Clinical trial results:
STRIKE – Treating Patients with Early Axial Spondyloarthritis to Target – a 1 Year Randomized Controlled Study Taking an Intense Treatment Approach Versus Routine Treatment

Summary

EudraCT number	2015-005398-18
Trial protocol	DE
Global end of trial date	21 December 2017

Results information

Result version number	v1 (current)
This version publication date	28 December 2018
First version publication date	28 December 2018

Trial information

Trial identification

Sponsor protocol code	W15-679

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02897115
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbvie Deutschland GmbH & Co.KG
Sponsor organisation address	House, Vanwall Business Park, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, Abbvie, 011 800-633-9110,
Scientific contact	Henning Kleine, Abbvie, henning.kleine@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 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 December 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare an intensified treat-to-target (T2T) treatment approach with standard of care (SOC) in reducing disease activity at Week 32 in patients with early axial spondyloarthritis (axSpA).

Protection of trial subjects:

The study was conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.
All subjects entering the study had to sign an informed consent that was explained to them and questions encouraged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2016
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	Germany: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	22
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study planned to enroll approximately 240 participants at 30 sites in Germany. Due to slow enrollment the study was terminated prematurely; At the time the decision to close the study was made 22 subjects were enrolled at 9 sites in Germany.

Pre-assignment

Screening details:

Twenty-six subjects were screened, 22 of whom were randomized. Four of the screened subjects were not randomized; one subject due to premature study termination by the sponsor, one subject withdrew consent during the screening period, and two subjects did not meet inclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treat-to-Target (T2T)

Arm description:

Participants initially received treatment with any non-steroidal anti-inflammatory drug (NSAID) at full anti-inflammatory dose for 4 weeks. After 4 weeks, if the Ankylosing Spondylitis Disease Activity Score (ASDAS) was ≥ 2.1 or treatment with NSAID 1 was not tolerated, treatment was changed to a second NSAID at full anti-inflammatory dose for 4 weeks. If ASDAS was ≥ 2.1 after 4 weeks of NSAID 2, participants were switched to receive a combination of NSAID and adalimumab 40 mg every other week for up to 48 weeks.

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

Dosage and administration details:

Adalimumab 40 mg administered every other week by subcutaneous injection for up to 48 weeks, depending on participants' disease activity.

Arm title	Standard of Care (SOC)

Arm description:

Participants received treatment as prescribed by their physician according to the local standard of care.

Arm type	Standard of Care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Treat-to-Target (T2T)	Standard of Care (SOC)
Started	14	8
Completed	3	0
Not completed	11	8
Early termination of study by sponsor	11	8

Baseline characteristics

Reporting groups	
Reporting group title	Treat-to-Target (T2T)
Reporting group description:	
Participants initially received treatment with any non-steroidal anti-inflammatory drug (NSAID) at full anti-inflammatory dose for 4 weeks. After 4 weeks, if the Ankylosing Spondylitis Disease Activity Score (ASDAS) was ≥ 2.1 or treatment with NSAID 1 was not tolerated, treatment was changed to a second NSAID at full anti-inflammatory dose for 4 weeks. If ASDAS was ≥ 2.1 after 4 weeks of NSAID 2, participants were switched to receive a combination of NSAID and adalimumab 40 mg every other week for up to 48 weeks.	
Reporting group title	Standard of Care (SOC)
Reporting group description:	
Participants received treatment as prescribed by their physician according to the local standard of care.	

Reporting group values	Treat-to-Target (T2T)	Standard of Care (SOC)	Total
Number of subjects	14	8	22
Age categorical Units: Subjects			
Adults (18-65 years)	14	8	22
Age continuous Units: years			
arithmetic mean	37.0	29.6	
standard deviation	± 9.49	± 7.96	-
Gender categorical Units: Subjects			
Female	8	4	12
Male	6	4	10

End points

End points reporting groups

Reporting group title	Treat-to-Target (T2T)

Reporting group description:

Participants initially received treatment with any non-steroidal anti-inflammatory drug (NSAID) at full anti-inflammatory dose for 4 weeks. After 4 weeks, if the Ankylosing Spondylitis Disease Activity Score (ASDAS) was ≥ 2.1 or treatment with NSAID 1 was not tolerated, treatment was changed to a second NSAID at full anti-inflammatory dose for 4 weeks. If ASDAS was ≥ 2.1 after 4 weeks of NSAID 2, participants were switched to receive a combination of NSAID and adalimumab 40 mg every other week for up to 48 weeks.

Reporting group title	Standard of Care (SOC)

Reporting group description:

Participants received treatment as prescribed by their physician according to the local standard of care.

Primary: Percentage of Participants With an Ankylosing Spondylitis Disease Activity Score (ASDAS) of Inactive Disease at Week 32

End point title	Percentage of Participants With an Ankylosing Spondylitis Disease Activity Score (ASDAS) of Inactive Disease at Week 32[1]

End point description:

ASDAS inactive disease is defined as ASDAS < 1.3. ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) as an objective measure of inflammation. The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease"; ≥ 1.3 to < 2.1 for "moderate disease activity"; ≥ 2.1 to ≤ 3.5 for "high disease activity" and > 3.5 for "very high disease activity."

End point type	Primary

End point timeframe:

Week 32

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: The study terminated early due to slow enrollment and no data were analyzed.

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: percentage of participants				
number (not applicable)				

Notes:

[2] - The study terminated early due to slow enrollment and no data were analyzed.

[3] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Assessment of Spondyloarthritis International Society (ASAS) Health Index (HI)

End point title	Change From Baseline in Assessment of Spondyloarthritis

	International Society (ASAS) Health Index (HI)

End point description:

The ASAS HI measures functioning and health across 17 aspects of health in patients with AS, including pain, emotional functions, sleep, sexual function, mobility, self care, and community life. The ASAS HI consists of 17 questions, each answered by the participant as agree (1) or disagree (0). The responses to the 17 dichotomous items are summed up to give a total score ranging from 0 to 17, with a lower score indicating a better and a higher score indicating an inferior health status.

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[4] - The study terminated early due to slow enrollment and no data were analyzed.

[5] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Work Productivity and Activity Impairment – Axial Spondyloarthritis (WPAI-axSpA)

End point title	Change From Baseline in Work Productivity and Activity Impairment – Axial Spondyloarthritis (WPAI-axSpA)

End point description:

The Work Productivity and Activity Impairment (WPAI) axSpA is an axSpA specific questionnaire consisting of 6 questions, based on patient recall of the previous 7 days. WPAI assesses work time missed due to illness (absenteeism), impairment at work due to health (presenteeism), overall work impairment due to health (an aggregate measure of both absenteeism and presenteeism), and total non-occupational activity impairment due to health. WPAI scores are expressed as impairment percentages, with higher scores indicating worse outcomes. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[6] - The study terminated early due to slow enrollment and no data were analyzed.

[7] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life-5 Dimensions (EQ-5D) Questionnaire

End point title	Change From Baseline in European Quality of Life-5 Dimensions (EQ-5D) Questionnaire

End point description:

The EQ-5D-3L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-3L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 3 levels of severity (1: indicating no problem, 2: indicating some/moderate problems, 3: indicating extreme problems). A single preference-weighted health utility index score was calculated by applying country-specific weights, with scores ranging from approximately 0 (death) to 1 (full health).

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[8] - The study terminated early due to slow enrollment and no data were analyzed.

[9] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Bath Ankylosing Spondylitis Disease Activity Index

End point title	Change From Baseline in the Bath Ankylosing Spondylitis Disease Activity Index

End point description:

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 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 where lower scores indicate less disease activity.

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - The study terminated early due to slow enrollment and no data were analyzed.

[11] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ASDAS Low Disease Activity

End point title	Percentage of Participants With ASDAS Low Disease Activity

End point description:

ASDAS low disease activity is defined as an ASDAS < 2.1. ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (CRP or ESR) as an objective measure of inflammation. The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease"; ≥ 1.3 to < 2.1 for "moderate disease activity"; ≥ 2.1 to ≤ 3.5 for "high disease activity" and > 3.5 for "very high disease activity."

End point type	Secondary

End point timeframe:

Week 32 and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: percentage of participants				
number (not applicable)				

Notes:

[12] - The study terminated early due to slow enrollment and no data were analyzed.

[13] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ASDAS Moderate Disease Activity

End point title	Percentage of Participants With ASDAS Moderate Disease Activity

End point description:

ASDAS moderate disease activity is defined as an ASDAS ≥ 1.3 to < 2.1. ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (CRP or ESR) as an objective measure of inflammation. The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease"; ≥ 1.3 to < 2.1 for "moderate disease activity"; ≥ 2.1 to ≤ 3.5 for "high disease activity" and > 3.5 for "very high disease activity."

End point type	Secondary

End point timeframe:

Week 32 and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: percentage of participants				
number (not applicable)				

Notes:

[14] - The study terminated early due to slow enrollment and no data were analyzed.

[15] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ASDAS High Disease Activity

End point title	Percentage of Participants With ASDAS High Disease Activity

End point description:

ASDAS high disease activity is defined as an ASDAS ≥ 2.1 to < 3.5. ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (CRP or ESR) as an objective measure of inflammation. The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease"; ≥ 1.3 to < 2.1 for "moderate disease activity"; ≥ 2.1 to ≤ 3.5 for "high disease activity" and > 3.5 for "very high disease activity."

End point type	Secondary

End point timeframe:

Week 32 and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: percentage of participants				
number (not applicable)				

Notes:

[16] - The study terminated early due to slow enrollment and no data were analyzed.

[17] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ASDAS Clinically Important Improvement

End point title	Percentage of Participants Achieving ASDAS Clinically Important Improvement

End point description:

ASDAS clinically important improvement is defined as a change from baseline ≤ -1.1.
ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (CRP or ESR) as an objective measure of inflammation. The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease"; ≥ 1.3 to < 2.1 for "moderate disease activity"; ≥ 2.1 to ≤ 3.5 for "high disease activity" and > 3.5 for "very high disease activity."

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: percentage of participants				
number (not applicable)				

Notes:

[18] - The study terminated early due to slow enrollment and no data were analyzed.

[19] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ASDAS Major Improvement

End point title	Percentage of Participants Achieving ASDAS Major Improvement

End point description:

ASDAS Major Improvement is defined as a change from baseline ≤ -2.0. ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (CRP or ESR) as an objective measure of inflammation. The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease"; ≥ 1.3 to < 2.1 for "moderate disease activity"; ≥ 2.1 to ≤ 3.5 for "high disease activity" and > 3.5 for "very high disease activity."

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[20]	0[21]		
Units: percentage of participants				
number (not applicable)				

Notes:

[20] - The study terminated early due to slow enrollment and no data were analyzed.

[21] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ASDAS

End point title	Change From Baseline in ASDAS

End point description:

ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (CRP or ESR) as an objective measure of inflammation. The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease"; ≥ 1.3 to < 2.1 for "moderate disease activity"; ≥ 2.1 to ≤ 3.5 for "high disease activity" and > 3.5 for "very high disease activity."

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[22]	0[23]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[22] - The study terminated early due to slow enrollment and no data were analyzed.

[23] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The Bath Ankylosing Spondylitis Functional Index (BASFI) is a validated index to determine the degree of functional limitation in patients with AS. BASFI consists of 10 questions assessing participants' ability to perform activities, on a numeric rating scale (NRS) ranging from 0 (easy to perform an activity) to 10 (impossible to perform an activity). The overall score is the mean of the 10 items and ranges from 0 (best) to 10 (worst).

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[24]	0[25]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[24] - The study terminated early due to slow enrollment and no data were analyzed.

[25] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ASDAS Inactive Disease at Week 52

End point title	Percentage of Participants With ASDAS Inactive Disease at Week 52

End point description:

ASDAS inactive disease is defined as ASDAS < 1.3. ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (CRP or ESR) as an objective measure of inflammation. The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease"; ≥ 1.3 to < 2.1 for "moderate disease activity"; ≥ 2.1 to ≤ 3.5 for "high disease activity" and > 3.5 for "very high disease activity."

End point type	Secondary

End point timeframe:

Week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[26]	0[27]		
Units: percentage of participants				
number (not applicable)				

Notes:

[26] - The study terminated early due to slow enrollment and no data were analyzed.

