2.0 Synopsis

<table>
<tr><td>Abbott Laboratories</td><td>Individual Study Table Referring to Part of Dossier:</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Adalimumab</td><td>Volume:</td><td rowspan="3"></td></tr>
<tr><td>Name of Active Ingredient:
Adalimumab</td><td>Page:</td></tr>
<tr><td colspan="3">Title of Study:
An Extension Study of A Randomized, Double-Blind, Placebo-Controlled, Phase III Study of the Human Anti-TNF Antibody Adalimumab Administered as Subcutaneous Injections in Korean Rheumatoid Arthritis Subjects Treated with Methotrexate</td></tr>
<tr><td colspan="3">Rationale for Abbreviated Clinical Study Report:
Efficacy was not examined in this open-label extension study; only safety data were collected and monitored.</td></tr>
<tr><td colspan="3">Coordinating Investigator:
Ho-Youn Kim, Division of Rheumatology, Department of Internal Medicine, The Catholic University Kang-Nam St. Mary's Hospital, #505 Banpo-Dong, Seocho-Ku, Seoul, 137-040, Korea</td></tr>
<tr><td colspan="3">Study Sites:
Six sites in Korea.</td></tr>
<tr><td colspan="3">Publications:
None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Open-Label Dose: 09 Jan 2004
Last Subject Last Open-Label Dose: 04 Nov 2005</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objective:
The objective of this extension study was to provide the option to subjects who completed the 24 week double-blind treatment (either adalimumab 40 mg eow or placebo) or open-label rescue treatment (adalimumab 40 mg eow sc) to continue into an open-label adalimumab 40 mg eow sc extension study if the investigator believed it was in the subject's best interest to continue adalimumab treatment until commercial availability in Korea or a maximum of 2 years of adalimumab exposure.
Therefore, this open-label extension (OLE) study was to evaluate the safety of subcutaneous (sc) injections of adalimumab 40 mg every other week (eow) for up to 2 years or until commercial availability in Korean rheumatoid arthritis (RA) subjects concomitantly treated with methotrexate (MTX).</td></tr>
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Methodology:

This study was an open-label extension (OLE) to the Phase 3 randomized, double-blind, placebo−controlled, 24-week study (Study M02-556) previously reported. The study was conducted at six sites in Korea to assess the long−term safety of the human anti−TNF antibody adalimumab administered via subcutaneous (sc) injection in Korean subjects with rheumatoid arthritis (RA) and concomitantly treated with methotrexate (MTX). Subjects who completed the 24-week double-blind treatment with either adalimumab 40 mg every other week (eow), placebo, or open-label rescue treatment (adalimumab 40 mg eow sc), had the option to continue into this extension study with open-label adalimumab 40 mg eow sc, if the Investigator felt it was in the subject's best interest to continue treatment until the drug became commercially available in Korea or for a maximum of two years of treatment.

Following 24 weeks of study treatment in the M02-556 study, a total of 118 subjects completed the double-blind portion of the study. Of these, 109 (56 on adalimumab 40 mg, 35 on placebo, and 18 who were on placebo and rescued) subjects enrolled into this OLE study. Eligible, consented subjects were administered adalimumab 40 mg eow sc at Week 26. Subjects were evaluated for safety every 4 months. Subjects who prematurely discontinued the extension study prior to study completion or commercial availability of study drug were examined one month following last dose of adalimumab for safety. Up to 70 days (5 half-lives) following the last dose of adalimumab, serious adverse events (SAEs) and non−serious adverse events (AEs) were elicited either via visits, telephone contacts or were spontaneously reported.

Safety assessments included vital signs, AE monitoring, review of concomitant medications, and fasted laboratory tests (hematology, chemistry and urinalysis).

Number of Subjects:

Planned: 120 subjects enrolled at 6 sites.

Enrolled: 109 subjects at 6 sites.

Completed: 77 subjects.

Analyzed: A total of 109 subjects were enrolled and received at least one injection of open-label study drug and were therefore included in the safety analysis.

Diagnosis and Main Criteria for Inclusion:

Subjects were Korean males and females aged 18 years or older who met the American College of Rheumatology (ACR) criteria for diagnosis of active RA, and had at both Screening and Baseline visits ≥6 swollen joints and ≥9 tender joints. Additional criteria required that subjects:

- Received folic acid (1-5 mg/day or leucovorin 1-5 mg/day) in addition to MTX.
- Completed the 24-week double-blind (including open-label rescue) portion of the study.

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

Test Product: Aqueous injection containing 50 mg/mL of adalimumab

Test Dose/Strength/Concentration: Adalimumab 40 mg/0.8 mL

Mode of Administration: sc injection

Lot Numbers: 08-692-S2, 10-882-S2, and 25-902-S2 (Lot # 07-635-S2 was administered to Subject 004-420 at Week 28 in error.)

Duration of Treatment:

Subjects were to receive open-label adalimumab 40 mg eow until the drug became commercially available in Korea or for a maximum of two years of treatment.

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

Not applicable for the OLE portion of the study.

Criteria for Evaluation

Efficacy:

Not applicable for this abbreviated clinical study report.

Safety:

Safety assessments included vital signs, AE monitoring, review of concomitant medications, and fasted laboratory tests (hematology, chemistry and urinalysis).

Adverse events included those events that were serious (SAEs), non-serious (AEs), and treatment−emergent (TEAEs). Serious AEs were collected from the time the subject signed the informed consent, and AEs and TEAEs were collected beginning at Week 26 (*i.e.*, the first OLE dose) until 70 days (5 half-lives) after the last dose of adalimumab, whether elicited during scheduled telephone contacts and/or study visits or spontaneously reported by the subject.

Laboratory and vital signs data were displayed over time and included changes from Baseline values during open-label adalimumab treatment.

Statistical Methods

Efficacy:

Not applicable for this abbreviated clinical study report.

Safety:

The safety analysis was performed on the safety population. The number and percentage of subjects who reported TEAEs were tabulated by MedDRA preferred term and system organ class, by relationship to study drug, and by severity. Treatment emergent AEs, which were serious, severe, or life-threatening, were described in detail. Listings of all AEs were provided. Laboratory parameters and vital signs over time and changes from Baseline values were summarized. Laboratory values outside the normal reference ranges were flagged, evaluated by shift tables, and listed.

Summary/Conclusions

Efficacy Results:

Not applicable for this abbreviated clinical study report.

Safety Results:

- Adverse events were reported by 82.6% of subjects, the majority (45%) of which were mild in severity. Severe AEs were reported in 6.4% of subjects, more than half of whom were judged by the Investigator to be not or probably not related to study drug.
- Eight (8) treatment-emergent AEs were reported at an incidence ≥5%. The most commonly reported AEs were upper respiratory tract infection (22.9%), rheumatoid arthritis (11.9%), myalgia (9.2%), pharyngolaryngeal pain and hypertension (both 6.4%) and anemia, fatigue, and insomnia (all 5.5%). Most of these commonly reported AEs are not unexpected (with the exception of hypertension) in the subject population given the age, underlying chronic inflammatory disease of RA and use of multiple concomitant immunosuppressive medications (including corticosteroids, DMARDs and TNF antagonist). Although hypertension was unexpectedly reported in 7 (6.4%) subjects, all cases were either moderate or mild in severity and assessed by the Investigator as not related or probably not related to study drug. One of these incidents was a worsening of the subject's pre-existing history of hypertension and attributed by the Investigator as such.
- The incidence of AEs possibly or probably related to study drug was 22%. The most common events possibly or probably related to study drug were upper respiratory tract infection (3.7%), herpes zoster (1.8%), and pneumonia (1.8%).
- No deaths occurred during the OLE portion of the study.
- Serious adverse events occurred in 15 subjects (13.8%). However, only nine of the subjects with 10 SAEs were judged by the Investigator to be probably or possibly drug-related.
- Discontinuations due to adverse events occurred in 14 subjects (12.8%) including 11 subjects with AEs judged to be at least possibly drug-related. Infectious adverse events were reported by 43.1% of subjects. The most commonly reported infections involved the respiratory tract.
- Nine subjects (8.3%) reported nine serious infectious AEs, eight of which were assessed by the Investigator to be either possibly or probably related to study drug.
- Four (3.7%) subjects reported an opportunistic infection. Three (2.8%) of these subjects reported serious opportunistic infections that were assessed by the Investigator as possibly related to study treatment. Adequate screening for tuberculosis prior to the initiation of anti-TNF therapy, and the adequate treatment of latent tuberculosis if diagnosed, are considered to be effective methods for reducing the incidence of tuberculosis during anti-TNF therapy. In addition, subjects should be monitored closely for any signs of tuberculosis during treatment with an anti-TNF compound since tuberculosis is generally well managed with timely diagnosis.
- No incidences of treatment-emergent malignancies or immunologic reactions were reported during the OLE portion of the M02-556 study.
- Clinically important changes in laboratory parameters were limited to increases in mean hemoglobin, hematocrit, RBC, and serum lipid values. Mean platelet counts, WBC and neutrophil percents decreased.
- Three (2.8%) subjects experienced isolated CTC Grade 3 hematology results during the OLE portion of the study. No other CTC Grade above 2 occurred during administration of open−label adalimumab.

- No clinically important changes were observed for vital signs (including blood pressure, heart rate, or body temperature).

Conclusions:

Adalimumab was generally safe and well tolerated when administered for up to two years in Korean RA subjects concomitantly treated with MTX as evaluated by the incidence and pattern of serious and non−serious adverse events, discontinuations due to adverse events, TNF inhibitor related events of interest, laboratory results and vital signs.