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 Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Axial Spondyloarthritis (SpA)		
Coordinating Investigator: [redacted] Germany		
Study Sites: 37 study sites in Australia, Belgium, Canada, Czech Republic, France, Germany, The Netherlands, Spain, United Kingdom, and the United States		
Publications: 2 manuscripts; 15 abstracts		
Studied Period (Years): First Subject First Visit: 11 August 2009 Last Subject Last Visit: 19 August 2013	**Phase of Development:** 3	

Objectives:

The objective of the study was to evaluate the efficacy and safety of adalimumab 40 mg given every other week (eow) subcutaneously (SC) compared to placebo for 12 weeks followed by open-label (OL) safety and efficacy assessments in subjects with active axial SpA not fulfilling the modified New York criteria for ankylosing spondylitis (AS) who had an inadequate response to or intolerance to ≥ 1 nonsteroidal anti-inflammatory drug (NSAID), or had a contraindication for NSAIDs, as defined by the investigator.

Methodology:

This was a Phase 3, placebo-controlled, double-blind (DB), randomized study with an OL period conducted in the US, Canada, Europe, and Australia in subjects with active non-radiographic axial SpA (nr-axSpA) who met the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial SpA but did not fulfill the modified New York criteria for AS and had an inadequate response to or intolerance to ≥ 1 NSAID, or had a contraindication for NSAIDs, as defined by the investigator. Approximately 194 adult subjects with nr-axSpA were planned to be enrolled.

Subjects were randomized in a 1:1 ratio to receive either adalimumab 40 mg SC eow or matching placebo for 12 weeks during the DB period.

Following the DB period, at Week 12, all remaining subjects entered the OL period of the study in which they received adalimumab 40 mg SC eow for up to an additional 144 weeks. At the Week 12 study visit, all subjects on placebo were started on active drug, and the subjects already on active drug continued on active drug.

Methodology (Continued):

The study included a 30-day screening period, a 12-week DB placebo-controlled treatment period, a 144-week OL (40 mg adalimumab eow) treatment period, and a follow-up phone call 70 days after the last dose of study drug.

This final clinical study report contains the results for the study through Week 156 (12 weeks of DB treatment and 144 weeks of OL treatment), presenting both data analyses for the overall population and post-hoc data analyses for a subpopulation who had objective evidence of inflammation based on a positive magnetic resonance image (MRI) of the sacroiliac (SI) joints or the spine, or an elevated C-reactive protein (CRP), at Baseline.

Number of Subjects (Planned and Analyzed):

Planned: 194 subjects

Analyzed:

Four analysis sets were used for efficacy analyses for the overall study population (all subjects received study drug according to their randomization assignment):

1. 192 subjects (intent-to treat [ITT] Analysis Set, defined as all randomized subjects who received ≥ 1 dose of blinded study drug) were analyzed only as a sensitivity analysis for the primary efficacy endpoint and ranked secondary efficacy variables due to investigator noncompliance at 1 investigative site, which led to exclusion of 7 subjects from the efficacy analyses. The treatment group for each subject was based on treatment assignment at the time of randomization, regardless of actual treatment that the subject received during the study.
2. 185 subjects (Full Analysis Set [FAS]), a subset of the ITT Analysis Set that excluded the 7 subjects from site with investigator noncompliance. The FAS was used to evaluate the primary efficacy endpoint.
3. 161 subjects (per-protocol population [PPP]), all FAS subjects who completed the DB portion of the study and did not have any major protocol violation during the DB period.
4. 183 subjects (Any Adalimumab Efficacy Set), all randomized subjects who received ≥ 1 dose of adalimumab any time during the study, with the exception of the 7 subjects from the site with investigator noncompliance.

Two analysis sets were used for safety analyses of the overall population:

1. 192 subjects who received ≥ 1 dose of study drug (placebo or adalimumab) (Safety Analysis Set).
2. 190 subjects who received ≥ 1 dose of adalimumab (Any Adalimumab Safety Set).

The 2010 ASAS recommendations for the use of anti-tumor necrosis factor (TNF) agents for the treatment of axial SpA stated that candidates for anti-TNF therapy, in addition to a diagnosis of axial SpA, should at least: have failed treatment with, or have a contraindication for, NSAIDs; have active disease defined as Bath AS Disease Activity Index (BASDAI) ≥ 4; and have an expert opinion that treatment is warranted, considering not only clinical features but also the presence of elevated serum acute phase reactants or imaging results. Consistent with these treatment recommendations, a subpopulation of the subjects in Study M10-791 was identified that had either a positive MRI of the SI joints or the spine, or an elevated CRP, as objective evidence of active inflammation at Baseline: this was referred to as the Adalimumab Target Population (ATP).

Number of Subjects (Planned and Analyzed) (Continued):

Four analysis sets were used for efficacy analyses of the ATP:

1. 147 subjects (ATP ITT, defined as all subjects from the ITT who had a positive MRI or an elevated CRP at Baseline) were analyzed only as a sensitivity analysis for the primary efficacy endpoint and ranked secondary efficacy variables.
2. 142 subjects (ATP FAS), all subjects from the FAS who had a positive MRI or an elevated CRP at Baseline.
3. 125 subjects (ATP PPP), all ATP FAS subjects who completed the DB period of the study and did not have any major protocol violation during the DB period.
4. 140 subjects (ATP Any Adalimumab Efficacy Set), all subjects from the Any Adalimumab Efficacy Set who had a positive MRI or an elevated CRP at Baseline.

Two analysis sets were used for safety analyses of the ATP:

1. 147 subjects from the Safety Analysis Set who had a positive MRI or an elevated CRP at Baseline (ATP Safety Analysis Set).
2. 145 subjects from the Any Adalimumab Safety Set who had a positive MRI or an elevated CRP at Baseline (ATP Any Adalimumab Safety Set).

Diagnosis and Main Criteria for Inclusion:

- Males and females ≥ 18 years of age who did not fulfill modified New York criteria for AS.
- No history or current diagnosis of psoriasis or psoriatic arthritis.
- Subjects must have had chronic back pain (of ≥ 3 months duration) with onset at < 45 years of age.
- MRI evidence of active inflammatory lesions of SI joints (past or present) with definite bone marrow edema/osteitis, suggestive of sacroiliitis associated with SpA plus ≥ 1 of the following clinical criteria or positive human leukocyte antigen-B27 (HLA-B27) plus ≥ 2 of the following clinical criteria: inflammatory back pain; history of arthritis (past or present); heel enthesitis (past or present); anterior uveitis confirmed by an ophthalmologist (past or present); Crohn's disease or ulcerative colitis (past or present); good prior response to NSAIDs; family history of SpA; positive HLA-B27; or elevated CRP.
- Subjects must have had an inadequate response to or intolerance to ≥ 1 NSAID, or had a contraindication for NSAIDs as defined by the investigator.
- Subjects must have had Baseline disease activity as defined by having a Total Back Pain visual analogue scale score ≥ 40 mm and BASDAI ≥ 4 on a 0 – 10 cm scale at both the Screening and Baseline visits.

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

Adalimumab 40 mg/0.8 mL, pre-filled SC syringes

Bulk Product Lot Numbers: [redacted]

Duration of Treatment: 156 weeks

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

Placebo for adalimumab

Bulk Product Lot Numbers: [redacted]

Criteria for Evaluation

Efficacy:

Efficacy measurements in this study were selected or designed to assess disease activity in subjects with nr-axSpA. The primary efficacy variable for this study was the proportion of subjects who achieved Assessment of Spondyloarthritis International Society-40 (ASAS40) response criteria at the Week 12 visit.

Ranked secondary efficacy variables analyzed at Week 12 were:

1. ASAS20 response
2. BASDAI 50
3. Mean change in Short Form-36 Health Status Survey™ Version 2 (SF-36v2) physical component summary (PCS) score
4. ASAS partial remission
5. ASAS5/6 response
6. Mean change in Health Assessment Questionnaire modified for the spondyloarthropathies (HAQ-S) total score
7. Mean change in high sensitivity (hs) CRP
8. Mean change in Spondyloarthritis Research Consortium of Canada (SPARCC) MRI score for SI joints
9. Mean change in SPARCC MRI score for the spine

Other secondary efficacy variables analyzed/summarized at various other time points were:

<u>Reduction of Signs and Symptoms Variables</u>

- ASAS 20/40/50/70 responses
- ASAS5/6 response
- ASAS partial remission
- Mean change in Patient's Global Assessment of Disease Activity (PTGA-disease activity)
- Total back pain
- Mean change in Bath AS Functional Index (BASFI)
- Inflammation/morning stiffness (mean of BASDAI questions 5 and 6)
- BASDAI50 response
- Mean change in BASDAI total score
- Mean change in hs-CRP and pooled CRP (hs-CRP or standard)
- Mean change in Ankylosing Spondylitis Disease Activity Score (ASDAS)
- Mean change in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
- ASDAS response
- ASDAS disease activity state
- Plantar fascia enthesitis
- Mean change in Physician's Global Assessment of Disease Activity (PGA-disease activity)
- Mean change in PTGA-pain
- Mean change in tender and swollen joint counts (TJC68 and SJC66)
- Mean change in dactylitis count

Criteria for Evaluation (Continued)

Efficacy (Continued):

Reduction of Signs and Symptoms Variables (continued)

- Anterior uveitis flares during study
- Nocturnal pain

Metrology Variables

- Mean change in BASMI component scores
- Mean change in $BASMI_{lin}$
- Mean change in $BASMI_2$
- Mean change in chest expansion

Health-Related Quality of Life Variables

- Mean change in HAQ-S total score
- Mean change in SF-36v2 PCS and Mental Component Summary (MCS) scores
- Health care resource utilization
- Mean change in Work Productivity and Activity Impairment – Specific Health Problem Questionnaire (WPAI-SHP)
- Patient Acceptable Symptom State (PASS)
- Mean change in Medical Outcomes Study (MOS) Sleep Scale
- Mean change in European Quality of Life – 5 Dimensions questionnaire (EQ-5D)

Biomarkers

- Matrix metalloproteinase-3 (MMP-3)
- Type II collagen C-telopeptide (CTX-II)
- Vascular endothelial growth factor-A ($VEGF_A$)

Safety:

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

Statistical Methods

Three Statistical Analysis Plans (SAPs) were prepared over the course of this study:

- A SAP (dated 26 January 2011), which was for an interim report of data with a data cutoff of 02 February 2011 (the date of the last subject's Week 24 visit). Data was unblinded on 16 February 2011.
- A SAP (dated 07 November 2011), which was for an interim report of data through Week 68 (12 weeks of DB + 56 weeks of OL treatment). Database lock for the Week 68 interim report occurred on 15 November 2011. This SAP was also used for an interim report of data through Week 68 (12 weeks of DB + 56 weeks of OL treatment) which also presented post-hoc data analyses for a subpopulation with either a positive MRI or an elevated CRP at Baseline to align with the most recent treatment recommendations from ASAS.
- A SAP (dated 26 August 2013), which was for this final CSR that presents data through Week 156. Database lock for this final CSR occurred on 29 August 2013.

Statistical Methods (Continued)

Efficacy:

The primary efficacy endpoint and secondary efficacy variables were analyzed for the FAS and for the ATP FAS. In order to evaluate the impact of major protocol violations on the results of the study, additional analysis of the primary efficacy variable were conducted on the PPP and the ATP PPP, which consisted of all FAS/ATP FAS subjects who completed the DB period (Week 12) of the study and did not have any major protocol violation during the DB portion. The ITT and ATP ITT sets were used as a sensitivity analysis for the primary efficacy endpoint and ranked secondary efficacy variables.

Two interim database locks were planned: the initial interim analysis was performed when all subjects had completed at least Week 24 of the study (blind was broken for DB analyses done at Week 24), and the subsequent interim analysis was performed when all subjects had completed up to Week 68 of the study. The DB study results for the primary efficacy endpoint and ranked secondary efficacy variables (at Week 12) were based on the first database lock. All statistical comparisons for the primary endpoint and secondary variables were done at Week 12 (end of the placebo-controlled period) unless otherwise stated. Hence, no adjustment to the *P* value was required for this interim reporting. Efficacy data during the 12 weeks after Week 12 (i.e., to Week 24) were presented for exploratory purposes, and no statistical comparisons were made.

Analyses of efficacy for the ATP were added after the Week 68 SAP was finalized.

The last available pretreatment values recorded on or before Day 1 (first DB injection) were considered as the Baseline value. To account for the missing data for the primary efficacy endpoint (ASAS40) and all categorical efficacy variables, a non-responder imputation (NRI) approach was used, i.e., subjects with missing ASAS40 responses at Week 12 were imputed as non-responders. The last observation carried forward (LOCF) rule was used to impute missing continuous efficacy data at Week 12. That is, the subject's last non-missing post-baseline value assessed in the study while receiving DB study drug was used in the analysis. In addition, an analysis using only the observed or reported data was performed as a sensitivity analysis.

The primary efficacy endpoint was the proportion of responders to ASAS40 response criteria at Week 12, 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. Subjects with missing ASAS40 response at Week 12 were treated as non-responders according to the NRI method. Sensitivity analyses of the primary efficacy endpoint were conducted using both LOCF method and observed case (OC) analyses for the ASAS40 response. The response rates were compared using a 2-sided Pearson's chi-square test with $\alpha = 0.05$ for all NRI, LOCF, and OC analyses.

The ranked secondary efficacy variables were tested in hierarchical order. The first secondary variable was tested at $\alpha = 0.05$; if the null hypothesis was rejected, the next hypothesis in sequence was tested at $\alpha = 0.05$; this process was to continue until the null hypothesis for a particular variable was accepted.

Discrete variables were summarized using count and percentages and were compared between adalimumab and placebo groups using Pearson's chi-square or Fisher's exact test (if $\geq 25\%$ of the cells had expected counts less than 5).

Statistical Methods (Continued)

Efficacy (Continued):

Continuous efficacy variables were summarized by summary statistics (number of subjects, mean, standard deviation, first quartile, median, third quartile, minimum, maximum) at Week 12. Change from Baseline at Week 12 in the continuous variables was compared between adalimumab and placebo groups using an analysis of covariance (ANCOVA) method adjusting for the Baseline score. This was done for both observed and LOCF imputed values.

The OL data (beyond Week 12) were summarized descriptively. No statistical comparison was done based on the randomized treatment group for OL data.

After the Week 156 (final) SAP was finalized, summaries of post-baseline TB test results for either the purified protein derivative (PPD) skin test or the QuantiFERON® Gold test were added.

During the Week 156 (final) analyses, DB efficacy tables were rerun only as necessary to reflect changes in the final database compared with the DB analyses from the Week 24 interim database (the Week 12 change in SPARCC MRI score for the spine and categorical HCRU score at Week 12). Otherwise, the DB efficacy and safety statistical source data is provided by the Week 24 interim analyses, while the Week 156 (final) analyses provide source data over the entire study through 156 weeks.

Safety:

Safety analyses were carried out using 2 safety analysis sets each for the overall study population (Safety Analysis Set, Any Adalimumab Safety Set) and for the ATP (ATP Safety Analysis Set and ATP Any Adalimumab Safety Set). Treatment-emergent and pretreatment and posttreatment AEs were summarized and reported.

Treatment-emergent AEs (TEAEs) were defined as AEs that began or worsened on or after the date of the first dose of study drug and no more than 70 days after the last dose of study drug. The number and percent of subjects experiencing TEAEs were tabulated by body system and Medical Dictionary for Regulatory Activities (MedDRA® version 15.1 and 14.0 [for the DB period only]) preferred term (PT). In addition, summary of TEAEs by severity and relationship to study drug were presented. TEAEs that were serious, severe, or life-threatening, and that led to premature study discontinuation were listed and described in detail.

Mean change in laboratory variables and vital signs variables at each visit was summarized for all treated subjects, and compared between treatment groups using a 1-way analysis of variance (ANOVA) for visits during the DB period. The last evaluation prior to the first dose of study drug was used as Baseline for analyses during the DB period using the Safety Analysis Set. The last evaluation prior to the first dose of adalimumab was used as Baseline for analyses during administration of adalimumab using the Any Adalimumab Safety Set. For selected parameters, a listing of all subjects with any laboratory determination meeting Common Toxicity Criteria (CTC) of Grade 3 or higher (based on common terminology criteria for AEs [CTCAE] v3.0) was provided. Shift tables for changes from Baseline according to the normal range were provided for laboratory variables.

Analyses of safety for the ATP (added after the Week 68 SAP was finalized) included: AEs (excluding tables summarizing AEs by MedDRA PT by maximum severity and by maximum relationship to study drug [severity and relationship to study drug per individual MedDRA PT is provided on the tabular listings for the ATP]), AEs per 100 patient-years (E/100 PYs), and select laboratory variables (a listing of all subjects with any laboratory determination during the DB period and for any adalimumab exposure meeting CTC of Grade 3 or higher [based on CTCAE v3.0] and shift tables for select laboratory parameters).

Summary/Conclusions

Efficacy Results:

Study M10-791 evaluated the efficacy of adalimumab 40 mg eow compared to placebo for 12 weeks in subjects with active nr-axSpA based on the ASAS axial SpA criteria, but not fulfilling the modified New York criteria for AS, who had an inadequate response to or intolerance to ≥ 1 NSAID, or had a contraindication for NSAIDs, as defined by the investigator.

