically significant changes from Baseline to Week 12 (shifts of severe disease to moderate and mild disease) were observed in the proportions of subjects with severe, moderate, or low disease activity as assessed by the DAS28. Clinically significant decreases from Baseline to Week 12 were observed in Patient's Assessment of Pain (-26.8), Patient's Global Assessment of Disease Activity (-29.1), and Physician's Global Assessment of Disease Activity (-40.1), $p < 0.001$.

Psoriatic Components

At Week 12, 64.7% of subjects achieved a PASI50 response and 47.1% of subjects achieved a PASI75 response. At Baseline, mean total plaque score was 8.9 ± 2.2 . At Week 12, it decreased by 4.0 to 5.1 ± 3.3 . This change was statistically and clinically significant ($p \leq 0.001$).

Physical Function

A statistically and clinically significant decrease in HAQ-DI from Baseline to Week 12 was observed (-0.44 ; $p < 0.001$).



Work Limitations Questionnaire

Results demonstrated statistically and clinically significant decreases in WLQ from Baseline to Week 12 in three of the four domains (physical, time, and output) indicating that adalimumab is effective in reducing the impairment in work-related productivity.

Subgroup Analyses:

In terms of subgroup analyses, comparable ACR response rates and PASI responses were observed between subjects who received adalimumab as monotherapy or as combination therapy, between subjects who received adalimumab as monotherapy or with 1 or ≥ 2 DMARDs, and between those subjects who had previously been treatment with biologic and those who had not.

Safety Results:

Overall, 81 subjects who received adalimumab eow reported a treatment-emergent AE (TEAE). The most frequently reported TEAEs, based on system organ class, were infections and infestations (26.7%). By preferred term, the most frequently reported TEAEs were headache, upper respiratory tract infection, and dizziness. Most subjects reported TEAEs that were mild (65.7%) and considered not related or unlikely to be related to study drug by the Investigator. A total of 11.9% of subjects reported TEAEs that were assessed as probably related to study drug by the Investigator.

Three subjects reported three treatment-emergent SAEs. Two of the events were reported during the 70-day follow-up period. A [REDACTED] female experienced a cerebral venous thrombosis on Day 94 and was hospitalized. This SAE was assessed by the Investigator as not related to study medication. A [REDACTED] male reported psoriatic arthropathy on Day 105 and was hospitalized for treatment. The causality of this event was not likely related to study drug. A cerebrovascular accident was reported in a [REDACTED] female on Day 72. Study medication was discontinued. The causality of this SAE was also considered to be not likely related to study drug. There were no deaths reported during the study.

Conclusions: redacted information 01Oct2014

Study W05-399, a Phase 3b, multicenter, open-label study in subjects with active PsA who had not adequately responded to prior PsA treatments, demonstrated results comparable to those observed in other studies of adalimumab for the treatment of PsA: adalimumab proved to be effective in treating the signs and symptoms of PsA, both arthritic and psoriatic, decreased disease activity, increased physical function, and improved the quality of life and the productivity of patients who had not adequately responded to prior PsA therapy.

In this study in subjects with active PsA, adalimumab 40 mg SC eow for up to 12 weeks was well-tolerated and had a safety profile similar to that observed when it is used to treat patients with rheumatoid arthritis or to that observed in PsA randomized clinical trials. There were no deaths in this study and only three SAEs were reported, none of which were considered to be possibly or probably related to study medication. Laboratory values and vital signs were unremarkable overall.