[27] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving a BASDAI 50 Response

End point title	Percentage of Participants Achieving a BASDAI 50 Response

End point description:

The BASDAI 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.
A BASDAI 50 response is defined as improvement of 50% or more from baseline in BASDAI score.

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[28]	0[29]		
Units: percentage of participants				
number (not applicable)				

Notes:

[28] - The study terminated early due to slow enrollment and no data were analyzed.

[29] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With ASDAS Very High Disease Activity

End point title	Percentage of Participants With ASDAS Very High Disease Activity

End point description:

ASDAS very high disease activity is defined as an ASDAS ≥ 3.5. ASDAS is a composite disease activity outcome measure which combines patient reported back pain, duration of morning stiffness, patient global assessment of disease activity, patient assessment of peripheral joint pain and swelling and an acute phase reactant (CRP or ESR) as an objective measure of inflammation. The overall score ranges from 0 with no defined upper score; published ranges for disease activity states as defined by the ASDAS are: < 1.3 for "inactive disease"; ≥ 1.3 to < 2.1 for "moderate disease activity"; ≥ 2.1 to ≤ 3.5 for "high disease activity" and > 3.5 for "very high disease activity."

End point type	Secondary

End point timeframe:

Week 32 and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[30]	0[31]		
Units: percentage of participants				
number (not applicable)				

Notes:

[30] - The study terminated early due to slow enrollment and no data were analyzed.

[31] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 20 Response

End point title	Percentage of Participants Achieving an Assessment of Spondyloarthritis International Society (ASAS) 20 Response

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, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[32]	0[33]		
Units: percentge of participants				
number (not applicable)				

Notes:

[32] - The study terminated early due to slow enrollment and no data were analyzed.

[33] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving an ASAS 40 Response

End point title	Percentage of Participants Achieving an ASAS 40 Response

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, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[34]	0[35]		
Units: percentage of participants				
number (not applicable)				

Notes:

[34] - The study terminated early due to slow enrollment and no data were analyzed.

[35] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving ASAS Partial Remission

End point title	Percentage of Participants Achieving ASAS Partial Remission

End point description:

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:

Week 32 and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[36]	0[37]		
Units: percentage of participants				
number (not applicable)				

Notes:

[36] - The study terminated early due to slow enrollment and no data were analyzed.

[37] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient's Global Assessment of Pain

End point title	Change From Baseline in Patient's Global Assessment of Pain

End point description:

The Patient's Global Assessment of Pain was assessed on a NRS from 0 (no pain) to 10 (pain as bad as it could be).

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[38]	0[39]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[38] - The study terminated early due to slow enrollment and no data were analyzed.

[39] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Tender Joint Count

End point title	Change From Baseline in Tender Joint Count

End point description:

An assessment of 68 joints was performed by physical examination of each joint. Joint pain/tenderness was classified as present (1), absent (0), replaced (9), or no assessment (NA).

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[40]	0[41]		
Units: tnder joints				
arithmetic mean (standard deviation)	()	()		

Notes:

[40] - The study terminated early due to slow enrollment and no data were analyzed.

[41] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The Patient's Global Assessment of Disease Activity was assessed using an NRS from 0 (no disease activity) to 10 (very severe disease activity).

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[42]	0[43]		
Units: nits on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[42] - The study terminated early due to slow enrollment and no data were analyzed.

[43] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physician's Global Assessment of Disease Activity

End point title	Change From Baseline in Physician's Global Assessment of Disease Activity

End point description:

The Physician's Global Assessment of Disease Activity was assessed using an NRS from 0 (no disease activity) to 10 (severe disease activity).

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[44]	0[45]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[44] - The study terminated early due to slow enrollment and no data were analyzed.

[45] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Active Inflammation of the Sacroiliac Joints and Spine

End point title	Change From Baseline in Active Inflammation of the Sacroiliac Joints and Spine

End point description:

Active inflammation of the sacroiliac (SI) joints as well as the cervical, thoracic and lumbar regions of the spine was assessed using magnetic resonance imaging (MRI). Images were scored by a central reader according to the Berlin MRI Score on a grading scale from 0 to 3, where Grade 0 indicates no active inflammation and Grade 3 indicates > 66% inflammation of the sacroiliac joints or > 50% active inflammation in the spine.