A total of 192 subjects were enrolled in this study (ITT Analysis Set); however, due to investigator noncompliance at a single investigative site, the 7 subjects enrolled at that site were excluded from the efficacy analyses. The remaining 185 subjects comprised the FAS, which was the basis for the primary analyses of efficacy. Data analyses are also performed for a subpopulation, defined as the ATP, that consisted of subjects who had objective evidence of inflammation at Baseline based on a positive MRI (i.e., SPARCC MRI score at Baseline of at least 2 for either the SI joints or the spine) or an elevated CRP at Baseline. Several ATP subsets were analyzed, including an ATP FAS consisting of 142 subjects. Post-hoc data analyses on this subpopulation were included in the Week 156 final analysis for this study.

The majority of subjects in the FAS and ATP FAS were female, white, and < 40 years old. The study population was similar across the adalimumab and placebo treatment groups in the FAS and ATP FAS. No significant differences in demographics, medical history, presenting Baseline disease activity and other disease characteristics, electrocardiogram, chest x-ray, or prior/concomitant medications were observed between the 2 treatment groups in either analysis set.

The primary efficacy endpoint of this study was ASAS40 response at Week 12, which was achieved by 36.3% of adalimumab-treated subjects versus 14.9% of placebo-treated subjects in the FAS and 40.6% of adalimumab-treated subjects versus 13.7% of placebo-treated subjects in the ATP FAS ($P < 0.001$ for both the FAS and ATP FAS; NRI). This finding was supported by sensitivity analyses using the ITT Analysis Set (34.7% versus 14.4%; $P = 0.001$ [NRI]) and the ATP ITT Analysis Set (39.4% versus 13.2%; $P < 0.001$ [NRI]).

Nine ranked secondary variables of this study were tested in hierarchical order for statistical significance between the adalimumab and placebo groups at Week 12; all 9 endpoints achieved statistical significance in favor of adalimumab in both the FAS and the ATP FAS.

Summary/Conclusions (Continued)
Efficacy Results (Continued):

		Adalimumab Versus Placebo	
	Ranked Secondary Variable	**FAS**	**ATP FAS**
1	ASAS20 response (n [%])	51.6% versus 30.9% (*P* = 0.004; NRI)	59.4% versus 31.5% (*P* < 0.001; NRI)
2	BASDAI50 response (n [%])	35.2% versus 14.9% (*P* = 0.001; NRI)	39.1% versus 13.7% (*P* < 0.001; NRI)
3	SF-36v2 Physical Component Summary (PCS) score (mean change from Baseline)	5.5 versus 2.0 (*P* = 0.001; OC)	6.9 versus 2.3 (*P* < 0.001; OC)
4	ASAS partial remission (n [%])	16.5% versus 5.3% (*P* = 0.014; NRI)	18.8% versus 5.5% (*P* = 0.014; NRI)
5	ASAS5/6 response (n [%])	30.8% versus 6.4% (*P* < 0.001; NRI)	34.8% versus 8.2% (*P* < 0.001; NRI)
6	HAQ-S total score (mean change from Baseline)	–0.3 versus –0.1 (*P* = 0.027; LOCF)	–0.3 versus –0.1 (*P* = 0.007; LOCF)
7	hs-CRP (mean change from Baseline)	–4.7 versus –0.3 (*P* < 0.001; LOCF)	–6.5 versus –0.8 (*P* < 0.001; LOCF)
8	SPARCC MRI score for SI joints (mean change from Baseline)	–3.2 versus –0.6 (*P* = 0.003; OC)	–4.3 versus –0.9 (*P* = 0.002; OC)
9	SPARCC MRI score for spine (mean change from Baseline)	–1.8 versus –0.2 (*P* = 0.001; OC)	–2.3 versus –0.5 (*P* = 0.004; OC)

OC = observed cases

In a sensitivity analysis of the ranked secondary variables using the ITT Analysis Set, the first 5 ranked variables met the criteria for statistical significance in favor of adalimumab as compared with placebo. Ranked secondary variable No. 6 (mean change from Baseline in HAQ-S total score) failed to reach statistical significance ($P = 0.096$) in the ITT Analysis Set (even though it met statistical significance in the ATP ITT Analysis Set, $P = 0.013$). Hence, the *P* values from the results of the remaining ranked secondary variables (No. 7 through No. 9, with *P* values ranging from < 0.001 to 0.003) based on the ITT Analysis Set are nominal in nature.

Using the ATP ITT Analysis Set, all 9 ranked secondary variables met the criteria for statistical significance in favor of adalimumab compared with placebo (*P* values ranged from < 0.001 to 0.013).

Additional supportive efficacy variables assessed using OC at Weeks 12 and 24 for the FAS, as well as additional OL data available through Week 156 (FAS) are presented in this final report by categories (see table below) that represent the effect of adalimumab on multiple components of active nr-axSpA. Many of these variables achieved statistical significance in favor of adalimumab at Week 12, with results being maintained at Week 24 through Week 156. Similar results were observed for the supportive secondary variables for the ATP FAS (see table below).

