Clinical trial results:
Whole-body MRI, MRI of sacroiliac joints and spine and circulating biomarkers in patients with spondyloarthritis treated with adalimumab (ASIM)

Summary

EudraCT number	2009-014348-12
Trial protocol	DK
Global end of trial date	18 August 2014

Results information

Result version number	v1 (current)
This version publication date	12 August 2017
First version publication date	12 August 2017

Trial information

Trial identification

Sponsor protocol code	ASIM (IMM 08-0061)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01029847
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Center for Rheumatology and Spine Diseases, Rigshospitalet
Sponsor organisation address	Valdemar Hansens Vej 17, Glostrup, Denmark, DK-2600
Public contact	Mikkel Østergaard, Center for Rheumatology and Spine Diseases, Rigshospitalet, mo@dadlnet.dk
Scientific contact	Mikkel Østergaard, Center for Rheumatology and Spine Diseases, Rigshospitalet, mo@dadlnet.dk

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	27 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2014
Global end of trial reached?	Yes
Global end of trial date	18 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of adalimumab on disease manifestations in axial and peripheral joints and entheses in patients with spondyloarthritis as assessed by whole-body MRI.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	50
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	50
Number of subjects completed	49

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Administrative error: 1

Period 1

Period 1 title	Part 1 - baseline to week 6
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab group

Arm description:

Adalimumab from baseline to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

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

Dosage and administration details:

Subcutaneous injection of 40 mg every other week

Arm title	Placebo group

Arm description:

Placebo from baseline to week 6 followed by Adalimumab from week 6 to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

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

Dosage and administration details:

Subcutaneous injection of inactive fluid every other week

Number of subjects in period 1[1]	Adalimumab group	Placebo group
Started	25	24
Completed	22	23
Not completed	3	1
Physician decision	1	-
Adverse event, non-fatal	1	-
Non-compliance	1	-
Family overloaded	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The group allocation was not known for one patient due to an administrative error. This patient has been excluded from all analyses.

Period 2

Period 2 title	Part 2 - week 6 to week 24
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab group

Arm description:

Adalimumab from baseline to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

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

Dosage and administration details:

Subcutaneous injection of 40 mg every other week

Arm title	Placebo group

Arm description:

Placebo from baseline to week 6 followed by Adalimumab from week 6 to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

Arm type	Placebo

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

Dosage and administration details:

Subcutaneous injection of 40 mg every other week

Number of subjects in period 2	Adalimumab group	Placebo group
Started	22	23
Completed	22	20
Not completed	0	3
Adverse event, non-fatal	-	1
Administrative error	-	1
Lack of efficacy	-	1

Period 3

Period 3 title	Part 3 - week 24 to week 48
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab group

Arm description:

Adalimumab from baseline to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

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

Dosage and administration details:

Subcutaneous injection of 40 mg every other week

Arm title	Placebo group

Arm description:

Placebo from baseline to week 6 followed by Adalimumab from week 6 to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

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

Dosage and administration details:

Subcutaneous injection of 40 mg every other week

Number of subjects in period 3	Adalimumab group	Placebo group
Started	22	20
Completed	20	19
Not completed	2	1
Adverse event, non-fatal	1	1
Non-compliance	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Adalimumab group
Reporting group description:	
Adalimumab from baseline to week 24. Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.	
Reporting group title	Placebo group
Reporting group description:	
Placebo from baseline to week 6 followed by Adalimumab from week 6 to week 24. Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.	

Reporting group values	Adalimumab group	Placebo group	Total
Number of subjects	25	24	49
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	39.9	35.1	
standard deviation	± 10.8	± 7.8	-
Gender categorical Units: Subjects			
Female	10	14	24
Male	15	10	25
Bath Ankylosing Spondylitits Disease Activity Index Units: Questionnaire based score from 0 to 10			
arithmetic mean	6.3	6.4	
standard deviation	± 1.2	± 1.5	-

End points

End points reporting groups

Reporting group title	Adalimumab group

Reporting group description:

Adalimumab from baseline to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

Reporting group title	Placebo group

Reporting group description:

Placebo from baseline to week 6 followed by Adalimumab from week 6 to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

Reporting group title	Adalimumab group

Reporting group description:

Adalimumab from baseline to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

Reporting group title	Placebo group

Reporting group description:

Placebo from baseline to week 6 followed by Adalimumab from week 6 to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

Reporting group title	Adalimumab group

Reporting group description:

Adalimumab from baseline to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

Reporting group title	Placebo group

Reporting group description:

Placebo from baseline to week 6 followed by Adalimumab from week 6 to week 24.
Clinical responders at week 24 continued subcutaneous injections of 40 mg adalimumab eow; clinical non-responders at week 24 were allowed to be treated with other drugs at the discretion of the investigator following local treatment guidelines.

Primary: Improvement in Bath Ankylosing Spondylitis Disease Activity Index of 50% or an absolute improvement of 2.0 at week 24

End point title	Improvement in Bath Ankylosing Spondylitis Disease Activity Index of 50% or an absolute improvement of 2.0 at week 24

End point description:

End point type	Primary

End point timeframe:

Week 24

End point values	Adalimumab group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: patients	18	14		

Statistical analyses

Statistical analysis title	BASDAI 50% or 2.0 response at week 24

Statistical analysis description:

Clinical responders as assessed by improvement in Bath Ankylosing Spondylitis Disease Activity Index of 50% or an absolute improvement of 2.0 at week 24.

Comparison groups	Adalimumab group v Placebo group
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Fisher exact

Post-hoc: Difference between Adalimumab group and Placebo group in change in Bath Ankylosing Spondylitis Disease Activity Index from baseline to week 6

End point title	Difference between Adalimumab group and Placebo group in change in Bath Ankylosing Spondylitis Disease Activity Index from baseline to week 6

End point description:

End point type	Post-hoc

End point timeframe:

Week 6

End point values	Adalimumab group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: Questionnaire based score from 0 to 10				
arithmetic mean (standard deviation)	-2.1 (± 2.2)	-0.6 (± 1.8)		

Statistical analyses

Statistical analysis title	Change in BASDAI from baseline to week 6

Statistical analysis description:

Difference between Adalimumab group and Placebo group in change in Bath Ankylosing Spondylitis Disease Activity Index from baseline to week 6.

Comparison groups	Adalimumab group v Placebo group
Number of subjects included in analysis	49
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.026
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All adverse events were collected from baseline and up to the final visit (Week 48).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Part 1 - Adalimumab group
Reporting group description: -	
Reporting group title	Part 1 - Placebo group
Reporting group description: -	
Reporting group title	Part 2 - Adalimumab
Reporting group description: -	
Reporting group title	Part 3 - Adalimumab
Reporting group description: -	
Reporting group title	Part 3 - Other treatment (not adalimumab)
Reporting group description: -	
Reporting group title	Adalimumab - entire study period (Part 1, Part 2 and Part 3)
Reporting group description: -	

Serious adverse events	Part 1 - Adalimumab group	Part 1 - Placebo group	Part 2 - Adalimumab
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 45 (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

Serious adverse events	Part 3 - Adalimumab	Part 3 - Other treatment (not adalimumab)	Adalimumab - entire study period (Part 1, Part 2 and Part 3)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 34 (2.94%)	0 / 6 (0.00%)	1 / 48 (2.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 6 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part 1 - Adalimumab group	Part 1 - Placebo group	Part 2 - Adalimumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 25 (12.00%)	3 / 24 (12.50%)	20 / 45 (44.44%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	3
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1

Non-serious adverse events	Part 3 - Adalimumab	Part 3 - Other treatment (not adalimumab)	Adalimumab - entire study period (Part 1, Part 2 and Part 3)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 34 (47.06%)	1 / 6 (16.67%)	27 / 48 (56.25%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 34 (5.88%)	0 / 6 (0.00%)	2 / 48 (4.17%)
occurrences (all)	2	0	2
Oedema peripheral			
subjects affected / exposed	2 / 34 (5.88%)	0 / 6 (0.00%)	2 / 48 (4.17%)
occurrences (all)	2	0	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 34 (5.88%)	0 / 6 (0.00%)	2 / 48 (4.17%)
occurrences (all)	2	0	2
Nausea			
subjects affected / exposed	0 / 34 (0.00%)	1 / 6 (16.67%)	3 / 48 (6.25%)
occurrences (all)	0	1	3
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 34 (0.00%)	1 / 6 (16.67%)	0 / 48 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	2 / 34 (5.88%)	0 / 6 (0.00%)	2 / 48 (4.17%)
occurrences (all)	2	0	2
Upper respiratory tract infection			
subjects affected / exposed	3 / 34 (8.82%)	0 / 6 (0.00%)	4 / 48 (8.33%)
occurrences (all)	3	0	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported