Clinical Investigation Report

Title: Effects of NSAIDs on RAdiographic Damage in AS a prospective randomised controlled trial

(a prospective randomized controlled trial on the effects of NSAID on spinal radiographic progression over 2 years in patients with ankylosing spondylitis)

Name or abbreviated title: ENRADAS

Clinical investigation plan ID: ENRADAS-01, EudraCT 2007-007637-39

Investigational device(s): Voltaren resinat (Zulassungsnummer 17982.00.00)

Sponsor /contact details: Charité - Universitäsmedizin Berlin

Coordinating investigator: Prof. Dr. med. Joachim Sieper

Statistician: Dr. Joachim Listing, Prof. Dr. Angela Zink, DRFZ Berlin

Start of trial: 22.08.2008

End of trial: 31.12.2013

Number of patients included: 180

Author(s) of report: Dr. Judith Rademacher

Version / date: Version 1.1 2021-06-30

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1. Summary

Title: Effects of NSAIDs on RAdiographic Damage in AS a prospective randomised controlled trial
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Sponsor: Charité - Universitäsmedizin Berlin
Investigational device(s): Voltaren resinat (Zulassungsnummer 17982.00.00)
Coordinating investigator: Prof. Dr. Joachim Sieper
Trial sites/ principle investigators: 19 trial sites, Prof. Dr. med. Joachim Sieper
Objective of the investigation: Before the study only one single controlled trial showed that non-steroidal anti-inflammatory drugs (NSAIDs) when continuously given is able to reduce radiographic progression in patients with ankylosing spondylitis over 2 years compared to treatment on demand. Therefore, the objective of this study was to confirm this finding in another randomised
Clinical endpoints: The primary endpoint was spinal radiographic progression between baseline and year 2 as measured by mSASSS. Secondary endpoints were radiographic progression of the patients completing the study and clinicial endpoints of disease acitivty measurement: BASDAI, ASDAS, BASFI, BASMI, C-reactive protein and erythrocyte sedimentation rate.

Study design: randomized controlled trial	**Number of patients (planned/ evaluated):** 360/180

Clinical investigation population (diagnosis and main inclusion criteria): patients with established AS who have moderate disease activity and who respond generally well to NSAIDS.
Clinical investigation method(s) used: laboratory assessments, imaging (conventional radiographs)
Ammendments: With Ammendment 1, Version 1 on 01 July 2009 performance of screening and baseline procedures (including randomisation, imaging, and patient drug supply) on the same day was allowed, concomitamt participation in any observational (non-therapeutic) study and concomitant therapy with a disease modifying antirheumatic drug (DMARD) such as methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, azathioprine) and systemic corticosteroids (≤10 md/day prednisolone equivalent) was allowed. Ammendment 2, Version 1 followed on 15 March 2010, 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 was taken out and sample size recalculation was performed. The number of patients need to be included in the trial in order to reveal differences in radiographic progression between two treatment group is 174 now (87 patients in each arm). The coordinatingl 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 studies sites were added, one study site excluded.

Date of the study start (first patient in): 22.08.2008	**Completion date (last patient out) or premature termination:** 31.12.2013

Statistical methods: The Mann–Whitney test was applied to compare the primary outcome - radiographic spinal progression - in patients with complete sets of radiographs at baseline and at 2 years. To account for differences in the mSASSS baseline status and the dependency of radiographic progression on the status at baseline, a non-parametric analysis of variance test for longitudinal data as proposed by Brunner et al was applied in addition. Furthermore, a generalised linear mixed model (GLM) approach was applied to take a possible bias caused by dropouts into account and to compare radiographic progression between the intention-to-treat (ITT) groups. GLMs were also applied to estimate baseline-adjusted mean changes and their 95% CIs. All tests applied were two-sided tests. p values<0.05 were considered to be statistically significant.

Summary of results: 62 of 85 patients enrolled in the continuous arm and 60 of 82 enrolled in the on-demand arm completed the study. The mSASSS progression was numerically higher in the continuous group (1.28 (0.7 to 1.9) vs 0.79 (0.2 to 1.4)) (p=0.39). If only patients were analysed who were either C reactive protein positive or had syndesmophytes at baseline, there was again a higher radiographic progression in the continuous versus the on-demand group: 1.68 (0.7 to 2.6) vs 0.96 (0.0 to 1.9) and 2.11 (1.1 to 3.1) vs 0.95 (0.0 to 1.9), respectively. There was no difference between the two treatment groups regarding adverse events. (Sieper et al, Annals of Rheumatic Diseases, 2015)

Conclusion: In our study, continuous treatment with diclofenac over 2 years did not reduce radiographic progression compared with on-demand treatment in AS.

2. Introduction

- *Statement placing the clinical investigation in the context of the development of the investigational device,*
- *Objective and hypotheses, target population, treatment and follow-up duration*
- *Guidelines that were followed .*

Ankylosing spondylitis (AS) is part of axial spondyloarthritis and defined by the presence of structural bone damage visible on X-rays in the sacroiliac joints and/or in the spine. The development of syndesmophytes in the spine contributes considerably to the restriction of spinal mobility and function, especially later in the course of the disease. Thus, next to an effective suppression of inflammation the prevention of structural damage, especially osteoproliferative changes in the spine, is an important treatment target (Sieper et al, ARD, 2017).

While tumour necrosis factor (TNF)-blockers are highly effective for the treatment of signs and symptoms, there is no short-term effect over 2–4 years of anti-TNF treatment on new bone formation in the spine of patients with established AS. Whether new bone formation can be prevented in case of earlier or longer treatment with TNF-blockers has still to be proven. Non-steroidal anti-inflammatory drug (NSAID) treatment is the first-line pharmaceutical therapy in patients with axSpA, based on their good efficacy for signs and symptoms. Moreover, limited data suggest that NSAIDs may also exhibit a disease-modifying effect in AS. It was already in 1976 that one study reported an inhibitory effect of phenylbutazone on the progression of ossification in a retrospective analysis, which was confirmed later by a prospective and randomised NSAID trial over 2 years in patients with AS starting with celecoxcib (Wanders et al, Arthritis Rheumatology 2005). In addition, a protective effect of a higher NSAID intake over time was shown in patients from a prospective spondyloarthritis inception cohort in Germany.

In the trial reported here, we aimed to confirm the inhibitory effect of NSAIDs on osteoproliferation in AS. Since we assumed that such an effect, if true, would represent a class effect rather than an effect of a particular type of NSAID, we used a different but commonly used NSAID, diclofenac, as a starting NSAID.

The Effects of NSAIDs on RAdiographic Damage in Ankylosing Spondylitis (ENRADAS) study was a prospective randomised controlled trial conducted in 19 centres in Germany between May 2008 and December 2013 (EudraCT 2007-007637-39). Patients aged 18–65 years fulfilling the 1984 modified New York criteria were eligible if they had active disease (back pain on a 0–10 numerical rating scale ≥4) that justified the start or continuation of an NSAID and had no contraindications for an NSAID therapy. TNF-blocker treatment was not allowed before and during the whole study. Proton pump inhibitor (PPI) could be added to the treatment. Plain radiographs of the cervical and lumbar spine had to be available to allow for randomisation. In order to reduce radiation exposure, existing radiographs of the spine were taken as baseline radiographs if not older than 24 months. Initially, we aimed to restrict the inclusion to patients with AS with at least one syndesmophyte at baseline in order to select for patients with a higher risk for radiographic progression. For feasibility reasons, however, this inclusion criterion was later omitted. The history or presence of gastroduodenal ulcers, chronic inflammatory bowel disease, cardiovascular disease (coronary heart disease, heart failure, stroke or transient ischaemic attack), renal insufficiency and known severe hypersensitivity reactions to NSAIDs were exclusion criteria.

3. Investigational device and methods

3.1 Investigational device description

- *Description of the investigational device, intended use, previous intended use or indications for use*
- *Any changes of the investigational device during the clinical investigation or any changes from the IB (raw materials, software, components, shelf-life, storage conditions, instructions for use, other changes).*

Voltaren® Resinat (diclofenac colestyramin) is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Voltaren, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.
The unique pharmacokinetics of Voltaren® Resinat provides a prompt onset of release as well as long lasting release of diclofenac. After an oral administration of one capsule Voltaren® Resinat detectable concentrations of diclofenac in plasma can be measured already after 20 minutes. Maximum plasma concentrations which can be found on average after 1.25 hours (range 0.33-2 hrs) are on average 0.7±0.22 µg/ml which is about one third of the concentration found for the equivalent dose of Voltaren tablets. Plasma levels of Voltaren® Resinat are detectable for up to 12 hours after oral administration.
The apparent volume of distribution (V/F) of diclofenac sodium is 0.12-0.17 l/kg. Diclofenac is more than 99% bound to human serum proteins, primarily to albumin. Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac. Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxy- and 5-hydroxy-diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects. However, diclofenac
metabolites undergo further glucuronidation and sulfation followed by biliary excretion. One diclofenac metabolite 4'-hydroxy- diclofenac has very weak pharmacologic activity.
Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Little or no free unchanged diclofenac is excreted in the urine. Approximately 60% of the dose is excreted in the urine and approximately 40% in the bile as conjugates of unchanged diclofenac plus metabolites. Because renal elimination is not a significant pathway of elimination for unchanged diclofenac (1% only), there is not risk of accumulation of diclofenac in patients with mild to moderate renal dysfunction. In patients with moderately impaired liver function (chronic hepatitis, liver cirrhosis without portal decompensation), the kinetics and metabolism of diclofenac is comparable to that of healthy people. Diclofenac is eliminated from plasma with a systemic clearance rate of 263±56 ml/min. The terminal half-life is approximately 1-2 hours.
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. Diclofenac cholestyramine (Voltaren Resinat) and PPI was provided as study drugs. This is an open, randomised, controlled multi-centre clinical trial. A placebo-controlled study over a period of 2 years would not be ethical given that active AS patients with an indication for NSAID treatment are included, and NSAIDs on demand are currently considered standard therapy in AS.

The intervention group was treated continuously with diclofenac cholestyramine (Voltaren Resinat) or any other NSAID in a daily dose of ≥50% of the maximal daily dose recommended by manufacturer together with a proton pump inhibitor (PPI) for gastroprotection for a period of 2 years. Diclofenac cholestyramine (Voltaren Resinat) and PPI was provided as study drugs. Assuming that retardation of radiographic progression of AS is a class effect of NSAIDs, investigators will have the possibility to choose any NSAID for the patient treatment.
Diclofenac in the maximal daily dose of 150mg was taken as 2 tablets a 75mg of Voltaren resinat. Therefore, the minimal daily dose of diclofenac in the continuous arm of this study is 75 mg. A dose of 150mg diclofenac per day has been the usual dose in several clinical trials in AS, and in other studies such as the VIGOR study or the MEDAL study. Moreover, diclofenac is generally regarded as highly effective, and the 150mg dose has been approved in rheumatic diseases including AS. PPI in standard dose (Pantozol 20mg) was available for all patients and should be given to patients with an increased risk for gastrointestinal complications or in case of gastrointestinal symptoms.
In Germany, diclofenac-cholestyramine (Voltaren Resinat) is one of the most frequently prescribed drugs in AS, therefore, we propose diclofenac as study drug in this trial. Moreover, diclofenac-cholestyramine 150mg was as effective as celecoxib 400 mg per day over 3 months in a recent randomised trial of 450 AS patients conducted in Germany with 83% of patients being on either drug at the end of the trial.
Safety data on a daily dose of 150mg diclofenac in AS patients are available from this trial and, even more important, from the large MEDAL study. The European Medicines Agency (EMEA) has concluded in a recent press release (October 24, 2006) that the benefit-risk balance for non-selective NSAIDs remains favourable. This conclusion was drawn following a review announced in September 2006 of new thrombotic cardiovascular safety data. Novartis Pharma GmbH, Germany, is prepared to provide the medication (diclofenac-cholestyramine) for the proposed trial without having other obligations nor obtaining any rights.

Batch Numbers of the used Voltaren Resinat®

Batch	Pharmacy			Elimination via Pharmacy			
	Date	Packages	Tabletts	Datum	study center	Pack.	Tbl.
Voltaren Resinat 75mg;	16.07.2008	18750	375000				
Ch.-B.: W0300;		↓		23.05.2011	1	149	2980
expiry date 03/2011		↓		23.05.2011	1		948
		↓		23.05.2011	St.-Zentrale	2490	49800
	23.05.2011	4800	96000	23.05.2011	Apotheke	4800	96000
				07.11.2012	PZ		4162
				01.11.2013	11		1140
				01.11.2013	36		103
				29.11.2013	10		373
Voltaren Resinat 75mg	11.10.2010	6250	125000	29.11.2012	10		190
Ch.-B.: W0511;				03.12.2012	1		1338
expiry date 08/2013				01.11.2013	St.-zentrale	900	18000
				01.11.2013	St.-zentrale	120	2400
				01.11.2013	1	32	640

				01.11.2013	9		269
				01.11.2013	10		16
				01.11.2013	11		779
				01.11.2013	36		701
				16.12.2013	11		189
	25.10.2013	1660	33200	25.10.2013	Apotheke	1660	33200
Voltaren Resinat 75mg	27.02.2013	450					
Ch.-B.: W0738; expiring 11/2015							

3.2 Clinical investigation plan (CIP)

- *Summary of the CIP, amendments with a rational for each amendment,*
- *Objectives, design, type, endpoints,*
- *Ethical considerations, quality assurance,*
- *Subject population (inclusion / exclusion criteria, sample size),*
- *Treatment and treatment allocation schedule*
- *Concomitant medications/treatments, duration of follow-up,*
- *Statistical analysis incl. Hypothesis or pass/fail criteria, sample size calculation,*
- *Statistical analysis methods.*

A summary of the CIP is given in the following trial flow scheme and study flowchart:

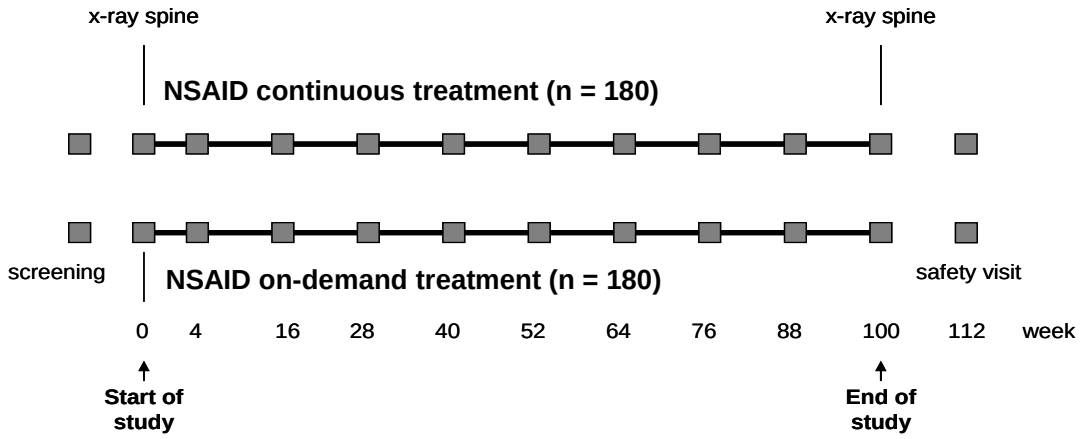


Figure: Schematic flow of the trial; ■ = visit

Subjects was screened within 28 days prior to administration of study medication to confirm that entrance criteria for the trial are met. The first visit after first treatment is four weeks later, thereafter every 12 weeks until week 100. Study visits serve to assess clinical efficacy and safety aspects. Radiographs of the cervical and lumbar spine are being taken at baseline (if not available) and at week 100. A final safety phone call will take place at week 112.

