Clinical trial results:
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

Summary

EudraCT number	2012-000646-35
Trial protocol	BE SK IT FI DE CZ DK SE GB IE NL NO ES PL
Global end of trial date	14 April 2017
Results information	
Result version number	v2 (current)
This version publication date	06 July 2018
First version publication date	04 March 2018
Version creation reason	• Correction of full data set An update is needed to align the results on clinicaltrials.gov with that of EudraCT.

Trial information

Trial identification	
Sponsor protocol code	M13-375
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01808118
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	AbbVie, Global Medical Services, 001 800-633-9110,
Scientific contact	Jaclyn Anderson , AbbVie, jaclyn.anderson@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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this multicenter, randomized, double-blind study was to evaluate the efficacy and safety of continuing versus withdrawing therapy with adalimumab 40 mg given every other week (eow) SC in maintaining remission in subjects with moderate to severe non-radiographic axial spondyloarthritis. 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 with open-label adalimumab (participants that flared at Weeks 60, 64 or 68 were allowed 12 weeks of rescue therapy and final visits were at Weeks 72, 76 or 80 respectively), plus a 70-day follow-up phone call. Participants in sustained Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease were randomized at Week 28 at a 1:1 ratio to receive either blinded adalimumab 40 mg eow or matching placebo.

Protection of trial subjects:

The investigator or his/her representative explained the nature of the study to the subject, and answered all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 April 2013
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	Australia: 62
Country: Number of subjects enrolled	Belgium: 36
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Czech Republic: 124
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Netherlands: 33
Country: Number of subjects enrolled	New Zealand: 8

Country: Number of subjects enrolled	Poland: 93
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United Kingdom: 47
Country: Number of subjects enrolled	United States: 98
Worldwide total number of subjects	673
EEA total number of subjects	447

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)	0
Adults (18-64 years)	663
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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.

Pre-assignment

Screening details:

Subjects with non-radiographic axial spondyloarthritis fulfilling the Assessment of Spondyloarthritis International Society (ASAS) axial SpA classification criteria, but not fulfilling the radiologic criterion of the modified New York criteria for ankylosing spondylitis enrolled in the study. This study included a 42-day screening period.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-label (OL) Adalimumab (Period 1)

Arm description:

40 mg every other week (eow), Weeks 0-28.

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

Dosage and administration details:

40 mg every other week (eow), Weeks 0-28. If participants flared during the double-blind period, they had an opportunity to receive at least 12 weeks of open-label adalimumab 40 mg eow.

Number of subjects in period 1	Open-label (OL) Adalimumab (Period 1)
Started	673
Completed	305
Not completed	368
Consent withdrawn by subject	24
Did not meet inclusion criteria	3
Adverse event, non-fatal	15
Noncompliance per sponsor	1
Enrolled in error	7

Nonconformance with inclusion criteria	3
Lost to follow-up	9
Did not meet criteria for remission	303
Investigator decision: site closure	2
Lack of efficacy	1

Period 2

Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Period 2)

Arm description:

Placebo every other week (eow), Weeks 28-68. Placebo was discontinued in participants who met the criteria for flare.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

every other week

Arm title	Double-blind Adalimumab (Period 2)

Arm description:

Adalimumab 40 mg every other week (eow), Weeks 28-68. Blinded adalimumab was discontinued in participants who met the criteria for flare.

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

Dosage and administration details:

40 mg every other week

Number of subjects in period 2	Placebo (Period 2)	Double-blind Adalimumab (Period 2)
Started	153	152
Completed	140	144
Not completed	13	8
Consent withdrawn by subject	7	6
Adverse event, non-fatal	4	-
Investigator no longer conducting trials	1	-
Switched to other therapy	1	-
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Open-label (OL) Adalimumab (Period 1)
Reporting group description:	
40 mg every other week (eow), Weeks 0-28.	

Reporting group values	Open-label (OL) Adalimumab (Period 1)	Total	
Number of subjects	673	673	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	663	663	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	37.3		
standard deviation	± 11.12	-	
Gender categorical			
Units: Subjects			
Female	343	343	
Male	330	330	

End points

End points reporting groups

Reporting group title	Open-label (OL) Adalimumab (Period 1)
Reporting group description:	
40 mg every other week (eow), Weeks 0-28.	

Reporting group title	Placebo (Period 2)
Reporting group description:	
Placebo every other week (eow), Weeks 28-68. Placebo was discontinued in participants who met the criteria for flare.	

Reporting group title	Double-blind Adalimumab (Period 2)
Reporting group description:	
Adalimumab 40 mg every other week (eow), Weeks 28-68. Blinded adalimumab was discontinued in participants who met the criteria for flare.	

Primary: Number of Participants Who Did Not Experience a Flare During Period 2 by Week 68

End point title	Number of Participants Who Did Not Experience a Flare During Period 2 by Week 68
End point description:	
The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). During Period 2 participants visited study sites at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68 or if they discontinued early from the study. A flare was defined as having any 2 consecutive study visits with ASDAS ≥ 2.100.	
End point type	Primary
End point timeframe:	
From Week 28 through 68	

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153[1]	152[2]		
Units: Participants	72	107		

Notes:

[1] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders
[2] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

Statistical analysis title	2-sided Pearson's chi-square test
Comparison groups	Double-blind Adalimumab (Period 2) v Placebo (Period 2)
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared

Secondary: Number of Participants With Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease at 12 Weeks After Initiation of Rescue Therapy

End point title	Number of Participants With Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease at 12 Weeks After Initiation of Rescue Therapy

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). ASDAS Inactive Disease is defined as a score of <1.300.

End point type	Secondary

End point timeframe:

Rescue Therapy Week 12

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[3]	36[4]		
Units: Participants	37	20		

Notes:

[3] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

[4] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving ASDAS Major Improvement at 12 Weeks After Initiation of Rescue Therapy

End point title	Number of Participants Achieving ASDAS Major Improvement at 12 Weeks After Initiation of Rescue Therapy

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-

reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). ASDAS Major Improvement is defined as a change from baseline ≤ –2.000.

End point type	Secondary

End point timeframe:

Baseline and Rescue Therapy Week 12

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[5]	36[6]		
Units: Participants	21	8		

Notes:

[5] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

[6] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving ASDAS Clinically Important Improvement at 12 Weeks After Initiation of Rescue Therapy

End point title	Number of Participants Achieving ASDAS Clinically Important Improvement at 12 Weeks After Initiation of Rescue Therapy

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). ASDAS Clinically Important Improvement is defined as a change from baseline ≤ –1.100.

End point type	Secondary

End point timeframe:

Baseline and Rescue Therapy Week 12

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[7]	36[8]		
Units: Participants	37	17		

Notes:

[7] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

[8] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 20 Response at 12 Weeks After Initiation of Rescue Therapy

End point title	Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 20 Response at 12 Weeks After Initiation of Rescue Therapy

End point description:

ASAS20 response was defined as improvement of ≥ 20% relative to baseline and absolute improvement of ≥ 1 unit (on a scale from 0 to 10) in ≥ 3 of the following 4 domains with no deterioration (defined as a worsening of ≥ 20% and a net worsening of ≥ 1 unit) in the potential remaining domain:
• Patient's Global Assessment of disease activity, measured on a numeric rating scale (NRS) from 0 (none) to 10 (severe);
• Pain, measured by the total back pain NRS from 0 (no pain) to 10 (most severe);
• Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which consists of 10 items assessing participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible);
• Inflammation, measured by the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/2 hours or more duration).

End point type	Secondary

End point timeframe:

Baseline and Rescue Therapy Week 12

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[9]	36[10]		
Units: Participants	46	19		

Notes:

[9] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

[10] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 40 Response at 12 Weeks After Initiation of Rescue Therapy

End point title	Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 40 Response at 12 Weeks After Initiation of Rescue Therapy

End point description:

ASAS40 response was defined as improvement of ≥ 40% relative to baseline and absolute improvement of ≥ 2 units (on a scale from 0 to 10) in ≥ 3 of the following 4 domains with no deterioration in the potential remaining domain:
• Patient's Global Assessment of disease activity, measured on a numeric rating scale (NRS) from 0 (none) to 10 (severe);
• Pain, measured by the total back pain NRS from 0 (no pain) to 10 (most severe);

• Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which consists of 10 items assessing participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible);
• Inflammation, measured by the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/2 hours or more duration).