Variable	% of Subjects or Mean Change from Baseline (FAS)											
	Week 12			Week 24			Week 68[a]			Week 156		
	PBO	ADA	*P* Value	PBO/ ADA	ADA/ ADA	Combined	PBO/ ADA	ADA/ ADA	Combined	PBO/ ADA	ADA/ ADA	Combined
Reduction of Signs and Symptoms Variables												
ASAS20	31.9%	53.4%	0.004	65.2%	72.0%	68.4%	77.6%	82.6%	80.0%	82.8%	82.8%	82.8%
ASAS40	15.4%	37.5%	< 0.001	55.1%	48.8%	52.0%	64.5%	69.6%	66.9%	68.8%	63.8%	66.4%
ASAS50	9.9%	31.8%	< 0.001	49.4%	43.9%	46.8%	60.5%	59.4%	60.0%	64.1%	53.4%	59.0%
ASAS70	4.4%	15.9%	0.010	27.0%	30.5%	28.7%	40.8%	36.2%	38.6%	48.4%	43.1%	45.9%
ASAS5/6	6.6%	31.8%	< 0.001	36.0%	50.0%	42.7%	44.7%	55.1%	49.7%	42.2%	53.4%	47.5%
ASAS partial remission	5.5%	17.0%	0.014	23.6%	29.6%	26.5%	35.5%	37.7%	36.6%	46.8%	39.7%	43.3%
BASDAI50	15.6%	36.4%	0.002	48.3%	52.4%	50.3%	61.8%	68.1%	64.8%	71.9%	67.2%	69.7%
PTGA-disease activity	–9.7	–22.5	< 0.001	–31.6	–34.6	–33.0	–40.0	–40.3	–40.2	–43.2	–40.8	–42.1
Total back pain	–11.5	–23.8	< 0.001	–34.0	–35.2	–34.5	–42.6	–42.7	–42.6	–45.7	–42.7	–44.3
Inflammation/morning stiffness (mean of BASDAI questions 5 and 6)	–1.2	–2.3	0.001	–3.5	–3.6	–3.6	–4.2	–4.0	–4.1	–4.5	–4.3	–4.4
BASDAI total score	–1.1	–2.0	0.005	–3.0	–3.2	–3.1	–3.8	–3.9	–3.9	–4.0	–3.9	–4.0
ASDAS clinically important improvement	14.1%	40.5%	< 0.001	64.0%	64.9%	64.4%	65.8%	74.6%	70.0%	67.2%	70.2%	68.6%
ASDAS major improvement	3.5%	20.2%	< 0.001	27.9%	22.1%	25.2%	43.8%	40.3%	42.1%	42.6%	36.8%	39.8%
ASDAS inactive disease state	4.5%	25.0%	< 0.001	29.2%	42.0%	35.3%	43.4%	52.2%	47.6%	48.4%	43.1%	45.8%
ASDAS score	–0.4	–1.1	< 0.001	–1.4	–1.5	–1.5	–1.8	–1.8	–1.8	–1.8	–1.7	–1.7

	% of Subjects or Mean Change from Baseline (FAS) (Continued)											
	Week 12			Week 24			Week 68[a]			Week 156		
Variable	PBO	ADA	*P* Value	PBO/ ADA	ADA/ ADA	Combined	PBO/ ADA	ADA/ ADA	Combined	PBO/ ADA	ADA/ ADA	Combined
Reduction of Signs and Symptoms Variables (continued)												
PGA-disease activity	–13.4	–21.7	0.024	–32.0	–34.8	–33.3	–39.7	–39.9	–39.8	–39.7	–39.3	–39.5
PTGA-pain	–10.1	–22.1	< 0.001	–33.6	–33.4	–33.5	–41.4	–39.4	–40.5	–43.2	–39.9	–41.6
hs-CRP	–0.4	–5.0	< 0.001	–4.6	–4.6	–4.6	–5.1	–3.6	–4.4	–3.6	–2.9	–3.3
Nocturnal pain	–8.5	–24.9	< 0.001	–32.4	–36.0	–34.1	–40.6	–42.3	–41.4	44.8	43.4	44.1
Health-Related Quality of Life Variables												
HAQ-S total score	–0.14	–0.28	0.025	–0.38	–0.40	–0.39	–0.52	–0.41	–0.47	–0.55	–0.41	–0.48
SF-36v2 PCS score	2.0	5.5	0.001	7.0	7.4	7.2	9.4	9.9	9.6	11.2	9.8	10.5
WPAI-SHP absenteeism	2.3	–7.2	0.005	–4.5	–6.4	–5.5	–3.4	–5.1	–4.2	1.9	1.9	1.9
WPAI-SHP presenteeism	–5.8	–12.3	0.070	–19.4	–17.3	–18.3	–22.1	–25.4	–23.6	–28.6	–21.7	–25.4
WPAI-SHP activity impairment	–3.6	–14.9	0.002	–18.7	–22.7	–20.6	–25.7	–30.8	–28.2	–34.4	–26.0	–30.3
WPAI-SHP overall work impairment	–5.7	–12.1	0.122	–20.8	–18.5	–19.6	–21.0	–24.7	–22.7	–26.9	–18.4	–22.8
MOS sleep scale quantity	–0.3	0.3	0.004	0.0	1.1	0.6	–0.1	0.2	0.1	0.2	0.3	0.3
EQ-5D (UK version)	0.04	0.12	0.037	0.17	0.20	0.18	0.23	0.21	0.22	0.31	0.19	0.25
EQ-5D (US version)	0.03	0.08	0.038	0.12	0.13	0.12	0.15	0.14	0.15	0.21	0.13	0.17

a. Results for SF-36, WPAI, MOS sleep scale, and EQ-5D are for Week 52 as these assessments were not administered at Week 68.

Notes: ADA/ADA = subjects originally randomized to adalimumab treatment (12-week DB period) followed by adalimumab treatment (OL period up to 156 weeks).
PBO/ADA = subjects originally randomized to placebo treatment (12-week DB period) followed by adalimumab treatment (OL period up to 156 weeks).

	% of Subjects or Mean Change from Baseline (ATP FAS)											
	Week 12			Week 24			Week 68[a]			Week 156		
Variable	PBO	ADA	*P* Value	PBO/ ADA	ADA/ ADA	Combined	PBO/ ADA	ADA/ ADA	Combined	PBO/ ADA	ADA/ ADA	Combined
Reduction of Signs and Symptoms Variables												
ASAS20	32.9%	60.3%	0.001	62.9%	82.5%	72.2%	81.4%	86.8%	83.9%	86.3%	84.8%	85.6%
ASAS40	14.3%	41.2%	< 0.001	51.4%	54.0%	52.6%	66.1%	73.6%	69.6%	70.6%	67.4%	69.1%
ASAS50	8.6%	35.3%	< 0.001	47.1%	47.6%	47.4%	61.0%	62.3%	61.6%	64.7%	54.3%	59.8%
ASAS70	4.3%	19.1%	0.007	28.6%	33.3%	30.8%	42.4%	41.5%	42.0%	51.0%	45.7%	48.5%
ASAS5/6	8.6%	35.3%	< 0.001	37.1%	55.6%	45.9%	52.5%	60.4%	56.3%	47.1%	54.3%	50.5%
ASAS partial remission	5.7%	19.1%	0.017	24.3%	31.7%	27.8%	37.3%	43.4%	40.2%	48.0%	45.7%	46.9%
BASDAI50	14.5%	39.7%	< 0.001	48.6%	54.0%	51.1%	62.7%	71.7%	67.0%	74.5%	69.6%	72.2%
PTGA-disease activity	–10.4	–26.5	< 0.001	–30.6	–37.8	–34.0	–40.1	–43.6	–41.8	–43.8	–43.5	–43.7
Total back pain	–10.0	–27.3	< 0.001	–32.3	–37.9	–35.0	–41.8	–45.1	–43.4	–44.4	–45.0	–44.7
Inflammation/morning stiffness (mean of BASDAI questions 5 and 6)	–1.3	–2.5	0.002	–3.5	–3.7	–3.6	–4.3	–4.1	–4.2	–4.5	–4.4	–4.5
BASDAI total score	–1.2	–2.2	0.005	–3.0	–3.4	–3.2	–3.9	–4.0	–3.9	–4.1	–4.1	–4.1
ASDAS clinically important improvement	13.4%	43.1%	< 0.001	65.2%	70.0%	67.4%	69.0%	78.8%	73.6%	70.8%	75.6%	73.1%
ASDAS major improvement	1.5%	26.2%	< 0.001	31.9%	26.7%	29.5%	48.3%	46.2%	47.3%	43.8%	40.0%	41.9%
ASDAS inactive disease state	4.4%	29.4%	< 0.001	30.0%	42.9%	36.1%	45.8%	50.9%	48.2%	49.0%	45.7%	47.4%
ASDAS score	–0.4	–1.3	< 0.001	–1.5	–1.7	–1.6	–1.9	–1.9	–1.9	–1.8	–1.9	–1.9

	% of Subjects or Mean Change from Baseline (ATP FAS) (Continued)											
	Week 12			Week 24			Week 68[a]			Week 156		
Variable	PBO	ADA	*P* Value	PBO/ ADA	ADA/ ADA	Combined	PBO/ ADA	ADA/ ADA	Combined	PBO/ ADA	ADA/ ADA	Combined
Reduction of Signs and Symptoms Variables (continued)												
PGA-disease activity	–13.9	–22.4	0.079	–29.3	–36.0	–32.5	–37.3	–40.5	–38.8	–37.5	–40.9	–39.1
PTGA-pain	–9.4	–25.8	< 0.001	–32.6	–35.8	–34.1	–42.0	–41.9	–42.0	43.8	43.1	43.5
hs-CRP	–0.9	–6.8	< 0.001	–5.9	–6.1	–6.0	–6.7	–4.9	–5.9	–4.6	–3.9	–4.2
Nocturnal pain	–7.1	–27.5	< 0.001	–29.8	–37.3	–33.4	–40.2	–45.4	–42.7	–43.9	–46.1	–44.9
Quality of Life Variables												
HAQ-S total score	–0.1	–0.3	0.007	–0.36	–0.43	–0.39	–0.53	–0.43	–0.48	–0.57	–0.42	–0.50
SF-36v2 PCS score	2.3	6.9	< 0.001	7.1	8.3	7.7	10.0	11.0	10.5	12.0	11.0	11.5
WPAI-SHP absenteeism	1.3	–8.9	0.017	–3.9	–7.6	–5.7	–3.8	–9.6	–6.4	1.3	0.9	1.1
WPAI-SHP presenteeism	–7.6	–14.4	0.041	–19.0	–17.1	–18.1	–23.1	–27.3	–24.9	–31.4	–23.9	–28.1
WPAI-SHP activity impairment	–4.6	–16.2	0.005	–18.9	–23.2	–21.0	–26.1	–31.5	–28.7	–35.4	–25.9	–30.8
WPAI-SHP overall work impairment	–8.4	–14.1	0.128	–20.2	–21.1	–20.6	–22.3	–29.2	–25.5	–30.4	–19.9	–25.6
MOS sleep scale quantity	–0.2	0.4	0.005	0.1	1.4	0.7	0.0	0.3	0.2	0.3	0.4	0.3
EQ-5D (UK version)	0.1	0.1	0.089	0.16	0.22	0.19	0.21	0.24	0.22	0.31	0.22	0.27
EQ-5D (US version)	0.0	0.1	0.095	0.11	0.14	0.12	0.14	0.16	0.15	0.21	0.15	0.18

a. Results for SF-36, WPAI, MOS sleep scale, and EQ-5D are for Week 52 as these assessments were not administered at Week 68.

Notes: ADA/ADA = subjects originally randomized to adalimumab treatment (12-week DB period) followed by adalimumab treatment (OL period up to 156 weeks).
PBO/ADA = subjects originally randomized to placebo treatment (12-week DB period) followed by adalimumab treatment (OL period up to 156 weeks).

Safety Results:

Results from Study M10-791 demonstrated that, compared to the known safety profile of adalimumab in other diseases, no new safety signals were identified for up to 156 weeks of adalimumab treatment in adult patients with nr-axSpA.

This is supported by the low incidence and frequency of SAEs and premature discontinuations from the study due to TEAEs. The safety results for the overall population during the DB period (Week 12, Safety Analysis Set) and the population that received any adalimumab at any time during the study (Any Adalimumab Safety Set) were similar to the safety results for the corresponding subsets of the ATP (ATP Safety Analysis Set, ATP Any Adalimumab Safety Set).

- One subject died (completed suicide) 40 days following discontinuation of OL adalimumab treatment. The event was considered not related to study drug by the investigator. Another subject died (cardiorespiratory failure in the setting of opiate toxicity) during the OL period on Day 649 of adalimumab treatment. The event was considered probably not related to study drug by the investigator. Both subjects were part of the ATP.

Observations during the DB period of this study were:

- Three subjects in the adalimumab treatment group and 1 subject in the placebo group of the Safety Analysis Set (2 subjects and 1 subject, respectively, in the ATP Safety Analysis Set) reported ≥ 1 SAE during the DB period. All individual PTs for SAEs were reported by 1 subject each. The majority of SAEs were considered not related or probably not related to treatment by the investigator.
- In the DB period, the proportion of subjects who prematurely discontinued from the study due to an AE was small (2 subjects [2.1%] and 1 subject [1.0%] in the adalimumab and placebo treatment groups, respectively, in the Safety Analysis Set; 2 subjects [2.8%] and 1 subject [1.3%], respectively, in the ATP Safety Analysis Set).
- More than half (58.8% of subjects administered placebo and 57.9% of subjects treated with adalimumab) of the subjects in the Safety Analysis Set (59.2% for both placebo- and adalimumab-treated subjects in the ATP Safety Analysis Set) reported ≥ 1 TEAE.
- More subjects in the adalimumab treatment group (32.6% in the Safety Analysis Set; 31.0% ATP Safety Analysis Set) compared with the placebo group (21.6% Safety Analysis Set; 21.1% ATP Safety Analysis Set) reported AEs that the investigator considered possibly or probably related to study drug. The most frequently reported TEAE that was possibly or probably related to study drug by the investigator was nasopharyngitis.
- The majority of TEAEs reported during the DB period were considered mild or moderate in severity (Safety Analysis Set and ATP Safety Analysis Set). All severe events reported by the 6 subjects in the Safety Analysis Set (4 of whom were in the ATP) were reported by only 1 subject each.
- No clinically meaningful differences in TEAEs were observed by subgroups (sex, age, weight, disease-modifying anti-rheumatic drug [DMARD] and NSAID use) examined (analysis performed on the Safety Analysis Set only).

Safety Results (Continued):

Observations among subjects treated with adalimumab at any time during this study were:

- SAEs were reported by 33 subjects (17.4%) in the Any Adalimumab Safety Set and by 25 (17.2%) in the ATP Any Adalimumab Safety Set. All individual PTs for SAEs were reported by 1 subject each, except for cellulitis and headache, which were each reported by 2 subjects in the Any Adalimumab Safety Set (only 1 of these subjects was part of the ATP). All SAEs in the ATP Any Adalimumab Safety Set were reported by 1 subject each. The majority of SAEs were considered not related or probably not related to treatment by the investigator.
- Among subjects who received treatment with adalimumab at any time during the study, 16 subjects (8.4%) in the Any Adalimumab Safety Set and 12 subjects (8.3%) in the ATP Any Adalimumab Safety Set prematurely discontinued due to a TEAE. All individual PTs for AEs leading to premature discontinuation from the study were reported by 1 subject each, with the exception of headache (2 subjects in the Any Adalimumab Safety Set who were not part of the ATP). The majority of events were considered probably or possibly related to treatment by the investigator.
- A total of 50.5% of subjects in the Any Adalimumab Safety Set (51.0% in the ATP Any Adalimumab Safety Set) reported TEAEs that were considered possibly or probably related to study drug by the investigator. In the Any Adalimumab Safety Set, the most frequently reported (≥ 4%) possibly or probably related TEAEs were nasopharyngitis (12.1%), bronchitis (7.9%), sinusitis (7.4%), upper respiratory infection (6.3%), and injection site reactions (5.8%). All other events were reported by < 4% of subjects.
- Twenty-five subjects (13.2%) in the Any Adalimumab Safety Set (19 subjects [13.1%] in the ATP Any Adalimumab Safety Set) reported ≥ 1 severe TEAE. All severe events were reported by 1 subject each, except for migraine, cough, and cellulitis, which were reported by 3 subjects each, and spondylitis which was reported by 2 subjects.

The safety and tolerability of adalimumab for up to 156 weeks was also demonstrated by evaluation of AEs of special interest. No cases of opportunistic infections (excluding oral candidiasis and TB), TB conversion (3 subjects had positive repeat TB test results, but these were not reported as AEs by the investigators), parasitic infections, legionella infections, malignancies (including lymphomas, nonmelanoma skin cancer, melanoma, hepatosplenic T-cell lymphoma, and leukemia), demyelinating disorders, cutaneous and noncutaneous vasculitis, gastrointestinal events (intestinal perforation-related events, intestinal stricture related events), reactivation of hepatitis B, cardiovascular events (including myocardial infarction, cerebrovascular accident, and congestive heart failure), interstitial lung disease, adalimumab administration-related medication errors, Steven-Johnson Syndrome, erythema multiforme related events, pancreatitis, sarcoidosis, progressive multifocal leukoencephalopathy, reversible posterior leukoencephalopathy, or amyotrophic lateral sclerosis were reported during the study. The following results were observed for the other AEs of special interest for adalimumab:

Infections: Infections were reported by 64.8% and 66.9% of subjects during any adalimumab exposure throughout the study in the Any Adalimumab Safety Set and ATP Any Adalimumab Safety Set, respectively. The most frequently reported infections (≥ 6%) in the Any Adalimumab Safety Set and the ATP Any Adalimumab Safety Set were nasopharyngitis, bronchitis, upper respiratory tract infection; sinusitis, and pharyngitis; all other infections were reported by < 6% of subjects each.

Safety Results (Continued):

Infections (continued):

There were no serious infections reported during the DB period. Eight subjects, 6 of whom were part of the ATP, reported serious infections during the OL period of the study; 3 subjects in the PBO/ADA treatment group and 5 subjects in the ADA/ADA treatment group. One of these subjects in the ADA/ADA treatment group developed a serious infection of TB during the OL period of the study and was discontinued from the study.

Injection site reactions: During the DB period of the study, injection site reaction-related TEAEs were reported by 8.4% of subjects in the adalimumab treatment group and 3.1% of subjects in the placebo group (Safety Analysis Set). Among subjects who received adalimumab at any time during the study, 11.1% of subjects in the Any Adalimumab Safety Set reported injection site reaction-related TEAEs. The most frequently reported injection site reaction-related TEAE terms in the DB period of the study and among subjects who received adalimumab at any time during the study were injection site reaction and injection site erythema. All injection site reaction-related TEAEs in the Any Adalimumab Safety Set were considered possibly or probably related to study drug by the investigator except for 2 events of injection site hematoma that were assessed as not related. The proportion of subjects in the ATP who reported injection-site reaction-related TEAEs was similar to that seen in the overall study population for both the DB period (9.9% and 3.9% of subjects in the adalimumab and placebo groups, respectively) and for subjects who received adalimumab at any time during the study (12.4%).

Lupus-like reactions: One subject experienced an event of lupus-like syndrome during the OL period on Day 591 relative to the first dose of adalimumab. The subject had previously reported a case of facial flushing that had resolved. The subject again reported facial flushing, which worsened with each injection, and joint pain. The subject was treated with naproxen, which controlled the joint pain symptoms, and study drug was permanently discontinued. The subject's symptoms were noted to be improving as of Day 771, but the event was recorded as still ongoing as of Day 918 (posttreatment Day 273). The event was considered serious based on persistent significant disability, and was considered probably related to study drug by the investigator.

Allergic reactions: Two subjects, 1 in each of the placebo and adalimumab treatment groups, reported nonserious allergic reaction-related TEAEs (urticaria and eyelid edema [part of the ATP]) during the DB period of the study (Safety Analysis Set). Among subjects who received adalimumab at any time during the study (Any Adalimumab Safety Set), allergic reaction-related TEAEs were reported in 15 subjects (7.9%). Drug hypersensitivity, rash, asthma, pruritus, and eye pruritus were reported by ≥ 2 subjects each; all but asthma were also reported by ≥ 2 subjects each in the ATP. The remaining events were reported by 1 subject each. One subject had serious allergic reaction-related AEs of cough and rash that were considered possibly related to study drug by the investigator. The majority of the events were considered probably not related or not related to study drug by the investigator. The majority of subjects who reported any treatment-emergent allergic reaction-related TEAEs were part of the ATP.

Hematologic disorders: Among subjects who received adalimumab at any time during the study (Any Adalimumab Safety Set), hematologic disorders were reported in 4 subjects (2.1%), 3 of whom were part of the ATP. None of the hematologic disorders was serious; all were considered not related to study drug by the Investigator, except one case of leukopenia which was considered possibly related.

Diverticulitis: One subject (part of the ATP) reported diverticulitis 10 days after the last dose of adalimumab. The event was considered possibly related to study drug by the investigator and was considered resolved within 10 days.

Safety Results (Continued):

Liver failure and other liver events: One subject (part of the ATP) in the adalimumab treatment group reported acute hepatitis with onset on Day 1 of the DB period of the study and was subsequently hospitalized and discontinued from study drug. The investigator considered this event probably not related to study drug. One subject experienced focal nodular hyperplasia of the liver 14 days after the last dose of adalimumab. As focal nodular hyperplasia is considered a benign process, no biopsy was performed. No treatment medication was given for the event. Study drug was permanently discontinued with the last dose administered on Day 384. The event was considered probably not related to study drug by the Investigator and was considered resolved as of Day 545 (posttreatment Day 161).

Pulmonary embolism: One subject (part of the ATP) who completed the DB period on placebo treatment and continued into the OL period of the study experienced a pulmonary embolism on Day 545 relative to the first dose of adalimumab. The subject reported a prior event of DVT that began on Day 466 and was ongoing at the time of onset of the pulmonary embolism. The subject temporarily discontinued study drug and was hospitalized, at which time the subject's NuvaRing was also removed. The event was considered resolved on Day 893, and study drug was reintroduced on Day 568. The investigator considered the event to be not related to study drug but more likely related to the contraceptive device, obesity, inactivity, and the DVT.

Ps condition worsening and new onset: Two subjects with no prior history of Ps, 1 of whom also was part of the ATP, discontinued adalimumab treatment due to an AE of Ps. The events were considered either possibly or probably related to study drug by the investigator.

Safety results in the ATP were consistent with those in the overall study population. No safety concerns were identified in the analysis of clinical laboratory and vital sign parameters.

Conclusions:

Efficacy results from this study demonstrated that adalimumab is an effective treatment for reducing the signs and symptoms in nr-axSpA subjects (i.e., subjects who met the ASAS classification criteria for axial SpA, but did not fulfill the modified New York criteria for AS) who had an inadequate response to or intolerance to ≥ 1 NSAID, or had a contraindication for NSAIDs. This was evidenced by the consistently significant improvements observed compared with placebo in various outcome measures that reflect the different aspects of the disease. Treatment response was maintained with continued adalimumab therapy of up to 156 weeks. Additionally, safety results from this study for up to 156 weeks of treatment in subjects with nr-axSpA were consistent with the known safety profile of adalimumab in other diseases, and no new safety signals were observed. Based on the ASAS recommendations on the use of anti-TNF therapy in axial SpA, data from a subpopulation of subjects who had objective evidence of inflammation at Baseline based on a positive MRI of the SI joints or the spine, or an elevated CRP, were analyzed. Efficacy and safety results in this subpopulation were consistent with those in the overall study population.