	Study Procedures	Screening	NSAID treatment phase										Follow-up
		≤ 28 days prior to BL	**BL W0**	**W 4***	**W 16***	**W 28***	**W 40***	**W 52***	**W 64***	**W 76***	**W 88*** [k]	**W 100* ** [a]/ ET[a]**	**W112**
		V 1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Screening Procedures	Informed Consent (S)	X											
	Inclusion/Exclusion Criteria (S)	X											
	Demographics (S)	X											
	Medical/Surgical History (S/ R)	X	X[b]										
Labora-tory	Pregnancy Test [c] (S)	X											
	Clinical Chemistry [d] (S)	X		X	X	X	X	X	X	X	X	X	
	Hematology [e] (S)	X		X	X	X	X	X	X	X	X	X	
	ESR, CRP (S/R)	X		X		X		X		X		X	
	Biomarker analysis	X						X				X	
Examination / History	Physical Examination (S/R)	X	X	X	X	X	X	X	X	X	X	X	
	Swollen joint count (S)	X						X				X	
	Vital Signs, including weight (S/R)	X		X	X	X	X	X	X	X	X	X	
	BASMI, chest expansion (S/R)	X		X		X				X		X	
	Spinal Pain Score	X				X						X	
Questionnaires	BASDAI (S/R)	X		X	X	X	X	X	X	X	X	X	
	BASFI (S/R)	X		X	X	X	X	X	X	X	X	X	
	SF-36™ Health Survey (S)	X						X				X	
	Patient's global (NRS) (S/R)	X		X	X	X	X	X	X	X	X	X	
	Pain (NRS) (S/R)	X		X	X	X	X	X	X	X	X	X	
	EQ-5D (S)	X						X				X	
	Nocturnal pain (NRS) (S)	X		X	X	X	X	X	X	X	X	X	
	Physician's global (NRS) (S/R)	X		X	X	X	X	X	X	X	X	X	
	PASS questions	X		X	X	X	X	X	X	X	X	X	
	Patient satisfactory	X		X	X	X	X	X	X	X	X	X	
Imaging	X-ray radiographs reading of cervical and lumbar spine [f] (R)		X									X	
	Magnetic Resonance Imaging of spine (MRI) [g]		X			X						X	
Other procedure	Adverse Events		X	X	X	X	X	X	X	X	X	X	X
	Follow-up phone call												x [i]
	NSAID/ PPI medication supply (S) [h]		X	X	X	X	X	X	X	X	X		
	Pill count			X	X	X	X	X	X	X	X	X	

Abbreviations: BL= baseline; W= week; V= visit; S= study specific procedure, R= routine procedure;

***** Weeks after first study drug administration (NSAIDs);

a. ET = early termination visit for subjects who prematurely terminate for any reason. In case of early termination all procedures from week 100 will have to be performed except the x-ray.

b. Interim history.

c. female patients will receive urine pregnancy test at screening; in case of a positive urine pregnancy test at screening a pregnancy has to be excluded, otherwise the patient has to be excluded from the study

d. ALT, AST, creatinine

e. Hemoglobin; WBC; platelets

f. radiographs of the cervical spine (lateral view) and lumbar spine (anterior-posterior view) are being taken at baseline and at week 100; available radiographs at the time of inclusion in the study was accepted as baseline radiographs as long as they are not older than 24 months. Radiographs of the spine will not be taken at screening to assess whether or not syndesmophytes are present; the presence of syndesmophytes must be retrieved from previously taken radiographs.

g. MRI of the spine in selected trial centers at baseline, week 28 and week 100

h. NSAID / PPI medication supply as needed
i. Follow-up phone call visit for assessment of adverse events for safety reason at week 112

Ammendments
Ammendment 1, Version 1 on 01 July 2009 was submitted to improve patient recruitment and facilitation of the trial conduction. Performance of screening and baseline procedures (including randomisation, imaging, and patient drug supply) 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 (personally or by phone) 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 concomitamt participation in any observational (non-therapeutic) study was allowed. Concomitant therapy with a disease modifying antirheumatic drug (DMARD) such as methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, azathioprine) and systemic corticosteroids (≤10 md/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 (daily NSAID) 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.

Ammendment 2, Version 1 followed on 15 March 2010, 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 syndesmopyhte and rely on the radiologist. Second, a patient cannot included at the first visit because radiographs need to be reviewed first (searching for a syndesmopyhte). 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 group is 174 now (87 patients in each arm). The coordinatingl investigator of the trial, principal investigator of the trial site 1 and legal representative of the sponosr has been changed: coordinating investigator, site 1 principal investigator and legal representative - Prof. Dr. Joachim Sieper, principal co-investigator - Dr. Martin Rudwaleit. 4 new studies sites are added, one study site is excluded.

Objectives:
1) To assess an effect of daily (continuous) versus on-demand NSAID treatment on radiographic progression in AS patients at risk for radiographic progression.
2) To study the safety of daily (continuous) vs on-demand NSAID therapy in AS over 2 years.

Design:
Randomised, controlled, multi-centre clinical trial on patients with ankylosing spondylitis.

Experimental intervention: continuous (daily) treatment with diclofenac or any other NSAID in a daily dose of ≥50% of the maximal daily dose recommended by manufacturer (diclofenac cholestyramine (Voltaren Resinat®) was provided).
Control intervention: treatment on-demand (as needed) with diclofenac or any other NSAID (diclofenac cholestyramine (Voltaren Resinat®) was provided). The treatment strategy of the control intervention (on-demand) reflects current clinical practice in AS.
Duration of intervention per patient: 2 years
Follow-up per patient: safety assessment 3 months after termination of the trial.

Primary Endpoint
Primary outcome was the radiographic change of the spine after 2 years of treatment in the intent-to-treat population. Radiographs of the cervical spine (lateral view) and the lumbar spine (lateral and anterior-posterior view) was taken before and after 2 yrs and scored by two independent trained readers according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). The two readers were blinded with respect to intervention arm (continuous vs on-demand) and to time point of radiographs (baseline vs follow-up).

Secondary Endpoints
In a secondary analysis the radiographic progression in the on-demand group was compared to the progression in the continuous-treatment group in the total population with substitution of missing radiographs. Furthermore, the proportions of any progression (change in the mSASSS ≥ 1) and change in the mSASSS > smallest detectable change (SDC) was compared between the groups in the per-protocol population. This analysis will also be repeated in the ITT population by substituting missing radiographs in dropouts by i) change (worsening) but also ii) no change (no worsening).
Safety was assessed as a secondary outcome parameter. Safety parameters include patient's in- and exclusion criteria, clinical history, physical examination including vital signs, safety blood tests, collection of adverse events and serious adverse events during the whole study time. Safety data was collected during the whole therapy and follow up phase.
Further secondary endpoints
Efficacy Evaluations:

- ASAS 20 response, ASAS 40
- BASDAI 50% improvement
- BASFI
- Mobility examinations: BASMI, chest expansion
- CRP, ESR
- Quality of Life: SF-36, EQ-5D
- Numeric Rating Scale (NRS) – physicians global, patients global, general pain, nocturnal pain
- Swollen and tender joint count

Ethical considerations
NSAIDs are the standard medical treatment in AS. Given the chance that NSAIDs may inhibit structural damage if given continuously (true DMARD effect) it is not unethical to treat patients continuously for a period of 2 years to test this hypothesis.
Adverse events of NSAIDs in the treatment of rheumatic diseases including ankylosing spondylitis are well known. Since in the intervention group Voltaren Resinat was taken daily for 2 years, a concomitant therapy with PPI is indicated to reduce the risk of gastrointestinal adverse events. In patients treated with Voltaren Resinat on demand a concomitant therapy with PPI is also recommended. The risk of a severe gastrointestinal adverse event is not different between patients treated with Cox-2 selective NSAIDs as compared to patients treated with non-selective NSAIDs in combination with PPI. A PPI in standard dose (such

as pantoprazol 20mg daily) was be provided to all study participants. Apart from GI toxicity there is no evidence that non-selective NSAIDs are disadvantageous over selective (Cox-2) NSAIDs. The overall absolute risk for a cardiovascular event is small for non-selective and selective NSAIDs. EMA has concluded in a press release (October 24, 2006) that the benefit-risk balance for non-selective NSAIDs remains favourable. This conclusion was drawn following a review announced in September 2006 of new thrombotic cardiovascular safety data. Furthermore, based on a recent large safety trial with NSAIDs over several years and on an AS trial over 12 weeks, the expected side effects, including gastrointestinal, cardiovascular, renal and hepatic adverse events, of a continuous treatment with 150mg diclofenac per day are well known and the patient's information contains detailed information on this. Because of younger age and less comorbidities of AS patients as compared to those with rheumatoid arthritis or osteoarthritis in most of the clinical trials even a lower number of serious adverse events than recently reported can be expected. An international safety review board (DSMB) reviewed the safety during the trial (for details see below). Insurance coverage was provided for all participating patients.
The study was be performed according to the Declaration of Helsinki from 1996 (according to Art. 3, Abs 2 der Richtlinie 2005/28/EG). Additionally it was the responsibility of all engaged in research on human beings to ensure that the study is performed in accordance with the international Good Clinical Practice standards and according to all local laws and regulations concerning clinical studies.
Written and informed consent from each subject participating in this study was obtained, after adequate explanation of aim, importance, anticipated benefits, and potential hazards and consequences of the study according to § 40 Abs 2 and § 40 Abs. 2a AMG.

Quality Assurance
The sponsor performed quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator reviewed the protocol, the investigator's brochure, the CRF´s and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AE´s and SAE´s. Quality control and quality assurance was provided by an external monitor who visited all participating study sites by regular intervals. During these site visits information recorded in the CRF´s was verified against source documents. The principal investigator reviewed all serious events and stated whether they are severe unexpected serious adverse reactions according to GCP and ICH guidelines. All participating study sites were well selected during pre-selection visits.

Subject Population
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.
- The patient is able and willing to take oral medications.
- The patient is capable of understanding and signing an informed consent form. The patient understands the study procedures, risks and benefits, and agrees to participate in the study giving written informed consent.
- No current therapy with anti-TNF agents. Any anti-TNF therapy must be stopped 4 weeks before screening.
- In case of DMARD-therapy (methotrexate ≤25 mg/week, sulfasalazine ≤3 g/day, leflunomide, azathioprine, or hydroxychloroquine), the dose must be stable for 4 weeks prior to baseline.

- In case of corticosteroid therapy, the dose must be stable within 2 weeks prior to baseline and must not exceed 10 mg (prednisolone equivalent) per day.

Exclusion Criteria

Patients meeting any of the following exclusion criteria were not enrolled:

- Complete ankylosis of the cervical and lumbar spine (the anterior part of at least one vertebral unit (lower part of the upper vertebra and upper part of the lower vertebra) of the cervical or lumbar spine on the lateral view on radiographs of at least one vertebral unit (lower part of the upper vertebra and upper part of the lower vertebra) of the cervical or lumbar spine must not show complete ankylosis).
- Exclusion criteria related to general health conditions
    - Patient has a history of any illness or has significant abnormalities on pre-study clinical or laboratory evaluation that, in the opinion of the investigator, contraindicates continuous therapy for at least 2 years with diclofenac or any other NSAID.
    - History of oesophageal, gastric, pyloric channel or duodenal ulceration documented by endoscopy or radiographic examination at any time before the screening visit, or any clinically relevant gastrointestinal bleeding.
    - Patient has, regardless of etiology, clinical gastrointestinal malabsorption
    - History of or current signs of coronary heart disease, myocardial infarction, stroke or transient ischemic attack or thrombotic events.
    - Uncontrolled hypertension; patients with medically controlled hypertension may participate
    - Evidence of impaired renal function, defined as serum creatinine greater than 1.5 mg/dl
    - History of inflammatory bowel disease (Crohn’ s disease, ulcerative colitis)
    - Patient has a history of or current signs of bleeding diathesis
    - Patient has a history of or current signs of peripheral arterial occlusive disease
    - Abnormal liver function (≥ 2x upper normal limit). Patients with known active hepatitis B or C must not participate.
    - Chronic or acute congestive heart failure (NYHA III or IV)
    - Patients with more than 2 risk factors for cardiovascular events (such as uncontrolled hypertension, hyperlipidemia, diabetes mellitus, smoking) in the past
    - Known reactions of bronchospasm, asthma, rhinitis or urticaria after intake of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs in the past
    - Patients with other chronic inflammatory articular disease or systemic autoimmune disease, e.g. Systemic lupus erythematosus, Sjögren’s syndrome, active rheumatoid vasculitis, a history of systemic diseases associated with arthritis.
    - Any active infection
    - History of HIV infection.
    - Patient has a history of neoplastic disease and does not meet one of the exceptions listed below. Patients with a history of leukaemia, lymphoma, melanoma, or myeloproliferative disease are ineligible for the study regardless of the time since treatment:
    - Exceptions:
        - □ patients with adequately treated basal cell carcinoma or carcinoma in situ of the cervix
        - □ patients with other malignancies which have been successfully treated ≥ 5 years prior to screening, where in the judgment of both the investigator and the treating physician, appropriate follow-up has

revealed no evidence of recurrence from the time of treatment through the time of screening.
    - Patients with a history of a severe psychological illness or condition such as to interfere with the patient's ability to understand the requirements of the study.
    - History of current evidence of abuse of “hard” drugs (e.g. cocaine/ heroine) or alcoholism.
    - Patient is allergic to or has hypersensitivity to aspirin, diclofenac sodium, other NSAIDs, or coxibs.
    - Women lactating, pregnant, nursing or of childbearing potential with a positive pregnancy test (urine test)
    - Patient is pregnant or nursing, or planning pregnancy within the projected duration of the study: Female patients of childbearing potential must have used adequate oral or barrier contraception or abstained from sexual contact at least 30 days prior to treatment and continue contraception through the treatment period or discontinuation visit. A highly effective method of birth control is defined as those which result in a low a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner. In addition, the patient must demonstrate a negative pregnancy test before baseline. Women who are postmenopausal, or surgically sterile (status posthysterectomy or who have had bilateral tubal ligation) are exempt from this requirement. Postmenopausal is defined as no menses for the previous 6 months.
- Exclusion criteria related to medications
    - Therapy with anti-TNF therapy within 4 weeks prior to screening
    - Previous treatment with any investigational agent within 4 weeks prior to screening (or less than 5 terminal half-lives of elimination) of day 1 dose
    - Combination with other NSAIDs including salicylates and Cox2-selective inhibitors
    - Patients are excluded from the study if one of the following concomitant medications is required at screening or is likely to be used during the study: phenytoine and/ or digoxin, selective serotonin-reuptake inhibitors (SSRI), ciclosporin, probenecid, sulfinpyrazone, chinolone-antibiotics, lithium, warfarin, heparin;
- Exclusion criteria related to lab findings
    - Any laboratory test result that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
- Exclusion criteria related to formal aspects
    - Patients who participate currently in another clinical trial with investigational drug. Participation in any observational (non-therapeutic) study is possible.
    - Patients who are underage or patients who are incapable to understand the aim, importance and consequences of the study and to give legal informed consent (according to § 40 Abs. 4 and § 41 Abs. 2 und Abs. 3 AMG).
    - Patients who are institutionalised due to regulatory or juridical order (according to AMG § 40 Abs 1, S 3, Nr 4 AMG)
- Exclusion criteria related to magnetic resonance imaging (MRI) investigation
        - □ these exclusion criteria apply only to those patients who are seen in one of the 4 MRI centers: 1) Charité Benjamin-Franklin, Rheumatology Department (Dr. Rudwaleit), 2) Rheumazentrum Ruhrgebiet (Prof. Braun), 3) Study center Munich, private practice (Prof. Kellner), 4) University of Tübingen (Prof. Kötter); of note: if patients have

contraindications for an MRI investigation but are otherwise eligible to participate in the study, they are allowed to participate in the study without undergoing MRI investigation.