End point type	Secondary

End point timeframe:

Baseline and Rescue Therapy Week 12

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[11]	36[12]		
Units: Participants	35	16		

Notes:

[11] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

[12] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving an ASAS 5/6 Response at 12 Weeks After Initiation of Rescue Therapy

End point title	Number of Participants Achieving an ASAS 5/6 Response at 12 Weeks After Initiation of Rescue Therapy

End point description:

An Assessment of Spondyloarthritis International Society (ASAS) 5/6 response is a 20% improvement in 5 out of the following 6 domains:
Patient's Global Assessment of disease activity, on a numeric rating scale (NRS) from 0 (none) to 10 (severe);
Pain, measured by total back pain NRS from 0 (no pain) to 10 (most severe);
Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which assesses participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible);
Inflammation: the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none) to 10 (very severe/2 hrs or more duration);
Spinal mobility: the lateral lumbar flexion score of the Bath AS Metrology Index (BASMI) on a scale from 0 (best mobility) to 10 (worst mobility);
High-sensitivity C-reactive protein level (lower levels = less inflammation).

End point type	Secondary

End point timeframe:

Baseline and Rescue Therapy Week 12

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[13]	33[14]		
Units: Participants	25	9		

Notes:

[13] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

[14] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving ASAS Partial Remission at 12 Weeks After Initiation of Rescue Therapy

End point title	Number of Participants Achieving ASAS Partial Remission at 12 Weeks After Initiation of Rescue Therapy

End point description:

Assessment in SpondyloArthritis International Society (ASAS) partial remission is defined as an absolute score of < 2 units on a 0 to 10 scale for each of the four following domains:

• Patient's Global Assessment of disease activity, measured on a numeric rating scale (NRS) from 0 (none) to 10 (severe);
• Pain, measured by the total back pain NRS from 0 (no pain) to 10 (most severe);
• Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which consists of 10 items assessing participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible);
• Inflammation, measured by the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/2 hours or more duration).

End point type	Secondary

End point timeframe:

Rescue Therapy Week 12

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[15]	36[16]		
Units: Participants	26	15		

Notes:

[15] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

[16] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 Response at 12 Weeks After Initiation of Rescue

Therapy

End point title	Number of Participants Achieving a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 Response at 12 Weeks After Initiation of Rescue Therapy

End point description:

The Bath Ankylosing Spondylitis (AS) Disease Activity Index assesses disease activity by asking the participant to answer 6 questions (each on a 10 point numeric rating scale [NRS]) pertaining to symptoms experienced for the past week. For 5 questions (level of fatigue/tiredness, level of AS neck, back or hip pain, level of pain/swelling in joints, other than neck, back or hips, level of discomfort from any areas tender to touch or pressure, and level of morning stiffness), the response is from 0 (none) to 10 (very severe); for Question 6 (duration of morning stiffness), the response is from 0 (0 hours) to 10 (≥ 2 hours). The overall BASDAI score ranges from 0 to 10. Lower scores indicate less disease activity. BASDAI50 is a 50% improvement from baseline in BASDAI score.

End point type	Secondary

End point timeframe:

Baseline and Rescue Therapy Week 12

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[17]	34[18]		
Units: Participants	41	18		

Notes:

[17] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

[18] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disability Index of Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S) at 12 Weeks After Initiation of Rescue Therapy

End point title	Change From Baseline in Disability Index of Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S) at 12 Weeks After Initiation of Rescue Therapy

End point description:

Health Assessment Questionnaire modified for spondyloarthropathies (HAQ-S) is a self-reported measure to assess the physical function and health-related quality of life. The Disability Index (DI) of HAQ-S is calculated as the mean of the following 8 category scores (range: 0 [without any difficulty] to 3 [unable to do]): Dressing and Grooming, Rising, Eating, Walking, Hygiene, Reach, Grip, and Activities. Five additional items in the functional status measure were included in the HAQ-S, including carrying heavy packages, sitting for long periods, able to work at a flat topped table, and (if the participant had a driver's license or a car) able to look in the rear view mirror and able to turn head to drive in reverse. The overall score ranges from 0 (no disability) to 3 (very severe, high-dependency disability). Negative mean changes
from baseline in the overall score indicate improvement.

