



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		
Title of Study: A Phase 3 Multicenter Study of the Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Active Ankylosing Spondylitis		
Investigator: [REDACTED] redacted information 14Nov2014		
Study Site(s): 11 sites in Canada		
Publications: 8 articles, 12 abstracts, 12 posters		
Studied Period (Years): First Subject First Visit: 15 December 2003 Last Subject Last Visit: 20 April 2009	Phase of Development: 3	
Objectives: The primary objectives of this study are to evaluate the efficacy and safety of 40 mg every other week (eow) subcutaneous (SC) adalimumab on: <ul style="list-style-type: none">• Reduction of signs and symptoms as measured with Assessment in Spondyloarthritis International Society (formerly Assessments in AS; ASAS) Working Group response criterion (ASAS 20) at Week 12.• Inhibition of progression of structural damage in the spine as measured with the change of the modified Stoke Ankylosing Spondylitis Spine Score (modified SASSS) from Baseline to Week 104. The secondary objectives of this study were to evaluate the effect of 40 mg eow adalimumab compared to placebo on: <ul style="list-style-type: none">• ASAS 20, ASAS 40, ASAS 50, and ASAS 70• Improvement in Bath AS disease activity index (BASDAI)• Bath AS functional index (BASFI)• Bath AS global index (BAS-G)• Bath AS metrology index (BASMI)• Edmonton AS metrology index (EDASMI)		



Objectives (Continued):

- Chest expansion
- Maastricht AS enthesitis score (MASES)
- Nocturnal pain VAS
- Total back pain VAS
- Partial remission
- Physician's global assessment of disease activity
- Patient's global assessment of disease activity
- Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue scale
- Swollen joint count for 44 joints (SJC 44)
- Tender joint count for 46 joints (TJC 46)
- Short form-36 health survey questionnaire (SF-36)
- C-reactive protein (CRP)
- Ankylosing Spondylitis Quality of Life questionnaire (ASQoL)
- Health Utilities Index Mark 3 (HUI-3)
- Disease Controlling Antirheumatic Therapy (ASAS 5/6) (including ASAS 40 and Partial Remission) outcome criteria
- Minimally clinically important state (MCIS), hereafter referred to as the Patient Acceptable Symptom State (PASS)
- Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) from Baseline to Week 104
- Safety assessment

Markers of articular cartilage damage (such as serum matrix metalloproteinase-3 (MMP-3), urine Type II collagen C-telopeptide (CTX-II) and serum Type I collagen N-telopeptide (NTx) were also examined.

However, for this 5-year open-label extension study report, the above secondary endpoints were not compared to placebo since placebo treatment was completed upon conclusion of the 24-week double-blind portion of the study, results from which were previously reported.



Methodology:

Study M03-606 is a Phase 3, placebo-controlled, double-blind, randomized, multicenter study designed to demonstrate the safety and efficacy of adalimumab in the treatment of active AS in subjects who have had an inadequate response or intolerance to one or more nonsteroidal anti-inflammatory drugs (NSAIDs) and who may have additionally failed disease-modifying antirheumatic drug (DMARD) therapy. Subjects were randomized in a 1:1 ratio to receive either 40 mg adalimumab eow SC or matching placebo during a 24-week placebo-controlled period. The 24-week placebo-controlled period of the study was followed by an open-label period during which subjects received 40 mg adalimumab eow SC for up to 236 weeks. The study was unblinded after all subjects completed the 24 week double-blind portion and results [REDACTED] were submitted to the agencies to support the indication of reducing signs and symptoms of active AS.

Subjects who failed to achieve ASAS 20 at Weeks 12, 16 or 20 had the following three options:

- Continue blinded study medication through Week 24;
- Receive early escape therapy (i.e., open-label adalimumab 40 mg eow SC prior to Week 24; defined as the "Early Escape Group"); or
- Discontinue from the study.

If a subject did not achieve a response based on ASAS 20 after at least 12 weeks of open-label treatment, increasing the frequency of adalimumab to 40 mg weekly was permitted (rescue therapy).

Number of Subjects (Planned and Analyzed):

Planned: 78 subjects

Enrolled: 82 subject

Analyzed: 82 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects were males and females aged 18 years or older who had an inadequate response to or intolerance to one or more NSAIDs and met the criteria for the diagnosis of active AS as defined by the Modified New York Criteria. Subjects must have fulfilled at least two of the following three criteria:

- BASDAI score ≥ 4 ,
- VAS score for Total Back Pain ≥ 40 mm (4 cm), or
- Morning stiffness ≥ 1 hour.

Additional criteria required that subjects:

- On sulfasalazine (SSZ; ≤ 3 g/day) and/or methotrexate (MTX; ≤ 25 mg/week) and/or hydroxychloroquine (≤ 400 mg/day) and/or prednisone (≤ 10 mg day) (and/or prednisone equivalents) and/or NSAIDs had maintained a stable dose for 4 weeks prior to Baseline.

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

Adalimumab, 40 mg/0.8 mL, SC: Lot numbers [REDACTED]

redacted information 14Nov2014



Duration of Treatment:

Subjects were to receive open-label adalimumab 40 mg eow for up to 236 weeks of treatment beyond the 24-week double-blind period. The total duration of exposure for any subject was not to exceed 5 years.

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

Placebo for adalimumab, 40 mg/0.8 mL, SC: Lot number [REDACTED] redacted information 14Nov2014

Criteria for Evaluation

Efficacy:

Primary Efficacy Endpoints

The first primary efficacy parameter was the ASAS Working Group response criterion (ASAS 20) at the 12-week primary endpoint. A subject was categorized as an ASAS 20 responder if the subject achieved the following:

Improvement of $\geq 20\%$ and absolute improvement of ≥ 10 units (on a scale of 0 to 100) from Baseline in ≥ 3 of the following 4 domains:

- Subject global assessment
- Pain
- Function
- Inflammation

There had to be an absence of deterioration in the potential remaining domain, where deterioration was defined as a change for the worse of $\geq 20\%$ and a net worsening of ≥ 10 units (on a scale of 0 to 100). These changes applied to each scale and not to an overall, global scale.

Subject global assessment was represented by the VAS global assessment score (0 to 100) scale. Pain was represented by the total back pain VAS score (0 to 100 scale). Function was represented by the BASFI score (0 to 100 scale). Inflammation was represented by the mean of the two morning stiffness-related BASDAI VAS scores (i.e., the average of items 5 and 6 of the BASDAI).

The second primary efficacy parameter was change in x-ray based on the modified Stoke Ankylosing Spondylitis Spine Score (modified SASSS) scoring method from Baseline to Week 104.

Secondary Efficacy Endpoints

Secondary efficacy variables included:

- The ASAS 20 response through Week 260.
- The ASAS 40, ASAS 50 and ASAS 70 responses through Week 260.
- The BASDAI 20, BASDAI 50, and BASDAI 70 responses through Week 260.
- Change in the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Patient Global Index (BAS-G), nocturnal pain score, the Bath Ankylosing Spondylitis Metrology Index (BASMI), and the Edmonton Ankylosing Spondylitis Metrology Index (EDASMI) through Week 260.
- Change in total back pain through Week 260.
- Change in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) through Week 260.
- Change in C-reactive protein (CRP) through Week 260.



Criteria for Evaluation

Efficacy:

Secondary Efficacy Endpoints (Continued)

- ASAS partial remission through Week 260.
- Physician's global assessment of disease activity through Week 260.
- Subject's global assessment of disease activity through Week 260.
- Change in biomarkers (serum MMP-3, urine CTX-II and Type I collagen NTx) through Week 260.
- Change in the SF-36 Health Survey index (the physical component summary and the mental component summary through Week 260.
- Change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale through Week 260.
- Change in Ankylosing Spondylitis Quality of Life questionnaire (ASQoL) through Week 260.
- Change in Health Utilities Index (HUI)-3 through Week 260.
- Percent of subjects achieving the minimal clinically important state (MCIS) through Week 260.
- Change in the swollen joint index (44 joints) through Week 260.
- Change in the tender joint index (46 joints) through Week 260.
- Change in the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index of disease activity score at 12 and 52 weeks.
- Change in the SPARCC MRI index of structural damage at 12 and 52 weeks.
- ASAS 5/6 response through Week 260.

Specific efficacy assessments (i.e., BASMI, EDASMI, MASES, SJC, TJC) must have been performed by an independent assessor. The independent assessor should not have performed any other study related procedures. A back-up independent assessor, who was trained and competent in performing such assessments, must have been identified. The training of all assessors must have been documented. If the independent assessor was not available, the pre-identified back-up assessor was to perform such assessments. The use of an independent assessor was to last for a minimum of six months to cover the double-blind treatment period.

Safety:

Safety was assessed by adverse events (AEs), physical examinations (PEs), vital signs and laboratory data.



Statistical Methods

Efficacy:

Descriptive statistics were provided to summarize efficacy variables. These included the number of observations, mean, standard deviation, 95% confidence interval, median, minimum, and maximum for continuous variables and counts and percentages for discrete variables.

The last available pre-treatment values recorded on or before Day 1 (first adalimumab injection date) were considered as Baseline. All changes and percent changes were calculated based on this baseline unless otherwise stated.

In general, the efficacy variables were presented as observed. Data were summarized for subjects receiving adalimumab only. Long-term data was summarized by duration of exposure to any adalimumab, as opposed to study visit.

Safety:

All subjects who received at least one dose of the study drug were included in the safety analysis. Treatment-emergent adverse events (TEAEs) included all AEs that either began on or after administration the first adalimumab injection. The number and percentage of subjects reporting TEAEs were tabulated by Medical Dictionary for Regulatory Activities (MedDRA[®]) preferred term (PT) and system organ class (SOC). TEAEs that were judged by the Investigator to be probably or possibly related to study drug were also tabulated. In addition, AEs summarized by severity and relationship to study drug were presented. Treatment-emergent adverse events (TEAEs) were tabulated. In addition, SAEs were collected between the signing of the informed consent and the first dose were reported separately. TEAEs which were serious, severe or life threatening were described in detail. All AEs were presented in the data listing.

The AE data before and after retreatment in Study M03-606 according to the definition of dose interruption were also provided.

All laboratory and vital signs values beyond the normal ranges were listed. For evaluation of both laboratory and vital sign values, the last evaluation prior to the first dose of adalimumab was used as Baseline for all analyses.

The baseline, minimum, maximum, and final value means was presented for subjects who had both baseline and post-baseline values. Categorical data was summarized using frequencies and percentages. The number of non-missing values was given.



Summary/Conclusions

Efficacy Results:

The study population was typical of an AS population, which is largely male, white, and HLA-B27 positive. No unexpected concomitant diseases, presenting Baseline disease characteristics, or prior/concomitant therapies were noted.

The results of the analyses for this study report support the findings from the 24-week placebo-controlled DB period CSR. The benefit and effectiveness of adalimumab seen during the first 24 weeks of treatment in reducing the signs and symptoms of active AS was maintained for up to 5 years (260 weeks). This includes parameters associated with disease controlling clinical response such as ASAS 40, ASAS 5/6, and ASAS partial remission.

Measures of biomarkers (MMP-3, CTX-II, and NTx) tended to decrease over the course of the study, which suggested that treatment with adalimumab may suppress the degradation of articular cartilage in subjects with active AS. The high degree of variability of these biomarker data, however, precludes any definitive or meaningful conclusions from being drawn.

Safety Results:

Adalimumab was generally safe and well-tolerated in Study M03-606 at SC doses up to 40 mg weekly for up to 5 years of treatment as evaluated by the incidence and pattern of SAEs and discontinuations due to AEs.

- Frequencies of SAEs are similar to those presented in previously submitted summaries of adalimumab in AS, and is not unusual taking increased time and exposure to study drug into account.
- The majority of events resulting in discontinuation of the study occurred in just one subject each.
- One treatment-emergent death occurred due to gastric cancer which was considered by the investigator as probably not related to study drug.
- Adalimumab was also generally safe and well-tolerated in Study M03-606 at SC doses up to 40 mg weekly for up to 5 years of treatment as evaluated by events of interest for TNF inhibitors.
- A considerable proportion, 86.6% (71/82), of subjects reported an infectious AE, however these were considered to be medically manageable.
- Overall 3.7% (3/82) of subjects treated with any dose of adalimumab reported a malignant AE. One of these events, gastric cancer, resulted in death.
- There were no opportunistic infections. There were no cases of TB. Two subjects were reported with a positive TB skin test during the study.
- One subject reported lupus-like syndrome.
- Overall, 17.1% (14/82) of subjects treated with any dose of adalimumab reported an injection site reaction. Most injection site reactions reported were mild and considered to be medically manageable.



Safety Results (Continued):

- Overall, 9.8% (8/82) of subjects treated with any dose of adalimumab reported a hepatic related AE. Most events were mild to moderate in intensity and assessed by the Investigator as possibly related or not related to study drug.
- Overall, 4.9% (4/82) of subjects treated with any dose of adalimumab reported any allergic reaction related AE. Most events were mild in intensity and assessed by the Investigator as possibly related to study drug.
- Two subjects out of 82, (2.4%), treated with any dose of adalimumab reported treatment-emergent hematologic related AEs.
- No subjects reported a congestive heart failure AE.
- No subjects reported a demyelinating AE.
- Adalimumab was safe and well tolerated for up to 5 years as evaluated by laboratory and vital sign results.
- No clinically significant changes in hematology or urinalysis laboratory results occurred during the study. Changes are similar to changes observed among adalimumab treated subjects in previously reported studies and are not judged to be clinically important.
- Most changes in clinical chemistry were not clinically significant. The increases in cholesterol and triglycerides observed in Study M03-606 have also been seen in prior studies in adalimumab-treated subjects and are probably related to correction of the dyslipoproteinemia associated with the inflammatory state.
- Four subjects with normal Baseline ALT values had post-Baseline ALT values $\geq 3.0 \times \text{ULN}$. All 4 of these subjects had post-Baseline ALT elevations that resolved on continued treatment with adalimumab. Two of the 4 subjects with post-Baseline ALT values $\geq 3.0 \times \text{ULN}$ had AEs reported in association with elevated ALT ($\geq 3.0 \times \text{ULN}$) values (ALT increased and hepatic steatosis).
- No clinically significant changes in vital signs were observed.

Conclusions:

Overall, the efficacy of adalimumab, up to a dose of 40 mg weekly, in reducing the signs and symptoms and improving the physical function of subjects with active AS who have had an inadequate response or intolerance to NSAID therapy was maintained for up to 5 years.

Additionally, adalimumab treatment for up to 5 years was generally safe and well tolerated and had a safety profile that was expected based on data from previous studies in the adalimumab clinical program with the recommended dose of 40 mg eow; increase in the dosing frequency to 40 mg weekly was also beneficial without an increase in AEs. There were no new safety findings in this study compared to findings in previous studies in the adalimumab clinical program.