- Patients who have claustrophobia
- Patients with a cardiac pacemaker
- Patients who have metal implants which are not compatible with an MRI examination
- Patients who have any other contraindication for MRI examination

Sample Size and Calculation

The assumptions for the statistical analysis made in the study protocol (initial version and amendment 1) were done from a precautious point of view requiring a high power (90%) to detect a difference, and considering lower mean differences between the groups and larger variances than those reported by Wanders et al.

On the other hand the possibility of larger differences in the primary outcome between the groups because of very strict inclusion criteria was not taken into account. Since these arguments are true, we therefore performed a power re-calculation of the ENRADAS trial by taking into considerations the following points:

- Up till March 2010 we enrolled 80 patients who already had syndesmophytes in the spine and were therefore at higher risk of radiographic progression. It is anticipated that 20-40% of patients included next will have radiographic evidences of syndesmophytes, even in absence of the syndesmophyte requirement in the changed study protocol. Therefore, more than 60% of the included patients in both arms are expected to have signs of radiographic damage in the spine. In these patients the difference between both treatment groups can be expected to be larger than in an unselected sample. Furthermore, our own findings and those of the OASIS cohort suggest an even higher radiographic progression rate in the on-demand group than those reported by Wanders et al in their unselected sample of AS patients. Therefore, we postulate that the treatment effect in the ENRADAS trial is at least as strong as the one seen in the trial by Wanders et al. and that we can, therefore, use the mean differences and their variances as they were reported by Wanders et al directly for the power calculations. In the original calculation we had assumed smaller differences between the treatment groups and larger variances.
- We now demand a power of 80%, which is regarded to be sufficient for this kind of study.

We assumed unequal variances in both groups and based the power calculation on Satterthwaite t-test. These new assumptions resulted in a sampler size per group of n=61 in the completer sample and by taking the dropout rate in a samples size of n=174.

Treatment

Patients were stratified according to the time period between radiographic examination and inclusion into the trial, resulting in the following groups: ≤3 months n=115, 4–6 months n=25, 7–9 months n=20, 10–12 months n=5 and 13–15 months n=2.

Using a block randomisation method, patients were randomised within these strata in a 1:1 ratio to treatment with diclofenac either continuously (at least 50% per day of the maximally recommended daily dose of 150 mg diclofenac) or on demand for a total period of 2 years, without a washout period for previous NSAID treatment. Each pill contained 75 mg of

diclofenac. Switching to another NSAID was allowed in case of intolerance or inefficacy. In switchers, equivalent dosages of NSAIDs were used.
The intervention group was treated continuously with diclofenac cholestyramine (Voltaren Resinat®) or any other NSAID in a daily dose of ≥50% of the maximal daily dose recommended by manufacturer together with a proton pump inhibitor (PPI) for gastroprotection for a period of 2 years. Diclofenac cholestyramine (Voltaren Resinat®) and PPI was provided as study drugs. Assuming that retardation of radiographic progression of AS is a class effect of NSAIDs, investigators will have the possibility to choose any NSAID for the patient treatment.
Diclofenac in the maximal daily dose of 150mg was taken as 2 tablets a 75mg of Voltaren resinat. Therefore, the minimal daily dose of diclofenac in the continuous arm of this study is 75 mg. A dose of 150mg diclofenac per day has been the usual dose in several clinical trials in AS [6], and in other studies such as the VIGOR study or the MEDAL study. Moreover, diclofenac is generally regarded as highly effective, and the 150mg dose has been approved in rheumatic diseases including AS. PPI in standard dose (Pantozol 20mg) was available for all patients and should be given to patients with an increased risk for gastrointestinal complications or in case of gastrointestinal symptoms.
In Germany, diclofenac-cholestyramine (Voltaren Resinat) is one of the most frequently prescribed drugs in AS, therefore, we propose diclofenac as study drug in this trial. Moreover, diclofenac-cholestyramine 150mg was as effective as celecoxib 400 mg per day over 3 months in a recent randomised trial of 450 AS patients conducted in Germany with 83% of patients being on either drug at the end of the trial.
Safety data on a daily dose of 150mg diclofenac in AS patients are available from this trial and, even more important, from the large MEDAL study. The European Medicines Agency (EMEA) has concluded in a recent press release (October 24, 2006) that the benefit-risk balance for non-selective NSAIDs remains favourable. This conclusion was drawn following a review announced in September 2006 of new thrombotic cardiovascular safety data. Novartis Pharma GmbH, Germany, is prepared to provide the medication (diclofenac-cholestyramine) for the proposed trial without having other obligations nor obtaining any rights.
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. Diclofenac cholestyramine (Voltaren Resinat®) and PPI was provided as study drugs. This is an open, randomised, controlled multi-centre clinical trial. A placebo-controlled study over a period of 2 years would not be ethical given that active AS patients with an indication for NSAID treatment are included, and NSAIDs on demand are currently considered standard therapy in AS.

Concomittant medication
The patients were asked for recent and current medications and treatments before screening. AS treatments and concomitant treatment were assessed throughout the entire trial.
During the study for the treatment of AS patients should only take study medication as defined in the study protocol. Medications for treatment of other diseases were allowed apart from those listed in the exclusion criteria and documented. Paracetamol and analgesics were allowed as rescue medication for the treatment of pain during the study. This type of medication if needed was prescribed by the treating physician.
Therapy with TNF blocking agents must be terminated within 4 weeks prior to screening. Previous treatment with any investigational agent must be terminated within 4 weeks prior to screening (or less than 5 terminal half-lives of elimination). Patients were excluded from the study if one of the following concomitant medications was required at screening or likely to be used during the study: lithium, warfarin, heparin, aspirin (any dose), non-study NSAID;

concomitant digoxin medication is allowed but serum drug levels should be monitored since diclofenac and other NSAIDs can increase blood levels of digoxin.

Statistical analysis

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. The intent-to-treat population comprises all study patients who have received at least one dose of study drug and who have available radiographs at baseline and after 2 years (end of study). 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. The smallest detectable change (SDC) in mSASSS scores for the two readers was calculated. In secondary analyses the proportion of patients with radiographic progression (change in mSASSS ≥ 1, and > SDC) will be compared between the groups by means of the chi-square test. Furthermore, analysis of covariance with baseline status as covariate and group as factor were applied to compare time-averaged values of global pain, patient global, BASDAI, BASFI, lateral spinal flexion, and tragus-to-wall distance. The corresponding analysis for skewed parameters (CRP) will be based on the non-parametric test for longitudinal data proposed by Brunner et al. (Brunner E, Langer F. Nichtparametrische Analyse longitudinaler Daten. Oldenburg Verlag, München Wien 1999, p.91-99). Fisher's exact test will be applied to compare event rates of serious and non-serious adverse events. Furthermore, Little's parametric dropout test and a non parametric dropout test developed more recently (see: Listing J, Schlittgen R: A nonparametric test for random dropout. Biometrical Journal 45 (2003) 113-127) will be used to compare the patient groups who have complete radiographs with the patients lost to follow up.

Efficacy analyses will be performed using the intention-to-treat (ITT) and the per protocol populations. In the safety analysis all patients receiving at least one dose of the study drug will be included.

Intent-to-treat population (ITT) includes all patients who have received at least one dose of study medication and in whom the primary outcome variable (mSASSS) was measured at baseline and after 2 years (complete dataset of the primary outcome variable).

Per protocol population includes all patients who complete the study without without major protocol violations. Not all protocol deviators and violators will be excluded from the per protocol population.

The safety population is defined to include all patients who received at least one dose of the trial medication and a safety follow-up, whether withdrawn prematurely or not.

Safety data will be analysed describing frequency and types of adverse events. All adverse events will be coded and tabulated by body system and preferred term for individual events within each body system, and will be presented in descending frequency. Adverse events will also be tabulated by severity and relationship to the study medication. Serious adverse events will be summarized separately.

4. Results

- *Initiation date, completion/suspension date, disposal of subjects and investigational devices,*
- *Subjects demographics, CIP compliance,*
- *Performance analysis provided for in the CIP,*
- *Summary of all adverse events and adverse device effects including of the severity, treatment needed, resolution, judgement concerning the causal relationship with investigational device or procedure,*
- *Table compiling all observed device deficiencies that could have led to a serious adverse device effect,*
- *Corrective actions taken during the investigation*
- *Subgroup analyses for special populations, as appropriate,*
- *Accountability of all subjects, description of how missing data or deviations were dealt with in the analysis, incl. subjects not passing screening tests, lost to follow-up, withdrawn or discontinued and the reason.*

Initiation Date: 22.08.2008

Completion Date: 31.12.2013

Subject demographics (Sieper et al, ARD 2017)

	Patients with complete sets of radiographs		**All patients**	
	Continuous (n=62)	**On demand (n=60)**	**Continuous (n=85)**	**On demand (n=82)**
Age, mean (SD)	40.7 (9.6)	45 (10.4)*	41.7 (10.4)	43.8 (10.8)
Males, n (%)	44 (71.0)	40 (66.7)	63 (74.1)	56 (68.3)
Disease duration in years, mean (SD)	12.8 (11.3)	17.0 (12.6)*	12.2 (10.3)	15.2 (12.4)
HLA-B27 positive, n (%)	55 (88.7)	55 (91.7)	71 (83.5)	68 (84)
BASDAI, mean (SD)	4.1 (1.5)	4.2 (1.5)	4.2 (1.6)	4.5 (1.6)
BASFI, mean (SD)	2.9 (2.1)	3.7 (2.2)*	3.1 (2.2)	3.9 (2.2)*
ASDAS (CRP), mean (SD)	2.7 (0.7)	2.8 (0.7)	2.7 (0.8)	2.9 (0.8)
CRP, mg/L, mean (SD)	7.8 (7.4)	12.5 (15.1)	8.4 (8.1)	12.9 (15.5)
CRP>5 mg/L, n (%)	33 (54.1)	35 (58.3)	46 (55.4)	47 (57.3)
BASMI, mean (SD)	2.1 (2.1)	3 (2.3)	2.2 (2.1)	2.7 (2.2)

	Patients with complete sets of radiographs		All patients	
	Continuous (n=62)	**On demand (n=60)**	**Continuous (n=85)**	**On demand (n=82)**
mSASSS, mean (SD)	10.9 (15.5)	16.4 (18.2)	11.3 (14.9)	14.0 (16.8)
Patients with syndesmophytes at baseline, n (%)	33 (53.2)	37 (61.7)	47 (55.3)	47 (57.3)
Current smoker, n (%)	36 (59)	20 (33.3)*	44 (52.4)	33 (40.2)
Previous smoker n (%)	14 (22.6)	20 (33.3)	19 (22.4)	23 (28.0)

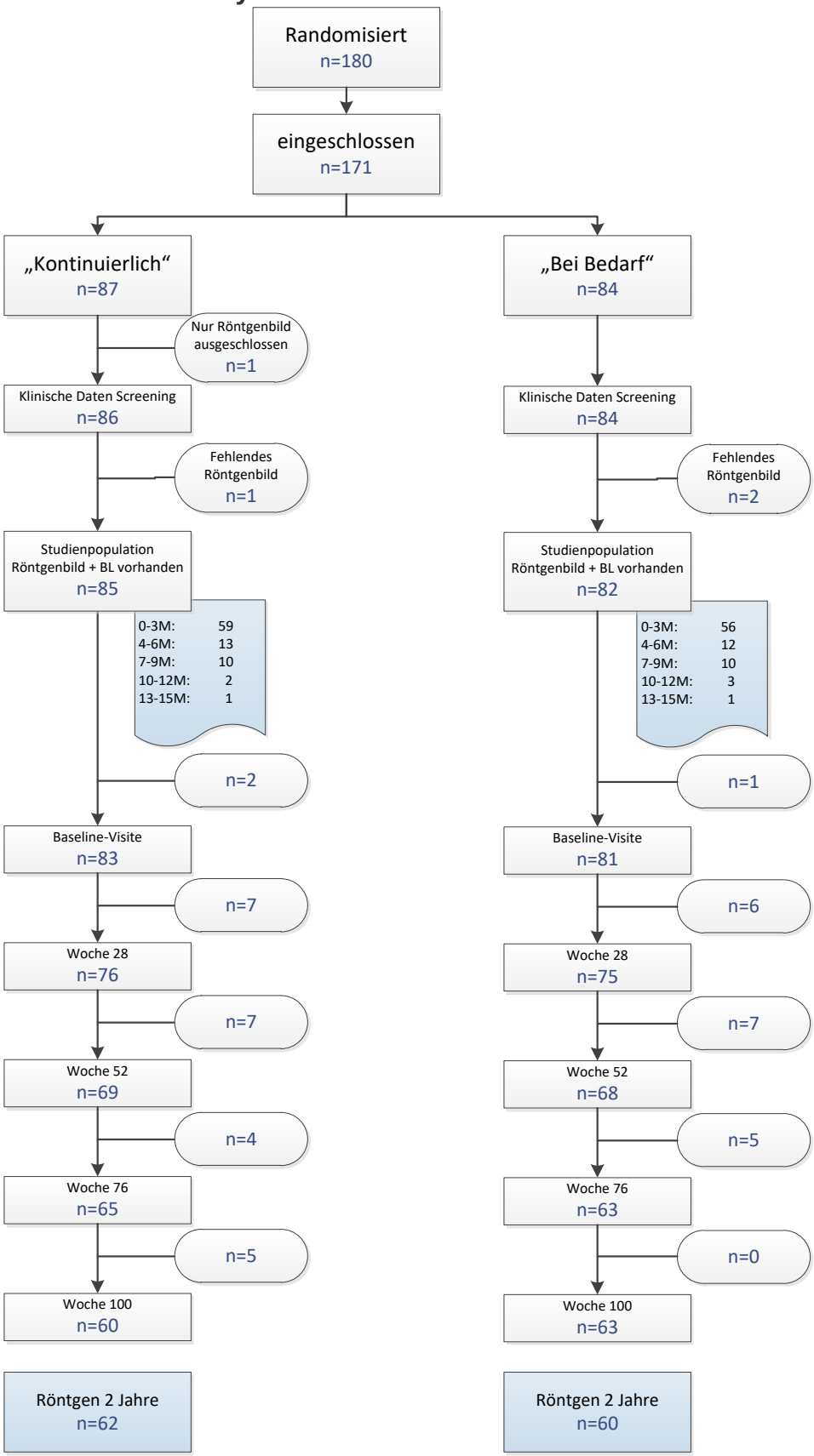
Values are means (SDs) if not otherwise specified. *Significant differences ($p<0.05$) between treatment groups. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; HLA, human leucocyte antigen; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

CIP Compliance

There were the following disrespects of the CIP which received an exceptional approval:

- 4 patients were simultaneously participating in a cohort study
- 1 patient took aspirine 100mg daily at inclusion
- 1 patient had the visits 6 and 7 each 2 weeks later than scheduled due to personal reasons

Performance Analysis



Included Patients per Centre

Centre, Screening				
Number of Center	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
1	45	26.95	45	26.95
3	6	3.59	51	30.54
7	9	5.39	60	35.93
8	2	1.20	62	37.13
9	5	2.99	67	40.12
10	16	9.58	83	49.70
11	15	8.98	98	58.68
13	1	0.60	99	59.28
18	5	2.99	104	62.28
27	1	0.60	105	62.87
30	4	2.40	109	65.27
31	14	8.38	123	73.65
34	3	1.80	126	75.45
36	23	13.77	149	89.22
38	1	0.60	150	89.82
39	1	0.60	151	90.42
40	5	2.99	156	93.41
42	8	4.79	164	98.20
45	3	1.80	167	100.00

Comparison of Baseline Data of Dropouts

group	Group	N	Label	N	Mean	Median	Std Dev
completer	Continous	60	mSASSS	60	**10.6**	3.25	15.5
			BASDAI, Screening	59	4.11	4.10	1.54
			BASFI, Screening	59	2.99	2.50	2.18
			BASMI, Screening	60	2.13	1.00	1.99
			pain, Screening	59	4.98	4.00	1.97
			BSG, Screening	59	19.0	16.0	14.0
			CRP in mg/l, Screening	59	7.65	6.00	7.49
	On demand	63	mSASSS	63	**15.9**	10.5	18.0
			BASDAI, Screening	63	**4.22**	4.30	1.47
			BASFI, Screening	63	3.74	3.20	2.14
			BASMI, Screening	63	2.90	3.00	2.26
			pain, Screening	63	5.14	5.00	1.52
			BSG, Screening	63	21.4	18.0	18.2
			CRP in mg/l, Screening	63	12.3	7.30	14.8
dropout	Continous	25	mSASSS	25	**12.8**	9.50	13.6
			BASDAI, Screening	25	4.34	4.20	1.89
			BASFI, Screening	25	3.45	3.20	2.15
			BASMI, Screening	22	2.45	1.50	2.48
			pain, Screening	25	5.84	6.00	2.15
			BSG, Screening	25	17.0	15.0	11.7
			CRP in mg/l, Screening	24	10.3	8.00	9.44
	On demand	19	mSASSS	19	**8.00**	2.00	10.3
			BASDAI, Screening	19	**5.35**	5.30	1.72
			BASFI, Screening	19	4.48	4.00	2.26
			BASMI, Screening	17	2.00	1.00	2.03
			pain, Screening	19	6.32	6.00	1.77
			BSG, Screening	19	18.5	14.0	18.7
			CRP in mg/l, Screening	19	14.8	6.00	18.0

Patients that terminated the study early and did not have Xrays after 2 years (dropouts) were compared to patients who completed the study (completer). Dropout patients in the “On Demand” group had higher BASDAI at baseline compared to completer in the on demand group (p=0.01). mSASSS at baseline was lower in patients on demand who dropped out compared to completers.

Follow-Up Data of Dropouts

Parameter	Completer	Dropouts	Difference Dropouts/Completer, p-Wert	Different Effect for Dropouts (Interaction Dropout*Group), p-Wert
BASDAI	3.15	3.66	0.040	0.55
BASFI	2.98	3.25	0.28	0.99
Pain	3.83	4.48	0.042	0.58
BSG	17.47	20.06	0.155	0.34
CRP	8.81	13.55	0.0003	0.52

Reasons for Dropout

Reason	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Not contactable	7	15.56	7	15.56
Worsening of AS	10	22.22	17	37.78
Concomittant disease	1	2.22	18	40.00
Not fulfilling of inclusion / exclusion criteria	2	4.44	20	44.44
Adverse events	11	24.44	31	68.89
Patient was no longer willing to participate	10	22.22	41	91.11
other	4	8.89	45	100.00

Imaging Data

Missing Values

mSASSS was only calculated if at least 16 spots were present. If data were missing at baseline on some levels, those were replaced by the values of the same scorer for the same level of Year 2. Same was done for missing data at baseline. If one level was missing at both time points, their value was replaced by 0.

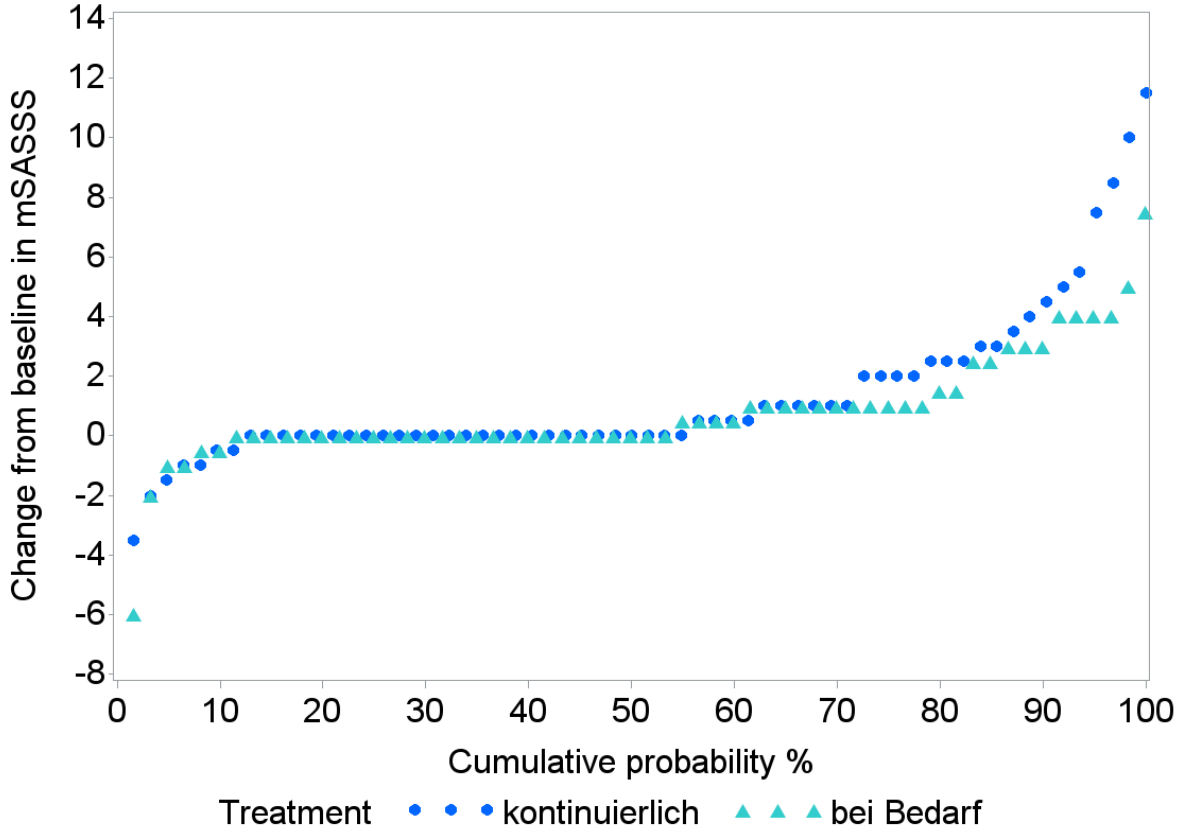
Completer Year 2

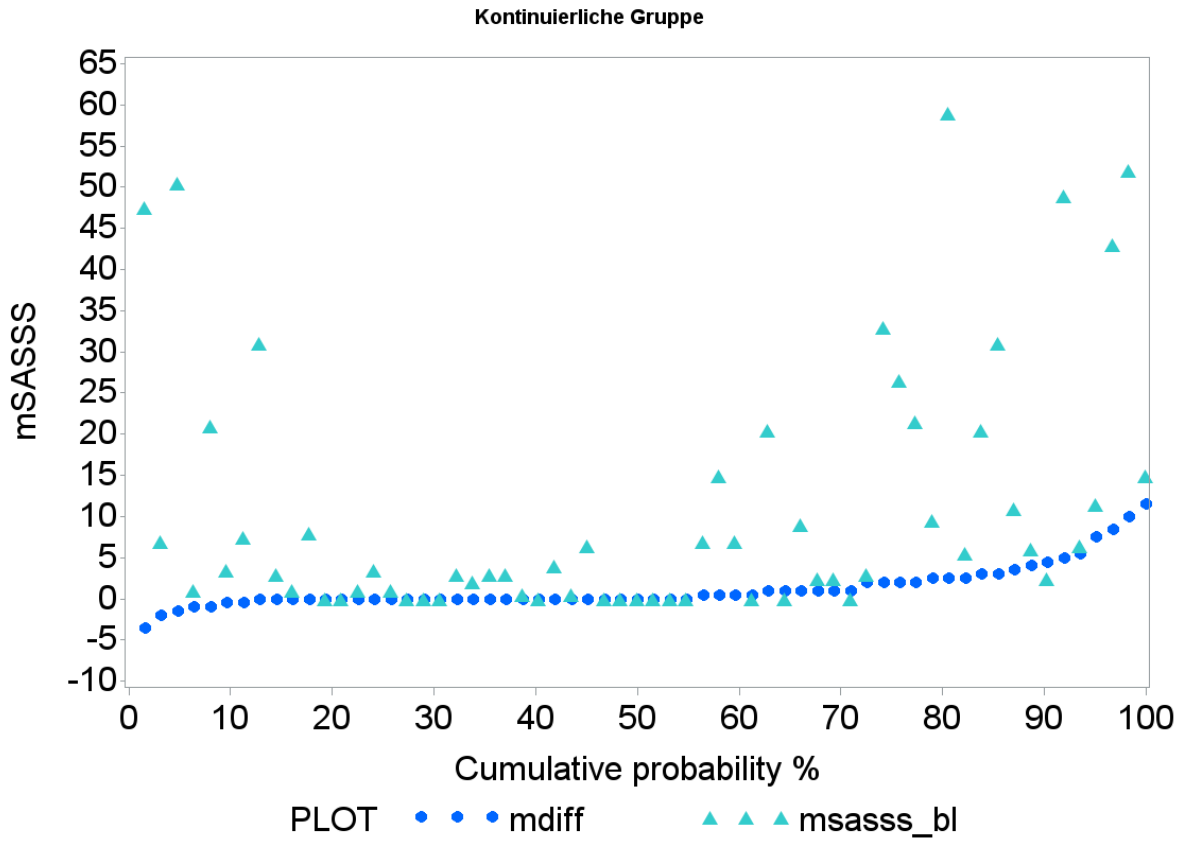
ICC was high for mSASSS: at baseline it was at 95.8%, at Year 2 at 94.7%. ICC for mSASSS difference and progression was at 50.1%. Smallest detectable change (SDC) score was 3.72 mSASSS points.

Group	N Obs	Variable	Label	N	Mean	Median	Std Dev	Minimum	Maximum
continuously	62	msasss_bl msasss_z2 mdiff	mSASSS-Progression	62 62 62	10.9 12.2 1.28	3.50 4.50 0	15.5 16.7 2.70	0 0 -3.5	59.0 62.0 11.5
on demand	60	msasss_bl msasss_z2 mdiff	mSASSS-Progression	60 60 60	16.4 17.2 0.79	10.8 11.8 0	18.2 18.6 1.87	0 0 -6.0	59.0 60.5 7.50

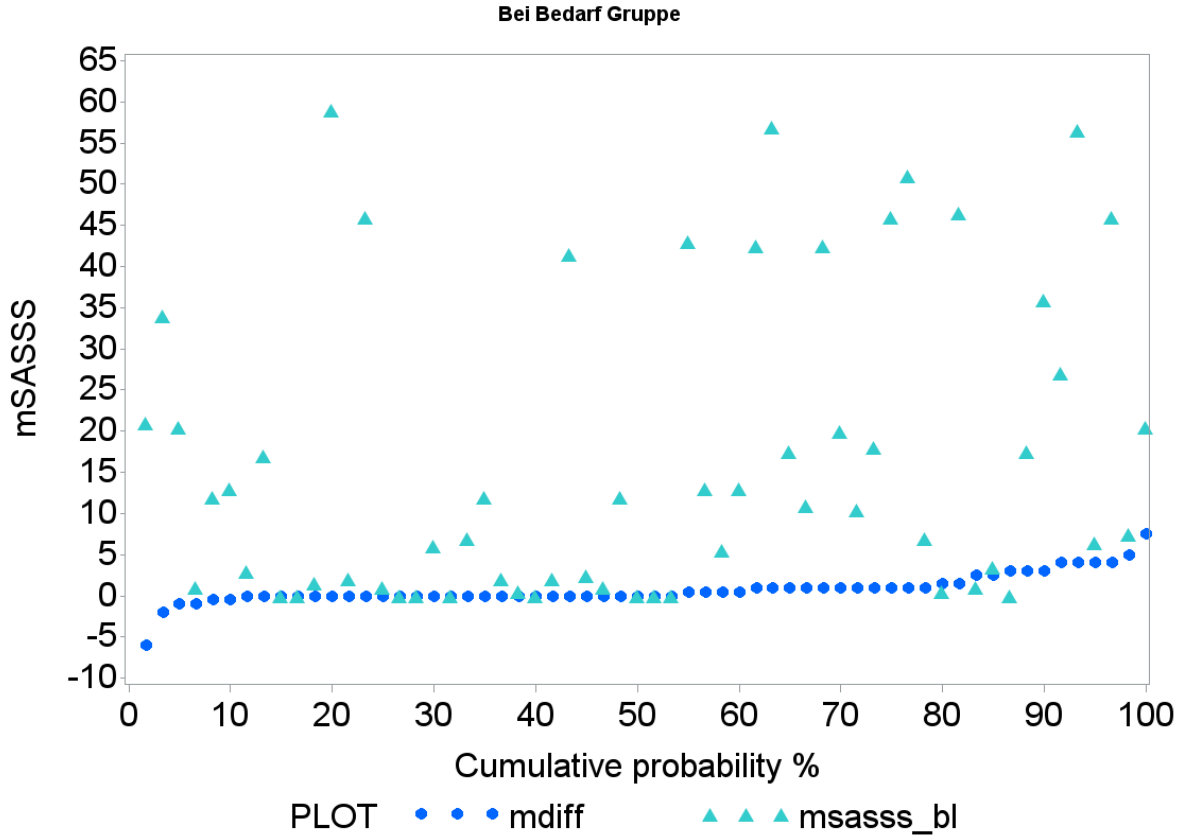
Mean mSASSS score at baseline and Year s (z2) are displayed in the table as well as their difference.

Cumulative-Probability-Plots radiographic progression of all Completer





Radiographic progression of patients of the continuously group



Radiographic progression of patients of the on demand group

Analysis of the imaging data ITT

Primary Outcome with GLM

All patients with mSASSS at baseline were included in the analyses oft he primary outcome of mSASSS progression between both treatment groups.

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
time	1	164	23.09	<.0001
group	1	164	0.95	0.3306
time*group	1	164	1.99	0.1601

The difference in progression between both groups was measured in this model via the term time*group. The different mSASSS levels at baseline were taken into account. A significant effect of time, but not a significant different progression between both groups was seen. Baseline is depicted as time 0, whereas Year 2 is time 1.

Least Squares Means										
Effect	**time**	**Group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
time*group	0	on demand	14.0247	1.7707	164	7.92	<.0001	0.05	10.5283	17.5211
time*group	0	continuously	11.2647	1.7286	164	6.52	<.0001	0.05	7.8516	14.6778
time*group	1	on demand	14.7311	1.8571	164	7.93	<.0001	0.05	11.0642	18.3980
time*group	1	continuously	12.5585	1.8132	164	6.93	<.0001	0.05	8.9782	16.1388
time	0		12.6447	1.2373	164	10.22	<.0001	.	.	.
time	1		13.6448	1.2977	164	10.51	<.0001	.	.	.

Least-Squares Means of mSASSS (Estimate) and its 95% CI

Effect	**time**	**Group**	**_time**	**Group**	**Estimate**	**Standard Error**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
time*group	0	on demand	0	continuously	2.7600	2.4746	0.2663	0.05	-2.1261	7.6461
time*group	0	on demand	1	on demand	**-0.7064**	0.2968	0.0185	0.05	-1.2924	-0.1203
time*group	0	on demand	1	continuously	1.4662	2.5344	0.5637	0.05	-3.5381	6.4705
time*group	0	continuously	1	on demand	-3.4664	2.5371	0.1737	0.05	-8.4759	1.5432
time*group	0	continuously	1	continuously	**-1.2938**	0.2919	<.0001	0.05	-1.8701	-0.7175
time*group	1	on demand	1	continuously	2.1726	2.5955	0.4038	0.05	-2.9523	7.2975

Differences of Least-Squares Means

mSASSS values in the continuously treated group increased about 1.3 points, and about 0.71 points in the on-demand group. This difference was not significant.

A sensitivity analysis was performed to evaluate whether risk factors for radiographic progression would influence this result.

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
time	1	162	0.47	0.4934
group	1	162	0.90	0.3443
time*group	1	162	2.34	0.1277
lgcrp*time	2	162	3.17	0.0448
sex	1	162	7.83	0.0058
HLA-B27	1	162	3.92	0.0495

Mixed linear Model comparing radiographic progression over time and the influence of sex, HLA-B27 and logCRP/time.

Sex and HLA-B27 positivity influence mSASSS at baseline. logCRP influences the evolution of mSASSS score over time significantly (p=0.045). However, the result of the primary outcome is not changed by taking into account the above mentioned covariates.

Least Squares Means											
Effect	time	Geschlecht, Screening	HLA-B27, Screening	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
gesch_01		male		13.0590	1.7846	162	7.32	<.0001	0.05	9.5348	16.5831
gesch_01		female		5.8593	2.4365	162	2.40	0.0173	0.05	1.0480	10.6706
b27_01			positiv	12.6103	1.4265	162	8.84	<.0001	0.05	9.7933	15.4274
b27_01			negativ	6.3079	2.9743	162	2.12	0.0355	0.05	0.4345	12.1813

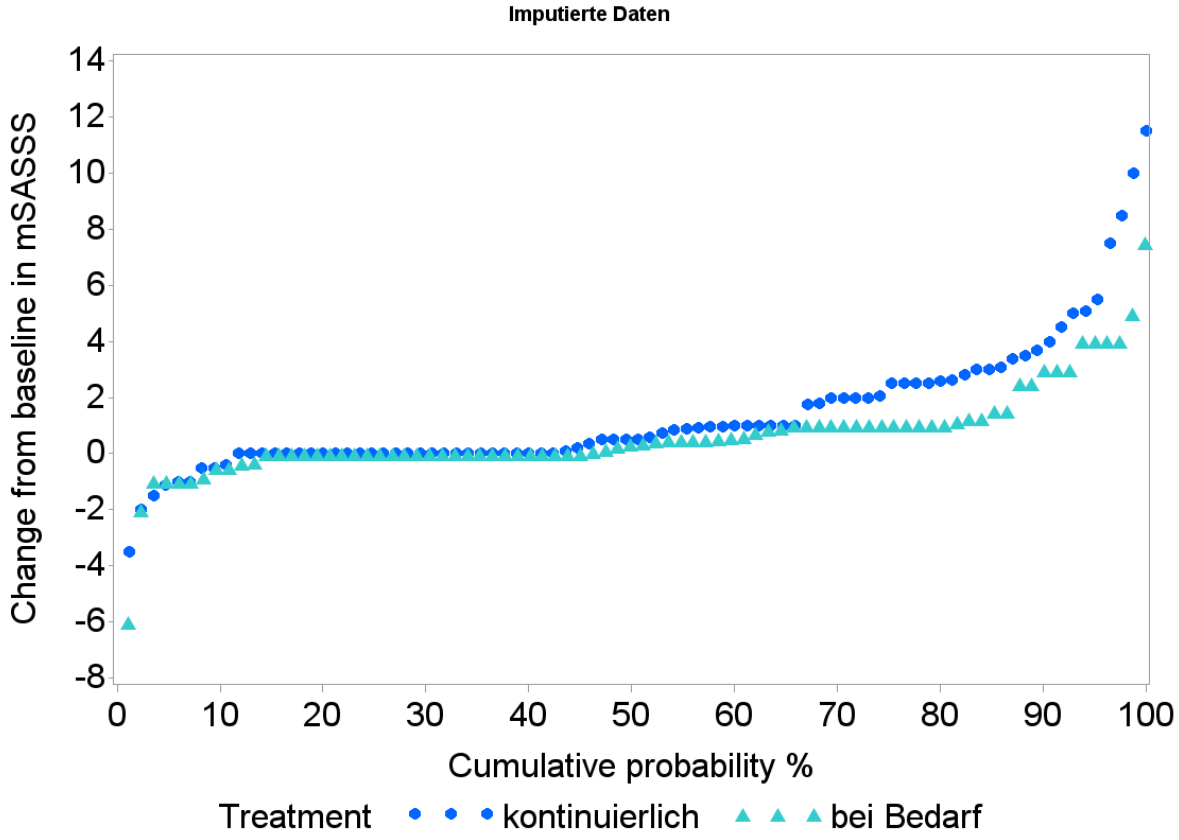
Effect	time	Group	_time	Group	Estimate	Standard Error	DF	Pr > |t|	Alpha	Lower	Upper
time*group	0	on demand	0	continuously	2.6350	2.3920	162	0.2723	0.05	-2.0886	7.3585
time*group	0	on demand	1	on demand	**-0.6932**	0.2970	162	0.0208	0.05	-1.2797	-0.1068
time*group	0	on demand	1	continuously	1.3011	2.4484	162	0.5959	0.05	-3.5338	6.1360
time*group	0	continuously	1	on demand	-3.3282	2.4505	162	0.1763	0.05	-8.1672	1.5109
time*group	0	continuously	1	continuously	**-1.3339**	0.2928	162	<.0001	0.05	-1.9120	-0.7557
time*group	1	on demand	1	continuously	1.9943	2.5058	162	0.4273	0.05	-2.9539	6.9425

Also when adjusting for sex, HLA-B27 positivity and log CRP, the difference between both treatment groups was not significantly.

Analysis with imputation of missing data

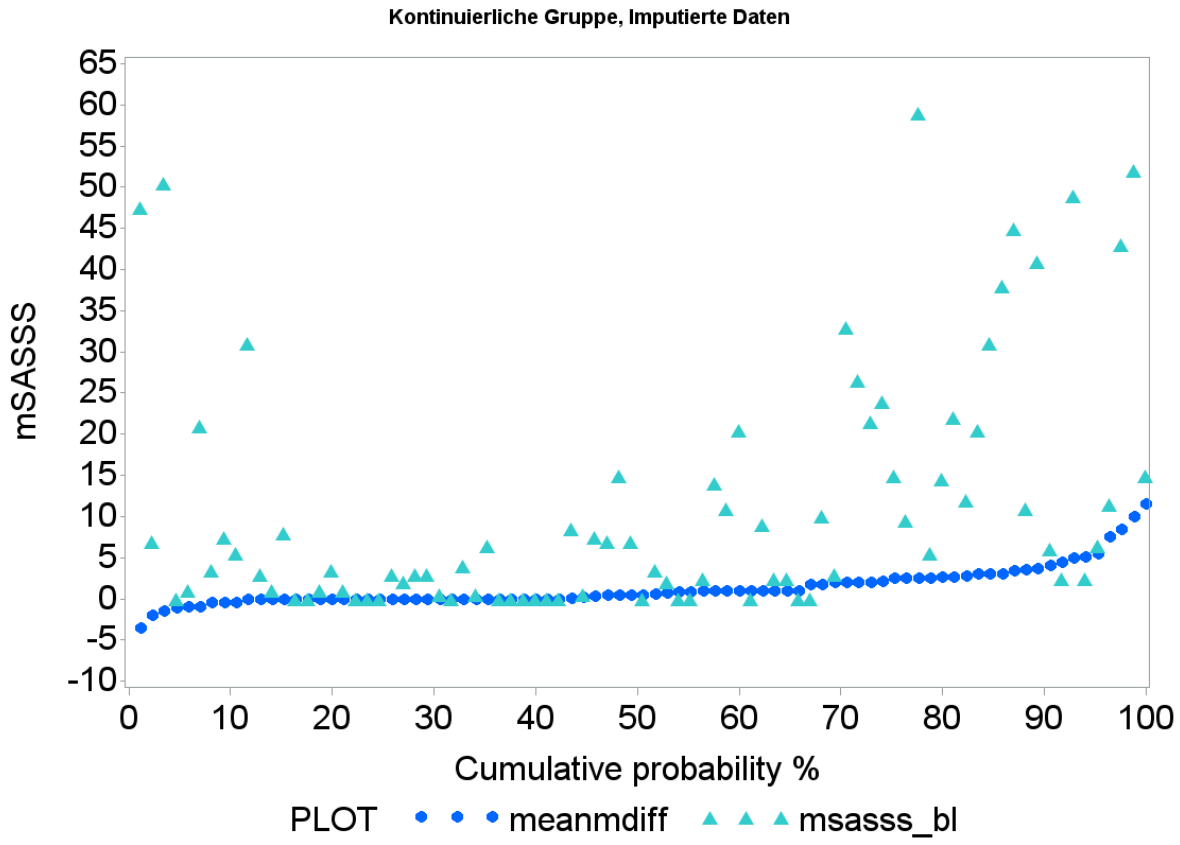
Additional analyses were done, were for all patients with missing Xray at year 2 the missing mSASSS value was imputed 10times. For the imputation mSASSS at baseline, the date of the Xray at baseline, CRP value at baseline were taken into account. Imputation was done per group. Thereby, graphical visualization via probability plots becomes applicable.

Figures

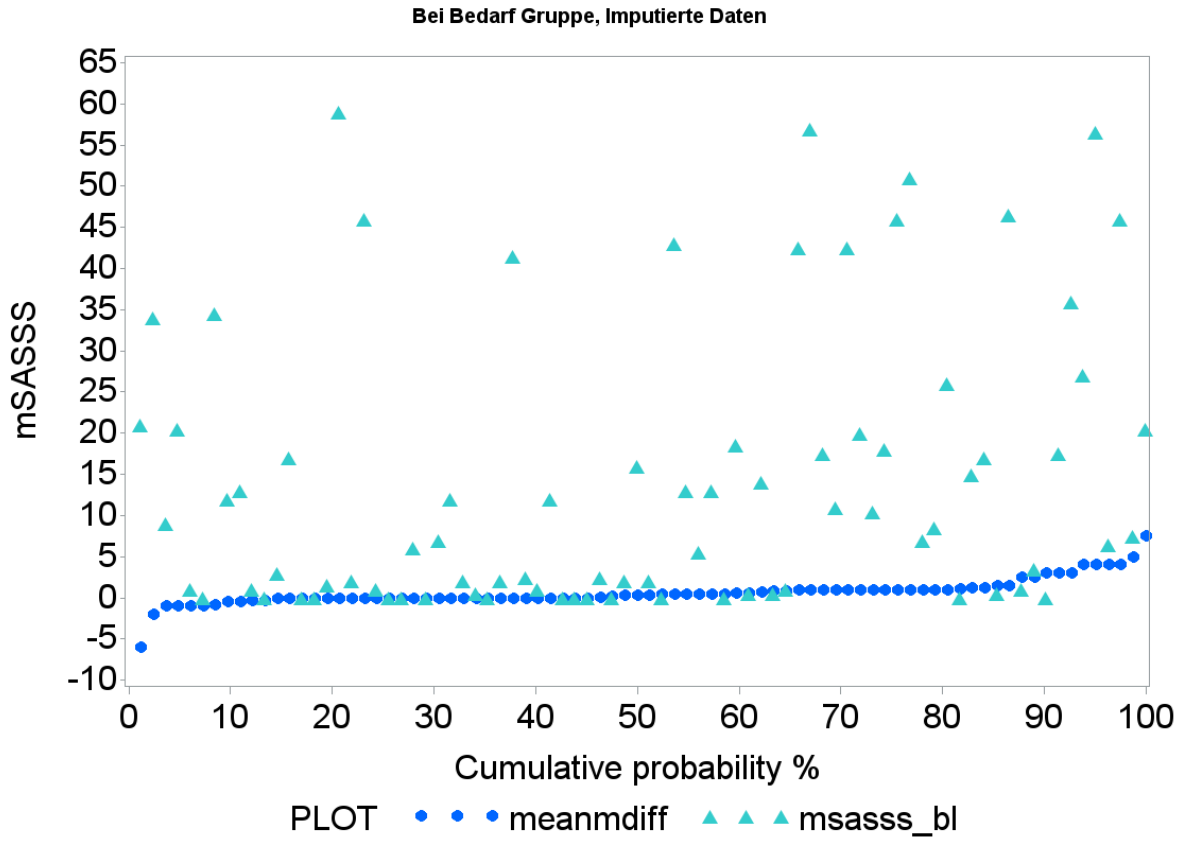


Probability plot of all patients ITT Population

Results of the ITT population do not differ from the completer analysis. There remains a non significant difference.



Continuously treated patients



On-demand Group

Age of Xrays

A further sensitivity analyses was performed with an covariant-analytical analyses (basis imputed data). Radiographic progression was supposed to by influenced by mSASSS at baseline, the time since the Xrays at baseline and CRP value. We hypothesized that progression is non-linearly dependent from baseline value, which is why we took mSASSS-BL².

Modell: mdiff= age_xray group msasss_bl crp_01 msasss_bl2

Parameter	group	age_xray	Estimate	Std Error	95% Confidence Limits		Minimum	Maximum	Pr > |t|
age_xray	.	0-3Mon	0.106826	0.402754	-0.68449	0.898144	-0.080065	0.393849	0.7909
age_xray	.	4-6Mon	0.947821	0.614521	-0.26546	2.161105	0.576152	1.409103	0.1249
age_xray	.	7-9Mon	0.400557	0.734750	-1.04963	1.850742	-0.098168	0.841717	0.5863
age_xray	.	10-15Mon	-0.090127	1.024064	-2.11111	1.930852	-0.791759	0.861072	0.9300
group	continuously	.	0.596113	0.423430	-0.24432	1.436543	0.314274	0.930126	0.1624
group	on demand	.	0	0	.	.	0	0	.
msasss_bl	.	.	0.049323	0.043241	-0.03630	0.134946	0.008420	0.087814	0.2563
crp_01	.	.	0.001634	0.015698	-0.02926	0.032524	-0.007940	0.010257	0.9172
msasss_bl2	.	.	-0.000400	0.000836	-0.00205	0.001250	-0.001090	0.000267	0.6330

Also this analysis shows a higher progression in the continuously treated group (difference of 0.6 mSASSS points) with a non-significant difference (p=0.16).
Patients where Xray were performed at 4-6 or 7-9 months before baseline showed higher mSASSS progression than those with recent Xrays within 3 months before baseline (0.85 and 0.30, respectively).

The same analyses was therefore performed for patients only with recent Xray: the difference in the progression was smaller (0.15 points) and still not significant.

Modell: mdiff= group msasss_bl crp_01 msasss_bl2

Parameter	group	Estimate	Std Error	95% Confidence Limits		DF	Minimum	Maximum	Pr > |t|
group	continuously	0.313432	0.399841	-0.48225	1.109117	80.149	-0.016043	0.660471	0.4354
group	on demand	0.155453	0.415391	-0.66351	0.974421	205.76	-0.029408	0.603638	0.7086
msasss_bl	.	0.075136	0.044995	-0.01408	0.164350	105.19	0.038925	0.119260	0.0979
crp_01	.	0.016017	0.017810	-0.01927	0.051306	111.53	0.004993	0.029111	0.3704
msasss_bl2	.	-0.001100	0.000875	-0.00283	0.000632	120.19	-0.001860	-0.000435	0.2110

Subgroup-Analyses

CRP-positive patients

Table of highcrp_01 by group			
highcrp_01(CRP>5mg/l, Screening)	group(Group)		
Frequency Col Pct	continuously	on demand	Total
0	28 45.90	25 41.67	53
➢ 5mg/L	33 54.10	35 58.33	68
Total	61 50.41	60 49.59	121 100.00
Frequency Missing = 1			

Patients with CRP > 5mg/L at Baseline

Sensitivity analyses were performed for patients with elevated CRP at baseline:

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
time	1	90	14.57	0.0002
group	1	90	0.25	0.6180
time*group	1	90	1.64	0.2039

Differences of Least Squares Means												
Effect	time	Group	_time	Group	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
time*group	0	on demand	0	continuously	2.2935	3.6481	90	0.63	0.5312	0.05	-4.9541	9.5410
time*group	0	on demand	1	on demand	**-0.8357**	0.4592	90	-1.82	0.0721	0.05	-1.7479	0.07653
time*group	0	on demand	1	continuously	0.6151	3.7559	90	0.16	0.8703	0.05	-6.8466	8.0768
time*group	0	continuously	1	on demand	-3.1292	3.7543	90	-0.83	0.4068	0.05	-10.5877	4.3294
time*group	0	continuously	1	continuously	**-1.6784**	0.4721	90	-3.56	0.0006	0.05	-2.6163	-0.7405
time*group	1	on demand	1	continuously	1.4508	3.8591	90	0.38	0.7079	0.05	-6.2160	9.1175

Least squares means

mSASSS-Progression was 0.83 in the on demand-group versus 1.68 in continuously treated patients, however, the difference was not significant (p=0.20).

Patients with syndesmophytes at baseline

Table of syndbl by group			
syndbl	**group(Group)**		
Frequency Col Pct	**continuously**	**on demand**	**Total**
0	38 44.71	35 42.68	73
1	47 55.29	47 57.32	94
Total	85 50.90	82 49.10	167 100.00

For the following analysis only patients with syndesmophytes at baseline were taken into account.

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
time	1	91	20.28	<.0001
group	1	91	1.42	0.2368
time*group	1	91	3.29	0.0730

A statistical trend was shown for a different progression between both groups (p=0.073).

Differences of Least Squares Means												
Effect	**time**	**Group**	**_time**	**Group**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
time*group	0	on demand	0	continuously	4.7014	3.3806	91	1.39	0.1677	0.05	-2.0138	11.4167
time*group	0	on demand	1	on demand	**-0.8947**	0.4571	91	-1.96	0.0534	0.05	-1.8026	0.01319
time*group	0	on demand	1	continuously	2.6000	3.4588	91	0.75	0.4542	0.05	-4.2705	9.4705
time*group	0	continuously	1	on demand	-5.5962	3.4562	91	-1.62	0.1089	0.05	-12.4614	1.2691
time*group	0	continuously	1	continuously	**-2.1014**	0.4834	91	-4.35	<.0001	0.05	-3.0616	-1.1413
time*group	1	on demand	1	continuously	3.4947	3.5327	91	0.99	0.3252	0.05	-3.5225	10.5119

mSASSS-Progression was 0.89 in on demand-group and 2.10 in continuously treated patients, there was again no significant difference (p=0.07).

Analysis without outliers

Analyses by NSAID Index

A) Difference between patients with NSAID index of <50 and ≥50:
NSAID index was present for 159 patients. 94 patients had an index of ≥50 and 65 patients an index of <50.

Baseline Variables and Radiographic Progression of Completers stratified by NSAID index

nsaid-Index ≥ 50	N Obs	Variable	Label	N	Mean	Median	Minimum	Maximum
0	65	basdai_01	BASDAI, Screening	64	4.35	4.25	1.30	8.10
		basfi_01	BASFI, Screening	64	3.59	3.10	0	8.60
		age_01	Age, Screening	65	41.8	41.0	22.0	66.0
		msasss_bl		65	12.9	7.00	0	59.0
		mdiff	mSASSS-Progression	49	**0.72**	0	-6.0	7.50
1	94	basdai_01	BASDAI, Screening	94	4.29	4.30	0.40	8.30
		basfi_01	BASFI, Screening	94	3.49	3.20	0.10	9.20
		age_01	Age, Screening	94	42.9	43.0	21.0	71.0
		msasss_bl		94	12.4	4.75	0	59.0
		mdiff	mSASSS-Progression	71	**1.27**	0	-3.5	11.5

Baseline BASDAI, BASFI, age and mSASSS are comparable between NSAID groups. However, mSASSS at baseline is higher in patients with an NSAID index above 50.

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
time	1	156	19.81	<.0001
nsaid50	1	156	0.01	0.9199
time*nsaid50	1	156	1.53	0.2178

NSAID index did not show any significant influence on radiographic progression over the 2 years.

Least Squares Means										
Effect	time	nsaid ≥ 50	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
time*nsaid50	0	1	12.3280	1.6682	156	7.39	<.0001	0.05	9.0328	15.6231
time*nsaid50	0	0	12.8615	1.9954	156	6.45	<.0001	0.05	8.9200	16.8030
time*nsaid50	1	1	13.5529	1.7436	156	7.77	<.0001	0.05	10.1089	16.9970
time*nsaid50	1	0	13.5536	2.0859	156	6.50	<.0001	0.05	9.4334	17.6738

Differences of Least Squares Means												
Effect	time	nsaid50	_time	_nsaid50	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
time*nsaid50	0	1	0	0	-0.5336	2.6009	156	-0.21	0.8377	0.05	-5.6710	4.6039
time*nsaid50	0	1	1	1	**-1.2250**	0.2752	156	-4.45	<.0001	0.05	-1.7686	-0.6813
time*nsaid50	0	1	1	0	-1.2256	2.6709	156	-0.46	0.6470	0.05	-6.5014	4.0502
time*nsaid50	0	0	1	1	-0.6914	2.6498	156	-0.26	0.7945	0.05	-5.9256	4.5428

Differences of Least Squares Means												
Effect	time	nsaid50	_time	_nsaid50	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
time*nsaid50	0	0	1	0	**-0.6920**	0.3312	156	-2.09	0.0383	0.05	-1.3463	-0.03777
time*nsaid50	1	1	1	0	-0.00065	2.7186	156	-0.00	0.9998	0.05	-5.3707	5.3694

Progression in patients with high NSAID index is 1.22 compared to 0.692 (not significant).

B) Difference between NSAID index of <75 and ≥75:

Baseline Variables and Radiographic Progression of Completers stratified by NSAID index

nsaid75	N Obs	Variable	Label	N	Mean	Median	Minimum	Maximum
0	106	basdai_01	BASDAI, Screening	105	4.31	4.20	1.20	8.30
		basfi_01	BASFI, Screening	105	3.64	3.20	0	8.60
		age_01	Age, Screening	106	42.9	43.0	22.0	66.0
		msasss_bl		106	12.9	6.75	0	59.0
		mdiff	mSASSS-Progression	79	0.97	0	-6.0	10.0
1	53	basdai_01	BASDAI, Screening	53	4.32	4.50	0.40	7.70
		basfi_01	BASFI, Screening	53	3.32	3.10	0.20	9.20
		age_01	Age, Screening	53	41.7	42.0	21.0	71.0
		msasss_bl		53	12.0	5.50	0	59.0
		mdiff	mSASSS-Progression	41	1.20	0	-3.5	11.5

At baseline, patients with lower NSAID index have higher mSASSS values.

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
time	1	156	21.48	<.0001
nsaid75	1	156	0.08	0.7756
time*nsaid75	1	156	0.22	0.6378

NSAID index had no influence on radiographic progression.

Least Squares Means										
Effect	time	nsaid index ≥ 75	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
time*nsaid75	0	1	11.9528	2.2093	156	5.41	<.0001	0.05	7.5889	16.3168
time*nsaid75	0	0	12.8476	1.5696	156	8.19	<.0001	0.05	9.7472	15.9481
time*nsaid75	1	1	13.0993	2.3093	156	5.67	<.0001	0.05	8.5377	17.6609
time*nsaid75	1	0	13.7823	1.6413	156	8.40	<.0001	0.05	10.5404	17.0243

Mean mSASSS score stratified by NSAID index

Differences of Least Squares Means												
Effect	time	nsaid75	_time	_nsaid75	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
time*nsaid75	0	1	0	0	-0.8948	2.7101	156	-0.33	0.7417	0.05	-6.2480	4.4584
time*nsaid75	0	1	1	1	**-1.1465**	0.3644	156	-3.15	0.0020	0.05	-1.8663	-0.4268
time*nsaid75	0	1	1	0	-1.8295	2.7522	156	-0.66	0.5072	0.05	-7.2659	3.6069
time*nsaid75	0	0	1	1	-0.2517	2.7923	156	-0.09	0.9283	0.05	-5.7672	5.2638
time*nsaid75	0	0	1	0	**-0.9347**	0.2624	156	-3.56	0.0005	0.05	-1.4529	-0.4165
time*nsaid75	1	1	1	0	-0.6830	2.8331	156	-0.24	0.8098	0.05	-6.2793	4.9133

Analyse stratified by syndesmophytes at baseline for all patients

Synd. at BL per patient	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0 Synd BL	73	43.71	73	43.71
1-4 Synd BL	47	28.14	120	71.86
>4 Synd BL	47	28.14	167	100.00

Analysis Variable : mdiff mSASSS-Progression							
sumsyndbl	N Obs	N	Mean	Median	Minimum	Maximum	Std Dev
0 Synd BL	73	52	0.43	0	-1.0	5.50	1.17
1-4 Synd BL	47	36	1.29	0.50	-2.0	11.5	2.55
>4 Synd BL	47	34	1.71	1.00	-6.0	10.0	3.13

mSASSS progression stratified by syndesmophytes at baseline

mSASSS progression is highest in the group of patients with more than 4 syndesmophytes at baseline.

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
time	1	163	27.56	<.0001
sumsyndbl	2	163	237.96	<.0001
time*sumsyndbl	2	163	2.99	0.0530

Syndesmophytes at baseline do not significantly influence radiographic progression (p=0.053).