End point type	Secondary

End point timeframe:

Baseline and Rescue Therapy Week 12

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[19]	17[20]		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.3 (± 0.55)	-0.4 (± 0.60)		

Notes:

[19] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

[20] - Rescued Population: subjects w/ available data who rcvd open-label rescue Tx after the DB period

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease at Weeks 28 and 68

End point title	Number of Participants With Ankylosing Spondylitis Disease Activity Score (ASDAS) Inactive Disease at Weeks 28 and 68

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). ASDAS Inactive Disease is defined as a score of <1.300.

End point type	Secondary

End point timeframe:

Weeks 28 and 68

End point values	Open-label (OL) Adalimumab (Period 1)	Placebo (Period 2)	Double-blind Adalimumab (Period 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	323[21]	153[22]	152[23]	
Units: Participants				
Week 28	295	0	0	
Week 68	0	51	87	

Notes:

[21] - Period 1: all enrolled subjects who received at least 1 dose of adalimumab

[22] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

[23] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving ASDAS Major Improvement at Weeks 28 and 68

End point title	Number of Participants Achieving ASDAS Major Improvement at Weeks 28 and 68

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). ASDAS Major Improvement is defined as a change from baseline ≤ –2.000.

End point type	Secondary

End point timeframe:

Baseline, Weeks 28 and 68

End point values	Open-label (OL) Adalimumab (Period 1)	Placebo (Period 2)	Double-blind Adalimumab (Period 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	323[24]	153[25]	152[26]	
Units: Participants				
Week 28	266	0	0	
Week 68	0	49	89	

Notes:

[24] - Period 1: all enrolled participants who received at least 1 dose of adalimumab

[25] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

[26] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving ASDAS Clinically Important Improvement at Weeks 28 and 68

End point title	Number of Participants Achieving ASDAS Clinically Important Improvement at Weeks 28 and 68

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). ASDAS Clinically Important Improvement is defined as a change from baseline ≤ –1.100.

End point type	Secondary

End point timeframe:

Baseline, Weeks 28 and 68

End point values	Open-label (OL) Adalimumab (Period 1)	Placebo (Period 2)	Double-blind Adalimumab (Period 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	323[27]	153[28]	152[29]	
Units: Participants				
Week 28	316	0	0	
Week 68	0	69	102	

Notes:

[27] - Period 1: all enrolled participants who received at least 1 dose of adalimumab

[28] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

[29] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 20 Response at Weeks 28 and 68

End point title	Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 20 Response at Weeks 28 and 68

End point description:

ASAS20 response was defined as improvement of ≥ 20% relative to baseline and absolute improvement of ≥ 1 unit (on a scale from 0 to 10) in ≥ 3 of the following 4 domains with no deterioration (defined as a worsening of ≥ 20% and a net worsening of ≥ 1 unit) in the potential remaining domain:
• Patient's Global Assessment of disease activity, measured on a numeric rating scale (NRS) from 0 (none) to 10 (severe);
• Pain, measured by the total back pain NRS from 0 (no pain) to 10 (most severe);
• Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which consists of 10 items assessing participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible);
• Inflammation, measured by the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/2 hours or more duration).

