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: Review of Safety and Efficacy with Adalimumab in Patients with Active Ankylosing Spondylitis – An Open-label Study to Evaluate the Response to Adalimumab in Patients Who Have Failed Standard Therapy on TNF-α Inhibitors (RHAPSODY)

Investigator: PD Dr med. Martin Rudwaleit, Charité University Medicine, Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin

Study Sites Multicenter (211 study sites in 15 countries - Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, and United Kingdom).

Publications: 7 abstracts

Studied Period (Years):	**Phase of Development:** 3b
First Subject First Visit: 20 Feb 2006 Last Subject Last Visit: 27 Mar 2007	

Objectives: The objective of this open-label study was to evaluate adalimumab 40 mg every other week (eow) subcutaneously (SC) in subjects with active ankylosing spondylitis (AS) in day-to-day clinical practice.

The safety and efficacy of adalimumab was to be analyzed overall and based on concomitant nonsteroidal anti-inflammatory drug (NSAID) use, concomitant steroid use, concomitant disease-modifying antirheumatic drug (DMARD) use, and prior exposure to other tumor necrosis factor (TNF) inhibitors (etanercept and infliximab).

The safety and efficacy of adalimumab in subjects with AS was to be evaluated based on the type of clinical presentation of the disease (axial, peripheral arthritis, and/or enthesitis). The number of subjects with total ankylosis of the spine was limited in previous phase 3 studies of adalimumab in AS; thus, limited experience was available for use of adalimumab in subjects with advanced, including total ankylosis of the spine. This study also allowed further analyses of safety and efficacy in subjects with advanced spinal ankylosis.

The safety and efficacy profile was to be evaluated by AS associated disorders including inflammatory bowel disease (IBD), psoriasis (Ps) and uveitis. For uveitis, a subgroup of subjects was to be defined by the presence of acute uveitis or chronic uveitis within 12 months prior study entry, or at the Screening Visit with the expectation that these subjects were at higher risk of uveitis attacks.

Methodology: This was an open-label, multi-national, multicenter Phase 3b study designed to further assess the safety and efficacy of adalimumab in the treatment of subjects with active AS currently receiving standard therapy for the symptoms of AS.

A total of approximately 1200 subjects having a diagnosis of active AS and fulfilling study eligibility criteria were planned for enrollment at approximately 250 study sites in Europe.

The study included a screening period, a study treatment period (Day 1 through Week 12), an optional study continuation period (Week 12 through Week 20), and a 70-day follow-up phone call.

A magnetic resonance imaging (MRI) sub-study was to be conducted in selected sites in Germany and France and an Ultrasound/Doppler of the Entheses sub-study was to be conducted in selected sites in France.

During the screening period, subjects were assessed for eligibility for the study. Eligible subjects were to return to the study site at Day 1 to enter into the treatment period.

During the treatment period, subjects were to receive adalimumab 40 mg eow SC. Safety and efficacy assessments were to be completed at Day 1, Week 2, Week 6 and Week 12. At the subject's Week 12 study visit, the investigator was to discuss the appropriate subsequent treatment with the subject.

During the optional continuation period, subjects with active uveitis at the Screening Visit or documented active uveitis within the 12 months prior to the Screening Visit were to be allowed to continue in the study up to Week 20 for further analyses of AS subjects with uveitis. Subjects with active uveitis and subjects without active uveitis (in instances where adalimumab was generally unavailable at a country level for the indication of AS) were allowed to enter the study continuation period. Subjects with and without active uveitis were dispensed study drug at Week 12 and were to continue to self-administer adalimumab 40 mg eow SC with their last administration of study drug occurring at Week 18. All of these subjects were then to return at Week 20 study visit for safety and efficacy assessments. Following Week 20, the investigator was to discuss the appropriate subsequent treatment with the subjects.

Following the discontinuation of study drug the investigator was to contact the subject approximately 70 days following study drug discontinuation. Any adverse events (AEs) that occurred within those 70 days, and prior to initiation of commercial adalimumab were to have been reported. The telephone contact could have been made in advance of 70 days for subjects that were known to have started on commercial adalimumab.

