SUPPLEMENTARY APPENDIX

Disease activity-guided tapering of biologics in patients with inflammatory arthritis:

A pragmatic, randomised, open-label, equivalence trial

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CONTENT

Supplementary Data S1: Important modifications to the BIODOPT trial protocol during the study period with dates of report to the relevant authorities.

Amendment number	Amendment date	Description of amendment
1	June 12th 2018	The Department of Rheumatology, South West Jutland, Esbjerg, was added as study site (but the site never included any patients)
2	September 24th 2018	The biosimilar drugs Imraldi and Amgevita (adalimumab) was added as approved study drugs as all patients treated with adalimumab per national guideline had to switch to biosimilar adalimumab in the form of Imraldi or Amgevita.
3	March 8th 2019	The biosimilar drug Zessly (infliximab) was added as approved study drug as all patients treated with infliximab per national guideline had to switch to biosimilar infliximab in the form of Zessly. Moreover, the eligibility criteria was revised to allow inclusion of patients in sustained LDA during ≥12 months.
4	September 5th 2019	The Department of Rheumatology, Silkeborg Regional Hospital, was added as study site
5	November 30th 2020	The biosimilar drugs Erelzi (etanercept) and Hyrimoz (adalimumab) was added as approved study drugs as all patients treated with etanercept or adalimumab per national guideline had to switch to biosimilar Erelzi or Hyrimoz, respectively.
6	March 20th 2020	Suspension of patient enrolment due to the national implication of the COVID-19 pandemic to the Danish health care system. Moreover, remote monitoring by telephone contact was allowed for the following visits: month 4, month 8, month 12, and month 24. The primary endpoint assessment (visit 18 month) was considered to be essential to the patients and the trial; therefore, the visit was conducted as an outpatient consultation. Similarly, subacute visits due to symptoms of flare were also considered to be essential; thus, encouraged to be conducted as an outpatient consultation.
7	April 2nd 2020	The inclusion period was closed 1 month before scheduled due to the continued national COVID-19 implication to the Danish health care system.
8	June 12th 2020	Remote monitoring, due to the implication of the COVID-19 pandemic, was lifted; thus, all trial visits were onwards conducted as an outpatient consultation in accordance with the trial protocol.

Supplementary Data S2: Information on randomisation and allocation.

A computer-generated allocation sequence was created in SAS PROC PLAN by senior biostatistician Robin Christensen (RC) who had no clinical involvement in the trial. Patients were allocated in permuted blocks of three to six stratified by trial site (Aalborg, Aarhus, Odense, or Silkeborg), diagnosis (RA, PsA, or axSpA) and biologic failure history (currently on biologic number ≤2, or ≥3). The allocation sequence was only accessible to RC and the independent data manager Johanne Hovgaard Winther (JHW). JHW entered the sequence into a dedicated electronic case report form (e-CRF) in Research Electronic Data Capture (REDCap). A randomisation ratio of 2:1 (tapering:control) was chosen to gain more data on the tapering group for exploratory sub-analyses; however, as discussed in the manuscript the trial is not powered for the sub-analyses. The unequal randomisation ratio with more patients allocated to the tapering group exposes a larger proportion of patients to the risk of flare. However, the potential harm is considered acceptable as previous studies have demonstrated that a tapering strategy can reduce the biological dose considerably without persistent deterioration in disease activity as flares are managed with biologic dose escalation for the majority of patients (1-11). Moreover, patients in the tapering group were suspected to potentially have the benefit of a dose-dependent lower risk of adverse events including serious infections (12). In REDCap, the patient was randomised when the physician clicked on the 'randomisation button' and the assigned intervention appeared on the computer screen.

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11. Ye W, et al. Tapering and Discontinuation of Biologics in Patients with Psoriatic Arthritis with Low Disease Activity. Drugs 2018;78:1705–15.
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Supplementary Data S3: Power and sample size considerations.

The sample size calculation was based on the primary efficacy endpoint 'disease activity' and a requirement of minimum 85% power. A clinically relevant reduction in Disease Activity Score28-C-Reactive Protein (DAS28-CRP) is acknowledged to be ΔDAS28-CRP >1.2 (1) and in Ankylosing Spondylitis Disease Activity Score (ASDAS) to be ΔASDAS >1.1 (2). A clinically unimportant change in disease activity was defined as 'less than half of the effect' that is considered a clinically relevant disease activity reduction; thus, the equivalence margin was prespecified to be ±0.5 disease activity points. Furthermore, the equivalence margins of ±0.5 was 'less than half of the effect' that is considered a clinically relevant flare in DAS28-CRP, i.e., ΔDAS28-CRP >1.2 (3), and fairly equal to half of the effect that is considered a clinically flare in ASDAS, i.e., ΔASDAS ≥0.9 (4).

With an alpha level of 0.05 using two one-sided tests (one-sided alpha of 0.025) and equivalence margins of ±0.5 disease activity points, assuming a mean difference of 0 and a common SD of 1.0 points, a total sample size of 156 participants would correspond to a statistical power of 80%. From this, it was decided to aim for a total sample size of 180 participants corresponding to an approximate power of 87%.

For the other primary endpoint, a sample size of 180 patients would yield a high statistical power of 99% when assuming that 30% and 5% of the patients (tapering vs continuation, respectively) would achieve ≥50% reduction in biologic dose compared to baseline. Additional power and sample size considerations have previously been described in details (5).

References

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Supplementary Table S1: Baseline demographics and disease characteristics by diagnosis analysed "as observed" based on the ITT population.

Variable	Tapering group N = 95	Control group N = 47
Rheumatoid arthritis	**N = 41**	**N = 20**
Female, n (%)	34 (83%)	14 (70%)
Age (years), mean (SD)	61.9 (11.6)	65.9 (7.8)
Disease duration (years), median (IQR)	16.3 (9.7;21.0)	16.8 (11.9;22.9)
Rheumatoid factor positive, n (%)	26 (63%)	16 (80%)
Anti-Citrullinated Peptide Antibody positive, n (%)	28 (68%)	17 (85%)
Erosive, n (%)	34 (83%)	19 (95%)
Concomitant methotrexate, n (%)[1]	26 (63%)	14 (70%)
HAQ-DI (0-3), median (IQR)	0.50 (0.00;0.88)	0.56 (0.13;1.22)
Pain VAS (0-100), median (IQR)	13.0 (6.0;22.0)	17.5 (4.8;35.8)
Patient Global Health VAS (0-100), median (IQR)	13.0 (3.0;30.0)	18.5 (5.8;42.0)
Tender joint count (0-68), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
CRP (mg/L), median (IQR)	2.3 (0.9;3.9)	1.7 (0.6;3.9)
Physician Global Health VAS (0-100), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
DAS28-CRP (0.96-9.4), mean (SD)	1.7 (0.4)	1.8 (0.5)
CDAI (0-76), median (IQR)	1.3 (0.7;2.4)	1.9 (0.5;3.8)
SDAI (0-86), median (IQR)	1.9 (0.7;3.6)	2.2 (0.7;4.8)
Psoriatic arthritis	**N = 18**	**N = 8**
Female, n (%)	7 (39%)	3 (38%)
Age (years), mean (SD)	48.1 (11.8)	46.1 (13.4)
Disease duration (years), median (IQR)	13.4 (6.4;20.0)	11.1 (4.5;25.1)
Concomitant methotrexate, n (%)[1]	10 (56%)	4 (50%)
HAQ-DI (0-3), median (IQR)	0.13 (0.00;0.50)	0.31 (0.00;0.39)
Pain VAS (0-100), median (IQR)	9.5 (1.8;23.8)	14.5 (8.0;19.0)
Patient Global Health VAS (0-100), median (IQR)	16.0 (1.0;36.5)	15.0 (6.5;26.8)
Tender joint count (0-68), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
SPARCC Enthesitis Index (0-16), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Dactylitis by number (0-20), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
PASI (0-72), median (IQR)	0.0 (0.0;1.1)	0.3 (0.0;0.4)
mNAPSI (0-130), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.8)
CRP (mg/L), median (IQR)	1.3 (0.5;3.6)	0.7 (0.5;4.7)
Physician Global Health VAS (0-100), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.8)
DAS28-CRP (0.96-9.4), mean (SD)	1.7 (0.3)	1.6 (0.5)
DAPSA (0-164), median (IQR)	2.8 (1.1;6.3)	2.7 (1.8;7.1)
In MDA, n (%)	14 (78%)	6 (75%)
Axial spondyloarthritis	**N = 36**	**N = 19**
Female, n (%)	11 (31%)	3 (16%)
Age (years), mean (SD)	42.5 (14.3)	40.6 (12.1)
Disease duration (years), median (IQR)	7.3 (4.2;10.9)	6.8 (4.3;14.3)
Ankylosing spondylitis, n (%)	23 (64%)	14 (74%)
HLA-B27 positive, n (%)	32 (89%)	15 (88%)[2]
Concomitant NSAIDs, n (%)	7 (19%)	3 (16%)
HAQ-DI (0-3), median (IQR)	0.00 (0.00;0.13)	0.00 (0.00;0.13)
Pain VAS (0-100), median (IQR)	3.5 (1.0;13.0)	7.0 (3.0;12.0)
Patient Global Health VAS (0-100), median (IQR)	4.5 (0.3;10.8)	10.0 (5.0;24.0)
Backpain[3] (0-100), median (IQR)	7.5 (2.0;17.0)	10.0 (4.0;15.0)
Morning stiffness[4] (0-100), median (IQR)	7.5 (1.0;16.0)	4.0 (1.0;14.0)
Peripheral pain/swelling[5] (0-100), median (IQR)	4.0 (0.3;11.0)	2.0 (0.0;15.0)
Tender joint count (0-68), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
SPARCC Enthesitis Index (0-16), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Dactylitis by number (0-20), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
PASI (0-72), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
mNAPSI (0-130), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
CRP (mg/L), median (IQR)	3.8 (1.4;4.0)	3.7 (1.0;3.9)
Physician Global Health VAS (0-100), median (IQR)	0.0 (0.0;1.0)	0.0 (0.0;1.0)
ASDAS (0.6-∞), mean (SD)	1.1 (0.4)	1.2 (0.3)
BASDAI (0-100), median (IQR)	8.5 (2.3;13.8)	11.0 (5.0;21.0)

N: number, SD: standard deviation, IQR: interquartile range, HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analog Scale, CRP: C-Reactive Protein, mg: milligram, L: litre, DAS28-CRP: Disease Activity Score 28-C-Reactive Protein, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, SPARCC: Spondyloarthritis Research Consortium of Canada, PASI: Psoriasis Area Severity Index, mNAPSI: modified Nail Psoriasis Severity Index, DAPSA: Disease Activity index for PSoriatic Arthritis, MDA: Minimal Disease Activity in PsA, HLA-B27: Human leukocyte antigen subtype B27, NSAIDs: Non-steroidal anti-inflammatory drugs, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.
[1]: RA, median MTX dose (IQR): 15.0 mg/week (10.0;5.0). PsA, median MTX dose (IQR): 13.8 mg/week (10.0;15.0). [2]: 2 missing values. [3]: BASDAI question 2. [4]: BASDAI question 5. [5]: BASDAI question 3

Supplementary Table S2: Baseline demographics and disease characteristics analysed by biologic mode of action based on the ITT population.

Variable	*TNFi treated, n = 129*	*Non-TNFi treated, n =13*
General characteristics		
Female, n (%)	61 (47%)	11 (85%)
Age (years), mean (SD)	50.5 (1.3)	67.5 (2.9)
Smoking, n (%)	20(16%)	4 (31%)
Body Mass Index (kg/m^2), median (IQR)	25.6 (23.3;29.3)	27.4 (22.2;29.8)
Arthritis characteristics		
Diagnosis:		
RA, n (%)	48 (37%)	13 (100%)
PsA, n (%)	26 (20%)	0 (0%)
AxSpA, n (%)	55 (43%)	0 (0%)
Disease duration (years), median (IQR)	11.9 (6.1;18.3)	13.3 (9.3;19.4)
Disease activity measures		
HAQ-DI (0.0-3.0), median (IQR)	0.13 (0.00;0.50)	0.63 (0.13;1.69)
Pain VAS (0-100 mm), median (IQR)	10.0 (3.0;17.5)	14.0 (5.5;31.0)
Fatigue VAS (0-100 mm), median (IQR)	19.0 (6.0;34.5)	29.0 (9.0;63.5)
Patient global health VAS (0-100 mm), median (IQR)	11.0 (3.0;22.5)	16.0 (4.0;39.5)
Short Form-36:		
Physical component summary (0-100), median (IQR)	51.2 (46.9;54.9)[1]	46.9 (39.2;51.7)
Mental component summary (0-100), median (IQR)	55.4 (47.4;59.5)[1]	54.9 (49.1;59.8)
Tender joint count (0-68), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;1.0)
Swollen joint count (0-66), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
CRP (mg/L), median (IQR)	2.8 (0.8;3.9)	1.0 (0.5;2.5)
Physician global health VAS (0-100 mm), median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Disease activity score[2], mean (SD)	1.46 (0.04)	1.68 (0.15)
In remission[3], n (%)	109 (85%)	13 (100%)
Arthritis treatment characteristics		
csDMARDs, n (%)	57 (44%)	6 (46%)
Combination csDMARDs, n (%)	3 (2%)	1 (8%)
MTX, n (%)	38 (43%)	2 (29%)
Duration of baseline bDMARD (years), median (IQR)	4.9 (2.3;9.2)	4.8 (2.7;6.1)
Baseline bDMARD therapy:		
TNF-α inhibitor, n (%)	129 (100%)	0 (0%)
IL-6 inhibitor, n (%)	0 (0%)	9 (69%)
T-cell co-stimulation blocker, n (%)	0 (0%)	4 (31%)
Repeated bDMARD failure[4], n (%)	4 (3%)	5 (38%)

N: number, SD: standard deviation, kg: kilogram, m^2: square metre, IQR: interquartile range, RA: rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analog Scale, CRP: C-reactive protein, mg: milligram, L:litre, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, MTX: methotrexate, bDMARD: biologic disease-modifying antirheumatic drug, TNF: Tumour necrosis factor, IL: Interleukin.

[1]: Missing values: one value for SF-36 PCS and for SF-36 MCS.

[2]: RA and PsA: Disease Activity Score (DAS)28-CRP and axSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS).

[3]: RA and PsA: DAS28-CRP <2.6 and axSpA: ASDAS <1.3.

Supplementary Table S3: Disease specific outcomes at 18 months follow-up analysed "as observed" based on the ITT population.

Outcome	Tapering group, N = 88			Control group, N = 46		
	N	Median	IQR	N	Median	IQR
Rheumatoid arthritis		N = 41			N = 19	
Biologics reduced by ≥50%[1], N/n (%)	41/14	34%	20% to 49%	19/1	5%	-5% to 15%
HAQ-DI (0-3)	40	0.50	0.03 to 0.88	19	0.50	0.25 to 1.25
Pain VAS (0-100)	41	19.0	5.5 to 28.5	19	27.0	7.0 to 35.0
Patient Global Health VAS (0-100)	41	17.0	3.0 to 27.0	19	25.0	6.0 to 37.0
Tender joint count (0-68)	41	0.0	0.0 to 1.0	19	0.0	0.0 to 1.0
Swollen joint count (0-66)	41	0.0	0.0 to 0.0	19	0.0	0.0 to 0.0
Physician Global Health VAS (0-100)	41	0.0	0.0 to 1.0	19	0.0	0.0 to 6.0
CRP (mg/L)	41	3.9	1.1 to 6.5	19	2.1	1.0 to 3.9
DAS28crp (0.96-9.4)	41	1.8	1.5 to 2.3	19	2.0	1.7 to 2.5
CDAI (0-76)	41	2.3	0.7 to 4.7	19	3.5	1.1 to 5.8
SDAI (0-86)	41	2.8	1.3 to 5.7	19	3.8	1.3 to 6.3
Psoriatic arthritis		N = 14			N = 8	
Biologics reduced by ≥50%[1], N/n (%)	14/5	36%	11% to 61%	8/0	0%	··
HAQ-DI (0-3)	14	0.00	0.00 to 0.28	8	0.06	0.0 to 0.25
Pain VAS (0-100)	14	17.0	10.3 to 25.0	8	12.5	4.0 to 18.3
Patient Global Health VAS (0-100)	14	12.0	6.5 to 26.5	8	15.5	0.0 to 26.5
Tender joint count (0-68)	14	0.0	0.0 to 0.0	8	0.0	0.0 to 0.0
Swollen joint count (0-66)	14	0.0	0.0 to 0.0	8	0.0	0.0 to 0.0
SPARCC Enthesitis Index (0-16)	13	0.0	0.0 to 0.0	8	0.0	0.0 to 0.0
Dactylitis by number (0-20)	13	0.0	0.0 to 0.0	8	0.0	0.0 to 0.0
PASI (0-72)	13	0.0	0.0 to 0.2	8	0.0	0.0 to 0.4
mNAPSI (0-130)	13	0.0	0.0 to 0.0	8	0.0	0.0 to 0.0
Physician Global Health VAS (0-100)	14	0.0	0.0 to 3.5	8	0.0	0.0 to 0.0
CRP (mg/L)	14	0.9	0.6 to 2.9	8	2.3	0.5 to 5.4
DAS28crp (0.96-9.4)	14	1.4	1.3 to 1.8	8	1.6	1.3 to 1.8
DAPSA (0-164)	14	3.2	2.2 to 5.5	8	3.1	0.9 to 4.6
In MDA, N/n (%)	14	12	86%	8	8	100%
Axial spondyloarthritis		N = 33			N = 19	
Biologics reduced by ≥50%[1], N/n (%)	33/16	48%	31% to 66%	19/0	0%	··
HAQ-DI (0-3)	33	0.00	0.00 to 0.25	17	0.00	0.00 to 0.31
Pain VAS (0-100)	33	12.0	1.0 to 26.0	17	9.0	2.5 to 14.5
Patient Global Health VAS (0-100)	33	13.0	3.0 to 30.0	17	12.0	5.5 to 28.5
Backpain[2] (0-100)	33	15.0	2.0 to 28.5	17	6.0	1.0 to 14.0
Morning stiffness[3] (0-100)	33	9.0	1.0 to 23.5	17	10.0	1.5 to 19.5
Peripheral pain/swelling[4] (0-100)	33	3.0	0.0 to 6.5	17	4.0	0.5 to 24.5
Tender joint count (0-68)	33	0.0	0.0 to 0.0	19	0.0	0.0 to 0.0
Swollen joint count (0-66)	33	0.0	0.0 to 0.0	19	0.0	0.0 to 0.0
SPARCC Enthesitis Index (0-16)	33	0.0	0.0 to 0.0	19	0.0	0.0 to 0.0
Dactylitis by number (0-20)	33	0.0	0.0 to 0.0	19	0.0	0.0 to 0.0
PASI (0-72)	33	0.0	0.0 to 0.0	19	0.0	0.0 to 0.0
mNAPSI (0-130)	33	0.0	0.0 to 0.0	19	0.0	0.0 to 0.0
Physician Global Health VAS (0-100)	33	0.0	0.0 to 3.5	17	0.0	0.0 to 0.5
CRP (mg/L)	33	3.9	1.7 to 5.3	19	3.9	1.8 to 3.9
ASDAS (0.6-∞)	33	1.2	1.0 to 1.8	17	1.2	1.0 to 1.4
BASDAI (0-100)	33	11.0	1.0 to 21.5	17	12.0	5.0 to 16.0

N: number, IQR: interquartile range, HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analog Scale, CRP: C-Reactive Protein, mg: milligram, L: litre, DAS28crp: Disease Activity Score 28crp, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, SPARCC: Spondyloarthritis Research Consortium of Canada, PASI: Psoriasis Area Severity Index, mNAPSI: modified Nail Psoriasis Severity Index, DAPSA: Disease Activity index for PSoriatic Arthritis, MDA: Minimal Disease Activity in PsA, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score. [1]: Compared to baseline biologic dose and analysed as percentage with 95%CI, [2]: BASDAI question 2, [3]: BASDAI question 5, [4]: BASDAI question 3.

Supplementary Table S4: Comparison between groups at 18 months based on the ITT population using non-responder imputation (Baseline Observation Carried Forward) and multiple imputation.

Outcome	Tapering group N = 95	Control group N = 47	Difference between groups (95%CI)[1]
Primary outcome			
Biologics reduced by ≥50%[2], n (%)	38 (40%)	1 (2%)	0.38 (0.27 to 0.49)
Disease activity score[3]	1.73 (0.12)	1.66 (0.14)	0.07 (-0.13 to 0.27)
Key secondary outcomes			
In remission[4], n (%)	67 (71%)	35 (74%)	-0.04 (-0.19 to 0.12)
In low disease activity[5], n (%)	83 (87%)	43 (91%)	-0.04 (-0.15 to 0.06)
Other secondary outcomes			
ΔHAQ-DI (0-3)	0.04 (0.06)	-0.02 (0.06)	0.06 (-0.02 to 0.14)
ΔPain VAS (0-100)	5.5 (2.7)	1.0 (3.0)	4.5 (0.1 to 8.9)
ΔFatigue VAS (0-100)	-1.8 (3.6)	-2.9 (4.0)	1.1 (-4.5 to 6.7)
ΔPatient Global Health VAS (0-100)	2.4 (3.2)	0.9 (3.5)	1.5 (-3.6 to 6.5)
ΔShort Form-36 PCS (0-100)	-1.6 (1.2)	-2.2 (1.3)	0.6 (-1.3 to 2.5)
ΔShort Form-36 MCS (0-100)	-1.3 (1.5)	-1.1 (1.7)	-0.2 (-2.6 to 2.2)
ΔPhysician Global Health VAS (0-100)	4.2 (1.6)	3.5 (1.8)	0.7 (-2.2 to 3.7)
ΔTender joint count (0-68)	-0.04 (0.4)	0.55 (0.4)	-0.59 (-1.19 to 0.004)
ΔSwollen joint count (0-66)	0.3 (0.2)	0.3 (0.2)	-0.03 (-0.33 to 0.28)
ΔCRP (mg/L)	2.6 (1.2)	0.4 (1.3)	2.3 (0.1 to 4.4)

N: number, CI: confidence interval, Δ: Change between 18 months and baseline, HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analog Scale, PCS: physical component summary, MCS: mental component summary, CRP: C-reactive protein, mg: milligram, L: litre.

Dichotomous outcomes were analysed as crude risk difference for the between group comparison using generalised linear models for binomial data; missing outcome values were handled using a worst, best, worst-best, best-worst, and as observed data sets. Continuous outcomes were analysed using repeated-measures linear mixed-effects models as least squares means with standard error; missing values were handled with non-responder imputation (Baseline Observation Carried Forward).

[1]: Analysed as tapering group – control group.

[2]: Compared to baseline biologic dose.

[3]: RA and PsA: Disease Activity Score (DAS)28-CRP, and axSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS).

[4]: RA and PsA: DAS28-CRP <2.6 and axSpA: ASDAS <1.3.

[5]: RA and PsA: DAS28-CRP ≤3.2 and axSpA: ASDAS <2.1.

Supplementary Table S5: Comparison between groups at 18 months based on the *per protocol* population.

Outcome	Tapering group N = 82	Control group N = 43	Difference between groups (95%CI)[1]
Primary outcome			
Biologics reduced by ≥50%[2], n/N (%)	32/82 (39%)	1/43 (2%)	0.37 (0.25 to 0.48)
Disease activity score[3]	1.79 (0.09)	1.75 (0.10)	0.04 (-0.15 to 0.23)
Key secondary outcomes			
In remission[4], n/N (%)	60/82 (73%)	31/41 (76%)	-0.02 (-0.19 to 0.14)
In low disease activity[5], n/N (%)	75/82 (91%)	38/41 (93%)	-0.01 (-0.11 to 0.09)
Other secondary outcomes			
ΔHAQ-DI (0-3)	0.04 (0.04)	-0.01 (0.05)	0.05 (-0.03 to 0.13)
ΔPain VAS (0-100)	7.7 (2.1)	3.8 (2.4)	3.8 (-0.7 to 8.4)
ΔFatigue VAS (0-100)	-0.9 (2.8)	-1.2 (3.2)	0.3 (-5.4 to 6.0)
ΔPatient Global Health VAS (0-100)	4.7 (2.6)	3.4 (2.9)	1.3 (-3.9 to 6.6)
ΔShort Form-36 PCS (0-100)	-2.3 (1.0)	-2.5 (1.1)	0.3 (-1.8 to 2.3)
ΔShort Form-36 MCS (0-100)	0.5 (1.2)	-0.4 (1.4)	0.9 (-1.7 to 3.4)
ΔPhysician Global Health VAS (0-100)	5.0 (1.1)	3.9 (1.4)	1.1 (-1.7 to 3.8)
ΔTender joint count (0-68)	-0.1 (0.3)	0.6 (0.3)	-0.7 (-1.3 to -0.1)
ΔSwollen joint count (0-66)	0.3 (0.1)	0.3 (0.1)	-0.03 (-0.32 to 0.26)
ΔCRP (mg/L)	3.2 (1.0)	0.7 (1.2)	2.5 (0.2 to 4.9)

N: number, CI: confidence interval, Δ: Change between 18 months and baseline, HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analog Scale, PCS: physical component summary, MCS: mental component summary, CRP: C-reactive protein, mg: milligram, L: litre.

The per-protocol population consisted of 88% (125/142) as 6% (8/142) were lost to follow up, 3% (5/142) discontinued their biological therapy due to an AE, 2% (3/142) switched biological therapy due to persistent flare, and 1% (1/142) only tapered one step due to investigator error.

Dichotomous outcomes were analysed as crude risk difference for the between group comparison using generalised linear models for binomial data. Continuous outcomes were analysed using repeated-measures linear mixed-effects models as least squares means with standard error.

[1]: Analysed as tapering group – control group.

[2]: Compared to baseline biologic dose.

[3]: RA and PsA: Disease Activity Score (DAS)28-CRP, and axSpA: Ankylosing Spondylitis Disease Activity Score (ASDAS).

[4]: RA and PsA: DAS28-CRP <2.6 and axSpA: ASDAS <1.3.

[5]: RA and PsA: DAS28-CRP ≤3.2 and axSpA: ASDAS <2.1.

Supplementary Table S6: Sub-group analyses on the primary efficacy endpoint '≥50% biologic dose reduction' i.e. patients receiving ≥50% reduced biologic dose at 18 months analysed "as observed" based on the ITT population.

Subgroup	Tapering group n/N (%)	Control group n/N (%)	Contrast within sub-groups[1] RD (95% CI)	Contrast between sub-groups[2] RD (95% CI)	p-value for interaction[2]
Overall	35/88 (40%)	1/46 (2%)	0.38 (0.27 to 0.49)	–	–
Diagnosis				-0.18 (-0.40 to 0.05)	0.122
RA or PsA[3]	19/55 (35%)	1/27 (4%)	0.31 (0.16 to 0.45)		
AxSpA[4]	16/33 (48%)	0/19 (0%)	0.48 (0.31 to 0.66)		
Sex				-0.06 (-0.29 to 0.17)	0.626
Female	19/48 (40%)	1/19 (5%)	0.34 (0.17 to 0.51)		
Male	16/40 (40%)	0/27 (0%)	0.40 (0.25 to 0.55)		
Age				0.11 (-0.11 to 0.33)	0.321
<55 years old	19/44 (43%)	0/23 (0%)	0.43 (0.29 to 0.58)		
≥55 years old	16/44 (36%)	1/23 (4%)	0.32 (0.16 to 0.48)		
Repeated biologics failure				0.54 (-0.10 to 1.19)	0.100
<3	34/83 (41%)	0/43 (0%)	0.41 (0.30 to 0.52)		
≥3	1/5 (20%)	1/3 (33%)	-0.13 (-0.77 to 0.51)		
Biologic mode of action				0.13 (-0.35 to 0.62)	0.590
TNFi	32/81 (40%)	0/40 (0%)	0.40 (0.29 to 0.50)		
Non-TNFi[5]	3/7 (43%)	1/6 (17%)	0.26 (-0.21 to 0.73)		
Disease activity				0.11 (-0.17 to 0.41)	0.428
Baseline remission	32/77 (42%)	1/39 (3%)	0.39 (0.27 to 0.51)		
Baseline LDA	3/11 (27%)	0/7 (0%)	0.27 (0.01 to 0.54)		

N: number, RD: risk difference, CI: confidence interval, RA: rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, TNFi: tumour necrosis factor alpha inhibitor, LDA: low disease activity.

[1]: Analysed as crude risk difference (i.e. risk in tapering group – risk in control group) using generalised linear models for binomial data.

[2]: Analysed using binary (logistic) regression.

[3]: Monitored by DAS28-CRP.

[4]: Monitored by ASDAS.

[5]: Treatment with abatacept or tocilizumab.

Supplementary Table S7: Sub-group analyses on the primary efficacy endpoint 'disease activity' i.e. disease activity at 18 months analysed "as observed" based on the ITT population.

Subgroup	Tapering group		Control group		Contrast within sub-groups[2]	Contrast between sub-groups[3]	p-value for interaction[3]
	n/N[1]	Mean (SE)	n/N[1]	Mean (SE)	Mean difference (95% CI)	Mean difference (95% CI)	
Overall	88/88	1.73 (0.08)	44/46	1.67 (0.09)	0.05 (-0.20 to 0.31)	–	–
Diagnosis						-0.18 (-0.67 to 0.32)	0.480
RA or PsA[4]	55/88	1.89 (0.09)	27/44	1.91 (0.12)	-0.02 (-0.33 to 0.30)		
AxSpA[5]	33/88	1.46 (0.12)	17/44	1.3 (0.11)	0.16 (-0.22 to 0.53)		
Sex						-0.49 (-0.97 to 0.001)	0.050
Female	48/88	1.83 (0.11)	19/44	2.07 (0.15)	-0.25 (-0.63 to 0.14)		
Male	40/88	1.61 (0.11)	25/44	1.37 (0.08)	0.24 (-0.07 to 0.55)		
Age						0.13 (-0.36 to 0.62)	0.607
<55 years old	44/88	1.55 (0.10)	22/44	1.44 (0.10)	0.12 (-0.20 to 0.44)		
≥55 years old	44/88	1.90 (0.11)	22/44	1.91 (0.15)	-0.01 (-0.38 to 0.37)		
Repeated biologics failure						0.25 (-0.75 to 1.26)	0.620
<3	83/88	1.69 (0.08)	41/44	1.61 (0.08)	0.08 (-0.17 to 0.33)		
≥3	5/88	2.36 (0.30)	3/44	2.53 (0.75)	-0.17 (-1.83 to 1.48)		
Biologic mode of action						0.03 (-0.76 to 0.82)	0.946
TNFi	81/88	1.68 (0.08)	38/44	1.59 (0.09)	0.08 (-0.17 to 0.35)		
Non-TNFi[6]	7/88	2.23 (0.29)	6/44	2.17 (0.38)	0.06 (-0.98 to 1.10)		
Disease activity						-0.26 (-1.01 to 0.50)	0.503
Baseline remission	77/88	1.72 (0.09)	38/44	1.69 (0.11)	0.02 (-0.26 to 0.30)		
Baseline LDA	11/88	1.81 (0.16)	6/44	1.53 (0.19)	0.28 (-0.28 to 0.83)		

N: number, SE: standard error, CI: confidence interval, RA: rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, TNFi: tumour necrosis factor alpha inhibitor, LDA: low disease activity.

[1]: Number of observations/number of patients in the "as observed" ITT population

[2]: Analysed as mean difference in tapering group – mean difference in control group using ANOVA.

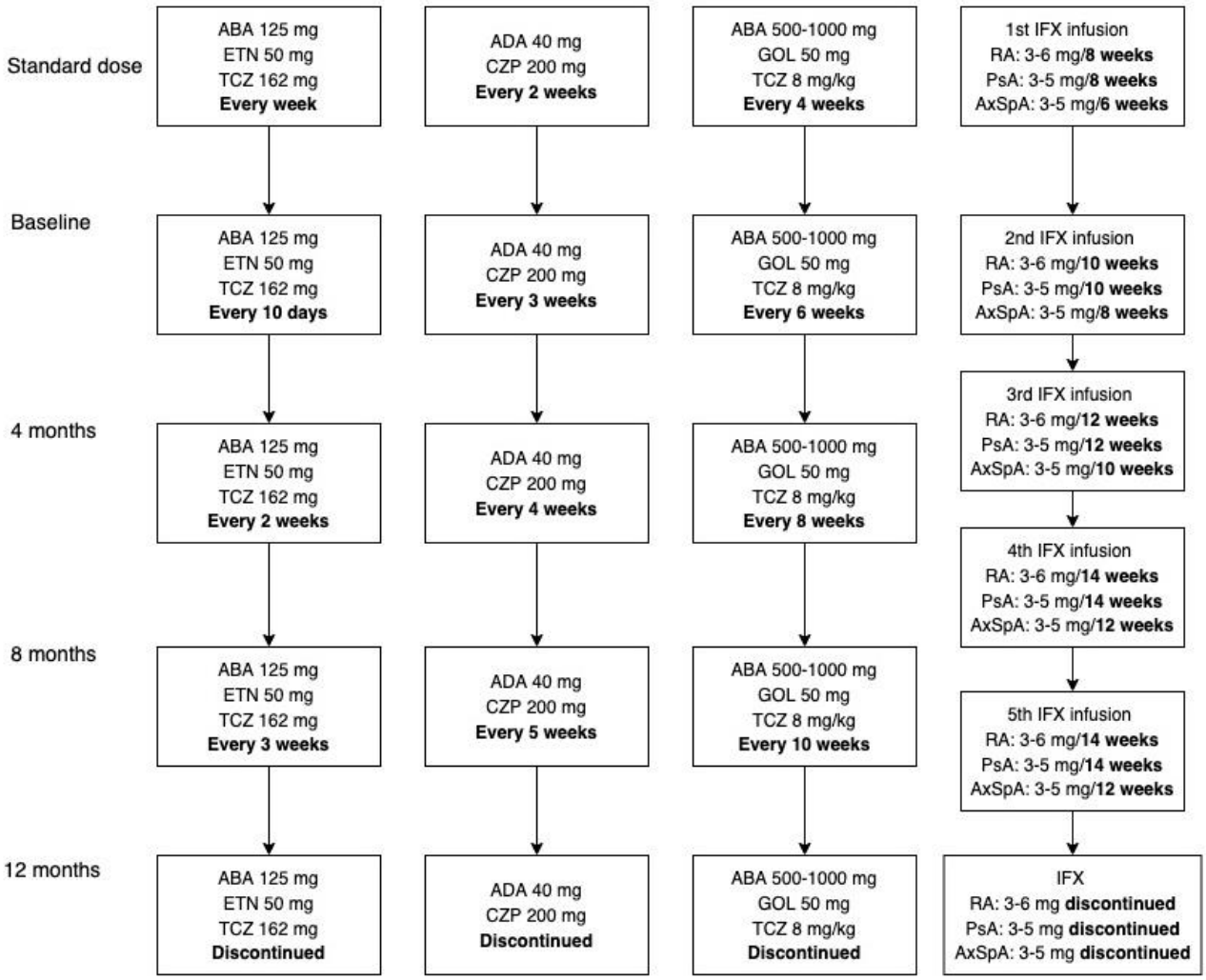
[3]: Analysed using ANOVA.

[4]: Monitored by DAS28-CRP.

[5]: Monitored by ASDAS.

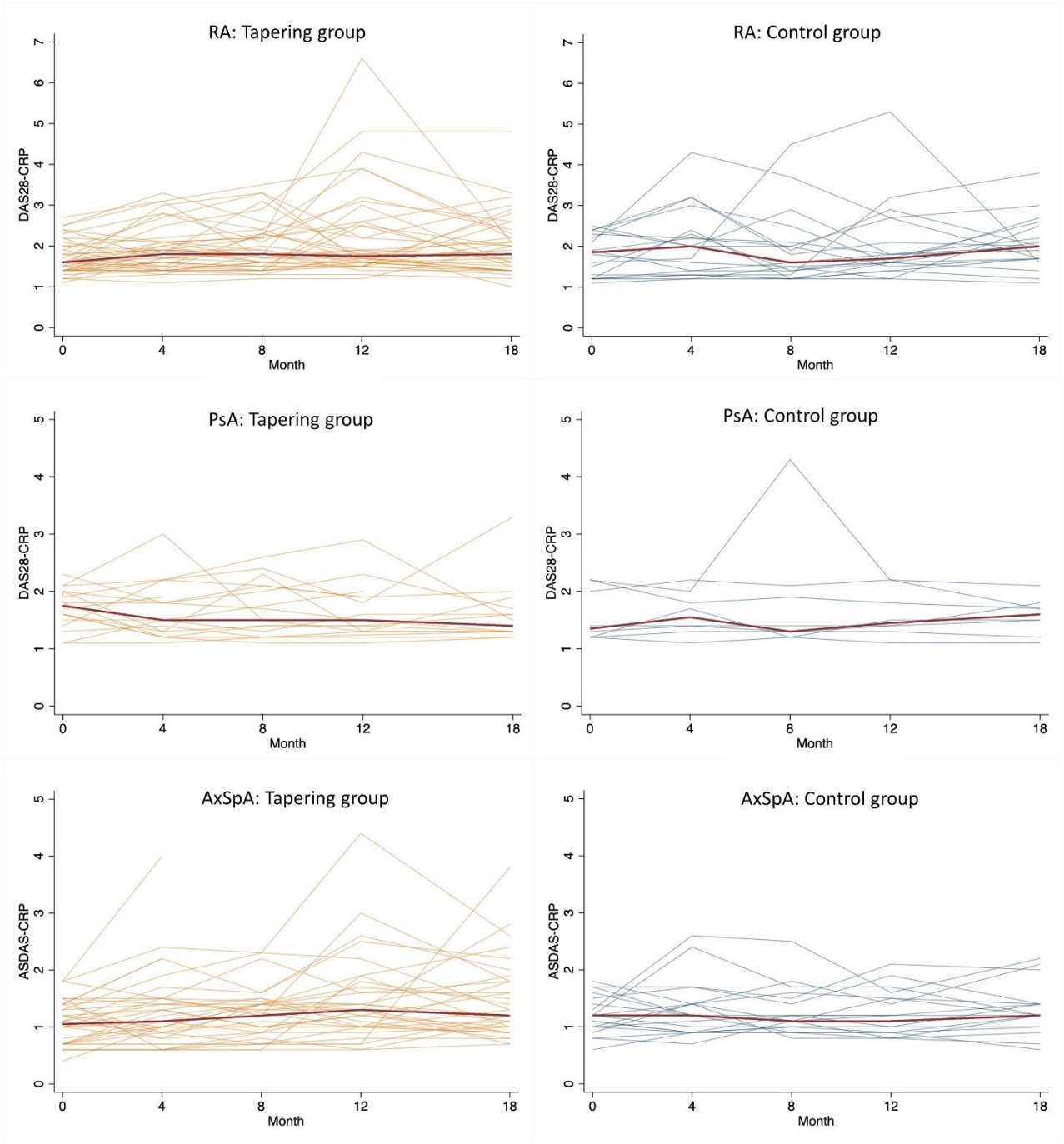
[6]: Treatment with abatacept or tocilizumab

Supplementary Figure S1*:* Overview of the disease activity-guided tapering algorithm applied for patients in the tapering group during the BIODOPT trial.



ABA: abatacept, mg: milligram, ETN: etanercept, TCZ: tocilizumab, ADA: adalimumab, CZP: certolizumab-pegol, GOL: goli-mumab, kg: kilogram, IFX: infliximab, RA: rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis.

Supplementary Figure S2*:* Spaghetti plots of disease activity during the study period in each trial group reported by diagnosis. The red line represents median disease activity.



Dose reduction and discontinuation of biological therapy in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis:

Protocol for a 18 months randomised, open label, parallel-group, multi-centre trial

Brief title: BIOlogical Dose OPTimisation (The BIODOPT trial)

This trial will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline and all other applicable regulatory requirements.

Sponsor-investigator: Salome Kristensen, MD, PhD

Coordinating investigator: Line Uhrenholt, MD

AUTHORS/COLLABORATORS

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TRIAL REGISTRATION

The Ethics Committee of Northern Region of Jutland

Danish Medicines Agency

Danish Data Protection Agency

The trial will be registered on EudraCT before enrolling patients.

TRIAL SITES

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PROTOCOL VERSION 7

December 16, 2017

Protocol number: 20170508

EudraCT number: 2017-001970-41

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ICH: International Conference on Harmonisation

GCP: Good Clinical Practice

LU: Line Uhrenholt

SK: Salome Kristensen

ASc: Annette Schlemmer

EMH: Ellen-Margrethe Hauge

RC: Robin Christensen

KHH: Kathrine Hyldig Hansen

REDCap: Research Electronic Data Capture

JHW: Johanne Hovgaard Winther

RA: Rheumatoid arthritis

SpA: Axial spondyloarthritis

PsA: Psoriatic arthritis

DAS28crp: Disease Activity Score28crp

ASDAS: Ankylosing Spondylitis Disease Activity Score

DAPSA: Disease Activity in Psoriatic Arthritis

IBD: Inflammatory bowel disease

T2T: Treat-to-target

LDA: Low disease activity

DMARD: Disease-modifying antirheumatic drugs

ETN: Etanercept

MTX: Methotrexat

RCT: Randomized controlled trial

ADA: Adalimumab

AS: Ankylosing spondylitis

IFX: Infliximab

PROMs: Patient Reported Outcome Measures

VAS: Visual Analog Scale

HAQ-DI: Health Assessment Questionnaire Disability Index

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASFI: Bath Ankylosing Spondylitis Functional Index

DRS: Dansk Reumatologisk Selskab (The Danish Rheumatology Society)

EULAR: European League Against Rheumatism

GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

RADS: Rådet for Anvendelse af Dyr Sygehusmedicin (The Council for the Use of Expensive Hospital Medicine)

ACR: American College of Rheumatology

ASAS: Assessment of SpondyloArthritis

SAA: Spondylitis Association of America

SPARTAN: Spondyloarthritis Research and Treatment Network

DOT: Dose optimisation tapering group

UC: Usual care group

CASPAR: ClASsification criteria for Psoriatic ARthritis

ABA: Abatacept

CZP: Certolizumab pegol

GOL: Golimumab

TCZ: Tocilizumab

DANBIO: Danish Rheumatology Database

IUD: Intrauterine device

SPARCC: Spondyloarthritis Research Consortium Canada enthesitis score

BASMI: Bath Ankylosing Spondylitis Metrology Index

CRP: C-reactive protein

OMERACT: Outcome Measures in Rheumatology

FMK: Fælles Medicin Kort (online medicine card)

ADAb: Anti-drug antibodies

NSAID: Non-Steroidal Anti-Inflammatory Drugs

e-CRF: Electronic Case Report Form

MRI: Magnetic Resonance Imaging

PASI: Psoriasis Area Severity Index

mNAPSI: Modified Nail Psoriasis Severity Index

ET: Early termination visit

FU: Telephone follow up visit

PtGH: Patient Global Health

SF-36: Short Form Health Survey 36

B-hcg: Blood test for Human Chorion Gonadotropin

ALAT: Alanine transaminase

BASP: Alkaline phosphatase

TSH: Thyroid-stimulating hormone

IgM-RF: IgM rheumatoid factor

Anti-CCP: Anti-cyclic citrullinated peptide

ANA: Antinuclear antibody

HLA-B27: Human leukocyte antigen subtype B27

CDAI: Clinical Disease Activity Index

SDAI: Simplified Disease Activity Index

MDA: Minimal Disease Activity criteria

SAP: Statistical analysis plan

ITT: Intention-to-treat

AE: Adverse event

SAE: Serious adverse event

SAR: Serious adverse reaction

SUSAR: Suspected unexpected serious adverse reaction

TMF: Trial master file

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6. INTRODUCTION

6.1. Summary

Background: The treatment of rheumatoid arthritis (RA), axial spondyloarthritis (SpA) and psoriatic arthritis (PsA) has undergone dramatic changes over the past 20 years mainly due to introduction of biological agents combined with close monitoring according to the treat-to-target principles. Recent studies have shown that a large proportion of patients with RA, SpA or PsA can maintain remission after tapering or even after withdrawal of the biological therapy.

Objectives: To evaluate whether a patient-involving dose optimisation tapering strategy for biological therapy will enable a superior dose-reduction (≥ 50%) while being equivalent in maintaining disease activity assessed 18 months from baseline compared with "usual care" (i.e. continuing biological therapy unchanged). The co-primary endpoint is thus:

1A Superiority: The proportion of patients who at 18 months is reduced to 50% or less of their inclusion dose of biological therapy.

1B Equivalence: Disease activity assessed 18 months from baseline

Key secondary endpoints at 18 months include the proportion of patients in remission and receiving reduced dose biological therapy and the proportion of patients in remission despite discontinuation of biological therapy. Exploratory objectives are to identify potential prognostic factors for flare after tapering of biological therapy and to explore potentially important factors associated with remission maintenance after the biological therapy is reduced or even discontinued.

Trial population: this trial will include participants with RA, SpA (including patients with PsA with axial involvement) and PsA (with peripheral involvement) in treatment with biological agents who have achieved sustained clinical remission for at least 1 year and who comply with all eligibility criteria. Remission is defined as Disease Activity Score28crp (DAS28crp) < 2.6 (Appendix 1) in patients with RA, Ankylosing Spondylitis Disease Activity Score (ASDAS) < 1.3 (Appendix 2) in patients with SpA and Disease Activity in Psoriatic Arthritis (DAPSA) ≤ 4 (Appendix 3) in patients with PsA.

Perspective: continuation of standard dose of biological therapy in patients with RA, SpA or PsA in sustained clinical remission will potentially lead to overtreatment and thus unnecessary side effects e.g. common and serious infections. Furthermore, biological therapy is costly and therefore, if dose optimisation (tapering or even withdrawal) is possible, benefits for society (incl. costs) would be anticipated. The outcome of this trial could lead to a significant change in the clinical management of biological therapy in patients with RA, SpA and PsA.

6.2. Background

6.2.1. Inflammatory conditions: epidemiology

RA, SpA and PsA are the three largest inflammatory arthritis groups in the rheumatology outpatient clinics. In Denmark, 0.7% of the population is estimated to suffer from RA (1), a disease characterised by peripheral, symmetric polyarthritis that can be accompanied by extra-articular manifestations like tenosynovitis, bursitis, rheumatoid nodules, serositis etc. (1). 0.5-2% of the Danish population is estimated to suffer from SpA (2), which is characterised by axial and possibly peripheral arthritis and can be accompanied by extra-articular manifestations like enthesitis, dactylitis, skin and nail psoriasis, inflammatory bowel disease (IBD) or uveitis (3). The prevalence of PsA is probably underestimated, as 0.1% of the population is estimated to suffer from PsA (4), while up to 30% of patients with skin psoriasis (prevalence 1-3%) is estimated to have PsA (5). PsA is characterised by peripheral and/or axial arthritis and can be accompanied by extra-articular manifestations like enthesitis, dactylitis, skin and nail psoriasis (5).

6.2.2. Inflammatory conditions: management

The treatment of RA has been significantly improved over the past 20 years partly due to the treat-to-target (T2T) principles, which consist of early diagnosis, defining a target (remission/low disease activity (LDA)) and applying tight control with adaptions of the arthritis treatment until the target is reached. This treatment strategy has been able to reduce arthritis activity compared to previous treatment regimes (6–11). Within the last years, the same treatment strategy has been shown to reduce arthritis activity in patients with PsA compared to previous treatment regimes (12). In daily clinical practice, SpA is treated after the T2T recommendations (13), but this is mainly based on expert opinions, as there currently is no clinical evidence of T2T in SpA (14–16). However, these individualized strategies is used as expert assessment finds it very likely to improve patient outcomes and long-term quality of life (13).

In addition to the T2T paradigm, biological agents has significantly improved treatment for patients with RA, SpA and PsA, thus increasing the numbers of patients in sustained clinical remission (17–33) – particularly patients with severe arthritis activity, as it is this group of patients that are candidates for biological therapy according to national and international guidelines.

6.2.3. Evidence Based Research: Tapering and withdrawal strategies

To avoid waste of research, no new studies should be initiated without a systematic review of the existing evidence (34). For the last two decades, the perception has been that biological therapy would be a lifelong treatment. However, recent studies indicate that a significant proportion of patients in clinical remission, can taper their biological therapy and still maintain remission (35–48). Currently, several tapering studies have been performed in patients with RA. However, these studies are often initiated by the pharmaceutical industry, thus involving only one biological drug per study and is often part two of an efficacy study (35,36,40,49,50); furthermore, in these studies, the population is often newly diagnosed and start biological therapy without prior disease-modifying antirheumatic drugs (DMARD) (36,40,49,50). Therefore, these patients do not necessarily need biological therapy and thus, it may be easier to taper the dose of the biological therapy and maintain remission or LDA (36,40,49,50). The PRESERVE trial, a major efficacy trial of etanercept (ETN), included, in contrast to the studies described above, patients with RA with moderate arthritis activity despite methotrexate (MTX) treatment (35). In part 2 of the trial it was found, that 82.6% of patients who continued standard dose ETN and 79.1% of patients who reduced ETN dose by 50% remained in LDA 1 year after, while significantly fewer patients who discontinued ETN maintained LDA (42.6%). In the DOSERA trial, a smaller Nordic randomised controlled trial (RCT), patients with RA from outpatients clinics who had achieved sustained LDA on ETN + MTX were included (37). The trial found, that 52% of patients who continued ETN in standard dose and 44% of those who reduced ETN dose by 50% had no flare over 48 weeks, while this only applied to 13% of patients who discontinued ETN (37). In a non-inferiority RCT with patients with RA, 20% of patients who gradually reduced dose of their biological therapy (adalimumab (ADA) or ETN) discontinued the treatment over 18 months while 43% received reduced doses and 37% had an arthritis flare (39). The dose optimisation of ADA and ETN was non-inferior to "usual care". Several studies have shown that discontinuation of biological therapy without prior dose reduction causes flare in up to 51% of patients with RA (49,51–56), however most patients regain remission after dose escalation to standard dose (49,51,54,56).

Dose optimisation of biological therapy in patients with SpA has been studied in several smaller trials. In the ANSWERS trial, a smaller RCT and ETN efficacy trial, 52% of patients with ankylosing spondylitis (AS) who reduced ETN dose by 50% (tapered group) and 83% of patients with AS who remained on ETN standard dose maintained remission 6 months after (45). However, only 4 out of 11 patients who had a flare in the tapered group needed dose increase of the biological therapy to stand-

ard dose. A small Dutch prospective observation study found that 53% of patients with AS who gradually reduced dose of their biological therapy (ADA, ETN or infliximab (IFX)) by 25% every 6 months remained in remission 24 months after dose optimisation (48). In the study, the mean dose of biological therapy over time corresponded to 62% of the standard dose regimen (48). Other studies have shown that discontinuation of biological therapy without prior dose reduction causes flare in 69-97.6% of patients with SpA (57–59), however most patients regain remission after dose escalation to standard dose (57–59).

Dose optimisation of biological therapy in patients with PsA has only been investigated in a few, smaller studies. In a prospective case-control study with 76 newly diagnosed patients with PsA and 55 with RA, 88.6% of patients with PsA and 17.6% of patients with RA (controls) were still in remission after 50% dose reduction of ADA, mean follow up were 28.9 and 24.2 months (42). A small Spanish cross-sectional study has shown that 27.5% of patients with PsA received reduced dose of their biological therapy, average time on reduced dose was 24.8 months (43). In this study, 42% received ADA 40 mg on average every 23.58 day, 28.6% received ETN 50 mg on average every 12.66 day and 28.6% received IFX average dose 3.77 mg/kg every 8 weeks. A minor, prospective observation study with patient with PsA has examined discontinuation of IXF without prior dose reduction. The study showed that 4 out of 4 patients had a flare, three patients after 2-6 months and one patient after 11 months (60).

Thus, the studies described above indicate that dose optimisation of biological therapy is possible in some patients with RA, SpA and PsA – especially by gradually reducing the dose, as abrupt discontinuation leads to flare in a significant proportion of patients. However, the studies above had a strict tapering algorithm without possibility of patient-involvement, which may cause patient dissatisfaction and lack of adherence to the algorithm.

In Rheumatology, Patient Reported Outcome Measures (PROMs) are essential together with clinical and paraclinical tests in the assessment of arthritis activity and judgement of treatment effect. In clinical practice in Denmark, the PROMs available include Visual Analog Scale (VAS) for pain, fatigue and global assessment of disease activity (Appendix 4), Health Assessment Questionnaire Disability Index (HAQ-DI) (Appendix 5) and for patients with SpA Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (Appendix 6) and Bath Ankylosing Spondylitis Functional Index (BASFI) (Appendix 7). Thus, the patient's own assessment of arthritis activity is taken into consideration at each visit in the outpatient clinic, allowing the patients to influence any treatment changes and adjustments.

6.2.4. Rationale for the BIODOPT trial

The tapering studies described above used a strict dose optimisation algorithms without the possibility of interactive patient-involvement. In daily clinical practice, such an approach may underestimate disease activity and cause dissatisfaction among the patients, thus reducing their adherence to the algorithm. Therefore, it seems rational to involve the patient in the dose optimisation and thus, this trial focus on PROMs to illustrate the patients' perception of arthritis activity during tapering. At each clinical visit, the physician evaluates the PROM data from the patient when considering if the patient has a flare. The patient-involvement in this trial also focus on patient educating regarding symptoms of arthritis flare so the patient is aware of symptoms that require assessment in the Rheumatology outpatient clinic.

To our knowledge, no specific national or international guidelines for dose optimisation of biological therapy in patients with RA, SpA or PsA are available. The Danish Rheumatology Society (Dansk Reumatologisk Selskab (DRS)) states in the new guideline for SpA that in absence of evidence, the results of several current studies regarding dose reduction and discontinuation of biological therapy are awaited (61). The same statement will be in the new DRS guideline for RA, which is currently being edited. Dose optimisation of biological therapy is not described in the DRS guideline for PsA from 2014 (5) and because of absence of evidence neither in the guidelines form European League Against Rheumatism (EULAR) (62) or Group for Research and Assessment of Psoriasis And Psoriatic Arthritis (GRAPPA) (63). In the absence of evidence, the Council for the Use of Expensive Hospital Medicine (Rådet for Anvendelse af Dyr Sygehusmedicin (RADS)) cannot provide general recommendations for dose optimisation of biological therapy in patients with RA, SpA and PsA, but abrupt discontinuation is not recommended (64–66). The American College of Rheumatology (ACR) and EULAR suggests dose optimisation of biological therapy by gradually reducing the dose in patients with RA (67,68); however ACR does not recommend discontinuation (68). In the 2017 Assessment of SpondyloArthritis (ASAS)/EULAR guideline it is recommended that dose optimisation by gradually reducing the dose of the biological therapy is considered in patients with SpA in sustained clinical remission for $\geq$ 6 months (69). ACR/Spondylitis Association of America (SAA)/Spondyloarthritis Research and Treatment Network (SPARTAN) guideline from 2016 recommend on the other hand continuation of biological therapy despite sustained remission due to lack of evidence (70). Thus, at present there are to our knowledge no specific guideline for dose optimisation of biological therapy in patients with RA, SpA or PsA. However, both from the individual patient's standpoint, as well as from a societal perspective, it would be advantageous if the biological therapy did not need

to be continued indefinitely but could either be reduced or even discontinued while maintaining sustained clinical remission. Thus, continuation of standard dose of biological therapy in patients in sustained clinical remission can lead to overtreatment and unnecessary side effects e.g. serious infections. In addition, biological therapy is costly and therefore dose optimisation is expected to cause considerable savings in the health budget.

An interactive patient-involvement in dose optimisation of biological therapy is to our knowledge a new approach of interest, but it seems plausible that the patient in this setting is more motivated for the dose reduction, thereby achieving better patient compliance to the algorithm. Thus, in this trial we will examine dose optimisation of biological therapy with a flexible patient-involving algorithm where the patient is an equal partner in their disease management, as expected and required by modern society (71).

7. RESEARCH HYPOTHESIS

The main trial hypothesis is that the use of an interactive patient-involving dose optimisation tapering algorithm for biological therapy will reduce use of biologics while the patients remain in persistent clinical remission.

8. OBJECTIVES AND AIMS

8.1. The primary objectives

To evaluate whether an interactive patient-involving dose optimisation tapering strategy for biological therapy will enable a significant dose-reduction while being equivalent in maintaining disease activity assessed 18 months from baseline compared with "usual care" (i.e. continuing biological therapy unchanged). The co-primary endpoints are thus:

1A Superiority: The proportion of patients who at 18 months is reduced to 50% or less of their inclusion dose of biological therapy.

1B Equivalence: Disease activity assessed 18 months from baseline

The aim of the BIODOPT trial is to assess whether disease activity corresponding to remission can be sustained when doses of biological agents are reduced (≥ 50%) or completely withdrawn.

8.2. The secondary objectives

Key secondary endpoints at 18 months include the proportion of patients in remission and receiving reduced dose biological therapy and the proportion of patients in remission despite discontinuation of biological therapy. Exploratory objectives are to identify potential prognostic factors for flare after

tapering of biological therapy and to explore potentially important factors associated with remission maintenance after the biological therapy is reduced or even discontinued (72–75).

9. METHODS

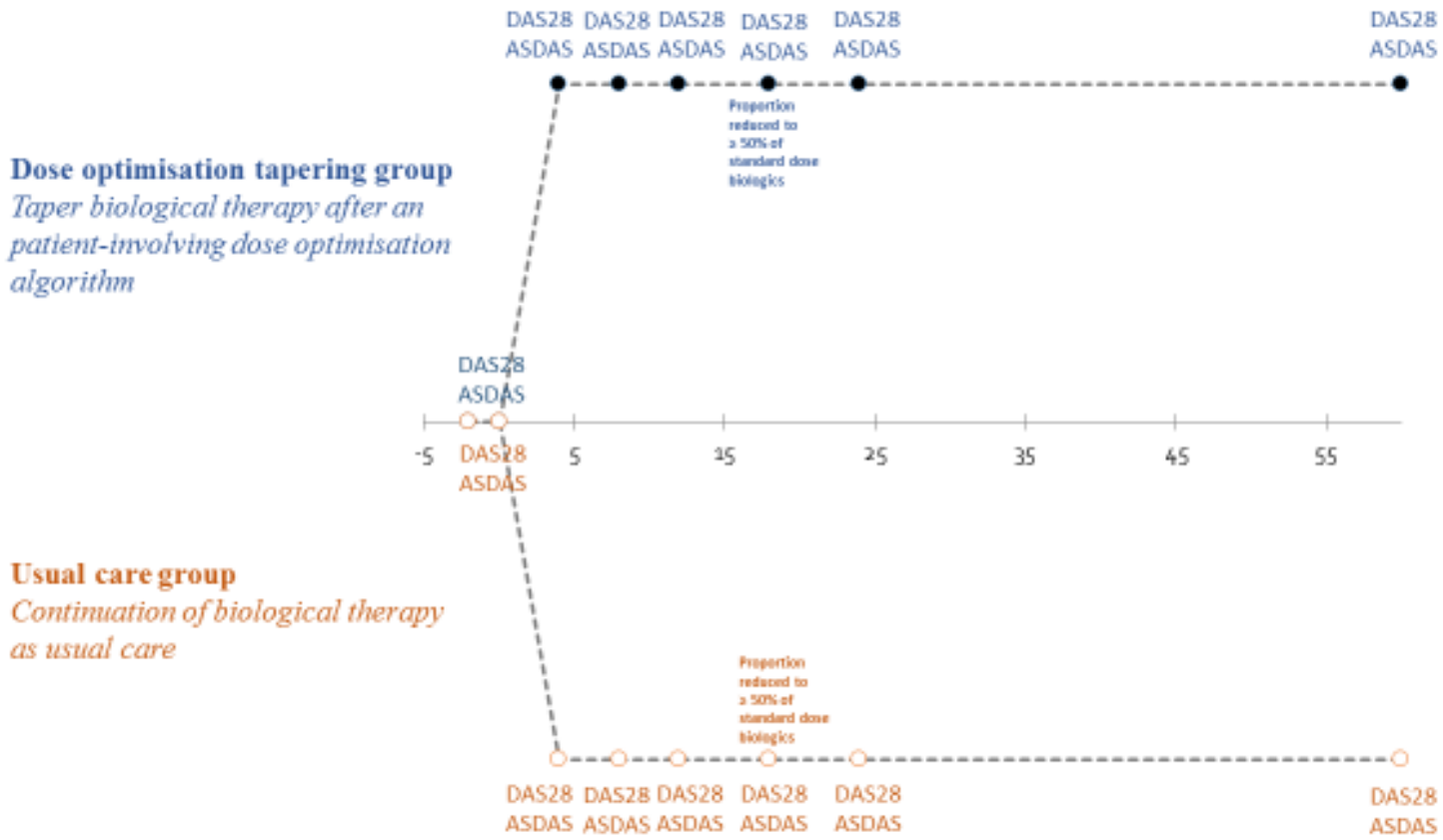
9.1. Trial design

A randomised controlled, open label, parallel-group, multicentre, equivalence trial of 18 months duration including patients with RA, SpA (including patients with PsA with axial involvement) and PsA (with peripheral involvement) in sustained clinical remission on biological therapy. The participants will be randomised in ratio 2:1 to dose optimisation tapering group (DOT) or usual care group (UC). After the intervention period (the first 12 months of the trial), a follow-up period starts which consist of three visits at 18, 24 and 60 months from baseline. Thus, the trial visits are:

- Baseline
- Visit at 4 months
- Visit at 8 months
- Visit at 12 months
- Visit at 18 months
- Visit at 24 months
- Visit at 60 months

Figure 1 illustrates the trial design with clinical visits, outcome assessments and milestones.

Figure 1: overview of the trial design



The participants will be randomised 2:1 into either a patient-involving dose optimisation tapering algorithm guided dose reduction of the biological therapy or usual care i.e. continuation of biological therapy as usual care. Disease activity will be monitored systematically throughout the trial by the CRP-based disease activity scores DAS28crp for patients with peripheral arthritis (RA and PsA) and ASDAS for patients with SpA. Trial visits are: baseline, visit at 4, 8, 12, 18, 24 and 60 months.

9.2. Setting

Four Rheumatology Outpatient Clinics in Denmark (Aalborg, Aarhus, Odense and Hjørring) will recruit and enrol patients from November 2017 to November 2018.

9.3. Participants

9.3.1. Recruitment

After submission and approval of the protocol to relevant authorities, the investigators of the four sites will recruit patients from their rheumatology outpatient clinics, see section 13.1. Recruitment procedures for detailed information. Recruiting will continue until the target population is achieved. The screening period is set to 12 months from November 2017 to November 2018.

9.3.2. Eligibility criteria

9.3.2.1. Inclusion criteria

A participant will be eligible for trial participation if he/she meets the following criteria:

- The participant is able and willing to provide written informed consent and comply with the requirements of this trial protocol.
- The participant is ≥ 18 years of age
- Meets the following diagnostic criteria:
    - Patients with RA: 2010 ACR/EULAR Classification Criteria for RA (Appendix 8) and/or 1987 ACR RA Criteria (Appendix 9)
    - Patients with SpA: 1984 modified New York Criteria for AS (Appendix 10) and/or 2009 ASAS Classification of SpA (Appendix 11) and/or axial PsA according to ClASsification criteria for Psoriatic ARthritis (CASPAR) (Appendix 12) and/or Moll & Wright Criteria (Appendix 13)
    - Patients with PsA: CASPAR Criteria and/or Moll & Wright Criteria
- Participants must be treated with abatacept (ABA), ADA, certolizumab pegol (CZP), ETN, golimumab (GOL), IFX or tocilizumab (TCZ) in stable dose (i.e. standard dose or reduced dose) during the last 12 months
- Participants must be in sustained clinical remission as defined in this protocol during the last 12 months measured by ≥ 2 registrations in the Danish Rheumatology Database (DANBIO)

- Female participants with childbearing potential: negative pregnancy test at baseline and practicing one of the following methods of safe birth control, for detailed information see section 12. Pregnancy:
    - Intrauterine device (IUD)
    - Hormonal contraception i.e. birth control pills, birth control implants, birth control patch, birth control vaginal ring or birth control shot (depot injection)
    - A vasectomized partner

9.3.2.2. Exclusion criteria

A participant cannot be included in the trial if he/she meets any of the following criteria:

- Inability to provide informed consent or unwilling to comply with the trial protocol
- Current oral prednisolone treatment
- Intra-articular or parenteral administration of corticosteroids or a short course of oral prednisolone within the last year
- Dose reduction of the biological therapy is not suitable judged by medical expert assessment due to e.g. patients with previously severe arthritis with difficult to reach remission on biological therapy or patients who previously have tried dose reduction of the biological therapy resulting in flare
- Female participants who is pregnant or breast-feeding or considering becoming pregnant while on biological therapy, MTX and/or leflunomide or within 3-6 months after the last dose, for detailed information see section 12. Pregnancy.
- Participants who have a history of psychiatric or psychological conditions that, in the opinion of the investigator, will affect the ability to participate in the trial
- Addictive or previous addictive behaviour defined as abuse of alcohol, hash, opioids or other euphoric substances
- Participants who is considered an unsuitable candidate for the trial for any reason by the investigator

Men treated with anti-TNF-α can continue their biological therapy during contraception as studies have found no adverse effect on seed quality and no increased risk of adverse effects in fetus/infant in the available studies as stated in the RADS guidelines (76–78).

Allergic reaction or significant sensitivity to constituents of the study drugs are not considered a relevant exclusion criterion in this trial as patients have been treated with the study drugs (biological therapy) > 1 year prior to inclusion.

9.4. DANBIO

DANBIO is a national Danish Rheumatology database where all adult patients with RA, SpA or PsA is recorded to assess arthritis activity. At each clinical visit, the patients' answers different PROMs on a touch screen in the rheumatology outpatient clinic, alternatively by DANBIO home access just before the clinical visit. In the database, the PROMs answered by the patient, the physicians registration of clinical findings e.g. swollen and tender joint count, enthesitis score by the Spondyloarthritis Research Consortium Canada Score (SPARCC) (Appendix 14) and Bath Ankylosing Spondylitis Metrology Index (BASMI) (Appendix 15) and the most recent C-reactive protein (CRP) level is uses to assess arthritis activity in order to conclude if the patient is in remission or not. Thus, the patient's own assessment of arthritis activity is taken into consideration at each visit in the rheumatology outpatient clinic, allowing the patients to influence any treatment changes and adjustments.

9.5. Remission criteria

In this trial, the following composite scores for the three different diseases are used to assess disease activity. All composite scores are published, validated and currently used for assessment of arthritis activity in trials and/or clinical practice. In this trial, remission is defined as:

RA: DAS28crp < 2.6 and no swollen joints assessed by 46 joint count for swollen and tender joints (46 joint count: Appendix 16)

SpA: ASDAS < 1.3. Additional peripheral involvement: no swollen joints assessed by 66/68 joint count for swollen and tender joints (66/68 joint count: Appendix 17)

PsA: DAPSA ≤ 4 and no swollen joints assessed by 66/68 joint count for swollen and tender joints.

DAS28crp was chosen for RA over CDAI as a review of patients with RA from the Department of Rheumatology at Aalborg University Hospital showed, that only 1 patient out of 31 in biological therapy, who fulfilled DAS28crp remission but not CDAI remission, had swollen joints – the remaining 30 patients was not in CDAI remission because of a high patient VAS global disease activity. ASDAS was chosen for patients with SpA over BASDAI as it is the recommended index by ASAS and EULAR (69). At present, there are to our knowledge no consensus regarding the preferred efficacy parameter (composite score) for patients with PsA either nationally or internationally. The

DAPSA was chosen in this trial as it is a stringent index that contains 66/68 joint count for swollen and tender joints and is one of the suggested efficacy scores by EULAR (62).

Peripheral arthritis is assessed by joint count – ultrasound assessment is thus not part of this trial, but can be used when in doubt to visualise the joint as done in daily clinical practice today. Arthritis assessed by ultrasound has synovial hypertrophy with grey tone and/or Doppler.

9.6. Flare criteria

In this trial, the Outcome Measures in Rheumatology (OMERACT) recommended DAS28 flare criteria for patients with RA is used (79). Currently, no consensus exist regarding which composite score to use for monitoring patients with PsA and thus no flare criteria exist. In this trial, the DAS28 flare criteria is also used for patients with PsA as it currently is the only flare criteria for patients with peripheral arthritis. The ASAS definition of ASDAS worsening for patients with SpA is used as flare criteria in this trial (80). Thus, in this trial, the following flare criteria is used:

RA and PsA: the following points must both be meet:

- ΔDAS28crp > 1.2 or ΔDAS28crp > 0.6 AND current DAS28crp $\geq$ 3.2
- Arthritis flare assessed by the physician

SpA: one of the following points must be meet:

- Inflammatory back pain AND ΔASDAS $\geq$ 0.9
- Additional peripheral involvement: $\geq$ 1 swollen joint assessed by 66/68 joint count AND arthritis flare assessed by the physician

Arthritis flare assessed by the physician requires exclusion of other reasons for flare e.g. infection, compliance problems or short pause with the biological therapy e.g. due to surgery. If the flare is not caused by dose reduction of the biological therapy, relevant examinations according to current guidelines is performed and the patient continues the biological therapy unchanged. However, patients with ongoing severe infection will pause the biological therapy until the infection is over according to general clinical practice. If the flare is caused by dose reduction of the biological therapy, the patient must increase the dose of the biological therapy to the last dose at which the arthritis was in remission – otherwise the patient is excluded from the trial due to non-compliance. Severe arthritis flare due to tapering that cannot be treated with standard dose of the biological therapy is treated in accordance with the national guidelines e.g. switch to another biological therapy. If the patient has symptoms of arthritis flare during tapering, but the arthritis is in remission assessed by the physician, the patient is

advised to continue tapering according to this protocol but may remain at the current dose after agreement between the patient and the physician.

As patients with PsA can have both axial and peripheral involvement, it is considered a flare if a patient with (peripheral) PsA have inflammatory back pain and an ASDAS flare. Similarly swollen joints in patients with SpA (including patients with PsA with axial involvement) is considered a flare. In Denmark, the indication for biological therapy for patients with RA, SpA or PsA is severe arthritis activity as described in DRS and RADS Guidelines (1,5,61,64–66). Thus, remission is assessed by the physician according to the above remission and flare criteria. However, in this trial other characteristics of SpA and PsA such as enthesitis, dactylitis, skin and nail involvement is also recorded – but the treatment is determined by the patient's peripheral or axial arthritis, because biological therapy for the manifestations mentioned above is not a part of rheumatology in Denmark. If the patient has symptoms of psoriasis flare during tapering, the Dermatological Department is contacted for dialogue and expert opinion in particular need for further examination or treatment adjustment e.g. dose escalation of the biological therapy. The same procedure applies to patient with symptoms of IBD flare during tapering (the Gastroenterology Department is contacted) or patient with symptoms of uveitis flare during tapering (the Ophthalmology Department is contacted). If the patient develop enthesitis or dactylitis during tapering, these conditions are treated according to general guidelines with physiotherapy and/or steroid injection.

9.7. Interventions

Participants will be randomised to one of two groups (2:1):

- Group 1: DOT, N = 120: dose optimisation of the biological therapy using an interactive patient-involving algorithm for disease activity guided dose reduction, i.e. stepwise increase of the dose interval until flare or discontinuation.
- Group 2: UC, N = 60: continuation of the biological therapy as usual care

9.8. Study drug

The study drugs in this trial are the biological therapies: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and tocilizumab. Standard dose of the biological therapies for patients with RA, SpA and PsA are according to RADS (64–66):

- Abatacept (ABA):
    - Subcutaneous: 125 mg every week
    - Intravenous: weight < 60 kg: 500 mg every 4 weeks
    - Intravenous: weight 60-100 kg: 750 mg every 4 weeks
    - Intravenous: weight > 100 kg: 1000 mg every 4 weeks
- Adalimumab (ADA): 40 mg subcutaneous every 2 weeks
- Certolizumab pegol (CZP):
    - 200 mg subcutaneous every 2 weeks
    - 400 mg subcutaneous every 4 weeks
- Etanercept (ETN):
    - 25 mg subcutaneous twice per week
    - 50 mg subcutaneous every week
- Golimumab (GOL): 50 mg subcutaneous every 4 weeks
- Infliximab (IFX):
    - RA: 6 mg/kg intravenous every 8 weeks
    - PsA: 5 mg/kg intravenous every 8 weeks
    - SpA: 5 mg/kg intravenous every 6 weeks
- Tocilizumab (TCZ):
    - Subcutaneous: 162 mg every week
    - Intravenous: 8 mg/kg every 4 weeks

The biological therapies are all approved and are nationally and internationally an established part of the treatment of patients with RA, SpA and PsA, however abatacept and tocilizumab only have indication for RA according to RADS (64–66). Detailed information of the biological therapies used in this trial as regards to use, management and risk profile is described in the summary of product characteristics by the European Medicines Agency. In brief, the positive effect on arthritis activity in patients with RA, SpA and PsA is well-documented and serious adverse events are rare. The most serious risks are infection e.g. respiratory infection, cystitis or skin infection, however this risk is expected to be reduced during this trial for the patients who taper their biological therapy. If the patient develop an infection while on biological therapy, he/she will be treated according to local guidelines. The physician judge if the infection is severe and the biological therapy must be paused for a brief period and/or if the patient must be treated with antibiotics.

9.9. Drug accountability

The biological therapies are all provided by the hospital pharmacy according to usual clinical practice in pre-filled syringes/pens (biological therapy in subcutaneous form) or pre-filled bottles (biological therapy in intravenous form). Skilled personnel will administer the intravenous agents at the trial sites in appropriately qualified intravenous infusion units. The biological drugs are all stored according to product-specific guidelines i.e. protected from light at 2°C-8°C. At the trial site, trained personnel will check the biological agents (study drug) for damage and verify proper identity and quantity as usual clinical practice. The trained personnel will also pack and label the biological agents used in this trial before administering it to participating patients (intravenous form) or handing it out to participating patients (subcutaneous form) (Appendix 18: labels for study drugs). Accurate and updated records of study drugs for the individual participant is registered by BATCH number in the patient's medical record and online medicine card (Fælles Medicin Kort (FMK)). The BATCH number of the biological therapy in intravenous form is registered when the drug is administrated at the rheumatology outpatient clinic. The BATCH number of the biological therapy in subcutaneous form is registered when the drug is handed over to the patient at the rheumatology outpatient clinic.

The patient's individual online medicine card (FMK) lists all medications, which the patient is currently treated with. At baseline, the patient receive a copy of the FMK and a patient diary (Appendix 19) and is informed to write down any changes in medication between the visits in this trial. In the patient diary, the date and the dose administered will be recorded. The patient also register in the diary if the study drug (biological therapy) is paused outside of the trial visits e.g. because of severe infection or operation. The dosing records will be reviewed and verified for compliance at each visit by the research personnel at the trial site, and the investigator will retain all relevant dosing information. The participant will also receive a written instruction for the dose reduction of the biological therapy at baseline (Appendix 20) and this instruction will be reviewed at each clinical visit.

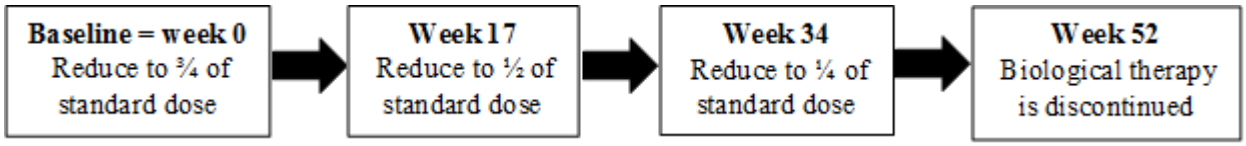
9.10. Dose optimisation tapering algorithm

At present, there are no specific guidelines nationally or internationally for dose optimisation of biological therapy in patients with RA, SpA or PsA in sustained clinical remission. In DOT, the dose of the biological therapy is gradually reduced over 1 year by prolonging the dosing intervals using an algorithm. The dose optimisation tapering algorithm is used in order to minimize the risk of flare due to rapid dose reduction. The participating patients follows the algorithm as long as their arthritis is in

remission. Due to IFX is administered at longer dosing intervals than the remaining biological therapies, the dose optimisation tapering algorithm for IFX is different. Thus, patients tapering IFX prolong the dosing interval with 2 weeks at each infusion, see section 9.10.2. Dose optimisation tapering algorithm for IFX, and can discontinue IFX 44-52 weeks after baseline, if possible. Patients tapering one of the remaining biological therapies reduce dose with approximately 25% every 4 months at clinical visits in the Rheumatology Outpatient Clinic, thus the biological agent can be discontinued 52 weeks after baseline, if possible. The participants is as usual practice asked for symptoms of arthritis flare when receiving the intravenous/subcutaneous biological agent at the rheumatology outpatient clinic. Patients will receive the scheduled infusion/receive the subcutaneous biologics after research personnel secure a full DANBIO registration including PROMs, CRP, joint count for swollen and tender joints and for patients with SpA BASMI. The patient is booked for an extra clinical visit within 7 days as described in section 9.13. Patient-involvement.

9.10.1. Dose optimisation tapering algorithm for ABA, ADA, CZP, ETN, GOL and TCZ

Figure 2: Outline of the algorithm for ABA, ADA, CZP, ETN, GOL and TCZ:



Dose optimisation/tapering algorithm for ABA, ADA, CZP, ETN, GOL and TCZ:

At baseline (week 0) the dose of the biological therapy is reduced as followed:

- Abatacept (ABA):
  - Subcutaneous: 125 mg every 10 days
  - Intravenous: weight < 60 kg: 500 mg every 6 weeks
  - Intravenous: weight 60-100 kg: 750 mg every 6 weeks
  - Intravenous: weight > 100 kg: 1000 mg every 6 weeks
- Adalimumab (ADA): 40 mg subcutaneous every 3 weeks
- Certolizumab pegol (CZP):
  - 200 mg subcutaneous every 3 weeks
  - 400 mg subcutaneous every 6 weeks
- Etanercept (ETN):

    - 25 mg subcutaneous every 5 days
    - 50 mg subcutaneous every 10 days
- Golimumab (GOL): 50 mg subcutaneous every 6 weeks
- Tocilizumab (TCZ):
    - Subcutaneous: 162 mg every 10 days
    - Intravenous: 8 mg/kg every 6 weeks

At week 17, the dose of the biological therapy is reduced as followed, if possible:

- Abatacept (ABA):
    - Subcutaneous: 125 mg every 14 days
    - Intravenous: weight < 60 kg: 500 mg every 8 weeks
    - Intravenous: weight 60-100 kg: 750 mg every 8 weeks
    - Intravenous: weight > 100 kg: 1000 mg every 8 weeks
- Adalimumab (ADA): 40 mg subcutaneous every 4 weeks
- Certolizumab pegol (CZP):
    - 200 mg subcutaneous every 4 weeks
    - 400 mg subcutaneous every 8 weeks
- Etanercept (ETN):
    - 25 mg subcutaneous every week
    - 50 mg subcutaneous every 14 days
- Golimumab (GOL): 50 mg subcutaneous every 8 weeks
- Tocilizumab (TCZ):
    - Subcutaneous: 162 mg every 14 days
    - Intravenous: 8 mg/kg every 8 weeks

At week 34, the dose of the biological therapy is reduced as followed, if possible:

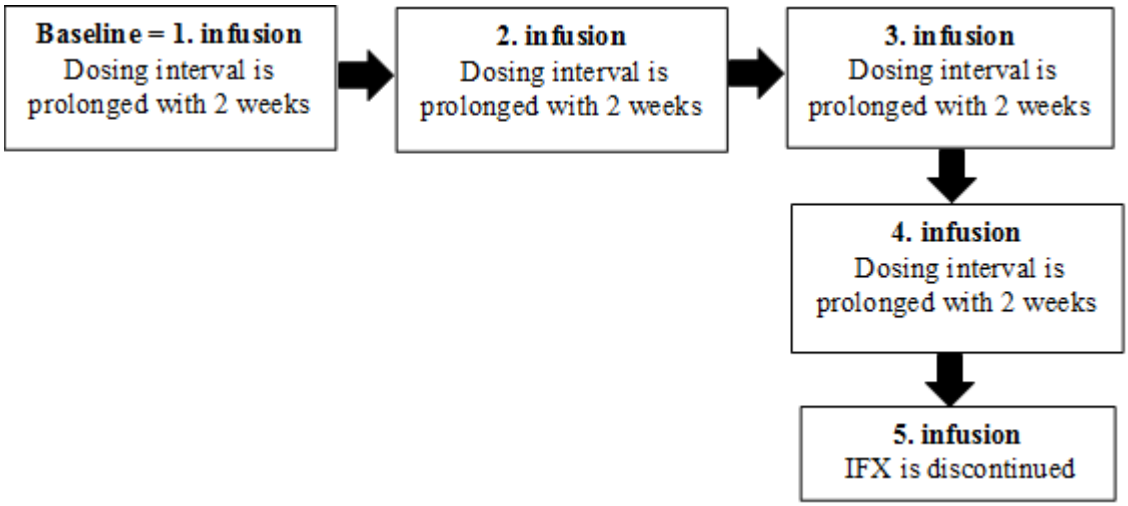
- Abatacept (ABA):
    - Subcutaneous: 125 mg every 21 days
    - Intravenous: weight < 60 kg: 500 mg every 10 weeks
    - Intravenous: weight 60-100 kg: 750 mg every 10 weeks
    - Intravenous: weight > 100 kg: 1000 mg every 10 weeks
- Adalimumab (ADA): 40 mg subcutaneous every 5 weeks
- Certolizumab pegol (CZP):
    - 200 mg subcutaneous every 5 weeks

  - 400 mg subcutaneous every 10 weeks
- Etanercept (ETN):
  - 25 mg subcutaneous every 10 days
  - 50 mg subcutaneous every 21 days
- Golimumab (GOL): 50 mg subcutaneous every 10 weeks
- Tocilizumab (TCZ):
  - Subcutaneous: 162 mg every 21 days
  - Intravenous: 8 mg/kg every 10 weeks

At week 52, the biological therapies are discontinued, if possible.

9.10.2. Dose optimisation tapering algorithm for IFX

Figure 3: Outline for the algorithm for IFX:



Dose optimisation tapering algorithm for IFX for patients with **RA** or **PsA**:

After the baseline visit, the following infusion administered to the patient is considered to be week 0 (first infusion):

- RA: infliximab (IFX) 3-6 mg/kg intravenous
- PsA: infliximab (IFX) 3-5 mg/kg intravenous

At week 10, the next infusion is given (second infusion):

- RA: infliximab (IFX) 3-6 mg/kg intravenous (10 weeks after last infusion)
- PsA: infliximab (IFX) 3-5 mg/kg intravenous (10 weeks after last infusion)

At week 22, the next infusion is given (third infusion):

- RA: infliximab (IFX) 3-6 mg/kg intravenous (12 weeks after last infusion)
- PsA: infliximab (IFX) 3-5 mg/kg intravenous (12 weeks after last infusion)

At week 36, the next infusion is given (fourth infusion):

- RA: infliximab (IFX) 3-6 mg/kg intravenous (14 weeks after last infusion)
- PsA: infliximab (IFX) 3-5 mg/kg intravenous (14 weeks after last infusion)

At week 52, IFX is discontinued, if possible (16 weeks after last infusion).

Dose optimisation/tapering algorithm for IFX for patients with **SpA**:

After the baseline visit, the following infusion administered to the patient at is considered to be week 0 (first infusion):

- SpA: infliximab (IFX) 3-5 mg/kg intravenous

At week 8, the next infusion is given (second infusion):

- SpA: infliximab (IFX) 3-5 mg/kg intravenous (8 weeks after last infusion)

At week 18, the next infusion is given (third infusion):

- SpA: infliximab (IFX) 3-5 mg/kg intravenous (10 weeks after last infusion)

At week 30, the next infusion is given (fourth infusion):

- SpA: infliximab (IFX) 3-5 mg/kg intravenous (12 weeks after last infusion)

At week 44, IFX is discontinued, if possible (14 weeks after last infusion).

9.10.3. Patients in reduced-dose biological therapy prior to trial entry

Patients in sustained clinical remission on reduced dose biological therapies (relative to standard dose as described above) are reduced to the nearest level at the first dose reduction at baseline. The dose of the biological therapy is thus reduced at baseline according to the following principles:

- The dose before tapering is > ¾ of the standard dose but ≤ full standard dose: the dose of the biological therapy is reduced at baseline to ¾ of the standard dose
- The dose before tapering is > ½ of the standard dose but ≤ ¾ of the standard dose: the dose of the biological therapy is reduced at baseline to ½ of the standard dose
- The dose before tapering is > ¼ of the standard dose but ≤ ½ of the standard dose: the dose of the biological therapy is reduced at baseline to ¼ of the standard dose
- The dose before tapering is ≤ ¼ of the standard dose: the biological therapy is discontinued at baseline

Thus, this patient group will reduce the dose of their biological therapy less at baseline compared to a patient receiving standard dose at baseline.

9.10.4 Anti-drug antibodies and dose optimisation

The formation of drug-neutralizing anti-drug antibodies (ADAb) is a concern when treating patients with biological agents because of the potentially risk of failure of the treatment. The risk of developing ADAb have been studied for anti-TNF-α with the highest risk for IFX and ADA and the lowest risk for ETN and GOL (81). Currently, only few studies have evaluated the risk of developing ADAb in patients treated with TCZ and ABA (82–84). To this date, the significance of ADAb in a patient receiving biological therapy is not fully understood. However, low drug levels of anti-TNF-α are generally associated with presence of ADAb among non-responders (81,85). It has been suggested, that low drug level of biologics could permit ADAb development and that high drug level could suppress ADAb development (81). Thus, this raise the possibility of increased ADAb development during tapering of biological therapy in patients in sustained clinical remission, thereby increasing the risk of secondary treatment failure. To this date however, no evidence supporting this hypothesis has been published. Recently one study examining tapering of ADA, ETN and IFX in patients with RA found presence of ADAb were infrequent and not a predictor for successful dose reduction or discontinuation (86). In this trial, ADAb and drug level of the biological agents is examined during tapering to further explore this topic.

9.11. Pause of the biological therapy

If the patient pause the biological therapy for over 3 months and are not willing to follow the dose optimisation tapering algorithm, the patient is discontinued from the trial due to lack of adherence. The pause of the biological agent can be one long pause lasting over 3 months or continuous pauses of a total value of over 3 months over 1 year. If the patient has an infection, the biological therapy should only be paused in the event of fever and need of antibiotic treatment judged by the physician. Thus, the biological therapy will not be paused by minor infections.

9.12. Concomitant treatment

At baseline, the patient's medicine incl. other arthritis treatments e.g. DMARD and Non Steroidal Anti-Inflammatory Drugs (NSAID) is recorded in the electronic Case Report Form (e-CRF) and in the FMK. DMARD includes MTX, salazopyrine, hydroxychloroquine or leflunomide. During the first 18 months of this trial, the dose of DMARD and NSAID recorded at baseline is maintained, except at the following circumstances:

- If the patient has side effects to DMARD or NSAID, the dose is reduced or the medication discontinued and the changes is registered in the e-CRF and FMK.
- If patients with SpA has symptoms of flare due to dose optimisation of the biological therapy, the physician can prescribe a short-term NSAID treatment of maximum 14 days concurrent with increasing dose of the biological therapy. This is recorded in the e-CRF and FMK. A short-term NSAID treatment of maximum 14 days is also allowed to treat flare caused by other reasons e.g. infection or surgery etc., as mentioned under section 9.6. Flare criteria.

Intra-articular steroid is allowed to treat flare due to dose optimisation of the biological therapy concurrent with increasing dose of the biological therapy. Intra-articular steroid is also allowed to treat flare caused by other reasons e.g. infection or surgery etc., as mentioned in section 9.6. Flare criteria.

9.13. Patient-involvement

Collaboration between patients and professionals in developing and disseminating research projects is relatively new. This trial has included a patient research partner in the scientific process as recommended by EULAR and as presented previously (87,88). The patient research partner Kathrine Hyldig Hansen (KHH) contributed to refinement of the trial protocol and approved the final manuscript.

This trial use patient-involvement during the dose optimisation of the biological therapy. At baseline, the patients are educated about symptoms of flare and to contact his/her rheumatology outpatient clinic if such symptoms occur. Thus, the patients must be examined for arthritis activity by research personnel incl. DANBIO registration within 7 days after he/she have contacted the outpatient clinic. At this visit, the physician assess if the arthritis has flared or not and discuss continuing tapering with the patient as described under section 9.6. Flare criteria.

In this trial, additional PROMs are used to assess arthritis activity than normal clinical practise in Rheumatology in Denmark. This in order to assess as many aspects as possible of the patient's experience during tapering of the biological therapy. The physician use the PROMs to determine if the patient has a flare and treatment changes must be made.

9.14. Trial visits

The trial procedures are listed in table 1A-1C below and described in detail in this section with exception of the collection of adverse events information, which is described in section 11. All trial data will be recorded in source documents and/or in the e-CRF.

9.14.1. Baseline

At baseline, the participants will receive adequate oral and written information about the trial and if he/she wishes to participate in the trial, the informed consent is signed. In addition, the participants will be screened to ensure they meet all inclusion criteria and none of the exclusion criteria. The participants then undergoes the following examinations depending on his/her disease:

- All participants: medical history, DANBIO registration and physical examination. In addition, blood test including biomarkers, see section 9.15.4 Laboratory tests. Radiological examinations are conducted in accordance with DRS guidelines for treatment change and not as part of this trial.
- Patients with RA: joint count 46 for swollen and tender joints
- Patients with SpA: joint count 66/68 for swollen and tender joints, BASDAI, BASFI and BASMI is registered together with registration of enthesitis by SPARCC, registration of dactylitis by number of affected fingers or toes, Psoriasis Area Severity Index (PASI) score for registration of skin involvement (Appendix 21) and modified Nail Psoriasis Severity Index (mNAPSI) score for registration of nail involvement (Appendix 22). The sacroiliitis degree judged by the New York criteria on radiographs of the sacroiliac joint is also registered. Radiological examinations and Magnetic Resonance Imaging (MRI) are conducted in accordance with DRS guidelines for treatment change and not as part of this trial.
- Patients with PsA: joint count 66/68 for swollen and tender joints, PASI score for registration of skin involvement, mNAPSI score for registration of nail involvement, SPARCC for registration of enthesitis and registration of dactylitis by number of affected fingers or toes. Radiological examinations are conducted in accordance with DRS guidelines for treatment change and not as part of this trial.

9.14.2. Visit at 4, 8, 12, 24 and 60 month

At the trial visits 4, 8, 12, 24 and 60 months from baseline, the participant undergoes the following examinations depending on his/her disease:

- All participants: DANBIO registration and blood test including serological test, see section 9.15.4 Laboratory tests.
- Patients with RA: joint count 46 for swollen and tender joints
- Patients with SpA: joint count 66/68 for swollen and tender joints, BASDAI, BASFI and

BASMI is registered together with registration of enthesitis by SPARCC, registration of dactylitis by number of affected fingers or toes, PASI score for registration of skin involvement and mNAPSI score for registration of nail involvement.

- Patients with PsA: joint count 66/68 for swollen and tender joints, PASI score for registration of skin involvement, mNAPSI score for registration of nail involvement, SPARCC for registration of enthesitis and registration of dactylitis by number of affected fingers or toes.

9.14.3. Visit at 18 month

At the trial visit 18 months from baseline, the participant undergoes the following examinations depending on his/her disease:

- All participants: DANBIO registration and blood test including serological test, see section 9.15.4 Laboratory tests. Radiological examinations are conducted in accordance with DRS guidelines for treatment change and not as part of this trial.
- Patients with RA: joint count 46 for swollen and tender joints
- Patients with SpA: joint count 66/68 for swollen and tender joints, BASDAI, BASFI and BASMI is registered together with registration of enthesitis by SPARCC and registration of dactylitis by number of affected fingers or toes, PASI score for registration of skin involvement and mNAPSI score for registration of nail involvement. MRI are conducted in accordance with DRS guidelines for treatment change and not as part of this trial.
- Patients with PsA: joint count 66/68 for swollen and tender joints, PASI score for registration of skin involvement, mNAPSI score for registration of nail involvement, SPARCC for registration of enthesitis and registration of dactylitis by number of affected fingers or toes.

9.14.4. Extra visits

All patients are instructed to contact the rheumatology outpatient clinic in case of symptoms of arthritis activity. In this case, research personnel must see the patient in the outpatient clinic to assessment of arthritis activity within 7 days.

9.14.5. Early termination visit

In case of early termination due to exclusion from the trial based on one of the safety measures or adverse events, see section 10. Harms and safety measures and 11. Adverse events, or at the patient's request, an early termination visit (ET) is offered. The ET must be completed within 2 weeks of the last dose of study drug (biological therapy), and preferably prior to the initiation of another therapy.

The ET is not conducted if the termination happens at one of the planned visits in this trial.

9.14.6. Telephone follow up

Patients who discontinue the trial early must be contacted by telephone 12 weeks after early termination for a telephone follow up (FU) to assessment of concomitant therapy and adverse events.

9.14.7. Overview of trial procedures

Trial procedures will be performed as summarized in the visit schedule presented in table 1A for patients with RA, table 1B for patient with SpA and table 1C for patients with PsA.

Table 1A: Trial procedures and outcome assessments for patients with RA:

	Baseline	4 month ± 2 weeks	8 month ± 2 weeks	12 month ± 2 weeks	18 month ± 2 weeks	24 months ± 4 weeks	60 month ± 4 weeks	Extra visit	ET	FU ± 12 weeks[1]
Clinical visit	X	X	X	X	X	X	X	X	X	
Inclusion and exclusion criteria	X									
Informed consent	X									
Randomisation	X									
Medical history	X									
PROMs according to this protocol	X	X	X	X	X	X	X	X	X	
Height, weight, blood pressure and pulse	X									
Physical examination	X									
46 joint count for swollen and tender joints	X	X	X	X	X	X	X	X	X	
Physician VAS for global disease activity	X	X	X	X	X	X	X	X	X	
Serum pregnancy test[2]	X									
CRP	X	X	X	X	X	X	X	X	X	
Haematology blood test	X	X	X	X	X	X	X	X	X	
Serum creatinine, ALAT, BASP	X	X	X	X	X	X	X	X	X	
IgM-RF, anti-CCP and ANA	X									
Serum uric acid, TSH and vitamin D	X									
Cytokines	X	X	X	X	X	X	X		X	
Druglevel and anti-drug-antibodies	X	X	X	X	X	X	X		X	
Adverse events assessment	X	X	X	X	X	X	X	X	X	X
Concomitant therapy assessment	X	X	X	X	X	X	X	X	X	X
Record of used/unused study drugs	X	X	X	X	X	X	X	X	X	

ET: early termination. FU: telephone follow up.

[1]: Performed 12 weeks from end of trial visit ± 2 weeks

[2]: Preformed on all women of childbearing potential

Table 1B: Trial procedures and outcome assessments for patients with SpA:

	Baseline	4 month ± 2 weeks	8 month ± 2 weeks	12 month ± 2 weeks	18 month ± 2 weeks	24 months ± 4 weeks	60 months ± 4 weeks	Extra visit	ET	FU ± 12 weeks[1]
Clinical visit	X	X	X	X	X	X	X	X	X	
Inclusion and exclusion criteria	X									
Informed consent	X									
Randomisation	X									
Medical history	X									
PROMs according to this protocol	X	X	X	X	X	X	X	X	X	
Height, weight, blood pressure and pulse	X									
Physical examination	X									
BASMI	X	X	X	X	X	X	X	X	X	
66/68 joint count for swollen and tender joints	X	X	X	X	X	X	X	X	X	
Physician VAS for global disease activity	X	X	X	X	X	X	X	X	X	
PASI score	X	X	X	X	X	X	X	X	X	
mNAPSI	X	X	X	X	X	X	X	X	X	
Enthesitis score by SPARCC	X	X	X	X	X	X	X	X	X	
Dactylitis by number of fingers/toes	X	X	X	X	X	X	X	X	X	
Serum pregnancy test[2]	X									
CRP	X	X	X	X	X	X	X	X	X	
Haematology blood test	X	X	X	X	X	X	X	X	X	
Serum creatinine, ALAT, BASP	X	X	X	X	X	X	X	X	X	
HLA-B27[3]	X									
IgM-RF, anti-CCP and ANA[4]	X									
Serum uric acid, TSH and vitamin D	X									
Cytokines	X	X	X	X	X	X	X		X	
Druglevel and anti-drug-antibodies	X	X	X	X	X	X	X		X	
Adverse events assessment	X	X	X	X	X	X	X	X	X	X
Concomitant therapy assessment	X	X	X	X	X	X	X	X	X	X
Record of used/unused study drugs	X	X	X	X	X	X	X	X	X	

ET: early termination. FU: telephone follow up.