End point type	Secondary

End point timeframe:

Baseline, Weeks 28 and 68

End point values	Open-label (OL) Adalimumab (Period 1)	Placebo (Period 2)	Double-blind Adalimumab (Period 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324[30]	153[31]	152[32]	
Units: Participants				
Week 28	315	0	0	
Week 68	0	72	107	

Notes:

[30] - Period 1: all enrolled participants who received at least 1 dose of adalimumab

[31] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

[32] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 40 Response at Weeks 28 and 68

End point title	Number of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 40 Response at Weeks 28 and 68

End point description:

ASAS40 response was defined as improvement of ≥ 40% relative to baseline and absolute improvement of ≥ 2 units (on a scale from 0 to 10) in ≥ 3 of the following 4 domains with no deterioration in the potential remaining domain:
• Patient's Global Assessment of disease activity, measured on a numeric rating scale (NRS) from 0 (none) to 10 (severe);
• Pain, measured by the total back pain NRS from 0 (no pain) to 10 (most severe);
• Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which consists of 10 items assessing participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible);
• Inflammation, measured by the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/2 hours or more duration).

End point type	Secondary

End point timeframe:

Baseline, Weeks 28 and 68

End point values	Open-label (OL) Adalimumab (Period 1)	Placebo (Period 2)	Double-blind Adalimumab (Period 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324[33]	153[34]	152[35]	
Units: Participants				
Week 28	302	0	0	
Week 68	0	70	100	

Notes:

[33] - Period 1: all enrolled participants who received at least 1 dose of adalimumab

[34] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders
[35] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving an ASAS 5/6 Response at Weeks 28 and 68

End point title	Number of Participants Achieving an ASAS 5/6 Response at Weeks 28 and 68

End point description:

An Assessment of Spondyloarthritis International Society (ASAS) 5/6 response is a 20% improvement in 5 out of the following 6 domains:
Patient's Global Assessment of disease activity, on a numeric rating scale (NRS) from 0 (none) to 10 (severe);
Pain, measured by total back pain NRS from 0 (no pain) to 10 (most severe);
Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which assesses participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible);
Inflammation: the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none) to 10 (very severe/2 hrs or more duration);
Spinal mobility: the lateral lumbar flexion score of the Bath AS Metrology Index (BASMI) on a scale from 0 (best mobility) to 10 (worst mobility);
High-sensitivity C-reactive protein level (lower levels = less inflammation).

End point type	Secondary

End point timeframe:

Baseline, Weeks 28 and 68

End point values	Open-label (OL) Adalimumab (Period 1)	Placebo (Period 2)	Double-blind Adalimumab (Period 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324[36]	153[37]	152[38]	
Units: Participants				
Week 28	253	0	0	
Week 68	0	49	87	

Notes:

[36] - Period 1: all enrolled participants who received at least 1 dose of adalimumab

[37] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders
[38] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving ASAS Partial Remission at Weeks 28

and 68

End point title	Number of Participants Achieving ASAS Partial Remission at Weeks 28 and 68

End point description:

Assessment in SpondyloArthritis International Society (ASAS) partial remission is defined as an absolute score of < 2 units on a 0 to 10 scale for each of the four following domains:

• Patient's Global Assessment of disease activity, measured on a numeric rating scale (NRS) from 0 (none) to 10 (severe);
• Pain, measured by the total back pain NRS from 0 (no pain) to 10 (most severe);
• Function, measured by the Bath Ankylosing Spondylitis Functional Index (BASFI) which consists of 10 items assessing participants' ability to perform activities on an NRS ranging from 0 (easy) to 10 (impossible);
• Inflammation, measured by the mean of the 2 morning stiffness-related Bath AS Disease Activity Index (BASDAI) NRS scores (items 5 [level of stiffness] and 6 [duration of stiffness]) each on a scale from 0 (none/0 hours) to 10 (very severe/2 hours or more duration).

End point type	Secondary

End point timeframe:

Baseline, Weeks 28 and 68

End point values	Open-label (OL) Adalimumab (Period 1)	Placebo (Period 2)	Double-blind Adalimumab (Period 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324[39]	153[40]	152[41]	
Units: Participants				
Week 28	224	0	0	
Week 68	0	41	64	

Notes:

[39] - Period 1: all enrolled participants who received at least 1 dose of adalimumab

[40] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

[41] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Achieving a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 Response at Weeks 28 and 68

End point title	Number of Participants Achieving a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 Response at Weeks 28 and 68

End point description:

