Clinical trial results:
A Multi-Center, Open-Label Efficacy, Safety, and Pharmacokinetic Study of Adalimumab in Japanese Subjects with Active Ankylosing Spondylitis

Summary

EudraCT number	2014-004532-18
Trial protocol	Outside EU/EEA
Global end of trial date	15 January 2011

Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	13 June 2015

Trial information

Trial identification

Sponsor protocol code	M10-239

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00667355
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	1 North Waukegan Road, North Chicago, IL, United States, 60064
Public contact	Global Medical Information, AbbVie, 001 800-633-9110,
Scientific contact	Hideyuki Hashiba, AbbVie, Hideyuki.Hashiba@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 January 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 January 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy, safety and pharmacokinetics of adalimumab in Japanese subjects with active ankylosing spondylitis

Protection of trial subjects:

Subject and/or legal guardian read and understood information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 41
Worldwide total number of subjects	41
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	39
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a 2-week screening period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Adalimumab

Arm description:

Adalimumab 40 mg or 80 mg subcutaneously administered every other week until approval of adalimumab for Ankylosing Spondylitis (AS) in Japan.

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	ABT-D2E7, Humira
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg or 80 mg every other week, subcutaneous

Number of subjects in period 1	Adalimumab
Started	41
Completed	30
Not completed	11
Other reason was not specified	5
Adverse event, non-fatal	5
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Adalimumab
Reporting group description:	
Adalimumab 40 mg or 80 mg subcutaneously administered every other week until approval of adalimumab for Ankylosing Spondylitis (AS) in Japan.	

Reporting group values	Adalimumab	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
<40 years	25	25	
Between 40 and 65 years	16	16	
>65 years	0	0	
Age continuous Units: years			
arithmetic mean	37.2		
standard deviation	± 12.17	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	32	32	

End points

End points reporting groups

Reporting group title	Adalimumab

Reporting group description:

Adalimumab 40 mg or 80 mg subcutaneously administered every other week until approval of adalimumab for Ankylosing Spondylitis (AS) in Japan.

Primary: Number of Subjects Achieving Assessment in Ankylosing Spondylitis 20 (ASAS 20) at Week 12

End point title	Number of Subjects Achieving Assessment in Ankylosing Spondylitis 20 (ASAS 20) at Week 12[1]

End point description:

ASAS measures symptomatic improvement in Ankylosing Spondylitis (AS) subjects. ASAS has 4 domains: patient global assessment of disease activity, pain, function, inflammation. ASAS 20 = at least 20% improvement (vs. baseline) and an absolute improvement ≥ 10 units on a 0 - 100 scale (0 = no disease activity; 100 = high disease activity) for ≥ 3 domains, and no worsening (defined as a worsening of ≥ 20% and a net worsening of ≥ 10 units) in the remaining domain. For all non-responder imputation (NRI) analyses, subjects with a missing value at a visit were imputed as a non-responder for that visit. Observed cases is based on a total of 40 subjects analyzed (vs. 41 subjects for the study and all other analysis sets) due to 1 subject who discontinued prior to Week 12.

End point type	Primary

End point timeframe:

Week 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were summarize for this end point per protocol.

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Subjects				
number (not applicable)				
Non-responder imputation (NRI), N = 41	30			
Last Observation Carried Forward (LOCF), N = 41	30			
Observed Cases, N = 40	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Achieving ASAS 20

End point title	Number of Subjects Achieving ASAS 20

End point description:

ASAS measures symptomatic improvement in Ankylosing Spondylitis (AS) subjects. ASAS has 4 domains: patient global assessment of disease activity, pain, function, inflammation. ASAS 20 = 20% improvement (vs. baseline) and an absolute improvement ≥ 10 units on a 0-100 scale (0 = no disease

activity; 100 = high disease activity) for ≥ 3 domains, and no worsening (defined as a worsening of ≥ 20% and a net worsening of ≥ 10 units) in the remaining domain. Analysis is based on non-responder imputation (NRI), for which subjects with a missing value at a visit were imputed as a non-responder for that visit.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Subjects				
number (not applicable)				
Week 12	30			
Week 24	30			
Week 48	32			
Week 72	32			
Week 96	27			
Week 120	21			
Final Visit	32			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Achieving ASAS 50