[1]: Performed 12 weeks from end of trial visit ± 2 weeks

[2]: Preformed on all women of childbearing potential

[3]: If the test was performed earlier and the answer can be found in the medical journal; the test should not be repeated

[4]: Performed on patients with additional peripheral involvement

Table 1C: Trial procedures and outcome assessments for patients with PsA:

	Baseline	4 month ± 2 weeks	8 month ± 2 weeks	12 month ± 2 weeks	18 month ± 2 weeks	24 months ± 4 weeks	60 months ± 4 weeks	Extra visit	ET	FU = 12 weeks[1]
Clinical visit	X	X	X	X	X	X	X	X	X	
Inclusion and exclusion criteria	X									
Informed consent	X									
Randomisation	X									
Medical history	X									
PROMs according to this protocol	X	X	X	X	X	X	X	X	X	
Height, weight, blood pressure and pulse	X									
Physical examination	X									
66/68 joint count for swollen and tender joints	X	X	X	X	X	X	X	X	X	
Physician VAS for global disease activity	X	X	X	X	X	X	X	X	X	
PASI score	X	X	X	X	X	X	X	X	X	
mNAPSI	X	X	X	X	X	X	X	X	X	
Enthesitis score by SPARCC	X	X	X	X	X	X	X	X	X	
Dactylitis by number of fingers/toes	X	X	X	X	X	X	X	X	X	
Serum pregnancy test[1]	X									
CRP	X	X	X	X	X	X	X	X	X	
Haematology blood test	X	X	X	X	X	X	X	X	X	
Serum creatinine, ALAT, BASP	X	X	X	X	X	X	X	X	X	
IgM-RF, anti-CCP and ANA	X									
Serum uric acid, TSH and vitamin D	X									
Cytokines	X	X	X	X	X	X	X		X	
Druglevel and anti-drug-antibodies	X	X	X	X	X	X	X		X	
Adverse events assessment	X	X	X	X	X	X	X	X	X	X
Concomitant therapy assessment	X	X	X	X	X	X	X	X	X	X
Record of used/unused study drugs	X	X	X	X	X	X	X	X	X	

ET: early termination. FU: telephone follow up.

[1]: Performed 12 weeks from end of trial visit ± 2 weeks

[2]: Performed on all women of childbearing potential

9.15. Clinical procedures

9.15.1. Medical history

At baseline, the patients' medical history will be recorded. Information about the following topics will be recorded:

- Predisposition for rheumatic disease, psoriasis and IBD
- Previous and current medical and surgical history
- Tobacco and alcohol consumption
- Social conditions: marital status (married/unmarried), education level and work life (working/ flex job/pension/sick leave/other)
- Medication:
    - Biological therapy
    - DMARD
    - Glucocorticoid treatment within the last year
    - Consumption of NSAID and other analgesics
    - Consumption of other medication
- Duration of remission on current biological therapy
- Previously treatment with other biological therapies than the current one
- Previously attempt to reduce the dose of the biological therapy
- Adverse reactions to current medications including biological therapy and DMARD
- Current symptoms of arthritis activity including symptoms of extra-articular disease

The above information about the participants is recorded to get insight into the participant's arthritis including the biological therapy and side effects to this prior to entry into the trial. In addition, information about predisposition to rheumatic diseases, previous medical history, tobacco and alcohol consumption, medication and social conditions are recorded for the analysis of demographic characteristics of participants who can reduce dose of their biological therapy and maintain remission and participants who cannot. Information from the participant's medical record will be obtained as a supplement to information from the patient himself/herself.

9.15.2. Patient reported outcome measures

In rheumatology, PROMs are used to gain insight into the patient's perception of arthritis activity, physical function etc. Prior to each visit at the rheumatology outpatient clinic in Denmark, the patients

fill out PROMs in the DANBIO database. In this trial, an additional PROM (Short Form Health Survey 36 (SF-36)) is used to assess the patients' health during tapering in order to highlight as many aspects as possible. The physician use the PROMs at each clinical visit to determine if the patient has a flare and treatment changes must be made. The PROMs included in this trial have all been published, validated and used for evaluating patients with RA, SpA and/or PsA. In this trial, the following PROMs are used:

- VAS: the left of the VAS scale (0 mm) signifies the absence of symptoms and the right end (100 mm) maximum activity in terms of the parameters assessed.
    - VAS Pain: the patient's assessment of pain within the last week on a 100 mm horizontal VAS scale (Appendix 4).
    - VAS Fatigue: the patient's assessment of fatigue within the last week on a 100 mm horizontal VAS scale (Appendix 4).
    - VAS Patient Global Health (PtGH): Patient's assessment: the patient's global assessment of disease activity (arthritis severity) within the last week on a 100 mm horizontal VAS scale (Appendix 4).
    - BASDAI: only used for patients with SpA. Consist of six questions regarding essential symptoms in axial arthritis on a 100 mm horizontal VAS scale (Appendix 6)
    - BASFI: only used for patients with SpA. Consist of ten questions regarding physical function on a 100 mm horizontal VAS scale (Appendix 7).
- HAQ-DI: assess the patient's physical function and consist of 20 questions regarding 8 different aspects of functional activities. Is answered by the patient on a scale from zero (no disability) to three (completely disabled) (Appendix 5).
- Short Form Health Survey 36 (SF-36): assess the patient's health and consist of 36 questions regarding 8 different aspects of health. The patient's answers is transformed into a score from 0 (maximum disability) to 100 (no disability) (Appendix 23).

9.15.3. Clinical assessments

In this trial, the following clinical assessments will be performed:

<u>All patients:</u>

- Physical examination is performed at baseline
- Height, weight and Body Mass Index is performed at baseline
- Blood pressure and pulse is measured at baseline

- Physician's global assessment of disease activity: the physician's global assessment of the patient's current disease activity on a 100 mm horizontal VAS scale is performed at each clinical visit (Appendix 24)

Patients with RA:

- 46 joint count for swollen and tender joints at each clinical visit (appendix 16)

Patients with PsA or SpA:

- 66/68 joint count for swollen and tender joints at each clinical visit (Appendix 17)
- Enthesitis score by SPARCC at each clinical visit (Appendix 14)
- Dactylitis count by number of affected fingers/toes
- PASI score for skin manifestation at each clinical visit (Appendix 21)
- mNAPSI score for nail manifestation at each clinical visit (Appendix 22)

Patients with SpA:

- BASMI at each clinical visit (Appendix 15)

9.15.4. Laboratory tests

The patients are as usual clinical practice monitored according to DRS guidelines with regular blood tests. In this trial, additional blood test are performed before each clinical visit as described below. The additional blood tests include biomarkers (drug level, anti-drug-antibodies and cytokines), which is examined to differentiate between patient who can taper the biological therapy successfully and patients who cannot. As drug level is measured when the concentration is lowest, i.e. just before the next dose of biological therapy, the blood tests are performed just before the next dose of biological therapy is administered prior to the clinical visit in the rheumatology outpatient clinic. That means:

- Patients treated with biological therapy in intravenous form: blood test are performed at the biochemistry department just before administration of the next intravenous dose of biological therapy at the rheumatology outpatient clinic. Thus the additional blood test does not require extra visits at the hospital for the patient.
- Patients treated with biological therapy in subcutaneous form: blood test are performed at the biochemistry department in connection to the patient pick up his/her biological agent at the rheumatology outpatient clinic. The visit is planned to just before the patients administer the next subcutaneous dose of biological therapy. Thus the additional blood test does not require extra visits at the hospital for the patient.

At the clinical visit, the physician notes the time of the previous and next administration of biological therapy.

All female patients with childbearing potential will undergo a serum pregnancy test (Human Chorion Gonadotropin test (B-hcg)) at screening as described in section 12. Pregnancy.

In this trial, blood sampling is performed by trained personnel at the biochemistry departments at the participating hospitals. At baseline 50 ml of blood is taken for analysis and at the remaining clinical visits 35 ml of blood is taken for analysis per visit. The patient should not be fasting for the blood tests. Routine analysis (all other analysis than biomarkers) will be analysed at the Departments of Biochemistry within a few days. Excess blood will be stored in the Danish Rheumatology Biobank for analysis of the biomarkers later on, see section 9.16. Biobank in the BIODOPT trial. In case of extra blood, this will also be stored in the biobank, see section 9.16. Biobank in the BIODOPT trial. Reference values for the blood tests mentioned below are the same at the four participating Rheumatology Departments.

Table 2: Overview of blood tests (including biomarkers)

Blood tests	Biomarkers
CRP	Cytokines
Differentiated white blood cell count	Drug-level
Haemoglobin	Anti-drug-antibodies
Platelets	
Creatinine	
ALAT and BASP	
Uric acid	
TSH	
Vitamin D status	
B-hcg	
ANA	
IgM-RF	
Anti-CCP	
HLA-B27	

9.15.4.1. Baseline blood tests

The baseline blood tests are performed just before administration of the next dose of biological therapy (as described above) after the baseline visit.

- All patients:
  - CRP
  - Haematology blood tests: haemoglobin, differentiated white blood cell count, platelets

  - Creatinine, alanine transaminase (ALAT), alkaline phosphatase (BASP), uric acid, thyroid-stimulating hormone (TSH) and vitamin D status
  - Biomarkers: cytokines, drug-level and anti-drug-antibodies
- Women of childbearing potential: B-hcg
- Patients with peripheral arthritis: IgM rheumatoid factor (IgM-RF), anti-cyclic citrullinated peptide (anti-CCP) antinuclear antibody (ANA)
- Patients with SpA: Human Leucocyte Antigen-B27 (HLA-B27) is performed if the test is not performed before or the result of a previous test cannot be found in the patient's medical record.

9.15.4.2. Blood test visit 4, 8, 12, 18, 24 and 60 months

The blood test in connection to visit 4, 8, 12, 18, 24 and 60 months is performed just before administration of the next dose of biological therapy (as described above) prior to the clinical visit.

- All patients:
  - CRP
  - Haematology blood tests: haemoglobin, differentiated white blood cell count, platelets
  - Creatinine, ALAT and BASP
  - Biomarkers: cytokines, drug-level and anti-drug-antibodies

9.15.4.3. Synovial fluid tests

Intra-articular steroid injection is only offered to the patient when the physician finds this necessary to treat a flare – and is thus not part of this trial. If synovial fluid is aspirated from the joint, this is analysed in according with local clinical practice, which may include the test listed in table 3. Reference values for the synovial fluid tests mentioned below are the same at the four participating Rheumatology Departments. Synovial fluid is not stored in the Danish Rheumatology Biobank.

Table 3: Synovial fluid tests – only done if synovial fluid is aspirated during arthrocentesis

Synovial fluid test
White blood cell count
Susceptibility test
Examination for crystals

9.16. Biobank in the BIODOPT trial

Participants will be asked for consent to store excess biological material (blood) in the Danish Rheumatology Biobank (Dansk Reuma Biobank), when signing the informed consent form. The purpose of storing biological material in the biobank is primarily to be able to repeat analyses if the first analyses of the samples has failed. In addition, some of the analyses are costly (the biomarkers), thus they are analysed together for more participants. Furthermore, the trial can raise new theories and questions that might be interesting to investigate later on. However, future studies will only be carried out after prior approval of the Danish Data Protection Agency and a new informed consent as a rule has been obtained. Moreover, the BIODOPT trial group has the right to the biological material in the Danish Rheumatology Biobank from this trial and thus, future studies will also need a prior approval of the BIODOPT trial group.

In addition, participants will be asked for a separate informed consent to store extra blood bank samples in the Danish Rheumatology Biobank. The purpose of this storage of extra biological material is future research purpose independent of this trial. At the baseline visit, the participants will be informed about the Danish Rheumatology Biobank and will recieve the information material "Forskning til gavn for fremtidens patienter – Patientinformation om prøver i Regionernes Bio- og GenomBank" and "Samtykke til opbevaring af biologisk materiale i Regionernes Bio- og GenomBank" and "Dit væv, dit valg".

The Danish Data Protection Agency has approved storage of excess and extra biologic material from this trial in the Danish Rheumatology Biobank approximately 25 ml blood at each visit. Samples for the biobank will be handled and prepared for storage by staff from the Danish Rheumatology Biobank and analysed in batches, then destroyed. The biological material will be stored at -80 °C in a freezer in the Danish Rheumatology Biobank under an ID-number, se section 14. Confidentiality.

9.17. Outcomes

All outcome measurements in this trial have been published and validated and used in the evaluation of patients with RA, SpA and/or PsA. All clinical and laboratory procedures in this trial are standard and generally accepted.

9.17.1. Primary outcome

The co-primary endpoint is:

1A Superiority: The proportion of patients who at 18 months is reduced to 50% or less of their inclusion dose of biological therapy.

1B Equivalence: Disease activity assessed 18 months from baseline.

9.17.2. Key secondary outcomes

At 18, 24 and 60 months: the proportion of patients in remission and receiving reduced dose biological therapy and the proportion of patients in remission despite discontinuation of biological therapy.

Changes from baseline to 4, 8, 12, 18, 24 and 60 months in the following composite scores:

- RA:
    - DAS28crp
    - Clinical Disease Activity Index (CDAI)
    - Simplified Disease Activity Index (SDAI)
- SpA:
    - ASDAS
    - BASDAI
- PsA:
    - DAPSA
    - DAS28crp
    - Minimal disease activity criteria (MDA)

Changes from baseline to 4, 8, 12, 18, 24 and 60 months in the following PROMs:

- All patients:
    - Patient's assessment of pain
    - Patient's assessment of fatigue
    - Patient's global assessment of disease activity
    - HAQ
    - SF-36
- Patients with SpA:
    - BASDAI
    - BASFI

Changes from baseline to 4, 8, 12, 18, 24 and 60 months in the following clinical assessment by the physician:

- All patients: the physician's global assessment of the patient's disease activity
- Joint count:
    - RA: 46 joint count for swollen and tender joints
    - SpA and PsA: 66/68 joint count for swollen and tender joints
- For patients with SpA
    - BASMI
- For patients with SpA or PsA:
    - PASI score
    - mNAPSI score
    - Enthesitis score by SPARCC
    - Dactylitis by number of affected fingers/toes

9.17.3 Tertiary (exploratory secondary) outcome

Changes from baseline to 4, 8, 12, 18, 24 and 60 months in the following biomarkers:

- All patients: cytokines
- All patients: drug-level
- All patients: anti-drug-antibodies

The following laboratory test will be assessed in terms of possible predictive factors for successful dose optimisation of the biological therapy:

- All patients:
    - CRP at the start of biological therapy
    - CRP at baseline of this trial
- Patients with peripheral arthritis:
    - IgM-RF seropositivity
    - Anti-CCP seropositivity
- Patients with SpA:
    - Presence of HLA-B27 positivity

9.18. Power and sample size considerations

1A: We assume that 30% of the patients allocated to DOT and 5% of patients allocated to the UC will meet primary endpoint 1A. These assumptions appear consistent with data from a newly published non-inferiority trial regarding dose optimisation of ADA and ETN in patients with RA (39),

where patients with RA treated with ADA or ETN and in DAS28crp LDA were included. For a comparison of two independent binomial proportions using Pearson's Chi-square statistic with a Chi-square approximation with a two-sided significance level of 0.05, a total sample size of 180 assuming an allocation ratio of 2 to 1 has an very high statistical power of 0.992 (99%) if the proportion of patients significantly reducing their biologics (≥50% reduction), are 30% and 5%, respectively.

1B: For the between-group comparison, members of The BIODOPT trial group (SK, AS, EMH and LU) decided a predefined margin of equivalence at ± 0.5 DAS28crp points for patients with RA or PsA with peripheral arthritis and ± 0.5 ASDAS points for patients with SpA or PsA with axial arthritis. This margin was based on less of half of the effect that is considered a clinically relevant reduction in DAS28crp level (ΔDAS28crp > 1.2) or ASDAS level (ΔASDAS > 1.1) corresponding to a clinically important improvement in arthritis activity. In a two one-sided test analysis for additive equivalence of two-sample normal means with bounds ± 0.5 for the mean difference and a significance level of 0.05, assuming a mean difference of 0 and a common standard deviation of 1.0, a total sample size of 180 participants assuming an allocation ratio of 2:1 yields a sufficient statistical power of 0.868 (87%).

Thus, inclusion of 180 patients in total during an inclusion period of 1 year is desired. First patient first visit (FPFV) is scheduled for 1st November 2017 and thus last patient first visit (LPFV) is scheduled for 1st November 2018. The trial lasts 5 years for each patient, who complete this trial, thus first patient last visit (FPLV) is scheduled for 1st November 2022 and last patient last visit (LPLV) for 1st November 2023.

9.19. Randomisation and group allocation

9.19.1. Sequence generation

All patients who fulfil the eligibility criteria and who provides written informed consent for participation will be enrolled and randomly allocated. A computer-generated randomisation sequence will be produced before any patients are enrolled, allocating participants in permuted blocks of 3 to 6. The randomisation sequence will be prepared by the senior biostatistician with no clinical involvement in the trial (RC). The sequence generation will be prepared with a 2:1 allocation ratio, stratified by trial site (Aalborg, Aarhus, Odense and Hjørring), diagnosis (i.e. RA, SpA or PsA) and repeated biologics failure (currently on biological agent number 3 or higher). We will use SAS PROC PLAN to generate the 24 mutually independent randomisation schedules (4 centres × 3 diagnoses × 2 biological agent "stages"); SAS statistical software (version 9.4.).

