

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		
Title of Study: A Multicenter, Randomized, Double-Blind, Study Comparing the Efficacy and Safety of Continuing Versus Withdrawing Adalimumab Therapy in Maintaining Remission in Subjects with Non-Radiographic Axial Spondyloarthritis		
Coordinating Investigator: Robert Landewé, Atrium Medical Center, Netherlands		
Study Sites: 107 sites in Australia, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, Germany, Ireland, Italy, Mexico, Netherlands, New Zealand, Poland, Russia, Slovakia, Spain, Switzerland, United Kingdom, and US		
Publications: 2 abstracts		
Studied Period (Years): First Subject First Visit: 16 April 2013 Last Subject Last Visit: 14 April 2017 (70-day follow-up call)	Phase of Development: 3b/4	
Objective: The objective of this study was to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given eow SC in maintaining remission in subjects with nonradiographic axial spondyloarthritis (nr-axSpA).		
Methodology: The study duration included a 42-day Screening Period, a 28-week open-label 40 mg adalimumab eow treatment period (Period 1), a 40-week double-blind placebo controlled eow treatment period (Period 2) with an opportunity to receive at least 12 weeks of rescue therapy (subjects that flared at Weeks 60, 64 or 68 were allowed 12 weeks of rescue therapy and final visits were 72, 76 or 80 respectively), plus a 70 day follow-up phone call. Subjects in sustained ASDAS inactive disease were randomized at Week 28 in a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo. Length of exposure depended on remission or flare status and ranged from 20 (first time Ankylosing Spondylitis Disease Activity Score [ASDAS] remission was calculated) to 80 weeks of treatment.		
Number of Subjects (Planned and Analyzed): Planned: 740 subjects Analyzed: Open-label full analysis set (FAS): 673 subjects Double-blind modified intent-to-treat (mITT) population: 305 subjects (153 placebo; 152 adalimumab)		

Diagnosis and Main Criteria for Inclusion:

Subjects enrolled in this study fulfilled the Assessment of SpondyloArthritis International Society (ASAS) axial spondyloarthritis (SpA) classification criteria, but not the radiologic criterion of the modified New York criteria for ankylosing spondylitis. Subjects were to have had an inadequate response to at least 2 nonsteroidal anti-inflammatory drugs (NSAIDs) over a 4-week period in total at maximum recommended or tolerated doses or an intolerance to or a contraindication for NSAIDs. Subjects were also to have had objective evidence of active inflammation in the sacroiliac (SI) joints or spine on magnetic resonance imaging (MRI) or elevated high sensitivity C-reactive protein (hs-CRP) at screening (elevated hs-CRP is defined as any level greater than the upper limit of normal for the lab) and Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥ 2.100 , Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 , and Patient's Assessment of Total Back Pain score ≥ 4 based on a Numeric Rating Scale (NRS) at both the Screening and Baseline Visits.

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

Adalimumab 40 mg/0.8 mL

Bulk lot numbers: 11-005882, 13-000648, 13-005618, 15-000609, 15-005871

Duration of Treatment: Up to 80 weeks.

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

Placebo for adalimumab 0.8 mL, vial

Bulk lot number: 12-007038, 14-002885, 15-005865

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the proportion of subjects who did not experience a flare during Period 2 by Week 68 of the study where a flare was defined as having any 2 consecutive study visits with ASDAS ≥ 2.100 .

Secondary efficacy variables included the following:

At 12 Weeks after initiation of rescue therapy

- ASDAS inactive disease
- ASDAS major improvement
- ASDAS clinically important improvement
- ASAS20, ASAS40, ASAS 5/6, ASAS partial remission
- BASDAI50
- Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S)

At Week 28 and Week 68

- ASDAS inactive disease
- ASDAS major improvement
- ASDAS clinically important improvement
- ASAS20, ASAS40, ASAS 5/6 and ASAS partial remission
- BASDAI50
- HAQ-S

Criteria for Evaluation (Continued)

Efficacy (Continued):

At Week 68

- Time to flare defined as ASDAS \geq 2.100 at 2 consecutive visits
- Time to partial flare defined as ASDAS \geq 1.300 but $<$ 2.100 at 2 consecutive visits
- Proportion of subjects who reach flare definition
- Proportion of subjects who reach partial flare definition

Other supportive efficacy variables that represent the effect of adalimumab on multiple components of nr-axSpA were assessed during the open-label and double-blind periods of the study.

Safety:

Adverse events (AEs), physical examination, vital signs, and clinical laboratory data were assessed throughout the study.

Statistical Methods

Efficacy:

Period 1

Efficacy endpoints in Period 1 were summarized using descriptive statistics. The analysis population was the FAS.

Period 2

The primary efficacy endpoint was the proportion of subjects who do not experience a flare in Period 2 by Week 68 of the study, where a flare was defined as having any 2 consecutive study visits with ASDAS \geq 2.100, and the response rate observed in the group randomized to adalimumab 40 mg eow was compared to that in the placebo group. The null hypothesis associated with this comparison states that there is no difference in response rates between the adalimumab and placebo groups; the alternative hypothesis is that the response rates are different. The response rates were tested using a 2-sided Pearson's chi square test with $\alpha = 0.05$. Subjects who discontinued during the double-blind period (Period 2) with missing flare data at Week 68 were treated as non-responders (flare) according to "non-responder imputation" criterion.

Chi-square test was used for statistical analysis of binary endpoints; mixed model repeated measure (MMRM) analysis was used for continuous endpoints; Log-rank test and Cox proportional hazard model were used for time to event endpoint. Descriptive statistics were also presented for all efficacy endpoints.

The analysis population for the efficacy endpoints is the mITT population (randomized and treated). The primary endpoint was also analyzed using the per-protocol population (PP).

Pharmacokinetic:

PK results and conclusions are presented in a separate PK report (R&D/17/0299).

Safety:

Adverse event analyses included all treatment-emergent AEs up to 70 days after adalimumab dose. Adverse event data will be summarized and presented using primary MedDRA system organ classes and preferred terms according to Version 19.1 of the MedDRA coding dictionary.

Statistical Methods (Continued)

Safety (Continued):

The following summary statistics for laboratory, and vital signs measurements were presented for subjects who have both Baseline and post-baseline values for laboratory tests and vital signs: the mean value at Baseline and at each respective protocol specified visit, and the mean, standard deviation, and median for changes from Baseline. Categorical data will be summarized using frequencies and percentages.

Summary/Conclusions

Efficacy Results:

A total of 673 subjects were enrolled in the study and received open-label treatment with adalimumab 40 mg eow. Throughout the 28-week open-label period (Period 1), improvements were observed in the proportion of subjects achieving ASAS20 response, ASAS40 response, ASAS partial remission, ASAS 5/6 response, ASDAS inactive disease, ASDAS clinically important improvement, ASDAS major improvement, BASDAI50 response, as well as the mean change from baseline in HAQ-S scores.

There were 305 subjects randomized into Period 2. Of these, 152 subjects were randomized to continue receiving adalimumab 40 mg eow and 153 subjects were randomized to have adalimumab withdrawn and begin receiving placebo in the 40-week double-blind period (Period 2).

The primary efficacy variable was the proportion of subjects who did not experience a flare in the double-blind period (Period 2) by Week 68 of the study, where a flare was defined as having any 2 consecutive study visits with ASDAS ≥ 2.100 . The proportion of subjects that did not experience flare was statistically significantly greater ($P < 0.001$) in the adalimumab group (70.4%) than in the placebo group (47.1%). Results of sensitivity and subgroup analyses were consistent with the primary efficacy analysis. Time to flare analysis demonstrated subjects in the placebo group had a statistically significant higher risk of flare and shorter time to flare than subjects continued on adalimumab. Disease flare was observed for some subjects at the first possible timepoint permitted by the protocol (8 weeks after randomization) with clear separation of the Kaplan-Meier survival curves of the 2 groups observed 12 weeks after randomization.