The Bath Ankylosing Spondylitis (AS) Disease Activity Index assesses disease activity by asking the participant to answer 6 questions (each on a 10 point numeric rating scale [NRS]) pertaining to symptoms experienced for the past week. For 5 questions (level of fatigue/tiredness, level of AS neck, back or hip pain, level of pain/swelling in joints, other than neck, back or hips, level of discomfort from any areas tender to touch or pressure, and level of morning stiffness), the response is from 0 (none) to 10 (very severe); for Question 6 (duration of morning stiffness), the response is from 0 (0 hours) to 10 (≥ 2 hours). The overall BASDAI score ranges from 0 to 10. Lower scores indicate less disease activity. BASDAI50 is a 50% improvement from baseline in BASDAI score.

End point type	Secondary

End point timeframe:

Baseline, Weeks 28 and 68

End point values	Open-label (OL) Adalimumab (Period 1)	Placebo (Period 2)	Double-blind Adalimumab (Period 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324[42]	153[43]	152[44]	
Units: Participants				
Week 28	317	0	0	
Week 68	0	72	103	

Notes:

[42] - Period 1: all enrolled participants who received at least 1 dose of adalimumab

[43] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

[44] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disability Index of Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S) at Weeks 28 and 68

End point title	Change From Baseline in Disability Index of Health Assessment Questionnaire Modified for the Spondyloarthropathies (HAQ-S) at Weeks 28 and 68

End point description:

Health Assessment Questionnaire modified for spondyloarthropathies (HAQ-S) is a self-reported measure to assess the physical function and health-related quality of life. The Disability Index (DI) of HAQ-S is calculated as the mean of the following 8 category scores (range: 0 [without any difficulty] to 3 [unable to do]): Dressing and Grooming, Rising, Eating, Walking, Hygiene, Reach, Grip, and Activities. Five additional items in the functional status measure were included in the HAQ-S, including carrying heavy packages, sitting for long periods, able to work at a flat topped table, and (if the participant had a driver's license or a car) able to look in the rear view mirror and able to turn head to drive in reverse. The overall score ranges from 0 (no disability) to 3 (very severe, high-dependency disability). Negative mean changes from baseline in the overall score indicate improvement.

End point type	Secondary

End point timeframe:

Baseline, Weeks 28 and 68

End point values	Open-label (OL) Adalimumab (Period 1)	Placebo (Period 2)	Double-blind Adalimumab (Period 2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324[45]	79[46]	112[47]	
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 28	-0.8 (± 0.58)	0 (± 0)	0 (± 0)	
Week 68	0 (± 0)	-0.8 (± 0.59)	-0.8 (± 0.63)	

Notes:

[45] - Period 1: all enrolled participants who received at least 1 dose of adalimumab

[46] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

[47] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Flare at Week 68

End point title	Time to Flare at Week 68

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). During Period 2 participants visited study sites at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68 or if they discontinued early from the study. A flare was defined as having any 2 consecutive study visits with ASDAS ≥ 2.100.

End point type	Secondary

End point timeframe:

From Week 28 through 68

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153[48]	152[49]		
Units: weeks				
median (confidence interval 95%)	999 (41 to 999)	999 (999 to 999)		

Notes:

[48] - 999= survival function >50%; median time to flare and upper 95% CI limit not estimable

[49] - 999= survival function >50%; median time to flare and lower/upper 95% CI limit not estimable

Statistical analyses

Statistical analysis title	Time to Flare at Week 68

Statistical analysis description:

The statistical test was performed at a 2-sided significance level of 0.05. Time to flare analysis showed statistically significant lower risk of flare in the adalimumab group than in the placebo group.

Comparison groups	Placebo (Period 2) v Double-blind Adalimumab (Period 2)
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Logrank

Secondary: Time to Partial Flare at Week 68

End point title	Time to Partial Flare at Week 68

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). During Period 2 participants visited study sites at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68 or if they discontinued early from the study. A partial flare was defined as having any 2 consecutive study visits with ASDAS ≥ 1.300 but <2.100.

End point type	Secondary

End point timeframe:

From Week 28 through 68

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153[50]	152[51]		
Units: weeks				
median (confidence interval 95%)	41 (41 to 999)	42 (42 to 999)		

Notes:

[50] - The upper 95% CI limit was not estimable due to low no. of subjects with events, indicated by 999.

[51] - The upper 95% CI limit was not estimable due to low no. of subjects with events, indicated by 999.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reaching Flare Definition by Week 68

End point title	Number of Participants Reaching Flare Definition by Week 68

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10

representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). During Period 2 participants visited study sites at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68 or if they discontinued early from the study. A flare was defined as having any 2 consecutive study visits with ASDAS ≥ 2.100.

End point type	Secondary

End point timeframe:

From Week 28 through 68

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153[52]	152[53]		
Units: Participants	81	45		

Notes:

[52] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders
[53] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reaching Partial Flare Definition by Week 68

End point title	Number of Participants Reaching Partial Flare Definition by Week 68

End point description:

The Ankylosing Spondylitis Disease Activity Score (ASDAS) tool is a self-administered questionnaire/objective laboratory evaluation. The questionnaire assesses disease activity, back pain, and peripheral pain/swelling on a numeric rating scale (from 0 (normal) to 10 (very severe)) and duration of morning stiffness on a numeric rating scale (from 0 to 10, with 0 being none and 10 representing a duration of ≥2 hours). The laboratory parameter is a measurement of high-sensitivity C-reactive protein (mg/L) (hs-CRP). Data from five variables (disease activity, back pain, duration of morning stiffness, peripheral pain/swelling, and hs-CRP) are combined to yield a score (0 to no defined upper limit). During Period 2 participants visited study sites at Weeks 28, 32, 36, 40, 44, 48, 52, 56, 60, 64 and 68 or if they discontinued early from the study. A partial flare was defined as having any 2 consecutive study visits with ASDAS ≥ 1.300 but <2.100.

End point type	Secondary

End point timeframe:

From Week 28 through 68

End point values	Placebo (Period 2)	Double-blind Adalimumab (Period 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153[54]	152[55]		
Units: Participants	98	62		

Notes:

[54] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders
[55] - mITT: randomized and rcvd ≥1 dose of double-blind study meds; missing data imputed as nonresponders

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from the time of study drug administration until 70 days after the last dose of study drug (up to 90 weeks).

Adverse event reporting additional description:

TEAEs and TESAEs are defined as any adverse event (AE) with an onset date that is after the first dose ofstudy drug until 70 days after the last dose of study drug and were collected whether elicited or spontaneously reported by the participant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Open-label (OL) Adalimumab (Period 1), Full Analysis Set

Reporting group description:

40 mg every other week (eow), Weeks 0-28. The Full Analysis Set included all participants who enrolled in the open-label period (Period 1) and received at least 1 dose of adalimumab.

Reporting group title	Placebo (Period 2)

Reporting group description:

Placebo every other week (eow), Weeks 28-68. Placebo was discontinued in participants who met the criteria for flare.

Reporting group title	Double-blind Adalimumab (Period 2)

Reporting group description:

Adalimumab 40 mg every other week (eow), Weeks 28-68. Blinded adalimumab was discontinued in participants who met the criteria for flare.

Reporting group title	Any Adalimumab Population

Reporting group description:

The Any Adalimumab Population consisted of all participants who received at least 1 dose of adalimumab any time during the study (including the open-label period, double-blind period and rescue period).

Serious adverse events	Open-label (OL) Adalimumab (Period 1), Full Analysis Set	Placebo (Period 2)	Double-blind Adalimumab (Period 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 673 (2.82%)	10 / 153 (6.54%)	1 / 152 (0.66%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
THYROID ADENOMA			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ADENOCARCINOMA GASTRIC			

subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE LEIOMYOMA			
subjects affected / exposed	2 / 673 (0.30%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	2 / 673 (0.30%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
VAGINAL PROLAPSE			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY MASS			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
INTENTIONAL SELF-INJURY			

subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FOOT FRACTURE			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCEDURAL PAIN			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 673 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY STENOSIS			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

VENTRICULAR FIBRILLATION			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUS TACHYCARDIA			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 673 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MIGRAINE			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OPTIC NEURITIS			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ILEUS			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
URETEROLITHIASIS			

subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	1 / 152 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETHRAL CYST			
subjects affected / exposed	0 / 673 (0.00%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
AXIAL SPONDYLOARTHRITIS			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BURSITIS			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ATYPICAL PNEUMONIA			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS			
subjects affected / exposed	2 / 673 (0.30%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CELLULITIS			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA LEGIONELLA			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	1 / 673 (0.15%)	0 / 153 (0.00%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
subjects affected / exposed	0 / 673 (0.00%)	1 / 153 (0.65%)	0 / 152 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Any Adalimumab Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 673 (4.16%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
THYROID ADENOMA			
subjects affected / exposed	0 / 673 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ADENOCARCINOMA GASTRIC			

subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
UTERINE LEIOMYOMA			
subjects affected / exposed	2 / 673 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	2 / 673 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
PAIN			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
VAGINAL PROLAPSE			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PULMONARY MASS			
subjects affected / exposed	0 / 673 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
INTENTIONAL SELF-INJURY			

subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
FOOT FRACTURE			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CLAVICLE FRACTURE			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PROCEDURAL PAIN			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CORONARY ARTERY STENOSIS			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

VENTRICULAR FIBRILLATION			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SINUS TACHYCARDIA			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
MIGRAINE			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
OPTIC NEURITIS			
subjects affected / exposed	0 / 673 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ILEUS			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
URETEROLITHIASIS			

subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
URETHRAL CYST			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
AXIAL SPONDYLOARTHRITIS			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BURSITIS			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ATYPICAL PNEUMONIA			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
APPENDICITIS			
subjects affected / exposed	3 / 673 (0.45%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

CELLULITIS			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA LEGIONELLA			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SEPSIS			
subjects affected / exposed	1 / 673 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
VIRAL INFECTION			
subjects affected / exposed	0 / 673 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Open-label (OL) Adalimumab (Period 1), Full Analysis Set	Placebo (Period 2)	Double-blind Adalimumab (Period 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	221 / 673 (32.84%)	51 / 153 (33.33%)	57 / 152 (37.50%)
Nervous system disorders			
HEADACHE			
subjects affected / exposed	45 / 673 (6.69%)	5 / 153 (3.27%)	7 / 152 (4.61%)
occurrences (all)	50	5	7
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	36 / 673 (5.35%)	5 / 153 (3.27%)	6 / 152 (3.95%)
occurrences (all)	39	5	7

Musculoskeletal and connective tissue disorders			
AXIAL SPONDYLOARTHRITIS			
subjects affected / exposed	36 / 673 (5.35%)	21 / 153 (13.73%)	10 / 152 (6.58%)
occurrences (all)	38	23	15
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	90 / 673 (13.37%)	20 / 153 (13.07%)	25 / 152 (16.45%)
occurrences (all)	103	23	32
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	57 / 673 (8.47%)	12 / 153 (7.84%)	20 / 152 (13.16%)
occurrences (all)	70	14	25

Non-serious adverse events	Any Adalimumab Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	275 / 673 (40.86%)		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	54 / 673 (8.02%)		
occurrences (all)	62		
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	42 / 673 (6.24%)		
occurrences (all)	48		
Musculoskeletal and connective tissue disorders			
AXIAL SPONDYLOARTHRITIS			
subjects affected / exposed	57 / 673 (8.47%)		
occurrences (all)	65		
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	117 / 673 (17.38%)		
occurrences (all)	151		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	80 / 673 (11.89%)		
occurrences (all)	114		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2013	- Added an assessment of dactylitis - Added a requirement to submit a local pelvic x-ray assessment to the central imaging vendor - Added an interim analysis after all subjects had completed Week 28
15 January 2015	- Added mercaptopurine (6-MP) in the list of stable Disease modifying anti-rheumatic drugs (DMARDs) within the exclusion criteria - Increased the screening period from less than or equal to 30 days to 6 weeks - Updated the rounding rule in reference to ASDAS calculation - Added the Optional Blood Sample Collection Sub-Study, which gave subjects the option to provide blood samples for future research.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported