2.0 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:

A Multi-center Randomized, Phase 2/3, Double-blind, Parallel-group, Placebo-controlled, Study to Assess the Safety and Efficacy of Adalimumab Administered as Subcutaneous Injections in Adult Chinese Rheumatoid Arthritis Subjects Treated With Methotrexate

Investigator:

[redacted] MD redacted information 14Nov2014

Study Sites:

11 sites across China

Publications:

Not applicable

Studied Period (Years):	**Phase of Development:** 2/3
First Subject First Visit: 06 September 2007 Last Subject Last Visit: 30 December 2009	

Objective:

The objective of this study was to determine the safety and efficacy profiles of subcutaneous (SC) every other week (eow) doses of 80 mg adalimumab, 40 mg adalimumab, compared to placebo, in adult Chinese subjects with active rheumatoid arthritis (RA) treated concomitantly with methotrexate (MTX).

Methodology:

This was a multi-center, Phase 2/3, randomized, DB, parallel group, placebo-controlled, safety and efficacy study in adult Chinese RA subjects. The duration of the study was approximately 116 weeks. This included a 4-week (28 days) Screening period, a 12-week DB period, a 90-week OL Period, and a 10-week (70 days) Follow-up period. The 70-day Safety Follow-up period was initiated after the last dose of study medication. Subjects received adalimumab as part of the study until it was approved for use in China and the study was stopped.

During the DB period, subjects with RA and concomitantly treated with MTX were enrolled at 11 clinical sites located throughout China. Subjects were randomly assigned to one of the three treatment groups in a 2:2:1 ratio: 80 mg adalimumab, 40 mg adalimumab, or placebo. From Week 0 to Week 10 subjects received blinded study drug. Subjects who successfully participated and completed Week 12 of the DB portion of the study participated in the OL period. All subjects in the OL received adalimumab 40 mg. Throughout the study, the study drug was administered SC eow.

Number of Subjects (Planned and Analyzed):

300 planned, 302 analyzed

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

A subject was eligible for study participation if he/she met the following criteria:

- Subjects must have met ACR criteria for diagnosis of active RA and have had at both the Screening visit and Week 0 visit at least 4 swollen joints (out of 66 assessed) and at least 6 tender joints (out of 68 assessed).
- Subjects must have failed prior treatment with one or more disease-modifying antirheumatic drugs (DMARDs).
- DMARDs (other than MTX) must have been discontinued for ≥ 28 days or at least 5 half-lives, whichever is greater, before the Week 0 visit.
- Traditional Chinese Medicines must have been discontinued for ≥ 28 days before the Week 0 visit.
- Subjects must have received at least 3 months of treatment with MTX (minimum 7.5 mg/week) and remained on a stable dose of MTX for ≥ 28 days prior to the Screening visit.
- Glucocorticoids equivalent to ≤ 10 mg of prednisone and prednisone equivalent must remain unchanged for at least 28 days prior to the Week 0 visit.
- Male or female ages 18 years and older.
- If female of child bearing potential, the result of serum pregnancy test performed at the Screening visit and a urine pregnancy test performed at the Week 0 visit was negative.
- If female, subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or was of childbearing potential and practicing one of the following methods of birth control throughout the study and for 150 days after study completion: condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD), contraceptives (oral or parenteral) for 3 months prior to study drug administration.
- Subject must have been able and willing to give written informed consent and to comply with the requirements of this study protocol.

Exclusion Criteria

Any of the following excluded the subject from this study:

- Any subject with a history of, or current, acute inflammatory joint disease of different origin (e.g., mixed connective tissue disease, seronegative spondyloarthropathy, psoriatic arthritis (PsA), Reiter's syndrome, systemic lupus erythematosus, fibromyalgia or any arthritide with onset prior to age 16 years.
- Wheelchair-bound or bedridden.
- Joint surgery involving joints to be assessed within this study, within 2 months prior to the Screening visit.
- Intra-articular, intramuscular or intravenous administration of corticosteroids within 28 days prior to the Screening visit.
- Requirement for any excluded medication.

- Received a live vaccine within 3 months prior to the Week 0 visit.
- Received investigational biological and chemical agents within 5 half-lives prior to the Screening visit or within a longer or shorter time period depending on the mechanism of action.
- Prior treatment with any TNF antagonist, including adalimumab.
- History of listeriosis, history of histoplasmosis, active tuberculosis (TB), persistent chronic or active infections requiring treatment with intravenous (IV) antibiotics, IV antivirals, or IV antifungals within 28 days or oral antibiotics, oral antivirals, or oral antifungals within 14 days prior to the Screening visit.
- History of neurologic symptoms suggestive of central nervous system demyelinating disease.
- Poorly controlled medical condition, such as uncontrolled diabetes with documented history of recurrent infections, unstable ischemic heart disease, congestive heart failure (CHF), recent cerebrovascular accidents and any other condition that, in the opinion of the Investigator, would put the subject at risk by participation in the protocol.
- History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix.
- History of Human Immunodeficiency Virus (HIV) or of being immunocompromised.
- History of clinically significant drug or alcohol abuse.
- Positive Hepatitis B surface antigen (HbsAg) and Hepatitis C virus antibody (HCV Ab) indicative of a previous or current infection.
- Chest x-ray (CXR) with calcified granuloma and/or pleural scarring.
- Positive tuberculin PPD 5 tuberculin unit (TU) dose skin test, ≥ 5 mm read at 48 to 72 hours (if negative, repeated 1 to 3 weeks later for two-step tuberculin testing).
- Demonstration of clinically significant laboratory abnormalities.
- Female subjects who were pregnant or breast-feeding or considering becoming pregnant during the study. There was to be at least a 150-day period between the last dose of study drug and either conception or initiation of breast-feeding in women of childbearing potential.
- The Investigator considered the subject, for any reason, to be unacceptable for study participation.

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

Adalimumab 80 mg (2 × 40 mg, 0.8 mL solution for injection in 1 mL pre-filled syringes), Adalimumab 40 mg (1 × prefilled syringe + 1 placebo syringe), Placebo (2 × placebo syringes); SC injection

Adalimumab lot numbers: [redacted]

Placebo lot number: [redacted]

Duration of Treatment:

Up to 116 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
None

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Criteria for Evaluation

Efficacy:

The primary efficacy analysis was a comparison of the rates of ACR20 response at Baseline and at Week 12.

Secondary efficacy variables includes: Proportion of subjects achieving ACR20 at Week 24, Proportion of subjects achieving ACR50 and ACR70 at Weeks 12 and 24, Change from Baseline in tender joint count (TJC) and swollen joint count (SJC) at Weeks 12 and 24, Change from Baseline in VAS scores at Weeks 12 and 24, Change from Baseline in HAQ scores at Weeks 12 and 24, and Change from Baseline in SF-36 scores at Weeks 12 and 24.

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 1 injection of adalimumab were to be included in the efficacy analysis. The efficacy analysis was to be done descriptively by presenting summary statistics and corresponding *P* values. The values at all visits as well as changes from baseline were summarized.

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

Summary/Conclusions

Efficacy Results:

Adalimumab 40 mg SC eow and 80 mg SC eow was shown to be efficacious in the treatment of RA in adult Chinese subjects concomitantly treated with MTX compared to placebo. During the double-blind period, subjects treated with 40 mg of adalimumab, 57.0% achieved ACR20 response at Week 12 ($P = 0.004$ versus placebo), and subjects treated with 80 mg of adalimumab, 51.2% achieved ACR20 response at Week 12 ($P = 0.026$ versus placebo).

During the OL period all subjects received 40 mg eow of adalimumab, and response rates in the 2 adalimumab groups were maintained to Week 92.

Safety Results:

Adalimumab 40 mg eow and 80 mg eow was shown to be safe and well-tolerated during the DB period.

Adalimumab was also generally safe and well-tolerated with a positive risk benefit ratio through 92 weeks of treatment as evidenced by the low incidence of AEs, AEs at least possibly related to the study drug, and severe AEs:

- Overall, the frequency of AEs was low with less than 50% of subjects reporting at least 1 AE in the DB period. With as much as 92 weeks of treatment, 69.4% of subjects who received any adalimumab reported at least 1 AE.
- The most frequently reported AEs (≥ 5% of subjects) during both the DB period and in subjects who received any adalimumab were upper respiratory tract infection, nasopharyngitis, and injection site pruritus. In addition, in the subjects who received any adalimumab, alanine aminotransferase increase was reported in 5.0% of subjects.
- The number of events and the number of at least possibly drug-related AEs per 100 PYs were lower among subjects who received any adalimumab (145.5 and 103.5, respectively) than during the DB period (412.1 and 315.0, respectively).
- Between 38.0% and 46.0% of subjects reported AEs that were considered to be at least possibly related to the study drug during the DB period, of which only upper respiratory tract infection, nasopharyngitis, and injection site pruritus were reported in ≥ 5% of subjects. More than 80% of subjects who received any adalimumab reported AEs that were considered to be at least possibly related to the study drug. Upper respiratory tract infection, nasopharyngitis and injection site pruritus were reported in ≥ 5% of subjects.

Adalimumab was generally safe and well-tolerated with a positive risk benefit ratio through 92 weeks of treatment as evidenced by the low incidence of SAEs and AEs leading to discontinuation.

- Eight subjects in the DB period and 28 subjects who received any adalimumab reported AEs which led to discontinuation.
- During the DB Period 3 (1.2%) subjects reported 1 serious AE each. Among subjects who received any adalimumab, 21 (71.0%) reported at least 1 SAE.
- There were 2 fatal treatment-emergent AEs in subjects who received any adalimumab; 1 subject died due to a myocardial infarction which was considered probably not related to study drug and 1 subject died due to a completed suicide > 70 days after termination of the study which was considered not related to study drug.

Adalimumab was generally safe and well-tolerated through 92 weeks of treatment as evidenced by clinical laboratory results.

Conclusions:

In this study, adalimumab at a dose of 40 mg eow and 80 mg eow SC in combination with MTX, markedly reduced arthritic signs, symptoms, and disability of RA and was generally well-tolerated with a positive benefit-risk ratio in this study Chinese RA patients.

There were no new safety findings in this study compared to findings in previous studies in the adalimumab clinical program.