Secondary efficacy variables during the double-blind period (Period 2) supported the primary efficacy variable with statistically significantly greater proportions of subjects in the adalimumab group achieving ASAS20 response, ASAS40 response, ASAS partial remission, ASAS 5/6 response, ASDAS inactive disease, ASDAS clinically important improvement, ASDAS major improvement, and BASDAI50 response compared with the placebo group at Week 68.

At Week 68, mean improvements in other supportive efficacy variables showed consistently greater improvement in subjects continued adalimumab vs. those withdrawn from treatment (placebo). BASFI, hs-CRP, SF-36 physical component score, physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of nocturnal back pain, patient's assessment of back pain, and patient's assessment of pain were statistically significantly greater in the adalimumab group compared with the placebo group.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Subjects who met flare criteria during the double-blind period (Period 2), received rescue therapy with open-label adalimumab 40 mg eow for at least 12 weeks and continued on open-label adalimumab through the duration of the subject's participation in the study. Following initiation of open-label rescue therapy the proportion of subjects with ASAS20 response, ASAS40 response, ASAS partial remission, ASAS 5/6, ASDAS inactive disease, ASDAS clinically important improvement, ASDAS major improvement, and BASDAI50 response increased through 12 weeks in both subjects who had been randomized to placebo and subjects who had been randomized to adalimumab in the double-blind period. The proportion of subjects achieving these responses was generally higher in subjects who had been randomized to blinded placebo compared with subjects who had been randomized to blinded adalimumab prior to restarting open-label adalimumab treatment; however, re-initiation of adalimumab did not result in all placebo-treated subjects regaining a state of remission.

Pharmacokinetic Results:

PK results and conclusions are presented in a separate PK report (R&D/17/0299).

Safety Results:

No deaths were reported during the study.

Among the Any Adalimumab Population, 516 (76.7%) subjects experienced an AE. The most frequently reported ($\geq 5\%$ of subjects) AEs were nasopharyngitis, upper respiratory tract infection, worsening of axial spondyloarthritis, headache, and diarrhea. Thirty-nine (5.8%) subjects reported AEs that were considered severe by the Investigator. The most frequently reported (≥ 2 subjects) severe AEs were worsening of axial spondyloarthritis (5 [0.7%] subjects); back pain (3 [0.4%] subjects); and fatigue, gastroenteritis, pneumonia, headache, and anxiety (2 [0.3%] subjects each).

Two hundred and fifty-four (37.7%) subjects reported an AE with a reasonable possibility of being related to study drug as determined by the Investigator.

During the open-label period (Period 1), 470 (69.8%) subjects experienced an AE.

Thirty (4.5%) subjects reported at least 1 severe AE and 224 (33.3%) subjects reported an AE with a reasonable possibility of being related to study drug as determined by the Investigator. During the double-blind period (Period 2), a similar percentage of subjects who received placebo (105 [68.6%]) reported an AE compared with subjects who received adalimumab (99 [65.1%]). Nine (5.9%) subjects from the placebo group and 3 (2.0%) subjects from the adalimumab group reported a severe AE. Forty-two (27.5%) subjects from the placebo group and 29 (19.1%) subjects from the adalimumab group reported an AE with a reasonable possibility of being related to study drug. After initiation of rescue therapy with open-label adalimumab, 56 (53.8%) subjects experienced an AE. Three (2.9%) subjects reported a severe AE and 19 (18.3%) subjects reported an AE with a reasonable possibility of being related to study drug.

Among the Any Adalimumab Population, 28 (4.2%) subjects reported a SAE. Eleven (1.6%) subjects reported a SAE considered by the Investigator as having a reasonable possibility of being related to study drug (2 subjects with appendicitis and 1 subject each for all other events).

Eighteen (2.7%) subjects experienced an AE leading to discontinuation of study drug (anxiety and injection site reaction in 2 subjects each and 1 subject each for all other events).

Summary/Conclusions (Continued)

Safety Results (Continued):

During the open-label period (Period 1), 19 (2.8%) subjects reported a SAE and 17 (2.5%) subjects experienced an AE leading to discontinuation of study drug. During the double-blind period (Period 2), a greater percentage of subjects who received placebo (10 [6.5%]) reported a SAE compared with subjects who received adalimumab (1 [0.7%]). Four (2.6%) subjects from the placebo group and no subjects from the adalimumab group experienced an AE leading to discontinuation of study drug. After initiation of rescue therapy, 4 (3.8%) subjects reported a SAE. No subjects experienced an AE leading to discontinuation of study drug.

Few AESIs were reported with the exception of infectious AEs (52.7% of subjects in the Any Adalimumab Population; 1.0% reporting serious infectious AEs, 0.1% reporting legionella infection, 0.3% reporting oral candidiasis, 0.4% reporting latent TB, and 0.1% reporting opportunistic infection excluding oral candidiasis and TB). Among the Any Adalimumab Population, injection site reaction was reported in 10.5% of subjects, allergic reactions including angioedema/anaphylaxis were reported in 2.5% of subjects, worsening/new onset psoriasis was reported in 1.0% of subjects, hematological disorders were reported in 0.9% of subjects, and malignancy (gastric adenocarcinoma), myocardial infarction, pulmonary embolism, and liver failure and other liver event (hepatic steatosis) were reported in 0.1% of subjects each. None of the following AESIs were reported during the study: diverticulitis, active TB, reactivation of hepatitis B, progressive multifocal leukoencephalopathy, lymphoma, NMSC, HSTCL, melanoma, leukemia, lupus-like reactions and systemic lupus erythematosus, vasculitis (cutaneous or non-cutaneous), sarcoidosis, autoimmune hepatitis, cerebrovascular accident, congestive heart failure, interstitial lung disease, intestinal perforation, pancreatitis, Stevens-Johnson syndrome, erythema multiforme, amyotrophic lateral sclerosis, reversible posterior leukoencephalopathy syndrome, and adalimumab administration-related medication error.

Across all periods of the study, only 1 subject had a CTC toxicity grade ≥ 3 hematology value (a single Grade 3 low neutrophil value during the open-label period, Period 1) that returned to normal by the next study visit. CTC toxicity grade ≥ 3 chemistry values were uncommon, having occurred in $\leq 1\%$ of subjects with the exception of increased ALT (8/668 [1.2%] subjects during the open-label period, Period 1). Most CTC toxicity grade ≥ 3 chemistry values improved or resolved by the final study visit value. Mean changes from Baseline in all laboratory parameters were small and not clinically significant with the exception of hs-CRP which decreased during the open-label and rescued periods, reflecting a decrease in systemic inflammation with adalimumab treatment, and increased over time in the placebo group during the double-blind period (Period 2), reflecting the return of systemic inflammation following removal of adalimumab treatment. During the study, mean changes from Baseline in vital sign values were small and not clinically meaningful.

Summary/Conclusions (Continued)

Conclusions:

Study M13-375 met the primary endpoint with the proportion of subjects not experiencing flare by Week 68 of Period 2 being higher in subjects who continued receiving adalimumab compared with subjects who had adalimumab withdrawn. Results of secondary and other efficacy endpoints supported the primary efficacy result. After treatment withdrawal, re-initiation of adalimumab did not result in all subjects regaining their previous state of remission. The results indicate that adalimumab 40 mg eow is effective in maintaining remission in subjects with nr-axSpA. Withdrawal of adalimumab therapy is associated with higher risk of both disease flare and inability to regain tight disease control.

Adalimumab was generally safe and well tolerated in Study M13-375; the safety profile was consistent with previous clinical trials for adalimumab and no new safety signals were observed.