



## 2.0 Synopsis

<b>Abbott Laboratories</b>	<b>Individual Study Table Referring to Item of the Submission:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b>		
<b>Name of Active Ingredient:</b> <b>Adalimumab</b>		
<b>Title of Study:</b> A Randomized, Double-Blind, Placebo-Controlled, Study of the Human Anti-TNF Antibody Adalimumab Administered as Subcutaneous Injections in Adult Chinese Rheumatoid Arthritis Subjects Treated with Methotrexate		
<b>Investigator:</b> Joung-Liang Lan, MD		
<b>Study Site:</b> Taichung Veterans General Hospital, Taiwan, R.O.C.		
<b>Publications:</b> None		
<b>Studied Period (Years):</b> First subject dosed: 20 October 2003 Last subject dosed: 28 April 2005	<b>Phase of Development: 3</b>	
<b>Objective:</b> This was a single-center, open-label extension portion of a Phase III, placebo-controlled, double-blind, randomized study (Study M02-573). The study, conducted in Taiwan, was designed to demonstrate the long-term safety of 40 mg subcutaneous (sc) injections of adalimumab administered every other week (eow) in Chinese subjects with rheumatoid arthritis [RA; as defined by the 1987-revised American College of Rheumatology (ACR) criteria] who had partial responses to methotrexate (MTX) and who had completed 12 weeks of treatment in the double-blind portion of the study (Study M02-573).		
<b>Methodology:</b> A total of 47 subjects were enrolled into the double-blind portion of the Study M02-573 and 43 subjects (32 from the adalimumab group, 11 from the placebo group) continued into the open-label extension portion of the study. Subjects who continued on open-label adalimumab treatment were evaluated for safety (e.g., adverse events [AEs], clinical laboratory parameters, vital signs) every four months starting at Week 14 (i.e., the start of the open-label portion of the study). The results of the double-blind portion of the study have already been reported (R&D/04/779). This abbreviated clinical study report presents safety data from only those subjects who continued in the open-label extension portion of Study M02-573.		



<p><b>Number of Subjects (Planned and Analyzed):</b> <b>Planned:</b> 48 (36 adalimumab group, 12 placebo group) <b>Entered Double-Blind Portion of Study:</b> 47 (35 adalimumab group, 12 placebo group) <b>Completed Double-Blind Portion of Study:</b> 43 (32 adalimumab group, 11 placebo group) <b>Entered Open-Label Portion of Study:</b> 43 (32 adalimumab group, 11 placebo group) <b>Completed Open-Label Portion of Study:</b> 33</p>
<p><b>Diagnosis and Main Criteria for Inclusion:</b> Subjects were Chinese males and females at least 18 years of age who: met ACR criteria for diagnosis of active RA and had at both screening and baseline visits <math>\geq 6</math> swollen joints and <math>\geq 9</math> tender joints. Additional criteria required that subjects must have:</p> <ul style="list-style-type: none"><li>• Received at least 1 prior DMARD besides MTX, but experienced no more than 4 failures on prior DMARDs</li><li>• Received therapy with MTX for at least 3 months prior to screening and were on a stable MTX dose for at least 4 weeks prior to screening and experienced insufficient efficacy with 10 to 15 mg MTX weekly</li><li>• Completed 12 weeks of treatment in the double-blind portion of the study</li></ul>
<p><b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b> <b>Test Product:</b> Aqueous injection containing 50 mg/mL adalimumab (Vial) <b>Dose/Strength/Concentration:</b> 40 mg/0.8 mL eow sc dosing</p>
<p><b>Duration of Treatment:</b> Subjects were to receive open-label adalimumab 40 mg every eow until one month after Veterans General Hospital, Taichung Taiwan (VGH-TC) formulary listing; however, the open-label extension portion of the study was terminated in April 2005 due to the availability of the commercial formulation to subjects in VGH-TC. All subjects who remained in the study at that time were transitioned to the commercial formulation.</p>
<p><b>Reference Therapy, Dose and Mode of Administration, Lot Number:</b> Not applicable for the open-label portion of the study.</p>
<p><b>Criteria for Evaluation:</b> <b>Efficacy:</b> Not applicable for this abbreviated clinical study report.</p>
<p><b>Safety:</b> Adverse events included those events that were serious (SAEs), non-serious (AEs), and treatment-emergent (TEAEs). AEs were collected from the time the subject signed the informed consent and AEs and TEAEs were collected beginning at Week 14 (<i>i.e.</i>, the start of the open-label portion of the study) until 70 days 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 adalimumab treatment.</p>
<p><b>Statistical Methods:</b> <b>Efficacy:</b></p>



Not applicable for this abbreviated clinical study report.

