Clinical trial results:
Intestinal Inflammation in Ankylosing Spondylitis assessed by Fecal Calprotectin, Capsular Endoscopy and Colonoscopy and the effects of Adalimumab on mucosal healing

Summary

EudraCT number	2009-018085-35
Trial protocol	DK
Global end of trial date	11 March 2014

Results information

Result version number	v1 (current)
This version publication date	26 March 2016
First version publication date	26 March 2016

Trial information

Trial identification

Sponsor protocol code	4682724

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01174186
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regionshospitalet Silkeborg
Sponsor organisation address	Falkevej 1, Silkeborg, Denmark, 8220
Public contact	Studieledelse, Regionshospitalet Silkeborg, +45 87222360, henngler@rm.dk
Scientific contact	Studieledelse, Regionshospitalet Silkeborg, +45 87222360, henngler@rm.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	09 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2014
Global end of trial reached?	Yes
Global end of trial date	11 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the proportion of otherwise intestinally low-symptomatic patients with intestinal ulcers in patients diagnosed with active spondyloarthritis and to illustrate the healing rate following treatment with the TNF-alpha inhibitor adalimumab

Protection of trial subjects:

The patients were informed orally and in writing. During the trial the patients could call a phone number day and night with questions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the rheumatologic outpatient clinics in the Central and North Denmark Regions on the basis of SpA activity. Patients ≥18 years with active SpA defined by expert opinion and a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 (and thus candidates for anti-TNF treatment) were eligible for inclusion and were a

Pre-assignment

Screening details:

Because NSAID can elevate fecal calprotectin, patients were subjected to a 4-week NSAID washout period, after which fecal calprotectin was measured. Depending on the fecal calprotectin level the patients were grouped into either a "calprotectin normal" (<50 mg/kg) or "calprotectin high" (≥100 mg/kg) category.

Pre-assignment period milestones

Number of subjects started	31[1]
Number of subjects completed	30

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient gave consent to join the study but withdrew his consent before completing NSAID wash-out period

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Calprotectin high

Arm description:

calprotectin high: Fecal calprotectin ≥100 mg/kg after NSAID wash-out period

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector, Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Loading dose of 80 mg. Hereafter 40 mg every other week

Arm title	Calprotectin normal

Arm description:

Faecal calprotectin <50 mg/kg after wash-out period

Arm type	Active comparator

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector, 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 1	Calprotectin high	Calprotectin normal
Started	15	15
Repeat endoscopy	15	15
Follow-up	15	15
Completed	15	12
Not completed	0	3
Lost to follow-up	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Calprotectin high
Reporting group description:	
calprotectin high: Fecal calprotectin ≥100 mg/kg after NSAID wash-out period	
Reporting group title	Calprotectin normal
Reporting group description:	
Faecal calprotectin <50 mg/kg after wash-out period	

Reporting group values	Calprotectin high	Calprotectin normal	Total
Number of subjects	15	15	30
Age categorical			
Age at baseline			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	15	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	34	32	
full range (min-max)	18 to 45	18 to 43	-
Gender categorical			
Units: Subjects			
Female	3	4	7
Male	12	11	23
HLA-B27 positive			
Positive meaning having MHC-class 1 allele B27			
Units: Subjects			
Positive	15	10	25
Negative	0	5	5
Disease duration			
Time from first symptom to inclusion			
Units: Years			
median	7	7	
full range (min-max)	1 to 24	1 to 26	-

Subject analysis sets	
Subject analysis set title	Follow-up baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Follow-up endoscopy in patients with intestinal inflammation or elevated calprotectin at baseline

Subject analysis set title	Follow-up 20 weeks
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with either elevated calprotectin at baseline or intestinal inflammation after 20 weeks of treatment

Subject analysis set title	Follow-up 12 weeks
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with elevated calprotectin at baseline or intestinal inflammation at endoscopy

Reporting group values	Follow-up baseline	Follow-up 20 weeks	Follow-up 12 weeks
Number of subjects	16	16	16
Age categorical			
Age at baseline			
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	16		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female			
Male			
HLA-B27 positive			
Positive meaning having MHC-class 1 allele B27			
Units: Subjects			
Positive			
Negative			
Disease duration			
Time from first symptom to inclusion			
Units: Years			
median			
full range (min-max)			

End points

End points reporting groups

Reporting group title	Calprotectin high
Reporting group description: calprotectin high: Fecal calprotectin ≥100 mg/kg after NSAID wash-out period	
Reporting group title	Calprotectin normal
Reporting group description: Faecal calprotectin <50 mg/kg after wash-out period	
Subject analysis set title	Follow-up baseline
Subject analysis set type	Sub-group analysis
Subject analysis set description: Follow-up endoscopy in patients with intestinal inflammation or elevated calprotectin at baseline	
Subject analysis set title	Follow-up 20 weeks
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with either elevated calprotectin at baseline or intestinal inflammation after 20 weeks of treatment	
Subject analysis set title	Follow-up 12 weeks
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with elevated calprotectin at baseline or intestinal inflammation at endoscopy	

Primary: Intestinal inflammation

End point title	Intestinal inflammation
End point description: Number of subjects at baseline with any intestinal ulceration	
End point type	Primary
End point timeframe: Baseline	

End point values	Calprotectin high	Calprotectin normal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Subject				
Present	12	1		
Absent	3	14		

Statistical analyses

Statistical analysis title	Intestinal inflammation between groups
Comparison groups	Calprotectin high v Calprotectin normal

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Lewis score at follow-up

End point title	Lewis score at follow-up

End point description:

Follow-up endoscopy in patients with intestinal inflammation or elevated faecal calprotectin at baseline

End point type	Primary

End point timeframe:

After 20 weeks of treatment

End point values	Follow-up baseline	Follow-up 20 weeks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: unit(s)				
arithmetic mean (full range (min-max))	398 (112 to 608)	33 (0 to 180)		

Statistical analyses

Statistical analysis title	Follow-up endoscopy

Statistical analysis description:

Comparison of Lewis score from baseline to 20 weeks after treatment onset

Comparison groups	Follow-up baseline v Follow-up 20 weeks
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.01
Method	Wilcoxon (Mann-Whitney)

Primary: Fecal calprotectin changes

End point title	Fecal calprotectin changes

End point description:

Changes in koncentration of calprotectin in faces

End point type	Primary

End point timeframe:

Baseline, 12 weeks and 20 weeks of treatment

End point values	Follow-up baseline	Follow-up 20 weeks	Follow-up 12 weeks	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	16	16	16	
Units: mg/kg				
arithmetic mean (standard deviation)	285 (± 186)	48 (± 33)	83 (± 67)	

Attachments (see zip file)	F-calpro.png

Statistical analyses

Statistical analysis title	Faecal calprotectin
Statistical analysis description: Change in calprotectin koncentration over time	
Comparison groups	Follow-up baseline v Follow-up 20 weeks v Follow-up 12 weeks
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	ANOVA

Secondary: MRI inflammation

End point title	MRI inflammation
End point description:	
End point type	Secondary
End point timeframe: Baseline to 52 weeks of follow-up	

End point values	Calprotectin high	Calprotectin normal		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	12		
Units: units				
arithmetic mean (inter-quartile range (Q1-Q3))	6.6 (2 to 12)	3.5 (0 to 4)		

Attachments (see zip file)	MRI intasah.png

Statistical analyses

Statistical analysis title	MRI score between groups
Statistical analysis description: Analysis of MRI scores between groups	
Comparison groups	Calprotectin normal v Calprotectin high
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	MRI score over time
Statistical analysis description: Comparison of MRI scores before and after treatment	
Comparison groups	Calprotectin high v Calprotectin normal
Number of subjects included in analysis	27
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Report for serious adverse events made annually. Here reported for entire study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	ICD
Dictionary version	10

Reporting groups	
Reporting group title	Calprotectin high
Reporting group description: calprotectin high: Fecal calprotectin ≥100 mg/kg after NSAID wash-out period	
Reporting group title	Calprotectin normal
Reporting group description: Faeacal calprotectin <50 mg/kg after wash-out period	

Serious adverse events	Calprotectin high	Calprotectin normal	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Dizziness	Additional description: 10 days after the start she gets dizziness and malaise. The patient goes to the family doctor, who admits patient. At the hospital examined with blood tests and physical examination. Discharged after 4 hours of stay in hospital.		
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastro intestinal bleeding	Additional description: 20 year old man wknown previous episodes that bleeding episodes from the gut hospitalized with nausea and dizziness. At the hospital found bleeding from the intestine surgically burned.		
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Calprotectin high	Calprotectin normal	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)	2 / 15 (13.33%)	
Skin and subcutaneous tissue disorders			
Dry skin	Additional description: Patients reporting dryness of skin after use of adalimumab		
subjects affected / exposed	3 / 15 (20.00%)	2 / 15 (13.33%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2011	A comparator group (calprotectin normal) was added to the study. Based on included subjects inclusion number was changed to n=15 in each group

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported