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:
Humira</td><td>Volume:NA</td><td>NA</td></tr>
<tr><td>Name of Active Ingredient:
Adalimumab</td><td>Page: NA</td><td>NA</td></tr>
<tr><td colspan="3">Title of Study:
Open-Label, Multi-country and Multi-Center Study to Asses the Clinical Efficacy and impact on QoL of the Fully Human Anti-TNF-alfa Monoclonal Antibody Adalimumab (Humira) when Added to Inadequate Standard Anti-Rheumatic Therapy in patients with Active Rheumatoid Arthritis in a period of 6 months treatment.</td></tr>
<tr><td colspan="3">Investigator:
Eduardo Acevedo, MD</td></tr>
<tr><td colspan="3">Study Site(s):
6 sites in Peru and 12 sites in Ecuador</td></tr>
<tr><td colspan="3">Publications: None</td></tr>
<tr><td colspan="2">Studied Period (Years): April 2007-March 2008
First Subject First Visit: 27 Apr 2007
Last Subject Last Visit: 02 Apr 2008</td><td>Phase of Development: IV</td></tr>
<tr><td colspan="3">Objectives
Safety: To demonstrate the safety of adalimumab in study patients receiving concomitant anti-rheumatic therapy.
Efficacy: To demonstrate the efficacy of adalimumab when added to preexisting inadequate standard anti-rheumatic therapy in patients with moderate to severely active RA.</td></tr>
<tr><td colspan="3">Methodology: A total of 220 subjects (120 from Peru and 100 from Ecuador) having a diagnosis of active RA fulfilling study eligibility criteria were enrolled at 18 sites. Study medication (40 mg) was administered by subcutaneous injection every other week. Efficacy, safety and QoL measurements were performed throughout the study. The follow up was every month for 6 months.</td></tr>
<tr><td colspan="3">Number of Subjects (Planned and Analyzed): 220 subjects</td></tr>
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Diagnosis and Main Criteria for Inclusion: A subject will be eligible for study participation if he/she meets the following criteria:

Males and females ≥18 years of age.

1. A negative pregnancy test (serum HCG) for women of childbearing potential prior to start of study treatment. [Non-childbearing potential is defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy)]

2. Use of a reliable method of contraception e.g. intra-uterine devices, condoms or hormone (oral, implantable, or injectable) contraceptives by all female patients of childbearing potential. Male patients with procreative capacity should also ensure that effective contraception is used during the study and for 70 days after study completion.

3. ACR criteria for diagnosis of RA for at least 3 months.

4. Active RA as defined by DAS28 ≥ 3.2 at study entry.

5. Unsatisfactory response or intolerance to prior DMARDs.

6. Able and willing to self-administer sc injections or have available a suitable person(s) to administer sc injections.

7. Able and willing to give written informed consent and to comply with the requirements of the study protocol.

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

Duration of Treatment: 6 months (28 weeks)

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Study drug was provided as prefilled syringes (40 mg adalimumab in 0.8 ml) for self-injections. The drug was given under the skin of the abdomen or the thigh. The total content of the syringe had to be injected. The syringes were stored in the original container at +2 to +8°C.

Criteria for Evaluation

Efficacy: This was an open-label study to establish whether patients with moderate to severely active RA showed response when adalimumab was added to the pre-existing inadequate standard anti-rheumatic therapy. No differentiation will be made between primary or secondary efficacy variables. Response was evaluated by change in disease activity score (DAS28) compared with study entry, ACR response criteria at 28 weeks. DAS28 and ACR response criteria as well as changes in individual ACR core set parameters were analyzed descriptively [redacted]

Pharmacokinetic: NA

Safety: Adverse Events, laboratory data, physical examinations and vital signs were assessed throughout the study.

Statistical Methods

Efficacy: The efficacy was performed on the set of patients who completed the 28 weeks of treatment with adalimumab. Since this is not a confirmatory study, no per-protocol analysis is planned.

Pharmacokinetic: NA

Safety: The safety analysis was performed on the set of patients who received at least one injection of adalimumab.

Summary/Conclusions

Efficacy Results: Mean DAS score improved from 6.3 to 3.7 and ACR20 response was of 51.6%, ACR50 of 22.5% and ACR70 of 9.3%. Clinical remission (DAS<2.6) was achieved in 55 patients (29%). Health Assessment Questionnaire (HAQ) improved from 1.77 to 0.65.

Pharmacokinetic Results: NA

Safety Results: Seventy-one percent of patients had an adverse event and 4.1% a serious adverse event. Four patients had TB during the study (incidence 3800 cases per 100,000-persons-year.

Conclusions: HUPE study showed that adalimumab therapy added to preexisting inadequate standard anti-rheumatic therapy in patients with moderate to severe disease was efficacious measured by DAS, ACR20 and HAQ improvement. Adalimumab was well tolerated but TB incidence was higher than expected and some adverse outcome occurred in patients with severe sepsis.