



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] Berlin, Germany redacted information 14Nov2014		
Study Sites: A total of 43 sites participated in this study from Belgium, France, Germany, Italy, The Netherlands, Spain, Sweden, United Kingdom, and the United States		
Publications: There have been 46 abstracts, 46 posters and 2 manuscripts as of the date of this report.		
Studied Period (Years): First Subject First Visit: 07 January 2004 Last Subject Last Visit: 22 July 2009	Phase of Development: 3	
<p>Objective: The objective of this study was to evaluate the safety and efficacy of adalimumab 40 mg given every other week (eow) subcutaneously (SC) compared to placebo in subjects with active AS who have had an inadequate response to or intolerance to one or more NSAIDs and who may have additionally failed one or more DMARD therapy. Active disease was defined as fulfilling at least two of the following three conditions:</p> <ul style="list-style-type: none"> • A Bath AS disease activity index (BASDAI) score ≥ 4 cm (40 mm) • A visual analog score (VAS) for total back pain ≥ 40 mm (4 cm) • Morning stiffness ≥ 1 hour <p>Active disease must have been present both at Screening and at Baseline prior to randomization.</p>		



Methodology: This was a Phase 3, placebo-controlled, double-blind, randomized, multicenter study in the United States and Europe, designed to demonstrate the safety and efficacy of adalimumab in the treatment of active AS in subjects who have had an inadequate response to, or who are intolerant to, treatment with at least one NSAID. Additionally, subjects may have failed one or more DMARDs (e.g., MTX, SSZ, hydroxychloroquine).

Three hundred and fifteen (315) subjects who met entry criteria for this study were enrolled at 43 study sites selected by Abbott Laboratories or its designee. Sites were selected based on their ability to adequately manage study-related requirements and activities, and to enroll eligible subjects. Subjects were randomized in a 2:1 ratio to receive either adalimumab or matching placebo. Subjects on active treatment received a SC injection of 40 mg adalimumab every other week (eow).

The duration of the study was 5 years and commenced with an initial 24-week double blind placebo-controlled period. All subjects then entered the open-label arm of the study where they received adalimumab 40 mg SC every other week for up to 236 weeks. The earliest time that the subjects may have entered the open-label arm of the study was at the Week 24 visit.

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

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

If the subject still did not achieve response based on ASAS20 after at least 12 weeks of treatment with adalimumab 40 mg sc eow in the open-label phase (Week 36 or later), increasing the frequency of adalimumab to 40 mg weekly may have been allowed (rescue therapy).

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.

Number of Subjects (Planned and Analyzed):

Planned: 282 subjects
Analyzed: 315 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects were males and females aged 18 or older with AS who had an inadequate response or intolerance to standard therapy with one or more NSAIDs and who did not have any significant co-morbidities, which would place the subject at risk, or affect the ability to assess safety and efficacy.

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

Test Product: 40 mg/0.8 mL adalimumab

Test Dose/Strength/Concentration: 40 mg/0.8 mL adalimumab/mL at Week 0 and every other week thereafter for up to 260 weeks.

Mode of Administration: SC injection

Bulk Product Lot Numbers [REDACTED]

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Duration of Treatment: 260 weeks
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Test Product: Matching placebo Test Dose/Strength/Concentration: Matching placebo/mL at Week 0 and every other week thereafter for up to 260 weeks. Mode of Administration: SC injection Bulk Product Lot Numbers: [REDACTED] redacted information 14Nov2014
Criteria for Evaluation Efficacy: The following efficacy variables were summarized by visit: <ul style="list-style-type: none">• ASAS 20• ASAS 40, ASAS 50, ASAS 70• Bath AS disease activity index (BASDAI)• Bath AS functional index (BASFI)• Bath AS global index (BAS-G)• Bath AS metrology index (BASMI)• Maastricht enthesitis score (MASES)• Nocturnal pain VAS• Total back pain VAS• Partial remission• Patient's Global Assessment of Disease Activity (PTGA)• Physician's Global Assessment of Disease Activity (PGA)• Swollen Joint Count for 44 joints (44 SJC)• Tender Joint Count for 46 joints (46 TJC)• Short Form-36 Health Survey Questionnaire (SF-36)• C-reactive Protein (CRP)• Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL)• Health Utilities Index –3 (HUI –3)• Work Productivity and Activity Impairment Questionnaire (WPAI-SHP)• Disease Controlling Antirheumatic Therapy (ASAS 5/6) outcome criteria• Minimally Clinically Important State (MCIS)• Modified Stoke Ankylosing Spondylitis Spine Score (modified SASSS) from Baseline to Week 104• Safety assessment <p>Chest expansion was also assessed as a secondary efficacy endpoint since the inception of the study. For the long-term, open-label (5-year) period, the above secondary endpoints were evaluated according to duration of adalimumab exposure.</p>
Safety: Adverse events, physical examination, vital signs and laboratory data were assessed throughout the study.



Statistical Methods

Efficacy:

The analysis of the reduction of signs and symptoms was measured with ASAS 20 at Week 12. ASAS 20 response rates of the adalimumab group were compared with the placebo group using Pearson's Chi-square test. The counts and percentages were calculated for total sample and by therapy group.

The primary analyses of the mSASSS were to be a comparison of the means at Baseline and Week 104. The detailed analysis method was described in a separate SAP, which was to be presented prior to the Week 104 database lock.

The primary analyses of the secondary discrete variables were a comparison of the placebo and adalimumab response rates at Week 12 and Week 24. Pearson's Chi-square test was used. If $\geq 25\%$ of the cells had expected counts less than 5, Fisher's exact test was used instead.

Safety:

All subjects who received at least one dose of the study drug were included in the safety analysis. Treatment-emergent AEs (TEAEs) included all AEs that either began on or after administration of study drug or pre-existing conditions that worsened on or after study drug administration. 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). Treatment-emergent AEs that are 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. Tabulations were presented by treatment group. Treatment-emergent AEs which were serious, severe or life threatening were described in detail. All AEs are presented in the data listings. Fisher's exact test was used to analyze AEs.

Abnormal changes in PEs were described as AEs. Laboratory values outside the reference ranges were flagged and evaluated. All laboratory and vital signs values beyond the normal ranges were listed. Laboratory parameters and vital signs were summarized over time, and changes from Baseline values were summarized. Shift tables for laboratory data were also provided.



Summary/Conclusions

Demographic and Baseline Characteristics: Baseline characteristics were comparable to those seen in the 24-week double-blind study report [redacted] and typical of an AS population, which is largely male (74.9%) and white (96.1%) with a mean age of 42.3 years, and mean weight of 81.1 kg.

Efficacy Results: For the primary analysis (where subjects who discontinued the study before Week 12 were considered as non-responders), 58.2% of the subjects in the adalimumab treatment group achieved an ASAS 20 response compared to 20.6% of the subjects in the placebo treatment group, a difference that was highly statistically significant ($P < 0.001$).

	Placebo (N = 107) n (%)	Adalimumab 40 mg eow (N = 208) n (%)	Difference Between Response Rates % (95% CI)	P value
ASAS 20 Response				
Responder	22 (20.6)	121 (58.2)	37.6 (27.4, 47.8)	< 0.001***
Non-responder	82 (76.6)	83 (39.9)	--	--
Missing	3 (2.8)	4 (1.9)	--	--

No significant difference was seen in the mSASSS change score between the OASIS cohort and subjects in this study and Study M03-606 based on the primary analysis of their Baseline and 2-Year radiographic results

Cohort	N	Mean Change from Baseline to Week 104 (se)	Between-cohort P value
OASIS	169	0.9 (0.22)	0.771
M03-606/607	307	0.8 (0.16)	--

The study population was typical of an AS population, which is largely male, white, and HLA-B27 positive. Concomitant diseases, presenting Baseline disease characteristics, or prior/concomitant therapies were typical of those found in subjects with AS.

Results from the 24-week double-blind portion of Study M03-607 [redacted] demonstrated that adalimumab was effective in reducing the signs and symptoms of active AS. In the adalimumab treatment group, 58.2% of subjects achieved a Week 12 ASAS 20 response (i.e., the primary efficacy endpoint for measuring the signs and symptoms of AS) compared to 20.6% of the subjects in the placebo treatment group, a difference that was statistically significant ($P < 0.001$).

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Summary/Conclusions (Continued)

Efficacy Results (Continued):

The results from the 24-week double-blind portion of Study M03-607 [REDACTED] also demonstrated that adalimumab improved physical function in subjects with AS. The statistically significant response observed in BASFI (-18.70; $P < 0.001$), SF-36 PCS (7.44; $P < 0.001$), and ASQoL (-3.58; $P < 0.001$) during the 24-week double-blind portion of the study was sustained through 5 years of treatment with adalimumab.

Additional results from the analyses for this study report support the findings from the previous 24-week placebo-controlled double-blind [REDACTED]. Results demonstrated the sustained benefit and effectiveness of adalimumab in reducing the signs and symptoms of active AS for up to 5 years (260 weeks):

- ASAS 50, ASAS 70, individual ASAS 20 components (Patient's Global Assessment of Disease Activity, Total Back Pain, BASFI [-27.27], Inflammation [morning stiffness]), and BASDAI 20/50/70 responses as well as mean changes from Baseline in BASDAI and CRP provided additional evidence of the long-term effectiveness and durability of adalimumab in reducing the signs and symptoms of active AS.
- Other secondary efficacy endpoints (mean changes from Baseline in BASMI, MASES, BAS-G, Nocturnal Pain, and Physician's Global Assessment of Disease Activity) up to 5 years demonstrated the long-term effectiveness of adalimumab in reducing the signs and symptoms of active AS.

Parameters associated with disease controlling clinical response demonstrated that adalimumab is both effective and sustains the response for up to 5 years (260 weeks) in subjects with active AS:

- ASAS 5/6 criteria and ASAS 40, and partial remission responses for up to 5 years provided evidence of the effectiveness of adalimumab and the ability to sustain a disease controlling clinical response in subjects with active AS.

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Safety Results:

The mean and median durations of adalimumab treatment were 1410.6 and 1748 days, respectively. Subjects received between 1 to 249 injections of adalimumab.

Results from Study M03-607 of adalimumab administered for up to 5 years at SC doses up to 40 mg weekly demonstrated that adalimumab is generally safe and well tolerated.

This was evidenced by the incidence and pattern of SAEs and discontinuations due to AEs.

- No treatment-emergent deaths occurred. (1 subject died due to adenocarcinoma at the gastroesophageal junction with liver metastases after the 70-day follow-up period, 450 days after last dose of adalimumab).
- Frequencies of SAEs are similar to those presented in previously submitted summaries of adalimumab in AS, and did not increase despite the increased time and exposure to study drug.
- Of TEAEs resulting in discontinuation from the study, a majority occurred in just 1 subject each. Ankylosing spondylitis, Ps, and urticaria were the only AEs reported in more than 1 subject that led to discontinuation of the study.

The safety and tolerability of adalimumab for up to 5 years was also demonstrated by TNF-inhibitor-related events of interest.

- In over 5 years of exposure to adalimumab, 78.5% (244/311) of subjects reported an infectious AE that were consistent with those seen in prior AS study reports.
- Few opportunistic infections (11) were reported and all were mild to moderate cases of candidiasis. No cases of TB were reported.
- Five subjects reported a TEAE of drug hypersensitivity, all of which were assessed to be not or probably not related to adalimumab, with one exception (Subject [REDACTED]).
- Forty-seven (15.1%) subjects treated with any dose of adalimumab reported an injection site reaction.
- Seven subjects reported malignancies, including one case of lymphoma.
- Two subjects who both had a previous history of CAD, MI, and hyperlipidemia reported new onset CHF.
- Fifty-four (17.4%) subjects treated with any dose of adalimumab reported any hepatic related AE.
- Ten (3.2%) subjects treated with any dose of adalimumab reported any allergic reaction related AE.
- One subject reported pleural effusion and lupus-like syndrome.

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Summary/Conclusions (Continued)

Safety Results (Continued):

- No subjects reported a demyelinating AE.
- One subjects out of 311, (0.3%), treated with any dose of adalimumab reported treatment-emergent hematologic related AEs.

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 with RA or PsA in previously reported studies and are judged to be not clinically important.
- Most changes in clinical chemistry were not clinically significant. The increases in cholesterol and triglycerides observed in Study M03-607 have also been seen in prior studies in subjects with RA and PsA and are probably related to correction of the dyslipoproteinemia associated with the inflammatory state.
- Eleven subjects had post-Baseline ALT values $\geq 3.0 \times \text{ULN}$. Three of these 11 subjects had abnormally high values at or prior to Baseline; 7 of the remaining 8 subjects had a single post-Baseline ALT elevation that resolved on continued treatment with adalimumab. Six of the 11 subjects had AEs reported in association with elevated ALT values. One subject reported a SAE of elevated liver enzymes with an ALT $< 3 \times \text{ULN}$.
- No clinically significant changes in vital signs were observed.

Conclusions:

Overall, long-term use of adalimumab 40 mg eow for up to 5 years was effective in reducing the signs and symptoms, improving the physical function and quality of life of subjects with active AS who have had an inadequate response or intolerance to NSAID therapy.

Additionally, treatment with adalimumab for up to 5 years and up to a dose of 40 mg weekly was generally safe and well tolerated and had a safety profile that was expected based on previous data from adalimumab treated subjects. This supports the findings from the 24-week double-blind portion of the study and demonstrates the sustained benefits observed through 5 years of treatment with adalimumab.