Least Squares Means										
Effect	time	sumsyndbl	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
time*sumsyndbl	0	>4 Synd BL	33.9362	1.1671	163	29.08	<.0001	0.05	31.6317	36.2407
time*sumsyndbl	0	1-4 Synd BL	8.9783	1.1797	163	7.61	<.0001	0.05	6.6489	11.3077
time*sumsyndbl	0	0 Synd BL	1.1712	0.9364	163	1.25	0.2128	0.05	-0.6779	3.0203
time*sumsyndbl	1	>4 Synd BL	35.4823	1.2721	163	27.89	<.0001	0.05	32.9704	37.9942
time*sumsyndbl	1	1-4 Synd BL	10.3077	1.2846	163	8.02	<.0001	0.05	7.7711	12.8442
time*sumsyndbl	1	0 Synd BL	1.6023	1.0228	163	1.57	0.1191	0.05	-0.4173	3.6220

Patients with and without syndesmophytes ate baseline

Syndesm. at BL	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	73	43.71	73	43.71
1	94	56.29	167	100.00

94 patients had syndesmophytes at baseline.

mSASSS-Progression for completer:

Analysis Variable : mdiff mSASSS-Progression							
Syndesm. at BL	N Obs	N	Mean	Median	Minimum	Maximum	Std Dev
0	73	52	0.43	0	-1.0	5.50	1.17
1	94	70	1.49	1.00	-6.0	11.5	2.83

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
time	1	164	20.80	<.0001
syndbl	1	164	114.17	<.0001
time*syndbl	1	164	6.17	0.0140

Patients with syndesmophytes at baseline have higher radiographic progression after 2 years (significant difference of 1.03 mSASSS points).

Least Squares Means										
Effect	time	syndbl	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
time*syndbl	0	1	21.5914	1.2781	164	16.89	<.0001	0.05	19.0677	24.1151
time*syndbl	0	0	1.1712	1.4426	164	0.81	0.4180	0.05	-1.6772	4.0197
time*syndbl	1	1	23.0566	1.3338	164	17.29	<.0001	0.05	20.4230	25.6903
time*syndbl	1	0	1.6030	1.5072	164	1.06	0.2891	0.05	-1.3730	4.5791

Comparison of CRP +/- patients

Patients with CRP levels above 5mg/l at baseline are regarded as CRP positive and compared to patients with normal CRP values.

CRP>5mg/l, Screening				
highcrp_01	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	72	43.11	72	43.11
1	95	56.89	167	100.00

Analysis Variable : mdiff mSASSS-Progression							
CRP>5mg/l, Screening	N Obs	N	Mean	Median	Minimum	Maximum	Std Dev
0	72	53	0.70	0	-3.5	5.50	1.62
1	95	69	1.30	0	-6.0	11.5	2.74

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
time	1	164	21.46	<.0001
highcrp_01	1	164	5.56	0.0195
time*highcrp_01	1	164	1.81	0.1800

Least Squares Means										
Effect	time	CRP>5mg/l, Screening	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
time*highcrp_01	0	1	15.0585	1.6243	164	9.27	<.0001	0.05	11.8513	18.2657
time*highcrp_01	0	0	9.4167	1.8559	164	5.07	<.0001	0.05	5.7521	13.0812
time*highcrp_01	1	1	16.3143	1.6955	164	9.62	<.0001	0.05	12.9664	19.6622
time*highcrp_01	1	0	10.1068	1.9373	164	5.22	<.0001	0.05	6.2816	13.9320

CRP positive patients show a higher progression compared to CRP negative patients, but differences are not significant (p=0.18).

Comparison of Smoking / Non smoking patients

Table of smoking_qual by group			
smoking_qual	**group(Group)**		
Frequency Row Pct Col Pct	**continuously**	**on demand**	**Total**
Non-smoking	20 23.53	25 30.49	45
Former smoking	19 22.35	24 29.27	43
Current smoking	46 54.12	33 40.24	79
Total	85 50.90	82 49.10	167 100.00

Analysis Variable : mdiff mSASSS-Progression							
smoking_qual	**N Obs**	**N**	**Mean**	**Median**	**Minimum**	**Maximum**	**Std Dev**
Non-smoking	45	31	0.63	0	-3.5	4.50	1.65
Former smoking	43	33	1.09	0	-1.0	5.50	1.66
Current smoking	79	58	1.23	0	-6.0	11.5	2.90

Mean mSASS progression

There was no significant difference in mSASSS progression between smoking and non-smoking patients.

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
time	1	163	19.11	<.0001
smoking_qual	2	163	0.59	0.5547
time*smoking_qual	2	163	0.72	0.4860

Least Squares Means										
Effect	**time**	**smoking_qual**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
time*smoking_qual	0	aktuell Raucher	11.5833	1.8100	163	6.40	<.0001	0.05	8.0092	15.1575
time*smoking_qual	0	Nichtraucher	12.2111	2.3830	163	5.12	<.0001	0.05	7.5055	16.9167
time*smoking_qual	0	früher geraucht	14.8953	2.4378	163	6.11	<.0001	0.05	10.0816	19.7091
time*smoking_qual	1	aktuell Raucher	12.7841	1.8934	163	6.75	<.0001	0.05	9.0454	16.5228
time*smoking_qual	1	Nichtraucher	12.7992	2.4952	163	5.13	<.0001	0.05	7.8721	17.7262
time*smoking_qual	1	früher geraucht	15.9603	2.5491	163	6.26	<.0001	0.05	10.9268	20.9937

Analysis with agenative method used for imputation of missing Xrays

For this analyses, the four most frequently missing places form SASSS scoring (hwk6_2, hwk7_1, hwk7_2, bwk1_1) were replaced by multiple imputation (10x).

Imputation as described above

Group	N Obs	Variable	Label	N	Mean	Median	Std Dev	Minimum	Maximum
continuously	62	msasss_bl msasss_z2 mdiff	 mSASSS-Progression	62 62 62	10.9 12.2 1.28	3.50 4.50 0	15.5 16.7 2.70	0 0 -3.5	59.0 62.0 11.5
on demand	60	msasss_bl msasss_z2 mdiff	 mSASSS-Progression	60 60 60	16.4 17.2 0.79	10.8 11.8 0	18.2 18.6 1.87	0 0 -6.0	59.0 60.5 7.50

Multiple imputation

Group	N Obs	Variable	Label	N	Mean	Median	Std Dev	Minimum	Maximum
continuously	62	msasss_bl msasss_z2 mdiff	 mSASSS-Progression	62 62 62	11.5 12.6 1.13	4.00 5.00 0	16.2 16.7 3.30	0 0 -9.0	59.0 62.0 13.5
on demand	60	msasss_bl msasss_z2 mdiff	 mSASSS-Progression	60 60 60	17.9 18.3 0.41	11.0 12.5 0	19.9 19.7 2.74	0 0 -11	61.5 62.5 9.50

When using the agenative method for imputation of missing data, mSASSS progression in the on demand group becomes smaller (0.79 vs. 0.41), whereas the continuously treated group does not change meaningful (1.28 vs 1.13). However, also when analyzing the 167 patients with imputed data by the agenative method, radiographic progression is not different between both treatment groups (p=0.88).

Clinicial Data at Follow-Up

As BASFI levels differ between the treatment groups at baseline, analyses of clincial data will be adjusted for baseline data.

BASDAI

Obs	Label	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	continuously vs on demand	-0.3440	0.2062	160	-1.67	0.0972	0.05	-0.7512	0.06319

Difference of BASDAI between treatment groups

Obs	Effect	group	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	group	on demand	3.4432	0.1461	160	23.57	<.0001	0.05	3.1548	3.7317
2	group	continuously	3.0992	0.1450	160	21.37	<.0001	0.05	2.8128	3.3856

BASFI

Obs	Label	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	continuously vs on demand	-0.1493	0.2098	160	-0.71	0.4778	0.05	-0.5636	0.2651

Obs	Effect	group	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	group	on demand	3.1166	0.1480	160	21.06	<.0001	0.05	2.8244	3.4088
2	group	continuously	2.9673	0.1465	160	20.25	<.0001	0.05	2.6779	3.2567

BASMI

Obs	Label	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	continuously vs on demand	-0.08975	0.1809	157	-0.50	0.6205	0.05	-0.4471	0.2676

Obs	Effect	group	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	group	on demand	2.4189	0.1281	157	18.88	<.0001	0.05	2.1659	2.6720
2	group	continuously	2.3292	0.1269	157	18.36	<.0001	0.05	2.0786	2.5798

Pain

Obs	Label	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	continuously vs on demand	-0.5380	0.2566	160	-2.10	0.0376	0.05	-1.0448	-0.03120

There was a significant difference in the mean pain score which was higher in the on demand group compared to the continuously group.

Obs	Effect	group	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	group	on demand	4.2352	0.1818	160	23.29	<.0001	0.05	3.8762	4.5943
2	group	continuously	3.6972	0.1814	160	20.38	<.0001	0.05	3.3390	4.0555

CRP

Obs	Label	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	continuously vs on demand	0.3197	1.1226	162	0.28	0.7762	0.05	-1.8972	2.5366

Obs	Effect	group	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	group	on demand	9.7661	0.7921	162	12.33	<.0001	0.05	8.2018	11.3304
2	group	continuously	10.0858	0.7840	162	12.86	<.0001	0.05	8.5376	11.6340

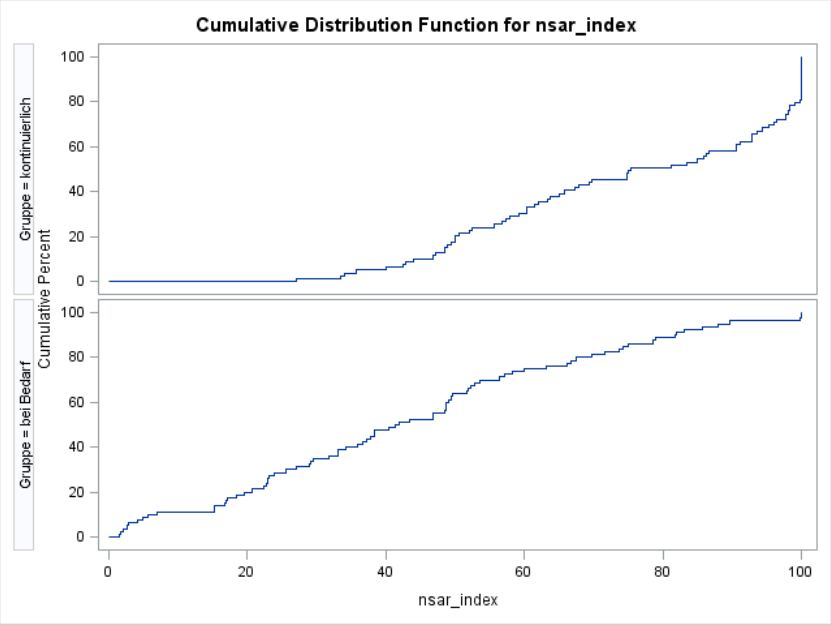
ESR

Obs	Label	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	continuously vs on demand	-0.9949	1.5167	158	-0.66	0.5128	0.05	-3.9904	2.0007

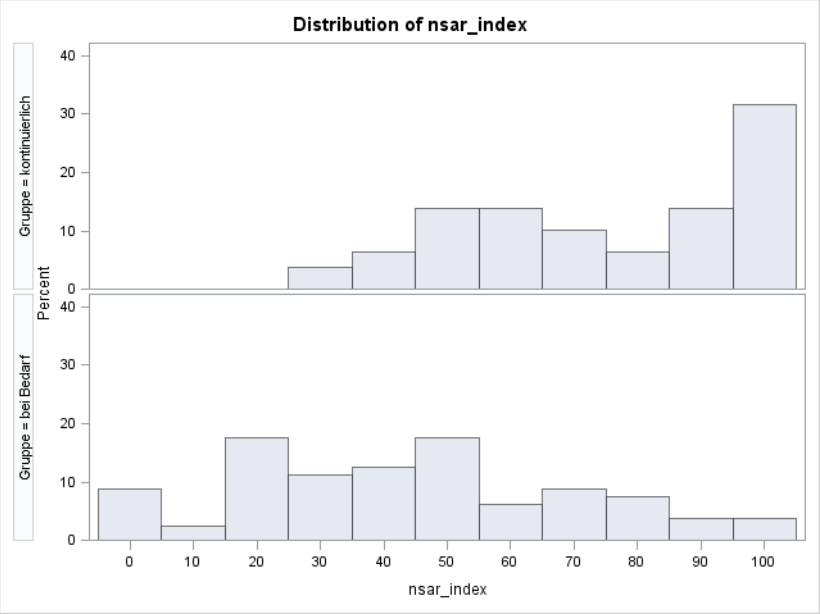
Obs	Effect	group	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
1	group	on demand	18.5895	1.0676	158	17.41	<.0001	0.05	16.4809	20.6981

Obs	Effect	group	Estimate	StdErr	DF	tValue	Probt	Alpha	Lower	Upper
2	group	continuously	17.5946	1.0755	158	16.36	<.0001	0.05	15.4704	19.7188

Compliance/NSAID-Index



Histogramm:



Analysis Variable : nsaid_index											
Group	N Obs	N	Mean	20th Pctl	30th Pctl	40th Pctl	50th Pctl	60th Pctl	70th Pctl	80th Pctl	90th Pctl
continuously	85	79	75	50	59	66	75	91	96	100	100
on demand	82	80	44	20	26	35	42	49	55	69	82

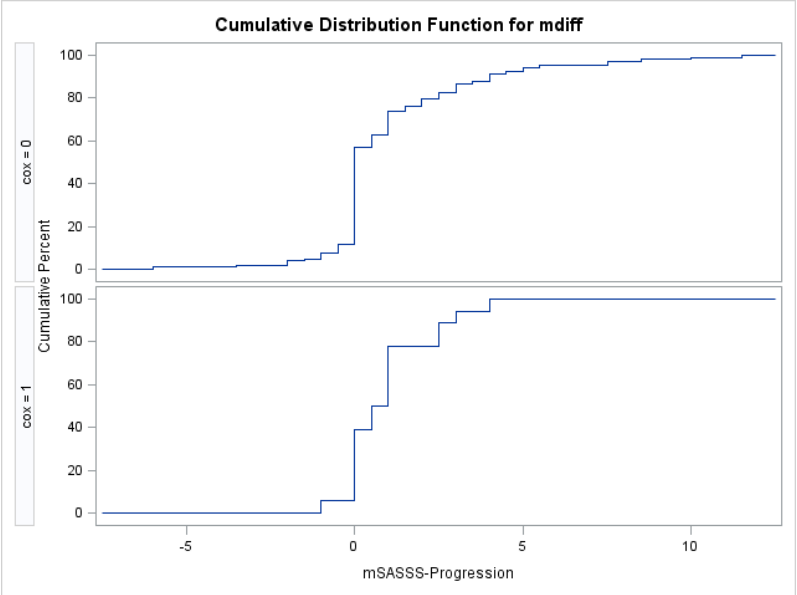
In the continuously group, 20% of the patients have a NSAID index of 50 or less, the NSAID index median of 75.
In the on demand group, 50% of the patients have a NSAID index of 42 or less.

COX2 inhibitors

19 patients changed to a Cox2 inhibitor during the study period (Etoricoxibe or Celecoxibe)

Time of COX2 inhibitor treatment:

Analysis Variable : cox2_duration								
Group	N Obs	N	Mean	Median	Lower Quartile	Upper Quartile	Minimum	Maximum
continuously	8	8	0.67	0.80	0.34	1.00	0.04	1.00
on demand	11	11	0.66	0.84	0.24	1.00	0.12	1.00



mSASSS Progression is similar in patients with and without coxibe treatment.

Syndesmophyte progression of Completers

A syndesmophyte is only counted, when scored by both readers. Progression is defined, if both readers scored 0 or 1 at baseline and 2 or 3 at year 2 (strict definition).

Syndesmophyte progression:

Table of group by syndneu			
group(Group)	syndneu		
Frequency Percent Row Pct Col Pct	0	1	Total
continuously	55 45.08 88.71 53.40	7 5.74 11.29 36.84	62 50.82
on demand	48 39.34 80.00 46.60	12 9.84 20.00 63.16	60 49.18
Total	103 84.43	19 15.57	122 100.00
Frequency Missing = 45			

7 (11.3%) of continuously treated patients versus 12 (20%) oft he On demand group showed the formation of a new syndesmophyte (p=0.22).

Radiographic progression and development of ankylosis

When taking into account the formation of ankylosis (mSASSS=2 at baseline of both scorers, and mSASSS of both readers =3 at Year 2), 13 (21%) patients of the continuously group and 12 (20%) of the On demand group showed a progression. When also taking into account other progression (0 to 1; 1 to 2; etc.) 34 patients in the continuously group and 17 in the On-demand group showed progression

Table of group by ankneu			
group(Group)	Formation of new syndesmophytes and ankylosis		
Frequency Percent Row Pct Col Pct	0	1	Total
continuously	49 40.16 79.03 50.52	13 10.66 20.97 52.00	62 50.82
on demand	48 39.34 80.00 49.48	12 9.84 20.00 48.00	60 49.18
Total	97 79.51	25 20.49	122 100.00
Frequency Missing = 45			

Adverse events

Therapy was overall well tolerated. There were 40 SAEs, out of which 21 occured in the On-Demand and the remaining 19 in the Continuously Treated group. No deaths occurred. There were 3 cases of acute myocardial infarct (2 in the continuously, 1 in the on-demand group), another case in the on-demand group hat angina pectoris. There were no severe gastrointestinal adverse events. One patient experienced an anemia, which might have been due to gastrointestinal bleeding.
In each group, there was 1 case of Colitis, in 2 cases in the on-demand group Crohn's disease occurred. There were no cases of liver toxicity or renal adverse events.

SAEs

meddraCode	pt_term	continuouslye Einnahme, N	Einnahme on demand, N
10002034	Anaemia	1	
10002383	Angina pectoris		1
10002556	Ankylosing spondylitis		1
10003011	Appendicitis	1	
10007025	Calculus ureteric	1	
10009657	Clostridium difficile colitis		1
10009887	Colitis	1	1
10011401	Crohn's disease		2
10012735	Diarrhoea		1
10012742	Diarrhoea infectious	1	
10013538	Diverticulitis		1
10013554	Diverticulum		1
10018498	Goitre	1	
10022016	Inguinal hernia		1
10022955	Iritis		1
10023203	Joint destruction		1
10028200	Multiple fractures	1	
10028596	Myocardial infarction	2	1
10029148	Nephrolithiasis		2
10029883	Obesity		1
10031161	Osteoarthritis	1	
10033647	Pancreatitis acute		1
10033664	Panic attack		1
10035598	Pleural effusion	1	
10037153	Psoriasis	1	
10039227	Rotator cuff syndrome		1
10042343	Subcutaneous abscess		1
10046788	Uterine haemorrhage	1	
10046798	Uterine leiomyoma	1	1
10047340	Vertigo	1	

10047571	Visual impairment	1	
10048015	Wolff-Parkinson-White syndrome	1	
10050584	Contusion	1	
10061000	Benign pancreatic neoplasm	1	
	SUMME	19	21

All SAE

All adverse events

AE

idSoc	soc_term	N gesamt	continuously, N	on demand, N	AE per 100 patient years, continuously group	AE per 100 patient years, on demand
10005329	Blood and lymphatic system disorders	7	3	4	2.27	3.01
10007541	Cardiac disorders	17	9	8	6.82	6.02
10010331	Congenital, familial and genetic disorders	0	0	0	0.00	0.00
10013993	Ear and labyrinth disorders	12	6	6	4.55	4.51
10014698	Endocrine disorders	6	2	4	1.52	3.01
10015919	Eye disorders	51	13	38	9.85	28.57
10017947	Gastrointestinal disorders	225	111	114	84.09	85.71
10018065	General disorders and administration site conditions	51	24	27	18.18	20.30
10019805	Hepatobiliary disorders	0	0	0	0.00	0.00
10021428	Immune system disorders	2	0	2	0.00	1.50
10021881	Infections and infestations	221	99	122	75.00	91.73
10022117	Injury, poisoning and procedural complications	25	13	12	9.85	9.02
10022891	Investigations	26	15	11	11.36	8.27
10027433	Metabolism and nutrition disorders	12	5	7	3.79	5.26
10028395	Musculoskeletal and	77	36	41	27.27	30.83

	connective tissue disorders					
10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7	3	4	2.27	3.01
10029205	Nervous system disorders	94	43	51	32.58	38.35
10036585	Pregnancy, puerperium and perinatal conditions	1	0	1	0.00	0.75
10037175	Psychiatric disorders	8	4	4	3.03	3.01
10038359	Renal and urinary disorders	12	5	7	3.79	5.26
10038604	Reproductive system and breast disorders	11	5	6	3.79	4.51
10038738	Respiratory, thoracic and mediastinal disorders	26	13	13	9.85	9.77
10040785	Skin and subcutaneous tissue disorders	36	16	20	12.12	15.04
10041244	Social circumstances	1	0	1	0.00	0.75
10042613	Surgical and medical procedures	13	6	7	4.55	5.26
10047065	Vascular disorders	21	11	10	8.33	7.52

SAE

idSoc	soc_term	N all	continuously, N	on demand, N	AE per 100 patient years, continuously group	AE per 100 patient years, on demand
10005329	Blood and lymphatic system disorders	1	1	0	0.76	0.00
10007541	Cardiac disorders	5	3	2	2.27	1.50
10013993	Ear and labyrinth disorders	1	1	0	0.76	0.00
10014698	Endocrine disorders	1	1	0	0.76	0.00
10015919	Eye disorders	2	1	1	0.76	0.75
10017947	Gastrointestinal disorders	8	1	7	0.76	5.26

10021881	Infections and infestations	5	2	3	1.52	2.26
10022117	Injury, poisoning and procedural complications	2	2	0	1.52	0.00
10027433	Metabolism and nutrition disorders	1	0	1	0.00	0.75
10028395	Musculoskeletal and connective tissue disorders	4	1	3	0.76	2.26
10029104	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	2	1	1.52	0.75
10037175	Psychiatric disorders	1	0	1	0.00	0.75
10038359	Renal and urinary disorders	3	1	2	0.76	1.50
10038604	Reproductive system and breast disorders	1	1	0	0.76	0.00
10038738	Respiratory, thoracic and mediastinal disorders	1	1	0	0.76	0.00
10040785	Skin and subcutaneous tissue disorders	1	1	0	0.76	0.00

5. Discussion and overall conclusion

- *Safety or performance results and any other endpoints,*
- *Assessment of risks and benefits,*
- *Discussion of clinical relevance and importance of their results in the light of other existing data,*
- *Any specific benefits or special precautions required for individual subjects or groups considered to be at risk,*
- *Implications for the conduct of future clinical investigations*
- *Any limitation of the clinical investigation.*

Out of the planned 37 rheumatological centers participating in Germany at this study, 19 centers included at least 1 patients and followed them up of the 2 year study duration for inclusion in the analysis. As recruiting for this study took longer than expected, two amendments with significant changes were done to facilitate recruitment. With these changes, recruitment could be finalized and the study successfully terminated.

ICC of both readers of Xrays was excellent with 95.8% at baseline and 94.7% at year 2.

The main result of this study was that no effect of a NSAID treatment on radiographic progression could be shown. Radiographic spinal progression was with 1.28 mSASSS points in the continuously treated group versus 0.79 in the on-demand group even higher, though not statistically significant. Thereby, the underlying hypothesis that continuously NSAID treatment is able to retard radiographic progression, could not be verified with this study. When taking into account the ASAS NSAID index ranging from 0 to 100, the continuously group had an NSAID index of 75 compared to 44 in the On-Demand-Group. As expected, also clinical parameters like BASDAI as activity index for AS decreased more in the group of patients under continuous NSAID treatment.

Interestingly, CRP and mSASSS values were higher in the On-demand group – both known risk factors for radiographic progression. Despite this increased risk at baseline in the On-demand group, this group sowed less progression than the continuously group.

Further analyses for the whole patient group could show, that known predictors of radiographic progression like baseline CRP and/or syndesmophytes at baseline were also associated with radiographic progression in our cohort of patients. When only analyzing subgroup of patients with high CRP or already present syndesmophytes at baseline, radiographic progression in the on-demand group was even lower compared to the continuously treated patients. These analyses showed, that in our ENRADAS study the continuously treatment with NSAID was not less effective than the On-Demand treatment. This result would also not have been different with a higher sample size, as a trend contrarily to the anticipated one was shown.

This study was started with diclofenac, however, change to another NSAID was possible. Interestingly, at the end of the study, 90% of the patients were still taking diclofenac, which is why we can only conclude, that diclofenac is not effective for retarding radiographic progression in AS. This questions whether a different effect of different NSAID on radiographic progression is possible. In the study of Wanders et al, 70 to 80% of the patients took Celecoxibe. Based on the current literature, such a different effect of diclofenac and celecoxibe can not be proven, but also not excluded. This should be further analysed in upcoming trials and basic research.

Even when calculating the NSAID intake based on the ASAS NSAID score irrespective of the treatment group, a higher NSAID intake was not associated with radiographic progression.

Besides the study of Wanders et al, which prospectively, randomized and controlled analysed the effect of NSAIDs on radiographic progression, 2 further studies pointed towards on effect of NSAID on radiographic progression: a retrospective analyses from the german GESPIC cohort and a retrospective study from 1976 in which 40 AS patients with continuous treatment with Phenylbutazon were compared to on-demand treatment. Here, a positive effect of continuously treatment could be shown.

Based on the results of our study, for upcoming studies evaluating the effect of NSAIDs on radiographic progression, the respective NSAID should be taken into account. Furthermore, a more clearer difference in the dose between both treatment groups seems recommendable.

Overall, the therapy was well tolerated. 40 SAEs were reported, out of which 21 occurred in the on-demand group and 19 in the continuously treated group. There were no deaths. 2 patients from the on-demand group and 1 from the continuously treated group experienced myocardial infarction. There were no severe gastrointestinal adverse events (ulceration, bleeding, perforation), no cases of acute liver or kidney toxicity. AEs occurred with similar frequency in both treatment groups.

To conclude, this study will significantly add to the ongoing discussion of the effect of NSAID on adiographic progression in AS.

6. Abbreviated terms and definitions

– *List of abbreviated terms and definitions of specialized or unusual terms*

AE	Adverse Event
AS	Ankylosing Spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BL	Baseline
BSG	Blutsenkungs-Geschwindigkeit
CRP	C-Reactive Protein
Den DF	Denominator Degrees of Freedom
DF	Degrees of Freedom
ICC	Intraclass Correlation
ITT	Intention-To-Treat
mSASSS	modified Stoke Ankylosing Spondylitis Spinal Score
N Obs	Number of observations
NSAID	Nichtsteroidale Antirheumatika
Num DF	Numerator Degrees of Freedom
pt	preferred term (meddra)
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
Synd	Syndesmophyt

7. Ethics

- *Confirmation that the CIP and any amendments to it were reviewed by the EC*
- *List of all ECs consulted (can be given in an annex)*

The clinicial investigational plan and any amendments were reviewed by the EC. A List of all ECs consulted is given.

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5	Dr. med.	Zinke	Silke	Berlin	EK Land Berlin
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8. Investigators and administrative structure

- *Description of the organisation of the clinical investigation,*
- *List of investigators, including their affiliations (can be given in annex),*
- *Names and addresses of any third parties (such as core laboratories, CROs, consultants or other contractors) that contributed to the clinical investigation (can be given in an annex),*
- *Names and addresses of the sponsor or sponsors' representative(s)*

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20	22	Dr. med. Volker Waltz	Rheuma-Praxis, Bad Bentheim
21	23	Dr. med. Gerd Kramer	Rheuma-Praxis, Remscheid
22	24	Dr. med. Siegfried Wassenberg	Evang. Krankenhaus, Ratingen
23	25	PD Dr. med. Hans-Eckard Langer	Rheuma-Praxis, Düsseldorf
24	26	Dr. med. Wolfgang Spieler	Rheuma-Praxis, Zerbst
25	27	Dr. med. Ulrich Schoo	Rheuma-Praxis, Rheine
26	28	Prof. Dr. med. Michael Hammer	St. Josefs-Stift, Sendenhorst
27	29	Prof. Dr. med. Mathias Schneider	Universitätsklinikum Düsseldorf
28	30	Prof. Dr. med. Jürgen Braun	Rheumazentrum Ruhrgebiet, Herne
29	31	Dr. med. Dorothea Pick	Rheuma-Praxis, Grafschaft b Bad Neuenahr-Ahrweiler
30	33	Dr. med. Andreas Kapelle	Rheuma-Praxis, Hoyerswerda
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34	37	Dr. med. Knut Kolitsch	Rheuma-Praxis, Katzhütte

35	38	Dr. med. Frank Mielke	Rheuma-Praxis, Berlin
36	39	Dr. med. Tadjana Schneider-Stiebler	Rheuma-Praxis, Wismar
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40	43	Dr. med. Thomas Linde	Rheuma-Praxis, Halle
41	44	Dr. med. Martin Viale Rissom	Rheuma-Praxis, Berlin

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2.	Prof. Dr. J. Sieper	Charité – Campus Benjamin Franklin, Berlin	
3.	Prof. Dr. J. Braun	Rheumazentrum Ruhrgebiet, Herne	
Independent Review of trial protocol			
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Trial Supporting facilities			
#	Name	Affiliation	Responsibility/Role
1.	Dr. J. Listing	Deutsches Rheumaforschungszentrum (DRFZ), Berlin	Biostatistical analyses
2.	Frau R. Bussar-Maatz	Koordinierungszentrum Klinische Studie KKS	Monitoring
Data Monitoring and Safety Board (DMSB)			
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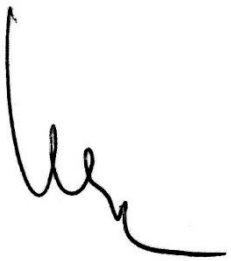

Prof. Joachim Sieper		30-06-2021
Name	Signature	Date