**Safety:**

The safety analysis was performed on the safety population. The number and percentage of subjects reporting TEAEs were tabulated by MedDRA preferred term and system organ class, by relationship to study drug, and by severity. TEAEs, which were serious, severe, or life-threatening, were described in detail. Listings were provided of all AEs. Laboratory parameters and vital signs over time and changes from Baseline values were summarized. Laboratory values outside the 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 97.7% of subjects, the majority of which were mild in severity (53.5%). Severe AEs were reported in 11.6% of subjects, all of which were judged by the Investigator to be not or probably not related to study drug.
- Twenty (20) treatment-emergent AEs were reported at an incidence of  $\geq 5\%$ . The most commonly reported AEs were upper respiratory tract infection (16 subjects, 37.2%), Sjogren's Syndrome (11 subjects, 25.6%), myofascial pain syndrome (10 subjects, 23.3%), insomnia (9 subjects, 20.9%) and chronic sinusitis, blood triglycerides increased, abdominal pain upper and constipation (5 subjects each, 11.6%). Of the most commonly reported AEs, upper respiratory tract infection and chronic sinusitis are not unexpected 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). In addition, Sjogren's Syndrome is related to the disease of interest (RA), and increased blood triglycerides are likely associated with correcting the dyslipidemia associated with the inflammatory response to adalimumab.
- The incidence of AEs possibly or probably related to study drug was 41.9%. The most common events possibly or probably related to study drug were blood triglycerides increased, tuberculosis, blood cholesterol increased, injection site erythema, hyperlipidemia and eczema.
- No deaths occurred during the open-label extension.
- Serious adverse events occurred in 13 subjects (30.2%). However, only four of the subjects with 11 SAEs were judged by the Investigator to be probably or possibly drug-related. Of these, three subjects developed tuberculosis and one subject developed palpitations, vertigo, abdominal pain, vomiting, asthenia, malaise, decreased appetite and abnormal hepatic function.
- Discontinuations due to adverse events occurred in eight subjects (18.6%) including five subjects with AEs judged to be at least possibly drug-related.
- Infectious adverse events were reported by 61% of subjects, all of which were mild or moderate in severity. The most commonly reported infections involved the respiratory tract.
- Five subjects (11.6%) reported six serious infectious AEs; of these, three (all of which were tuberculosis) were judged by the Investigator to be probably related to study drug.
- Three subjects (7.0%) developed tuberculosis. One subject was on concomitant sulfasalazine, MTX and prednisolone and developed tuberculosis after 14 months of exposure to adalimumab treatment. The other two subjects were on concomitant MTX and prednisolone and developed tuberculosis after 12 and 7 months of exposure to adalimumab treatment, respectively. Such combination therapy may increase the risk of developing serious infections as well as tuberculosis and, therefore, subjects on combination immunosuppressive therapy need to be closely monitored for any signs of infection and treated appropriately. 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.



- There were no malignancies reported in this study.
- One subject (2.3%) reported a treatment-emergent immunologic reaction of drug hypersensitivity that was mild and judged by the Investigator to be not related to study drug.
- Clinically important changes in laboratory parameters were limited to increases in mean hemoglobin, hematocrit, and RBC, and increases in mean serum lipids. One subject experienced CTC Grade 3 elevation of ALT and AST at Week 30. This ALT/AST elevation was reported as an AE, attributed to tuberculosis and judged by the Investigator to be not related to study drug.

**Conclusions:**

Overall, adalimumab was generally safe and well-tolerated in subjects with long-term exposure as evaluated by the incidence of AEs, drug-related AEs, severity of AEs, SAEs and discontinuations due to AEs.

**Date of Report:** 16 December 2005