Number of Subjects (Planned and Analyzed): A total of 1200 subjects were planned, 1250 were enrolled and analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects were eligible for enrollment if they had a diagnosis of AS according to the modified New York Criteria for Ankylosing Spondylitis; documented active AS based on the opinion of a physician for at least 3 months; had active AS with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 at the Screening Visit; was over the age of 18, and able and willing to self-administer SC injections or have available a suitable person to administer SC injections. Main criteria for inclusion also included: unsatisfactory response to standard AS therapies in accordance with the current national guidelines for treatment of AS with TNF inhibitors (if applicable) including a minimum of failing at least one NSAID; study enrollment in accordance with the current National guidelines (if applicable) for treatment of AS with TNF inhibitors; females were to be postmenopausal, sterile and not pregnant or breast-feeding and practicing at least one of the acceptable methods of birth control specified in the protocol; for women of childbearing potential, a negative pregnancy test (serum HCG) prior to start of study treatment; and subjects had to be evaluated for active and latent tuberculosis (TB) infection by purified protein derivative (PPD) skin test, T Spot-TB test, chest x-ray (CXR) including a detailed review of the subject's medical history, and guidelines regarding the treatment of latent tuberculosis had to be followed prior to the administration of adalimumab.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: All subjects received open-label adalimumab (0.8 mL SC injection of 50 mg/mL adalimumab solution for injection [40 mg adalimumab] eow).

Duration of Treatment: Twelve weeks with the potential for extension to 20 weeks depending on availability of commercial adalimumab at that time.

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

Not applicable. This is a single-arm open-label study.

Criteria for Evaluation

Efficacy: Efficacy was to be evaluated based on:

Axial ankylosing spondylitis signs and symptoms - ASAS 20/40/50/70, ASAS 5/6, BASDAI score, BASDAI 20/50/70, BASFI score, BASMI, Nocturnal pain VAS, and Total back pain VAS, Patient's global assessment of disease activity, Physician's global assessment of disease activity, CRP, and the reduction in the number of or discontinuation of NSAIDs compared to study entry.

Patient Reported Outcomes – SF-36™ Health Status Survey, WPAI-SHP, MOS-Sleep Scale, and patient's assessment of current treatment for AS.

Enthesitis assessment – change of MASES and change in fascia plantaris enthesitic sites.

Peripheral assessment – Change in TJC46/SJC44

AS Associated Disorders

Psoriasis – Physician's global assessment for Ps, Patient's assessment of improvement of Ps

Inflammatory Bowel Disease – Patient's assessment of improvement of IBD

Uveitis – The preventive effect of adalimumab on uveitis attacks will be assessed by the number of acute flares per patient years during adalimumab treatment in comparison with the flare rate during the last year before enrolling into the clinical study.

Safety: Safety assessments included AEs monitored throughout the study, physical examination results, vital signs measurements, and clinical lab results. Safety variables were to be analyzed for the subgroups of subjects with concomitant NSAIDs, corticosteroids, DMARD(s), and for subjects with adalimumab monotherapy separately, as well as for subjects with or without prior exposure to TNF inhibitors (infliximab or etanercept).

Statistical Methods

Efficacy: All subjects who received at least one injection of adalimumab were to be included in the efficacy analysis. The efficacy analysis was to be done descriptively by presenting summary statistics and confidence intervals. The values at all visits as well as changes from Baseline were to be summarized.

Efficacy variables were to be evaluated based on the type of clinical presentation of the disease (axial, peripheral arthritis, and/or enthesitis) and were to be analyzed for the subgroups of subjects with concomitant NSAIDs, steroids, DMARD(s) and for subjects with adalimumab monotherapy (without concomitant DMARD) separately, as well as for subjects with or without prior exposure to other biologics. Comparisons between the respective subgroups (with concomitant DMARD(s) vs. adalimumab monotherapy; with vs. without prior exposure to other biologics) were to be done using adequate statistical models that account for relevant confounders. All comparisons were to be

descriptive. Further details regarding the statistical analysis, including the identification of confounders, were to be specified in the statistical analysis plan.

Safety: All subjects who received at least one injection of adalimumab were to be included in the safety analysis. Treatment-emergent AEs were to be summarized. Treatment-emergent AEs were defined as events with an onset date after the first adalimumab injection up to 70 days after the last adalimumab injection, except for those subjects that switched to commercial adalimumab. Serious adverse events (SAEs) with onset before the first adalimumab injection were to be considered as pre-treatment SAEs. In case of increasing severity of an existing AE, the worsening was to be considered as a new AE with a new onset date.

AEs were to be tabulated by system organ class and preferred term, whereby the most current implemented Medical Dictionary for Regulatory Activities (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 to be 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 to be described by statistical characteristics. In addition, shift tables and listings were to be provided for abnormal values, whereby the normal ranges of the analyzing laboratory were to be used.

Safety variables were to be analyzed for the subgroups of subjects with concomitant DMARD(s) and for subjects with adalimumab monotherapy separately, as well as for subjects with or without prior exposure to other biologics. Comparisons between the respective subgroups (with concomitant DMARD(s) vs. adalimumab monotherapy; vs. without prior exposure to other biologics) were to be done using adequate statistical models that account for relevant confounders. All comparisons were to be descriptive.

Further details regarding the statistical analysis, including the identification of confounders, were to be specified in the statistical analysis plan.

Summary/Conclusions

Efficacy Results: The effectiveness and durability of adalimumab in reducing the axial signs and symptoms of active AS were shown by:

- ASAS 20/40/50/70 responses of 69.9%, 53.7%, 48.4%, and 28.7%, respectively at Week 12 with all rates maintained at Week 20.
- 55.3% of subjects achieving an ASAS 5 out of 6 response at Week 6 and maintained at Week 12 (58.0%) and at Week 20 (59.4%).
- Reductions in each of the four ASAS components (patient global assessment of disease activity, total back pain, BASFI, and inflammation) appearing to contribute equally to the improvement in ASAS.
- Partial remission being achieved by 27.7% of the subjects at Week 12 and improved further to 36.6% at Week 20.
- The BASDAI (scale 0-10) being reduced by a mean of -3.3 at Week 12 and sustained at Week 20 representing a remarkable improvement in the disease activity of AS.
- BASDAI20/50/70 responses of 79.7%, 57.2%, and 38.3%, respectively at Week 12 and maintained at Week 20.
- Reduction in nocturnal pain VAS scale showing a mean –34.2 reduction at Week 12, and sustained at Week 20 representing an improvement in physical function.

- Reduction from Baseline in the subject and physician global disease assessments of –35.3 ± 30 and –36.5 ± 22.4, respectively at Week 12 representing improvement in the AS disease of study subjects.
- Reductions in levels of CRP and ESR showing a reduction in the inflammatory response to adalimumab treatment. At Week 6 there was an initial reduction (1.5 ± 2.5 SD) from Baseline in the level of CRP, which was sustained at Weeks 12 and 20. At Week 12 the mean change for ESR was –15.7 ± 20.0.
- A total of 26.5% of subjects who were on concomitant NSAIDs at Baseline discontinued use of NSAIDs during the study period, i.e. at the subject's final visit: Week 12, 20 or ET visit.

The mean change from Baseline in the health-related questionnaires SF-36 PCS and MCS, WPAI-SHP, and the MOS- Sleep Scale, show subjects reported improvement in quality of life in areas of general health, physical function, mobility, pain, vitality, social functioning and mental health; work productivity and activity impairment; and sleep.

- At Week 12, the mean change from Baseline for SF-36: PCS was 10.1 ± 10.2 and the mean change for SF-36: MCS was 5.9 ± 11.3.
- At Week 12, the mean change from Baseline and percent change in the following WPAI-SHP components were:
    - Percent Work Time Missed (only in subjects with employment) was −6.5 ± 25.9 and −51.0% ± 136.1%.
    - Percent Impairment while working (only in subjects with employment) was –23.1 ± 28.1 and –44.3% ± 57.2%.
    - Percent Overall Work Impairment (only in subjects with employment) was –25.2 ± 29.3 and –44.5% ± 61.5%.
    - Percent Activity Impairment for all subjects was –26.7 ± 28.6 and -39.1% ± 54.0%.

  The decrease in WPAI-SHP at Weeks 6, 12 and 20 indicates improvement in study subjects' ability to work and perform regular activities.
- Changes in sleep scales at Weeks 6, 12 and 20 indicate that adalimumab was effective in improving study subjects sleep.
- The proportion of subjects reporting optimal sleep increased from 35.1% to 47.7%, 51.5%, and 54.5% at Weeks 6, 12, and 20, respectively.

Adalimumab demonstrated improvement in peripheral arthritis (defined as TJC >0 and/or SJC > 0) and enthesitis (defined as MASES > 0 or Fascia Plantaris Score > 0).

ASAS40, ASAS 5 out of 6, partial remission, BASDAI, and BASDAI50 responses were similar in the subgroups as defined in the Statistical Methods efficacy section except for subjects who were taking prior anti-TNF therapy. The proportion of subjects achieving response was higher in subjects with no prior anti-TNF therapy compared to those with prior anti-TNF therapy. Adalimumab showed effectiveness in subjects who had been treated with prior anti TNF inhibitors in the past and switched to adalimumab after failure, loss of response over time and /or intolerance of the prior anti-TNF.

Adalimumab showed effectiveness in the AS associated disorders Ps, IBD, and uveitis.

Safety Results: Adalimumab was generally safe and well tolerated as evaluated by the occurrence and nature of AEs and the incidence of deaths, SAEs and discontinuations due to AEs.

- There were no deaths reported during the study.
- Serious AEs occurred in only 43 (3.4%) subjects of the 1250 subjects, included 14 (1.1%) subjects with SAEs that were considered by the investigator to be at least possibly related or probably related to study drug.
- There was one pregnancy reported during this study. The subject chose to have an elective abortion (preferred term of "abortion induced"). The induced abortion was reported as an SAE.
- Discontinuations due to AE occurred in 65 (5.2%) subjects, included two events of headache, one event of alanine transferase increased, one event of aspartate transferase increased, and one event of pain in extremity that were considered by the investigator as possibly or probably related to study drug.

Adalimumab was generally safe and well tolerated as evaluated by TNF inhibitor-related events of interest.

- Infectious AEs were reported by 20.5% (256/1250) adalimumab-treated subjects. The infections reported in ≥ 1% of subjects included nasopharyngitis (5.1%; 64/1250), pharyngitis (1.6%; 20/1250), viral infection (1.3%; 16/1250), sinusitis (1.2%; 15/1250), rhinitis (1.1%; 14/1250), upper respiratory tract infection (1.1%; 14/1250), urinary tract infection (1.1%; 14/1250), and influenza (1.0%, 12/1250).
- A total of 5 (0.4%) of the 1250 subjects experienced serious infections (acute tonsillitis, viral infection, myringitis, botonous fever, and cellulitis), all of which were considered at least possibly related to study drug by the Investigator.
- There were no treatment-emergent malignancies reported.
- One subject reported treatment-emergent CNS demyelinating disease considered by the Investigator as possibly related. The subject, a 34 year-old male, experienced optic neuritis on Day 86 (43 days after last treatment), and optic atrophy (worsening of visual ability) on Day 87 (44 days after last treatment). Both events were of moderate severity and considered by the Investigator as possibly related.
- Fifteen (1.2%) subjects reported treatment-emergent immunologic reactions. Of these, eleven were considered by the investigator to be at least possibly related to study drug. None of these events were serious and all were moderate to mild in severity. Two were considered by the investigator to be due to hypersensitivity to adalimumab.
- Sixty-five (5.2%) subjects reported treatment-emergent injection site reaction during treatment with adalimumab. All events were considered at least possibly related by the investigator. None of these events were serious and all were moderate to mild in severity.
- Three (0.2%) subjects reported treatment-emergent opportunistic infections (candidiasis) during treatment with adalimumab. All were considered by the investigator to be at least possibly related to study drug. None were serious and all were mild to moderate in severity.
- One (0.1%) subject reported three events of treatment-emergent CHF during treatment with adalimumab. All were considered by the investigator to be at least possibly related to study drug. Two events were serious and severe.
- No treatment-emergent events of TB, lupus/lupus like reactions, and serious allergic reactions were observed.

The safety profile of adalimumab is unaffected by concomitant NSAIDs, concomitant oral steroids, and prior TNF inhibitors used in standard care for AS. Subjects on concomitant DMARDs were less likely to report a treatment-emergent AE while on adalimumab (OR = 0.067; p = 0.003).

There were 25 (2.0%) subjects who reported 27 events of treatment-emergent uveitis, representing 7.4 events per 100 PY. Three of the 27 events were reported as iritis by three different subjects. Each iritis event was considered either not related, probably not related, or possibly related to study drug by the Investigator. One event of iridocyclitis was reported in one subject. All events were non-serious with the exception of one serious and all events were mild to moderate with the exception of one serious event, which was severe. Two subjects reported new onset of uveitis.

The rate of 15 flares per 100 PY before adalimumab treatment is consistent with reported rates for the AS population in the literature. Adalimumab effectively reduced the rate of anterior uveitis flares in AS by more than 50%.

Adalimumab was generally safe and well tolerated as evaluated by assessments of serum chemistries, hematologic values and urinalyses.

- ALT elevations ≥ 3.0xULN were observed in 18 of 1250 adalimumab-treated subjects (1.4%). AST elevations ≥ 3.0xULN were observed in 12 of 1250 adalimumab-treated subjects (0.96%).

  Thirty-seven subjects had clinical chemistry values that were considered potentially clinically significant in two of four parameters (ALT, AST, alkaline phosphatase. and total bilirubin. Seven of the 37 subjects experiencing 11 events of increased ALT and/or AST were withdrawn from the study. Of the 11 events, all were considered by the investigator not to be serious; six events were mild in severity, three were severe and two were moderate; and six were considered not related, three possible or probably related, and two probably not related.
- Other laboratory and urinalysis evaluations did not demonstrate important clinical effects of adalimumab.

Conclusions: Adalimumab was generally safe and well tolerated at a dose of 40 mg eow SC. Adalimumab markedly reduced the signs and symptoms of AS, improved the quality of life, work productivity and sleep in patients with active disease who had an inadequate response to prior therapy. Adalimumab reduced the incidence of uveitis flares in subjects with ankylosing spondylitis.

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