End point title	Number of Subjects Achieving ASAS 50

End point description:

ASAS measures symptomatic improvement in Ankylosing Spondylitis (AS) subjects. ASAS has 4 domains: patient global assessment of disease activity, pain, function, inflammation. ASAS 50 = at least 50% improvement (vs. baseline) and an absolute improvement ≥ 20 units on a 0-100 scale (0 = no disease activity; 100 = high disease activity) for ≥ 3 domains, and no worsening (defined as a worsening of ≥ 20% and a net worsening of ≥ 10 units) in the remaining domain. Analysis is based on NRI, for which subjects with a missing value at a visit were imputed as a non-responder for that visit.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Subjects				
number (not applicable)				
Week 12	23			
Week 24	26			

Week 48	26			
Week 72	25			
Week 96	19			
Week 120	17			
Final Visit	27			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Achieving ASAS 70

End point title	Number of Subjects Achieving ASAS 70

End point description:

ASAS measures symptomatic improvement in Ankylosing Spondylitis (AS) subjects. ASAS has 4 domains: patient global assessment of disease activity, pain, function, inflammation. ASAS 70 = at least 70% improvement (vs. baseline) and an absolute improvement ≥ 30 units on a 0-100 scale (0 = no disease activity; 100 = high disease activity) for ≥ 3 domains, and no worsening (defined as a worsening of ≥ 20% and a net worsening of ≥ 10 units) in the remaining domain. Analysis is based on NRI, for which subjects with a missing value at a visit were imputed as a non-responder for that visit.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Subjects				
number (not applicable)				
Week 12	13			
Week 24	16			
Week 48	18			
Week 72	17			
Week 96	15			
Week 120	13			
Final Visit	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Achieving Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI 50)

End point title	Number of Subjects Achieving Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI 50)

End point description:

BASDAI is a validated self assessment tool used to determine disease activity in subjects with Ankylosing Spondylitis (AS). Utilizing a Visual Analog Scale (VAS) of 0-10 (0=none and 10=very severe) subjects answered 6 questions measuring discomfort, pain, fatigue, and morning stiffness. BASDAI 50 = at least 50% improvement (vs. baseline) in BASDAI. Analysis is based on NRI, for which subjects with a missing value at a visit were imputed as a non-responder for that visit.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Subjects				
number (not applicable)				
Week 12	27			
Week 24	26			
Week 48	25			
Week 72	28			
Week 96	22			
Week 120	18			
Final Visit	29			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Patient's Global Assessment of Disease Activity

End point title	Mean Change from Baseline in Patient's Global Assessment of Disease Activity

End point description:

Subject's assessment of disease activity using a Visual Analog Scale (VAS) of 0 – 100 mm (0 = none and 100 = severe). Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: mm on scale				
arithmetic mean (confidence interval 95%)				

Week 12	-34.6 (-42.8 to -26.33)			
Week 24	-37.3 (-45.99 to -28.69)			
Week 48	-39.5 (-47.52 to -31.51)			
Week 72	-39.7 (-48.14 to -31.32)			
Week 96	-37.1 (-45.96 to -28.34)			
Week 120	-40.1 (-48.61 to -31.53)			
Final Visit	-40.6 (-48.81 to -32.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Total Back Pain

End point title	Mean Change from Baseline in Total Back Pain

End point description:

Subject assessed his/her back pain by using a Visual Analog Scale (VAS) of 0 – 100 mm (0 = no pain and 100 = most severe pain). Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: mm on scale				
arithmetic mean (confidence interval 95%)				
Week 12	-35.6 (-43.68 to -27.59)			
Week 24	-37 (-45.05 to -28.85)			
Week 48	-38.6 (-46.68 to -30.53)			
Week 72	-39.3 (-47.53 to -31.01)			
Week 96	-36.4 (-44.33 to -28.4)			
Week 120	-39.2 (-46.98 to -31.36)			
Final Visit	-40.2 (-47.8 to -32.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI)

End point title	Mean Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI)

End point description:

BASFI is a validated self assessment tool that determines the degree of functional limitation in AS subjects. Utilizing a VAS of 0–100 mm (0=easy, 100=impossible), subjects answered 10 questions assessing their ability in completing normal daily activities or physically demanding activities. The BASFI score is a mean score of the 10 questions. Analysis is based on last observation carried forward (LOCF).