End point type	Secondary

End point timeframe:

Baseline and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[46]	0[47]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[46] - The study terminated early due to slow enrollment and no data were analyzed.

[47] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Swollen Joint Count

End point title	Change From Baseline in Swollen Joint Count

End point description:

An assessment of 66 joints was performed by physical examination of each joint. Joint swelling was classified as present (1), absent (0), replaced (9), or no assessment (NA).

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[48]	0[49]		
Units: swollen joints				
arithmetic mean (standard deviation)	()	()		

Notes:

[48] - The study terminated early due to slow enrollment and no data were analyzed.

[49] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: ange From Baseline in Dactylitis Count

End point title	ange From Baseline in Dactylitis Count

End point description:

Dactylitis is characterized by swelling of the entire finger or toe. Each digit on the hands and feet was rated as 0 for no dactylitis or 1 for dactylitis present. The dactylitis severity score is the sum of the individual scores for each digit. The dactylitis severity score, ranging from 0 to 20, is the number of digits on the hands and feet with dactylitis present.

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[50]	0[51]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[50] - The study terminated early due to slow enrollment and no data were analyzed.

[51] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in C-reactive Protein (CRP)

End point title	Change From Baseline in C-reactive Protein (CRP)

End point description:

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[52]	0[53]		
Units: mg/L				
arithmetic mean (standard deviation)	()	()		

Notes:

[52] - The study terminated early due to slow enrollment and no data were analyzed.

[53] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Erythrocyte Sedimentation Rate (ESR)

End point title	Change From Baseline in the Erythrocyte Sedimentation Rate (ESR)

End point description:

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[54]	0[55]		
Units: mm/hr				
arithmetic mean (standard deviation)	()	()		

Notes:

[54] - The study terminated early due to slow enrollment and no data were analyzed.

[55] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With New Onset Anterior Uveitis

End point title	Number of Participants With New Onset Anterior Uveitis

End point description:

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[56]	0[57]		
Units: participants				

Notes:

[56] - The study terminated early due to slow enrollment and no data were analyzed.

[57] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Maastricht Ankylosing Spondylitis Entheses Score (MASES)

End point title	Change From Baseline in Maastricht Ankylosing Spondylitis Entheses Score (MASES)

End point description:

The Maastricht Ankylosing Spondylitis Enthesitis Score quantitates inflammation of the entheses (enthesitis) by assessing pain at 13 entheses (sites where tendons or ligaments insert into the bone). All sites were scored as 0 (absent) or 1 (present). The MASES is the sum of all site scores (from 0 to 13).

End point type	Secondary

End point timeframe:

Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[58]	0[59]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[58] - The study terminated early due to slow enrollment and no data were analyzed.

[59] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Linear Bath Ankylosing Spondylitis Metrology Index (BASMIlin)

End point title	Change From Baseline in Linear Bath Ankylosing Spondylitis Metrology Index (BASMIlin)

End point description:

The linear Bath Ankylosing Spondylitis Metrology Index (BASMIlin) is a composite score based on 5 direct measurements of spinal mobility: lateral lumbar flexion, tragustowall distance, lumbar flexion, intermalleolar distance, and cervical rotation angle. The total score ranges from 0 to 10, where higher scores indicate more limited mobility.

End point type	Secondary

End point timeframe:
Baseline, week 32, and week 52

End point values	Treat-to-Target (T2T)	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[60]	0[61]		
Units: units on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[60] - The study terminated early due to slow enrollment and no data were analyzed.

[61] - The study terminated early due to slow enrollment and no data were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 52 weeks.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Standard of Care (SOC)
Reporting group description: Participants received treatment as prescribed by their physician according to the local standard of care.	
Reporting group title	Treat-to-Target (T2T)
Reporting group description: Participants initially received treatment with any non-steroidal anti-inflammatory drug (NSAID) at full anti-inflammatory dose for 4 weeks. After 4 weeks, if the Ankylosing Spondylitis Disease Activity Score (ASDAS) was ≥ 2.1 or treatment with NSAID 1 was not tolerated, treatment was changed to a second NSAID at full anti-inflammatory dose for 4 weeks. If ASDAS was ≥ 2.1 after 4 weeks of NSAID 2, participants were switched to receive a combination of NSAID and adalimumab 40 mg every other week for up to 48 weeks.	

Serious adverse events	Standard of Care (SOC)	Treat-to-Target (T2T)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
CHOLECYSTITIS CHRONIC			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Standard of Care (SOC)	Treat-to-Target (T2T)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	12 / 14 (85.71%)	
Vascular disorders			
HYPERTENSION			

subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
MENSTRUATION IRREGULAR			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
OVARIAN CYST			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
VULVOVAGINAL INFLAMMATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	1 / 8 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Psychiatric disorders			
MOOD ALTERED			
subjects affected / exposed	1 / 8 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
DEPRESSION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
SLEEP DISORDER			

subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
LACERATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
POST-TRAUMATIC NECK SYNDROME			
subjects affected / exposed	1 / 8 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 8 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
DYSAESTHESIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
MIGRAINE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
HEADACHE			
subjects affected / exposed	0 / 8 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
LYMPHADENOPATHY			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
DYSPEPSIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
ANAL FISSURE			

subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
ABDOMINAL PAIN			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 8 (12.50%)	3 / 14 (21.43%)	
occurrences (all)	1	4	
TOOTHACHE			
subjects affected / exposed	1 / 8 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
GASTRITIS			
subjects affected / exposed	0 / 8 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
NAUSEA			
subjects affected / exposed	0 / 8 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	1 / 8 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
URTICARIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
PSORIASIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 8 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
AXIAL SPONDYLOARTHRITIS			

subjects affected / exposed	3 / 8 (37.50%)	2 / 14 (14.29%)	
occurrences (all)	3	3	
BACK PAIN			
subjects affected / exposed	0 / 8 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	3	
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
NECK PAIN			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	3 / 8 (37.50%)	4 / 14 (28.57%)	
occurrences (all)	3	4	
GASTROENTERITIS			
subjects affected / exposed	2 / 8 (25.00%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
CYSTITIS			
subjects affected / exposed	1 / 8 (12.50%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
BRONCHITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
SINUSITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	4	
RHINITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
PULPITIS DENTAL			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
URINARY TRACT INFECTION			

subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
WOUND INFECTION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 8 (12.50%)	0 / 14 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2016	Key changes include: • Updated Section 5.2.2, Exclusion criteria. Rationale: Amended the criteria upon Ethics Committee's request, to reflect that vulnerable subjects are not eligible to participate in the study. • Updated Section 5.4.1, Discontinuation of Individual Subjects. Rationale: Upon Ethics Committee's request, provided more detailed clarification on the reasons for premature study discontinuation of individual subjects by cross-referencing to Section 6.1.7. • Updated Section 5.4.2, Discontinuation of Entire Study. Rationale: Upon Ethics Committee's request, provided more detailed clarification on the reasons for premature study termination. • Updated Section 6.1.7, Toxicity Management. Rationale: Amended Section text with information on management of selected laboratory abnormalities.
30 March 2017	The second protocol amendment was written to increase the number of sites to 30. Key changes included: • Updated Section 1.2, Synopsis. Rationale: Added change in BASMIlin to secondary objectives in Objectives and Criteria for Evaluation subsections to align with Section 5.3.1, Table 1 – Study Activities; increased the number of participating study sites to allow for faster enrollment; and aligned the Statistical Methods subsection with the respective wording concerning the safety analyses in Section 8.1.6 of the protocol. • Updated Section 5.1, Overall Study Design and Plan: Description, and Section 5.5.1, Treatments Administered. Rationale: Provided clarification regarding NSAIDs to be used in case of escalation to Escalation Step 2 due to intolerance to NSAID 2. • Updated Section 6.1, Medical Complaints. Rationale: Changed Section title from 'Adverse Events' to 'Medical Complaints' to align with new protocol template. • Updated Section 6.1.3, Relationship to Humira. Rationale: Updated definitions of reasonable versus no reasonable possibility to align with new protocol template.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported