



Clinical trial results: Effects of NSAIDs on Radiographic Damage in AS (ENRADAS) – a prospective randomised controlled trial - Amendment 2

Summary

EudraCT number	2007-007637-39
Trial protocol	DE
Global end of trial date	31 December 2013

Results information

Result version number	v1
This version publication date	01 March 2022
First version publication date	01 March 2022
Summary attachment (see zip file)	ClinicalInvestigationreportENRADAS (ClinicalInvestigationReport_ENRADAS_V1.1.pdf)

Trial information

Trial identification

Sponsor protocol code	ENRADAS-01
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité Universitätsmedizin Berlin
Sponsor organisation address	Hindenburgdamm 30, Berlin, Germany, 12203
Public contact	Fabian Proft, Charité Universitätsmedizin Berlin, Fabian.Proft@charite.de
Scientific contact	Fabian Proft, Charité Universitätsmedizin Berlin, Fabian.Proft@charite.de

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	30 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2013
Global end of trial reached?	Yes
Global end of trial date	31 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess an effect of daily (continuous) versus on-demand NSAID (diclofenac) treatment on radiographic progression in AS patients at risk for radiographic progression. Radiographic change (mean) of the spine after 2 years will be assessed in the per-protocol population.

Protection of trial subjects:

Regular assessments

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 August 2008
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	Germany: 167
Worldwide total number of subjects	167
EEA total number of subjects	167

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)	167
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Full recruitment in Germany from 22.08.2008 until 31.12.2011

Pre-assignment

Screening details:

Inclusion Criteria

- Diagnosis of AS according to the 1984 modified New York criteria
- Age 18 to 65 years.
- Active disease defined by a score ≥ 4 (VAS scale 0-10) of the BASDAI question 2 (related to back pain) at screening without NSAID therapy for at least 48 hours.
- A clinical indication for NSAID therapy based on signs and symptoms.
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Period 1

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

Blinding implementation details:

n.a.

Arms

Are arms mutually exclusive?	Yes
Arm title	Continuous

Arm description:

Experimental intervention: continuous (daily) treatment with diclofenac or any other NSAID in a daily dose of $\geq 50\%$ of the maximal daily dose recommended by manufacturer (diclofenac cholestyramine (Voltaren Resinat®) was provided).

Arm type	Experimental
Investigational medicinal product name	Diclofenac
Investigational medicinal product code	17982.00.00
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Diclofenac 75mg bid

Arm title	On Demand
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Arm description:

The comparator group was treated with diclofenac cholestyramine (Voltaren Resinat) or any other NSAID on-demand (as needed) for 2 years (with PPI being added as needed) as this strategy reflects very much current clinical practice in AS.

Arm type	Active comparator
Investigational medicinal product name	Diclofenac
Investigational medicinal product code	17982.00.00
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Diclofenac 75mg bid. On Demand

Number of subjects in period 1	Continuous	On Demand
Started	85	82
Completed	60	63
Not completed	25	19
Protocol deviation	25	19

Baseline characteristics

Reporting groups

Reporting group title	Continuous
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Reporting group description:

Experimental intervention: continuous (daily) treatment with diclofenac or any other NSAID in a daily dose of $\geq 50\%$ of the maximal daily dose recommended by manufacturer (diclofenac cholestyramine (Voltaren Resinat®) was provided).

Reporting group title	On Demand
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Reporting group description:

The comparator group was treated with diclofenac cholestyramine (Voltaren Resinat) or any other NSAID on-demand (as needed) for 2 years (with PPI being added as needed) as this strategy reflects very much current clinical practice in AS.

Reporting group values	Continuous	On Demand	Total
Number of subjects	85	82	167
Age categorical			
Units: Subjects			
Adults (18-64 years)	85	82	167
Age continuous			
Units: years			
arithmetic mean	41.7	43.8	-
standard deviation	± 10.4	± 10.8	-
Gender categorical			
Units: Subjects			
Male	63	56	119
Female	22	26	48
HLA-B27			
Units: Subjects			
positive	71	68	139
negative	14	14	28
CRP			
C-reactive Protein			
Units: Subjects			
CRP > 5mg/L	46	47	93
CRP \leq 5mg/L	39	35	74
syndesmophytes at baseline			
Units: Subjects			
Patients with	47	47	94
Patients without	38	35	73
Disease duration			
Units: years			
arithmetic mean	12.2	15.2	-
standard deviation	± 10.3	± 12.4	-
BASDAI			
Bath Ankylosing Spondylitis Disease Activity Index			
Units: Score			
arithmetic mean	4.2	4.5	-
standard deviation	± 1.6	± 1.6	-
BASFI			

The Bath Ankylosing Spondylitis Functional Index			
Units: Score			
arithmetic mean	3.1	3.9	
standard deviation	± 2.2	± 2.2	-
ASDAS			
Ankylosing Spondylitis Disease Activity Score			
Units: Score			
arithmetic mean	2.7	2.9	
standard deviation	± 0.8	± 0.8	-
CRP			
C-reactive Protein			
Units: mg/L			
arithmetic mean	8.4	12.9	
standard deviation	± 8.1	± 15.6	-
BASMI			
Bath Ankylosing Spondylitis Metrology Index			
Units: Score			
arithmetic mean	2.2	2.7	
standard deviation	± 2.1	± 2.2	-
mSASSS			
Modified Stoke Ankylosing Spondylitis Spinal Score			
Units: Score			
arithmetic mean	11.3	14.0	
standard deviation	± 14.9	± 16.8	-

End points

End points reporting groups

Reporting group title	Continuous
Reporting group description: Experimental intervention: continuous (daily) treatment with diclofenac or any other NSAID in a daily dose of $\geq 50\%$ of the maximal daily dose recommended by manufacturer (diclofenac cholestyramine (Voltaren Resinat®) was provided).	
Reporting group title	On Demand
Reporting group description: The comparator group was treated with diclofenac cholestyramine (Voltaren Resinat) or any other NSAID on-demand (as needed) for 2 years (with PPI being added as needed) as this strategy reflects very much current clinical practice in AS.	
Subject analysis set title	Non-smoking
Subject analysis set type	Intention-to-treat
Subject analysis set description: progression between smoking and non-smoking patients	
Subject analysis set title	Former smoking
Subject analysis set type	Intention-to-treat
Subject analysis set description: progression between smoking and non-smoking patients	
Subject analysis set title	Current smoking
Subject analysis set type	Intention-to-treat
Subject analysis set description: progression between smoking and non-smoking patients	

Primary: Change of the mSASSS-Progression

End point title	Change of the mSASSS-Progression
End point description: ICC was high for mSASSS: at baseline it was at 95.8%, at Year 2 at 94.7%. ICC for mSASSS difference and progression was at 50.1%. Smallest detectable change (SDC) score was 3.72 mSASSS points. Mean mSASSS score at baseline (bl) and Year 2 (z2) are displayed in the table as well as their difference. For more information see attached summary: ClinicalInvestigationreportENRADAS/ClinicalInvestigationReport_ENRADAS_V1.1.pdf	
End point type	Primary
End point timeframe: 2 years	

End point values	Continuous	On Demand		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	60		
Units: Score				
arithmetic mean (standard deviation)				
msasss_bl	10.90 (\pm 15.50)	16.40 (\pm 18.20)		
msasss_z2	12.20 (\pm 16.70)	17.20 (\pm 18.60)		
mdiff	1.28 (\pm 2.70)	0.79 (\pm 1.87)		

Statistical analyses

Statistical analysis title	Analysis of the imaging data ITT
Statistical analysis description: The primary outcome (mean radiographic progression in patients treated continuously vs patients treated on demand) will be assessed in an intent-to-treat analysis by means of the Mann-Whitney test	
Comparison groups	Continuous v On Demand
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	equivalence ^[1]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %

Notes:

[1] - The analysis was based on the mean mSASSS scores of both readers for each patient. In a further intent-to-treat analysis of all patients who entered the study but who have missing radiographs after 2 years, missing radiographic scores of dropout patients will be substituted by the overall mean of radiographic progression in the total sample as well as by an estimate calculated by means of linear regression (in the total sample) with baseline mSASSS as predictor.

Primary: Comparison of Smoking / Non smoking patients

End point title	Comparison of Smoking / Non smoking patients
End point description: There was no significant difference in mSASSS progression between smoking and non-smoking patients.	
End point type	Primary
End point timeframe: 2 years	

End point values	Non-smoking	Former smoking	Current smoking	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	31	33	58	
Units: Score				
arithmetic mean (standard deviation)	0.63 (± 1.65)	1.09 (± 1.66)	1.23 (± 2.90)	

Statistical analyses

Statistical analysis title	Analysis Variable : mdiff mSASSS-Progression
Comparison groups	Non-smoking v Former smoking v Current smoking

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Completers Data after 2 years

End point title	Completers Data after 2 years
End point description:	For more information see attachment: Comparison of Baseline Data of Dropouts
End point type	Secondary
End point timeframe:	After 2 years

End point values	Continuous	On Demand		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	82		
Units: Score				
arithmetic mean (standard deviation)				
mSASSS	10.60 (± 15.50)	15.90 (± 18.00)		
BASDAI, Screening	4.11 (± 1.54)	4.22 (± 1.47)		
BASFI, Screening	2.99 (± 2.18)	3.74 (± 2.14)		
BASMI, Screening	2.13 (± 1.99)	2.90 (± 2.26)		
pain, Screening	4.98 (± 1.97)	5.14 (± 1.52)		
BSG, Screening	19.00 (± 14.00)	21.40 (± 18.20)		
CRP in mg/l, Screening	7.65 (± 7.49)	12.30 (± 14.80)		

Attachments (see zip file)	Comparison of Baseline Data of Dropouts/comparison
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Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of Baseline Data of Dropouts

End point title	Comparison of Baseline Data of Dropouts
End point description:	Patients that terminated the study early and did not have Xrays after 2 years (dropouts) were compared to patients who completed the study (completer). For more information see attachment: Comparison of

Baseline Data of Dropouts

End point type	Secondary
End point timeframe:	
2 years	

End point values	Continuous	On Demand		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	19		
Units: Score				
arithmetic mean (standard deviation)				
mSASSS	12.8 (± 13.6)	8.00 (± 10.30)		
BASDAI, Screening	4.34 (± 1.89)	5.35 (± 1.72)		
BASFI, Screening	3.45 (± 2.15)	5.58 (± 2.26)		
BASMI, Screening	2.45 (± 2.48)	2.00 (± 2.03)		
pain, Screening	5.84 (± 2.15)	6.32 (± 1.77)		
BSG, Screening	17.00 (± 11.70)	18.50 (± 18.70)		
CRP in mg/l, Screening	10.30 (± 9.44)	14.80 (± 18.00)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

2 years

Adverse event reporting additional description:

for detailed informations see attachment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.1
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Reporting groups

Reporting group title	continuously
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Reporting group description: -

Reporting group title	on demand
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Reporting group description: -

Serious adverse events	continuously	on demand	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 85 (22.35%)	21 / 82 (25.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
All events related to Neoplasms benign, malignant and unspecified			
subjects affected / exposed	2 / 85 (2.35%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
All events related to the reproductive system and breast disorders			
subjects affected / exposed	1 / 85 (1.18%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
All events related to the Renal and urinary disorders			

subjects affected / exposed	1 / 85 (1.18%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
All events related to the Psychiatric disorders			
subjects affected / exposed	0 / 85 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
All events related to injuries, poisoning and procedural complications			
subjects affected / exposed	2 / 85 (2.35%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
All events related to the cardiac disorder			
subjects affected / exposed	3 / 85 (3.53%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
All Events related to the blood and lymphatic system	Additional description: idSoc = ID System Organ Class; idSoc 10005329		
subjects affected / exposed	1 / 85 (1.18%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
All events related to the ear and labyrinth disorder			
subjects affected / exposed	1 / 85 (1.18%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
All events related to the eye disorder			

subjects affected / exposed	1 / 85 (1.18%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
All events related to the gastrointestinal disorder			
subjects affected / exposed	1 / 85 (1.18%)	7 / 82 (8.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
All events related to the skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 85 (1.18%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
All events related to the endocrine disorder			
subjects affected / exposed	1 / 85 (1.18%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
All events related to the musculoskeletal and connective tissue disorder			
subjects affected / exposed	1 / 85 (1.18%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
All events related to infections and infestations			
subjects affected / exposed	2 / 85 (2.35%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
All events related to the Metabolism and nutrition disorder			

subjects affected / exposed	0 / 85 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	continuously	on demand	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 85 (100.00%)	82 / 82 (100.00%)	
Investigations			
overall			
subjects affected / exposed	85 / 85 (100.00%)	82 / 82 (100.00%)	
occurrences (all)	442	520	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2009	<p>Version 1 was submitted to improve patient recruitment and facilitation of the trial conduction. Performance of screening and baseline procedures on the same day was allowed, but start of study medication (NSAID) must be delayed until laboratory reports confirming the patient's eligibility have been obtained. Patient will be informed about the laboratory results by the investigator and whether he/she is allowed to start treatment with NSAID. Date of the patient contact and date of treatment initiation must be recorded in the source documents. The concomitant participation in any observational (non-therapeutic) study was allowed. Concomitant therapy with a disease modifying antirheumatic drug such as methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, azathioprine) and systemic corticosteroids (≤ 10 mg/day prednisolone equivalent) was allowed. Any NSAID can be chosen as study medication (diclofenac was supplied as the free study drug), assuming that the retardation of radiographic progression of AS is a class effect of NSAIDs which is based on several observations. This will facilitate the recruitment of patients who are treated already on demand with an NSAID. The NSAID dose in the continuous treatment arm can be varied between 50% and 100% of the maximally daily recommended dose (not 100% only). Again, this will increase the acceptance of both the patients and the rheumatologists to participate in the study. The rationale behind this is based on the assumption that the daily (continuous) therapy with NSAIDs is more relevant for inhibiting bone formation than the actualy dose. Hospitalization which has been planned prior to the screening visit due to pre-existing concomitant conditions (i.e. elective hospitalizations) will not be considered as serious adverse events (SAE). For study visits from week 16 to week 112 visit the time window for the conduct of a study visit was broadened to +/- 28-days.</p>
15 March 2010	<p>Amendment 2, Version 1, also to improve the patient recruitment and facilitation of the trial conduction as well as administrative changes. Requirement of a syndesmophyte as an inclusion criterium has been taken out. This requirement may in fact hamper the inclusion for three reasons: First, rheumatologists do not always feel confident in identifying a syndesmophyte and rely on the radiologist. Second, a patient cannot be included at the first visit because radiographs need to be reviewed first (searching for a syndesmophyte). Third, more AS patients are potentially eligible for the study because syndesmophytes are found in 50-70% of AS patients on average, but not in all patients. Thus, skipping this inclusion requirement will facilitate the inclusion of patients. The sample size recalculation has been performed. The number of patients need to be included in the trial in order to reveal differences in radiographic progression between two treatment groups is 174 now (87 patients in each arm). The coordinating investigator of the trial, principal investigator of the trial site 1 and legal representative of the sponsor has been changed: coordinating investigator, site 1 principal investigator and legal representative - Prof. Dr. Joachim Sieper, principal co-investigator - Dr. Martin Rudwaleit. 4 new study sites are added, one study site is excluded.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26242443>