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: mm on scale				
arithmetic mean (confidence interval 95%)				
Week 12	-19.4 (-24.49 to -14.34)			
Week 24	-20.5 (-25.84 to -15.08)			
Week 48	-21.9 (-28.39 to -15.51)			
Week 72	-22.2 (-29.44 to -14.89)			
Week 96	-22.1 (-28.72 to -15.54)			
Week 120	-21.8 (-28.07 to -15.51)			
Final Visit	-21.6 (-27.65 to -15.49)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in C-Reactive Protein (CRP)

End point title	Mean Change from Baseline in C-Reactive Protein (CRP)

End point description:

CRP is a marker of inflammation and measured in mg/dL. A higher level is consistent with inflammation. Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: mg/dL				
arithmetic mean (confidence interval 95%)				
Week 12	-1.2 (-1.6 to -0.83)			
Week 24	-1.3 (-1.76 to -0.89)			
Week 48	-1.4 (-1.78 to -0.95)			
Week 72	-1.3 (-1.74 to -0.83)			
Week 96	-1.4 (-1.84 to -0.94)			
Week 120	-1.3 (-1.76 to -0.76)			
Final Visit	-1.2 (-1.67 to -0.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Achieving Assessment in Ankylosing Spondylitis (ASAS) 5/6.

End point title	Number of Subjects Achieving Assessment in Ankylosing Spondylitis (ASAS) 5/6.

End point description:

ASAS 5/6 consists of 6 domains: the 4 used in ASAS 20 (patient global assessment of disease activity, pain, function, inflammation) plus spinal mobility and an acute phase reactant, C Reactive Protein (CRP). Achieving ASAS 5/6 requires a 20% improvement compared to baseline in ≥ 5 domains (each domain measured on a 0 - 100 scale [0 = no disease activity; 100 = high disease activity]). Analysis is based on NRI, for which subjects with a missing value at a visit were imputed as a non-responder for that visit.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Subjects				
number (not applicable)				
Week 12	28			
Week 24	29			

Week 48	31			
Week 72	28			
Week 96	25			
Week 120	20			
Final Visit	29			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Achieving Assessment in Ankylosing Spondylitis 40 (ASAS 40)

End point title	Number of Subjects Achieving Assessment in Ankylosing Spondylitis 40 (ASAS 40)

End point description:

ASAS measures symptomatic improvement in Ankylosing Spondylitis (AS) subjects. ASAS = 4 domains: patient global assessment of disease activity, pain, function, inflammation. ASAS 40 = at least 40% improvement (vs. baseline) and an absolute improvement ≥ 20 units on a 0-100 scale (0 = no disease activity; 100 = high disease activity) for ≥ 3 domains, and no worsening in remaining domain. Analysis is based on NRI, for which subjects with a missing value at a visit were imputed as a non-responder for that visit.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Subjects				
number (not applicable)				
Week 12	26			
Week 24	26			
Week 48	27			
Week 72	28			
Week 96	24			
Week 120	18			
Final Visit	26			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Achieving Assessment in Ankylosing Spondylitis Partial Remission

End point title	Number of Subjects Achieving Assessment in Ankylosing Spondylitis Partial Remission

End point description:

Partial remission is defined as a score of less than 20 units (on a scale of 0–100; 0=no disease activity and 100=high disease activity) in each of the 4 Assessments in Ankylosing Spondylitis (ASAS) domains: patient global assessment of disease activity, pain, function, and inflammation. Analysis is based on NRI, for which subjects with a missing value at a visit were imputed as a non-responder for that visit.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Subjects				
number (not applicable)				
Week 12	15			
Week 24	16			
Week 48	17			
Week 72	20			
Week 96	15			
Week 120	13			
Final Visit	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI)

End point title	Mean Change from Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI)

End point description:

BASMI is an objective measure of spinal mobility. The BASMI score is composed of 5 measures: tragus to wall distance, lumbar flexion, cervical rotation, lumbar side flexion, and intermalleolar distance. Each measure was scored 0-2 (0=normal mobility/mild disease involvement, 1=moderate disease involvement, 2=severe disease involvement) to give a final total score ranging from 0 to 10. The higher the BASMI score, the more severe was the subject's limitation of movement due to their AS. Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: units on scale				
arithmetic mean (confidence interval 95%)				
Week 12	-0.4 (-0.79 to -0.02)			
Week 24	-0.5 (-0.9 to -0.17)			
Week 48	-0.6 (-1.07 to -0.23)			
Week 72	-0.5 (-0.95 to -0.06)			
Week 96	-0.6 (-1.03 to -0.13)			
Week 120	-0.7 (-1.09 to -0.22)			
Final Visit	-0.6 (-1 to -0.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Chest Expansion

End point title	Mean Change from Baseline in Chest Expansion

End point description:

Chest expansion is the difference in centimeters between full expiration and full inspiration, measured at the 4th inter-costal space. An increase in chest expansion represents improvement. Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: cm				
arithmetic mean (confidence interval 95%)				
Week 12	0.7 (0.3 to 1.03)			
Week 24	0.4 (0.16 to 0.66)			
Week 48	0.8 (0.4 to 1.17)			
Week 72	1 (0.56 to 1.46)			
Week 96	0.6 (0.19 to 1.11)			

Week 120	1.1 (0.55 to 1.72)			
Final Visit	1.2 (0.54 to 1.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)

End point title	Mean Change from Baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)

End point description:

Assessment of enthesitis was performed in the following 7 domains: 1) 1st costochondral joint left and right, 2) 7th costochondral joint left and right, 3) posterior superior iliac spine left and right, 4) anterior superior iliac spine left and right, 5) iliac crest left and right, 6) 5th lumbar spinous process and 7) proximal insertion of Achilles tendon left and right. Each domain was graded for the presence (1) and absence (0) of tenderness yielding total MASES ranging from 0 (no tenderness) to 13 (worst possible score; severe tenderness). Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Week 12	-1 (-1.71 to -0.39)			
Week 24	-1.1 (-1.76 to -0.53)			
Week 48	-1.3 (-1.9 to -0.74)			
Week 72	-1.1 (-1.72 to -0.48)			
Week 96	-1.4 (-1.98 to -0.85)			
Week 120	-1.4 (-1.96 to -0.77)			
Final Visit	-1.4 (-1.96 to -0.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Nocturnal Pain

End point title	Mean Change from Baseline in Nocturnal Pain

End point description:

Nocturnal pain assessed by subjects using a Visual Analog Scale (VAS) of 0 – 100 mm (0 = no pain and 100 = worst possible pain). Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: mm on scale				
arithmetic mean (confidence interval 95%)				
Week 12	-30 (-39.71 to -20.29)			
Week 24	-31.7 (-41.92 to -21.54)			
Week 48	-35.8 (-45.04 to -26.61)			
Week 72	-34.6 (-43.45 to -25.77)			
Week 96	-33.4 (-43.14 to -23.69)			
Week 120	-35 (-44.1 to -25.85)			
Final Visit	-35.3 (-44.52 to -26.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Swollen Joint Count for 44 Joints (SJC 44)

End point title	Mean Change from Baseline in Swollen Joint Count for 44 Joints (SJC 44)

End point description:

The number of swollen joints among 22 anatomical joints for both the right and left side of the body were assessed by a joint evaluator where the presence of a swollen joint was scored as 1 and absence as 0. The total SJC was derived by the sum of the scores for a range of SJC from 0 (best possible score; no swollen joints) to 44 (worse possible score; all joints swollen). Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: SJC				
arithmetic mean (confidence interval 95%)				
Week 12	-1.1 (-1.91 to -0.38)			
Week 24	-1.1 (-1.81 to -0.34)			
Week 48	-1.1 (-1.97 to -0.32)			
Week 72	-1.3 (-2.17 to -0.37)			
Week 96	-1.2 (-1.99 to -0.44)			
Week 120	-1.2 (-2.01 to -0.43)			
Final Visit	-1.2 (-1.94 to -0.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Tender Joint Count for 46 Joints (TJC 46)

End point title	Mean Change from Baseline in Tender Joint Count for 46 Joints (TJC 46)

End point description:

The number of tender or painful joints among 23 anatomical joints for both the right and left side of the body were assessed by a joint evaluator where the presence of a tender or painful joint was scored as 1 and absence as 0. The total TJC was derived by the sum of the scores for a range of TJC from 0 (best possible score; no tender or painful joints) to 46 (worst possible score; all joints tender or painful). Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: TJC				
arithmetic mean (confidence interval 95%)				
Week 12	-1.5 (-3.86 to 0.94)			
Week 24	-1.4 (-3.66 to 0.87)			
Week 48	-1.3 (-3.6 to 0.96)			

Week 72	-1.6 (-4 to 0.88)			
Week 96	-1.6 (-3.63 to 0.46)			
Week 120	-1.6 (-3.69 to 0.56)			
Final Visit	-1.6 (-3.69 to 0.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in 36-Item Short Form (SF-36) Questionnaire

End point title	Mean Change from Baseline in 36-Item Short Form (SF-36) Questionnaire

End point description:

SF-36 is a standardized survey evaluating 8 aspects of functional health and well being: physical and social functioning, physical and emotional role limitations, bodily pain, general health, vitality, mental health. These are summarized in a physical component summary (PCS) and mental component summary (MCS) score. The score for a section is an average of the individual question scores, which are scaled 0-100 (0=lowest level of functioning; 100=highest level of functioning). Analysis is based on LOCF.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 72, 96, 120, and Final Visit

End point values	Adalimumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: units on scale				
arithmetic mean (confidence interval 95%)				
PCS Week 12	9.6 (6.81 to 12.4)			
PCS Week 24	10.6 (7.51 to 13.67)			
PCS Week 48	11.4 (8.69 to 14.06)			
PCS Week 72	11.3 (8.29 to 14.3)			
PCS Week 96	12.3 (9.25 to 15.37)			
PCS Week 120	12.1 (9.07 to 15.19)			
PCS Final Visit	12.6 (9.75 to 15.53)			
MCS Week 12	7 (3.07 to 10.87)			
MCS Week 24	7 (3.62 to 10.34)			

MCS Week 48	6.1 (2.52 to 9.59)			
MCS Week 72	6.7 (2.94 to 10.53)			
MCS Week 96	5.8 (2.55 to 9.09)			
MCS Week 120	6.1 (2.63 to 9.59)			
MCS Final Visit	5.9 (2.44 to 9.42)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events reported from the time of first study drug administration until 70 days following discontinuation of study drug administration were collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Adalimumab

Reporting group description:

Adalimumab 40 mg or 80 mg subcutaneously administered every other week until approval of adalimumab for Ankylosing Spondylitis (AS) in Japan.

Serious adverse events	Adalimumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 41 (14.63%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Periodontitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Intervertebral discitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Adalimumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 41 (97.56%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation			
subjects affected / exposed	8 / 41 (19.51%)		
occurrences (all)	11		
Pharyngolaryngeal pain			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Investigations			
Weight increased			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	5		
C-reactive protein increased			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	6		
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 6		
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	8 / 41 (19.51%) 11 3 / 41 (7.32%) 4 4 / 41 (9.76%) 5		
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all) Hepatic function abnormal subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3 9 / 41 (21.95%) 9		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Dermatitis contact subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 11 3 / 41 (7.32%) 3 3 / 41 (7.32%) 3		
Musculoskeletal and connective tissue disorders			

Ankylosing spondylitis subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 7		
Back pain subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4		
Arthralgia subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Myalgia subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 4		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	22 / 41 (53.66%) 55		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 41 (17.07%) 12		
Pharyngitis subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 6		
Gastroenteritis subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 4		
Influenza subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4		
Rhinitis subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Metabolism and nutrition disorders Hyperlipidaemia subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2008	Added the maximal limited dose of codeine phosphate and dihydrocodeine phosphate for antitussive (prohibited medications); added transdermal NSAIDs preparation to the list of restricted therapy
19 March 2008	Added the procedure to confirm the reason in the case when a subject was not able to receive the maximal recommended dose of NSAIDs.
02 April 2009	Changed the procedure for protocol deviation and protocol change due to the change of GCP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported