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, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of Adalimumab in Adult Chinese Subjects with Active Ankylosing Spondylitis

Coordinating Investigator:

Prof. Feng Huang, [redacted]

Study Sites:

Nine sites in China.

Publications:

None.

Studied Period (Years):	**Phase of Development:** 3
First Subject First Screening Visit: 20 January 2010 Last Subject Last Visit: 16 February 2011	

Objective:

The objective of this study was to evaluate the efficacy and safety of adalimumab every other week (eow) subcutaneously (SC) compared with placebo in Chinese subjects with active ankylosing spondylitis (AS) who had had an inadequate response to, or who were intolerant to 1 or more nonsteroidal anti-inflammatory drugs (NSAIDs).

Methodology:

Adult subjects with active AS were randomized in a 2:1 ratio to receive treatment with adalimumab 40 mg eow or matching placebo, given SC, in the 12-week double-blind (DB) phase. Randomized subjects received one SC injection of the appropriate DB study medication (adalimumab 40 mg or matching placebo) at Week 0 and then eow until Week 10. Subjects who completed the DB phase were allowed to participate in the 12-week open-label (OL) phase, during which all subjects received treatment with adalimumab 40 mg eow, starting at Weeks 12 through 22. A follow-up visit occurred 70 days after the last dose of study drug (in DB or OL phases) to obtain information on any ongoing or new adverse events (AEs).

Number of Subjects (Planned and Analyzed):

Enrollment was planned for 330 subjects. A total of 344 subjects comprised the Intent-to-Treat (ITT) analysis set for the primary efficacy analyses and were analyzed as the Safety analysis set.

Diagnosis and Main Criteria for Inclusion:

Subjects at least 18 through 65 years of age with active AS, diagnosed according to the Modified New York criteria, with a history of an inadequate response or intolerance to at least 1 NSAID as defined by the investigator. Active AS was defined by fulfillment of at least 2 of the following 3 criteria at the Screening and Baseline visits: Bath AS Disease Activity Index (BASDAI) score of ≥ 4 cm, total back pain score on a visual analog scale (VAS) of ≥ 40 mm, and presence of morning stiffness for at least 1 hour.

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

Adalimumab 40 mg/0.8 mL, administered eow as a SC injection solution in 1 mL, prefilled syringe. The lot number was 09-022455.

Duration of Treatment:

The duration of the study was up to 38 weeks, and included a 30-day Screening Period, a DB, placebo-controlled treatment period of up to 12 weeks, an open-label (OL) treatment period of up to 12 weeks, and a 70-day follow-up visit for subjects who completed the DB and OL periods or who prematurely discontinued the study.

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

Placebo matching adalimumab, administered eow as a SC injection solution in 1-mL, prefilled syringe (DB period only). The lot number was 08-018846.

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the proportion of subjects meeting the Assessment in Spondylarthritis International Society (ASAS) Working Group criteria for an ASAS20 response at Week 12.

Secondary efficacy variables were as follows:

- Proportion of subjects achieving an ASAS40 response at Week 12
- Proportion of subjects achieving ASAS5/6 response at Week 12
- Proportion of subjects achieving ASAS partial remission at Week 12
- Change from Baseline in Patient's Global Assessment of Disease Activity (PTGA) score at Week 12
- Change from Baseline in total back pain VAS score at Week 12
- Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) score at Week 12
- Change from Baseline in Inflammation score at Week 12 (mean of responses to Questions 5 and 6 of the BASDAI)
- Proportion of subjects achieving BASDAI50 response at Week 12
- Change from Baseline in BASDAI score at Week 12
- Change from Baseline in high sensitivity C-reactive protein (hs-CRP) value at Week 12

Criteria for Evaluation (Continued)

Efficacy (Continued):

- Change from Baseline in AS Disease Activity Score (ASDAS) total score at Week 12
- Proportion of subjects achieving each of the ASDAS disease state categories at Week 12 (Inactive, Moderate, High, Very High)
- Proportion of subjects achieving an ASDAS clinically important improvement and a major improvement at Week 12
- Change from Baseline in Physician's Global Assessment of Disease Activity (PGA) score at Week 12
- Change from Baseline in Bath Ankylosing Spondylitis Global Index (BAS-G) score at Week 12
- Change from Baseline in Patient's Global Assessment of Pain VAS score at Week 12
- Change from Baseline in nocturnal pain VAS score at Week 12
- Change from Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) score at Week 12
- Change from Baseline in swollen joint count (SJC) (44 joints) at Week 12
- Change from Baseline in tender joint count (TJC) (46 joints) at Week 12
- Change from Baseline in Bath Ankylosing Spondylitis Metrology Index ($BASMI_2$) score at Week 12
- Change from Baseline in the linear BASMI ($BASMI_{lin}$) at Week 12
- Change from Baseline in chest expansion score at Week 12
- Change from Baseline in Health Assessment Questionnaire for AS (HAQ-S) total score at Week 12
- Change from Baseline in the Short-Form 36 Version 2 (SF-36 v2) Physical Component Score (PCS) score at Week 12
- Change from Baseline in SF-36 v2 at Week 12
- Change from Baseline in Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI-SHP) score at Week 12

Safety:

Adverse events (including serious adverse events [SAEs] and AEs of special interest for adalimumab), clinical laboratory tests (hematology, chemistry, urinalysis, and liver function tests), vital signs, and chest x-rays were assessed.

Statistical Methods

Efficacy:

The primary and secondary efficacy analyses were performed on the ITT analysis set. The treatment difference in the primary efficacy variable between the adalimumab 40 mg and placebo groups was compared using a two-sided Pearson's Chi-square test at a 2-sided alpha level of 0.05. All statistical comparisons of secondary efficacy variables were conducted between the adalimumab 40 mg group and placebo group at Week 12 at a 2-sided alpha level of 0.05. A 2-sided Pearson's Chi-square test at a 2-sided alpha level of 0.05 was used to compare the adalimumab 40 mg and placebo groups for all discrete secondary efficacy variables; in instances where 25% or more of the cells have expected counts of less than 5, a Fisher's exact test was used. The change from Baseline at Week 12 in all continuous secondary efficacy variables was compared between the adalimumab 40 mg and placebo groups using an analysis of covariance (ANCOVA) that included the Baseline score as a covariate.

In the efficacy analyses, missing or incomplete data were to be handled using the nonresponder imputation (NRI), the last observation carried forward (LOCF) method, or observed case (OC) method, as appropriate.

Safety:

The number and percentages of subjects experiencing treatment-emergent adverse events (TEAEs) were tabulated using the Medical Dictionary for Regulatory Activities (MedDRA®) version 13.1 system organ class (SOC) and preferred term (PT). Summaries by severity and relationship to study drug were provided. Serious, severe, or life-threatening TEAEs, and TEAEs leading to discontinuation, were listed and described in detail.

Other safety variables, such as clinical laboratory and vital sign data, were described by descriptive statistics. Shift tables and listings were provided for abnormal values based on the normal range of the analyzing laboratory (for clinical laboratory parameters) or criteria prespecified by the sponsor (for vital signs).

Summary/Conclusions

Efficacy Results:

This was a Phase 3, placebo-controlled, double-blind (DB), randomized, multicenter study conducted in Chinese subjects with active AS who had an inadequate response to, or were intolerant to, treatment with at least 1 NSAID. A total of 344 subjects were enrolled and included in the primary efficacy population (ITT Analysis Set).

The majority of subjects in the ITT Analysis Set were male, < 40 years old, and HLA-B27 positive. The study population was similar across treatment groups. No significant differences in demographics, medical history, presenting Baseline disease activity and other disease characteristics, ECG, CXR, or prior/concomitant medications were observed between treatment groups.

The primary efficacy endpoint of this study was ASAS20 response at Week 12, which was achieved by 67.2% of adalimumab-treated subjects compared to 30.4% of placebo-treated subjects ($P < 0.001$; NRI).

Secondary and additional endpoints presented in this report represent the effect of adalimumab on multiple components of active AS. Nearly all of these endpoints achieved statistical significance in favor of adalimumab at Week 12, with results being sustained or improving further at Week 24.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

The efficacy of adalimumab in reducing the signs and symptoms of AS was further supported by statistically significant results at Week 12 in favor of the adalimumab treatment group over placebo for ASAS40/50/70, ASAS5/6, BASDAI, BASDAI50, ASDAS total score, PGA, PTGA-Pain, Total Back Pain, nocturnal pain, hs-CRP, and MASES. There was also a significantly greater proportion of subjects in the adalimumab group compared to placebo who achieved remission-like states based on the ASAS partial remission (21.8% versus 3.5%, $P < 0.001$) and ASDAS inactive disease state category (40.2% versus 5.2%, $P < 0.001$).

Subjects in the adalimumab treatment group had statistically significant improvement in spinal mobility and function at Week 12 compared to those in the placebo group. Statistically significant mean decreases (improvement) compared to placebo at Week 12 for $BASMI_{lin}$ (–0.5 versus –0.2; $P < 0.001$) and $BASMI_2$ (–0.8 versus –0.4; $P = 0.012$) were noted. Likewise, there was statistically significantly greater improvement in BASFI at Week 12 in the adalimumab group compared to placebo. No statistically significant difference in change from Baseline in chest expansion was observed between the adalimumab and placebo treatment groups at Week 12, however, subjects participating in this study had mean Baseline chest expansion values that were already close to what can be expected from the normal population.

Statistically significant differences in favor of the adalimumab treatment group over placebo in mean change from Baseline in the HAQ-S total score, SF-36, WPAI-SHP (presenteeism, overall work impairment, and activity impairment), and BAS-G were observed at Week 12.

After 12 weeks of OL adalimumab treatment, improvement was seen at Week 24 for the PBO/ADA treatment group in all efficacy variables, in most cases matching the level of response in the ADA/ADA treatment group. At Week 24, subjects in the ADA/ADA treatment group sustained their Week 12 response or had further improved.

Therefore, adalimumab was an effective treatment for reducing the signs and symptoms of AS in Chinese subjects with inadequate response to, or intolerance to, at least one NSAID.

Safety Results:

Results from Study M11-991 demonstrated that adalimumab treatment is generally safe and well tolerated in Chinese AS subjects for up to 24 weeks of therapy. This conclusion is supported by the low incidence and frequency of SAEs and discontinuations due to AEs.

- In the DB period, there was only 1 subject with an SAE in the adalimumab group, a case of pelvic inflammatory disease which led to discontinuation from the study, and 1 subject with 2 SAEs in the placebo group (fibroadenoma of the breast and intraductal papilloma of the breast).
- During the OL period, 4 additional subjects reported SAEs: 1 subject had viral hepatitis; 1 subject had peritoneal tuberculosis, pulmonary tuberculosis, and tuberculosis pleurisy; 1 subject had concussion, contusion, and skin laceration; and 1 subject had an induced abortion.
- During the DB period, 4 subjects in the adalimumab treatment group discontinued due to AEs, including 2 subjects who withdrew due to AEs of ALT increased and AST increased. An additional 3 subjects discontinued due to AEs during the OL period, for an AE-related discontinuation rate of 2.0% among subjects receiving any adalimumab.
- No deaths were reported during the study.

Summary/Conclusions (Continued)

Safety Results (Continued):

Adalimumab was generally safe and well tolerated during 12 weeks of DB therapy and during 12 weeks of OL therapy, as suggested by the types and frequencies of AEs.

- During the DB period, AEs were more frequent in the adalimumab treatment group with 35.4% of subjects reporting at least 1 AE (incidence rate of 338.4 events/100 PY) compared with the placebo group in which 22.6% of subjects reported at least 1 AE (incidence rate of 136.9 events/100 PY). This difference was largely due to more hepatic related AEs in the adalimumab treatment group compared to the placebo group, a majority of which were mild ALT and/or AST elevations. However, all AEs reported during the DB period of the study were considered mild or moderate in severity.
- Among subjects who received adalimumab at any time during the study, the most frequently reported possibly or probably related AEs were increased ALT (10.5%), increased AST (7.6%), upper respiratory tract infection (5.8%), injection site erythema (1.5%), decreased white blood cell count (1.5%), decreased platelet count (1.2%), pharyngitis (1.2%), and increased blood alkaline phosphatase (1.2%). All other possibly or probably related events were reported by < 1% of subjects.
- Among subjects who received adalimumab at any time during the study, 3 experienced severe AEs, each of which was also reported as a SAE (viral hepatitis in 1 subject; peritoneal tuberculosis, pulmonary tuberculosis, and tuberculosis pleurisy in 1 subject; and concussion, contusion, and skin laceration in 1 subject).
- Subgroup analysis by Baseline characteristics indicates that, among subjects treated with adalimumab, more subjects who were male, younger (< 40 years versus ≥ 40 years), or on concomitant DMARDs at Baseline experienced hepatic related AEs. However, all hepatic related AEs were laboratory abnormalities that were not associated with clinical signs and symptoms and all were assessed to be mild or moderate by the investigator. Although there were some minor differences in rates of hematologic AEs in certain subgroups, all of the events were assessed as being mild to moderate by the investigator and most were laboratory abnormalities.

Summary/Conclusions (Continued)

Safety Results (Continued):

The safety and tolerability of adalimumab for up to 24 weeks was also demonstrated by evaluation of TNF-inhibitor-related events of interest. No cases of malignancy, HSTCL, leukemia, melanoma, parasitic infection other than opportunistic infection, lupus-like syndrome, allergic reaction, cutaneous vasculitis, noncutaneous vasculitis, diverticulitis, intestinal perforation related events, intestinal stricture related events, myocardial infarction, cerebrovascular accident, pulmonary embolism, psoriatic condition and worsening, medication error related events, Stevens-Johnson syndrome, erythema multiforme, congestive heart failure, interstitial lung disease, pancreatitis, sarcoidosis, progressive multifocal leukoencephalopathy, reversible posterior leukoencephalopathy, or amyotrophic lateral sclerosis were reported during the study. The following results were observed for the other AEs of special interest:

Infections: Infections were reported in 17.5% of subjects during any adalimumab exposure throughout the study. The most frequently reported infections were upper respiratory tract infection, nasopharyngitis, and pharyngitis; all other infections were reported by < 1% of subjects each. Only 1 serious infection (pelvic inflammatory disease) was reported during the DB period of the study. One subject who received adalimumab during the DB period had a serious infection (peritoneal tuberculosis, pulmonary tuberculosis, and tuberculosis pleurisy) during the OL period of the study. One subject who received placebo during the DB period followed by OL adalimumab had a serious infection (viral hepatitis) during the post-treatment follow-up period. All 3 serious infections were assessed by the investigator as possibly related to study drug.

Tuberculosis: No cases of TB were reported during the DB period of the study. One subject experienced TB during the OL period of the study.

Injection site reactions: During the DB period of the study, injection site reactions were reported by 2.6% of subjects in the adalimumab treatment group and 0% of subjects in the placebo group. Among subjects who received adalimumab at any time during the study, 2.9% reported injection site reactions.

Hematologic related events: During the DB period of the study, hematologic related AEs were reported by 4.4% of subjects in the adalimumab treatment group and 1.7% of subjects in the placebo group. Among subjects who received adalimumab at any time during the study, 5.6% reported hematologic events. The most frequently reported hematologic-related AE terms in the DB period of the study were decreased white blood cell count and thrombocytopenia. Among subjects who received adalimumab at any time during the study, decreased white blood cell count, decreased platelet count, and leukopenia were reported most often. Almost all events were considered mild, the majority were considered possibly or probably related to study drug by the investigator, and none were serious AEs.

Summary/Conclusions (Continued)

Safety Results (Continued):

Hepatic related events: During the DB period, hepatic related events were reported in 11.8% of subjects in the adalimumab treatment group and 1.7% of subjects in the placebo treatment group. However, all reported hepatic related events were laboratory abnormalities not associated with clinical signs or symptoms. Only 11 subjects in the adalimumab group had ALT or AST elevations ≥ 3 × ULN. In the Any Adalimumab Analysis Set, 53 (15.5%) subjects had hepatic events. All of these events involved elevation of liver function test values, most frequently elevations of ALT and AST. Six subjects had hepatic AEs after initiation of treatment with adalimumab (DB or OL) that were assessed as moderate in severity by the investigator, while the rest had AEs assessed as mild. Only 2 subjects were discontinued from study drug due to a hepatic event; both had a prior medical history of fatty liver. The majority of these hepatic related AEs were considered possibly or probably related to study drug by the investigator.

Adalimumab was generally safe and well tolerated. No safety concerns were identified in the analysis of other clinical laboratory and vital signs parameters.

Conclusions:

Adalimumab was an effective treatment for reducing the signs and symptoms of AS in Chinese subjects with inadequate response to, or intolerance to, at least 1 NSAID. Additionally, adalimumab was generally safe and well tolerated.