9.19.2. Allocation concealment mechanism and implementation

The allocation will be concealed in a password-protected computer file only accessible by the senior biostatistician (RC) and the independent data manager (JHW). The randomisation sequence will be entered into the e-CRF in REDCap by the data manager (JHW). The participants will be given their trial number and randomization group when the physician "clicks" on "the randomise button", which will appear after finalising the baseline visit, depending on the stratum the patient represent. The randomization number and assigned intervention will then be visible on the screen. Thus, the patients are given consecutive screening and randomization numbers, independent of the trial site with concealed group allocation.

9.19.4. Blinding

The interventions in this trial are not blinded.

9.20. Statistical methods

All data analyses will be carried out according to a pre-established statistical analysis plan (SAP). All descriptive statistics and tests will be reported in accordance to the recommendations of the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network (89): the CONSORT statement (90,91). In order to evaluate the empirical distributions of the continuous outcomes, visual inspection will be applied to suggest whether an assumption of normality (Gaussian distribution) is reasonable. All analyses will be conducted according to the intention-to-treat (ITT) principle; i.e., analysing participant outcomes according to the group to which they were randomised, even if some participants do not follow the DOT and UC algorithm.

All statistical analyses will be performed on blinded group allocations. Unblinding will be done after completion of all the pre-specified statistical analyses (according to the 18 months assessment). To evaluate the longitudinal effects of the intervention (DOT vs. UC during the 18 months trial period), all continuous outcome variables (e.g. disease activity [1B]) will be analysed using a multilevel repeated-measures linear mixed effects model, with participant as random effect factor based on a restricted maximum likelihood model. The model will include group (DOT vs UC), diagnosis, biologics failure history, and centre status as fixed effects, with the baseline value of the relevant variable as a covariate. To assess the adequacy of the linear models describing the observed data - and checking assumptions for the systematic and the random parts of the models — we will investigate the model

features via the predicted values and the residuals; that is, the residuals have to be normally distributed (around 0) and be independent of the predicted values.

For the equivalence analyses (e.g. according to disease activity), imputations will not be used to replace missing data in the primary analyses, but will be included in a sensitivity analysis to assess the effect of missing data. According to Piaggio et al (91), equivalence is declared if the entire 2-sided 95% CI is within the equivalence margin. Thus, a 2-sided 95% CI for the difference in disease activity at 18-months follow-up between groups will be derived from the repeated-measures mixed linear model and equivalence will be declared if the 95% CI of disease activity level is completely within the pre-specified equivalence range (−0.5 units to +0.5 units).

Categorical changes for dichotomous end points (e.g. number of participants who achieve a significant reduction in biologics [≥50%] while assessed after 18 months) will be analysed with the use of logistic regression with the same fixed effects and covariates as the respective analysis of covariance. For the superiority tests (e.g. co-primary endpoint 1A), we set the statistical significance at the conventional level of .05. Results will be expressed as estimates of the differences between groups, with 95% CIs to represent precision of the estimates. All analyses will be performed using commercially available statistical software.

9.21. Data management

Data will be collected from the baseline visit until the end of the 60 months visit unless the patient is excluded from the trial or withdraw his/her consent, as described under section 9.23. Removal of participants from the trial.

This trial uses an e-CRF in REDCap where access to trial data is restricted to research members of the trial team by username and password. REDCap is a secure, web-based application for building and managing online databases and is designed to support data collection for research studies. REDCap use data logging to create an audit trail thereby registering e.g. who is looking at, changing or entering data. In the eCRF the following data will be entered: medical history, inclusion and exclusion criteria, informed consent, randomisation number, PROMs according to this protocol, physical examination incl. height, weight, BMI, blood pressure and pulse, 46 or 66/68 joint count for swollen and tender joints, BASMI, physician VAS for global disease activity, PASI score, mNAPSI, SPARCC score, number of dactylitis, CRP, serum pregnancy test at baseline, HLA-B27, IgM-RF, anti-CCP, AE, concomitant therapy and record of used/unused study drugs. In this trial, data quality will be promoted through the REDCap features real-time data entry validation (e.g. for dates and

range checks) and required data entry at each clinical visit. In addition, investigators at each trial site will review and update the e-CRF in REDCap to accuracy with date and signature when this is requested. The e-CRF in REDCap and source documents are available to research personnel in the BIODOPT trial at the respective trial site so they can enter data in the e-CRF as needed. Source documents are defined as original documents and records such as medical records including outpatient records, papers with assessment of swollen and tender joints, papers with vital parameters, laboratory results, medicine list including the participants' diary of medicine changes and dispensed biological therapy by BATCH number. PROMs entered by the patient in DANBIO as described in this protocol is also considered as source documents.

All trial-related information from this trial will be stored securely, see section 14. Confidentiality. All trial-related data will be identified by a coded ID number to maintain participant confidentiality, however, this does not apply for records that contain names or other personal identifiers, such as informed consent forms, which will be stored safely as described in section 14. Confidentiality. The code for the ID numbers will be stored safely in a locked file cabinet in areas with limited access away from all other trial-related data. The code for the ID numbers will be destroyed 15 years after the end of this trial. All biological material will be safely stored in the Danish Rheumatology Biobank as described in section 9.16 Biobank in the BIODOPT trial.

9.22. Participant retention

Once a participant is enrolled and randomised, the trial site will make every reasonable effort to follow the participant for the entire trial period. It is estimated that the rate of dropout will be approximately 10%.

9.23. Removal of participants from the trial

A participant may withdraw from the trial at any time. The investigator can discontinue any patient's participation for any reason, including an AE, safety concerns or failure to comply with the protocol. Participants will also be withdrawn from the trial if any of the following occur:

- Death
- Significant abnormal laboratory results or AEs, which rule out continuation of the study drug (biological therapy), as determined by the investigator
- Lack of adherence to the protocol
- If the patient pause the biological therapy for over 3 months and are not willing to follow the

dose optimisation tapering algorithm, the patient is discontinued from the trial due to lack of adherence. The pause of the biological therapy can be one long pause lasting over 3 months or continuous pauses of a total value of over 3 months over 1 year.

- Women who becomes pregnant while treated with biological therapy, MTX or leflunomide or within the period from last dose of these medications, where pregnancy is not recommended.
- If the flare is caused by dose reduction of the biological therapy, the patient must increase the dose of the biological therapy to the last dose at which the arthritis was in remission – otherwise the patient is excluded from the trial due to compliance-problems.

If a participants terminates the trial early, the procedures outlined for the ET visit must be completed. The date and reason for early termination will be recorded in the source document and/or in the e-CRF. Data collected from the participant is included in the trial until the date for early termination if the baseline visit has been completed. Participants who is excluded from the trial prematurely will be replaced by new participants and will be treated according to national guidelines by DRS and RADS.

9.24. Discontinuation of the entire trial

The sponsor-investigator, the principal investigators and the BIODOPT trial group may jointly proceed to discontinue the trial at any time if extreme circumstances would necessitate this e.g. extreme, unanticipated adverse events or extreme, unexpected difference in remission between the treatment groups. In addition, the Danish Medicine Agency and/or the local Ethics Committee can discontinue the trial at any time if this is found necessary.

10. HARMS AND SAFETY MEASURES

In this trial, the patients with RA, SpA or PsA does not start treatment with new drugs, but instead participants in DOT reduce dose of already initiated biological therapy. During this trial, the patients in DOT may experience a flare due to dose reduction of the biological therapy. This is treated with rapid return to the previous dose of the biological therapy where the patient was in remission. Rapid intervention is important when treating a flare, therefore the patient is educated about symptoms of flare and to not hesitate to contact the rheumatology outpatient clinic. If the patient experience symptoms of flare, the research personnel must see him/her in the outpatient clinic to assessment of arthritis activity within 7 days. For the participants in UC, the risk of arthritis flare is considered unchanged compared with prior to entry in this trial.

The seven visits in this trial comprise approximately 1 hour per visit over 5 years. Patients will be closely monitored by frequent clinical visits, possible at slightly higher frequencies and with more intensive assessment compared to usual care. This ensures that any symptoms of flare is detected so that relevant medical examination and treatment changes can be conducted.

Participation in this trial can have impact on the patients travel insurance for the patients in DOT as the dose of the biological therapy is changed (reduced). At baseline the patient is thus informed about this aspect and is advised to contact their travel insurance agency long before a scheduled travel to clarify whether the patient is covered by his/her travel insurance. Participation is this trial is not expected to have an impact on travel insurance for the patients in UC.

Additional harms for the participants in this trial are discomfort and risk of a small hematoma in the skin during blood sampling or arthrocentesis. In addition, there is a very small risk of infection due to penetration of the skin with a needle. The patient is informed of these risks at baseline. To minimize these risks, the site of needle penetration is disinfected with alcohol prior to blood sampling or arthrocentesis. Arthrocentesis is performed under sterile conditions according to procedure for minor surgical procedures and performed by an experienced physician only if this is necessary judged by the physician – thus arthrocentesis is not part of this trial. Blood sampling is done by experienced bio analysts and in connection to a visit in the rheumatology outpatient clinic. This to avoid more transportation to the hospital than necessary.

After the end of the trial participants will be treated according to national guidelines by DRS and RADS. There are no risk associated with the remaining part of this trial, although unforeseen risks or harms can occur. Participation in this trial has thus minimal risks, which are offset by the benefits.

The trial is expected to contribute with new knowledge about dose optimisation of biological therapy in patients with RA, SpA and PsA in sustained clinical remission and thus to positively benefit the individual patient and the society.

11. ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation participants administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. The principal investigators will monitor each patient for clinical and laboratory evidence of AE at each clinical visit throughout the trial. The investigators will assess and register any AE in detail including date of onset, description, severity, duration, outcome, relationship to study drug and any actions taken. All AE in this trial will be registered regardless of

how the research personnel become aware of it e.g. in response to a query, observed by site personnel or reported spontaneously by the patient. All AE reported from baseline to the end of this trial will be registered and followed to a satisfactory conclusion. Any worsening of a pre-existing condition, excluding RA, SpA and PsA, is considered an AE. Laboratory abnormalities are only an AE if they result in discontinuation from the trial, necessitate therapeutic medical intervention and/or if the investigator considers them an AE. A treatment-related AE is in this trial defined as any AE reported by the participants with onset or worsening from baseline until 5 half-lives after discontinuation of the study drug. An elective surgery/procedure is not considered an AE if the surgery/procedure is performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to trial entry. However, it is considered an AE if the pre-existing condition unexpectedly worsens during the trial period and e.g. causes surgery to take place earlier than planned. The investigators will use the following definitions to rate the severity of an AE:

- Mild: the AE is transient and easily tolerated by the participant
- Moderate: the AE causes the participant discomfort and interrupts the participant's usual activities
- Severe: the AE causes considerable interference with the participant's usual activities and may be incapacitating or life-threatening

The investigators will use the following definitions to assess the relationship of an AE to the use of a study drug:

- Probably related: an AE that has a strong temporal relationship to the study drug or recurs in rechallenge and other aetiology is unlikely or significantly less likely
- Probably not related: an AE that has little or no temporal relationship to the study drug and/or a more likely alternative aetiology exists.
- Not related: an AE that is caused by an underlying or concurrent illness or effect of another drug and is not related to the study drug

A serious adverse event (SAE) and serious adverse reaction (SAR) is defined as an event or side effect that, irrespective of dose, results in death, is life threatening, causes hospitalization or prolongation of a hospital stay, results in significant or permanent invalidity or incapacity or leads to congenital abnormality or malformation. All SAE/SAR reported from baseline to the end of this trial will be registered and followed to a satisfactory conclusion. The investigators must report any SAE or SAR to the BIODOPT trial group within 24 hours of the site being made aware of the SAE/SAR.

This is done by e-mailing the SAE forms (Appendix 25) to the sponsor-investigator (SK) and coordinating investigator (LU). The coordinating investigator (LU) will ensure that sponsor-investigator (SK) is notified about all SAE/SAR.

A SAR can be a suspected unexpected serious adverse reaction (SUSAR), which is defined as a serious side effect that may or may not be dose related, but is unexpected, as it is not consistent with current information. If the BIODOPT trial group judge that a SAE/SAR is a SUSAR, SK and LU are responsible for reporting it to the medical products agency, the local ethics committee and to the Danish Medicines Agency. A SUSAR that is life threatening must be reported to the Danish Medicines Agency and the local Ethics Committee within 7 days, if not life threatening within 15 days. The sponsor-investigator (SK) and the coordinating investigator (LU) are responsible for informing the principal investigators of any SUSARs.

The section "adverse reactions" in the product information of the biological therapies are used as referral documents for assessment of adverse events or adverse reactions in this trial.

12. PREGNANCY

At present, treatment with biological therapy is not permitted during pregnancy attempt for women and is not permitted in pregnant women or breastfeeding women. These rules also applies to patients treated with MTX or leflunomide for both men and women during pregnancy attempt. In this trial, female participants must use safe contraception like any other patient treated with biological therapy, MTX and/or leflunomide. The following methods of contraception are considered safe in this trial:

- IUD
- Hormonal contraception i.e. birth control pills, birth control implants, birth control patch, birth control vaginal ring or birth control shot (depot injection)
- A vasectomized partner

In accordance with the product information of the biological therapies, female participants must use safe contraception as described above for the following periods after discontinuation of their biological therapy:

- Abatacept: 3.5 months
- Adalimumab: 5 months
- Certolizumab pegol: 5 months
- Etanercept: 3 months
- Golimumab: 6 months

- Infliximab: 6 months
- Tocilizumab: 3 months

Safe contraception must be used 6 months after the last dose of MTX and up to 2 years after the last dose of leflunomide, however, patients treated with leflunomide can undergo a wash-out period after local guidelines. The BIODOPT trial group must be contacted within one working day after research personnel learns that a female trial participant has become pregnant during the trial or within the time period listed above for the different biological therapies. Female participants who become pregnant during the trial will have their study drug (biological therapy) discontinued if the pregnancy is proceeded. Data regarding the outcome of any pregnancy in at female trial participant treated with the study drugs will be collected. The medical outcome of an induced or a spontaneous abortion is considered a SAE and must be reported to the BIODOPT trial group within 24 hours of learning of the event.

13. ETHICS

13.1. Ethical consideration

In this trial, the participants does not start treatment with new drugs, but instead dose of the biological therapy is reduced in DOT and remained unchanged in UC. Prior studies have found no considerable adverse events when tapering biological therapy in patients with RA, PsA or SpA in sustained clinical remission as a flare is treated successfully when escalating to full dose biological therapy in most patients (37,41,42,46,48,92–94) – however, in a smaller proportion of patients switching to a different biological agent can be necessary to gain remission after a flare (38,41,46,93). Participants will be educated about symptoms of arthritis flare at baseline and will be closely monitored for arthritis activity every 4 month during the first year of the trial (the period of dose optimisation in DOT). Arthritis flare will be treated as described in this protocol, see section 9.6. Flare criteria. Continuation of standard dose biological therapy in patients in sustained clinical remission can lead to overtreatment and thus unnecessary side effects e.g. common and serious infections. Therefore it is expected, that DOT will have a smaller risk of side effects incl. infections and that UC will have an unchanged risk of side effects incl. infection. For the individual patient however, there is no guaranteed benefits for participating in this trial other than extra close monitoring of their arthritis due to extra visits at the outpatient clinic.

The amount of blood taken during the trial is 260 ml divided into 7 visits, which is considered acceptable for the participants. There are no risk associated with the remaining part of this trial, although

unforeseen risks or harms can occur. This trial is expected to contribute with new knowledge about dose optimisation of biological therapy in patients with RA, SpA and PsA in sustained clinical remission and thus to positively benefit the individual patient and the society. In light of the above, we consider it ethically justifiable to conduct the trial. This trial is conducted in accordance with the Helsinki Declaration and was initiated by the BIODOPT trial group – no pharmaceutical companies are involved and there are no conflicts of interest. This protocol and all its appendix' is submitted for approval to the local Ethics Committee for the Region of Northern Jutland and the Danish Medicines Agency. The trial has been reported to the Danish Data Protection Agency through the Regions joint notification system (Regionernes fælles paraplyanmeldelse) and EudraCT. The trial will be registered at EudraCT before start of participant enrolment. This trial will be conducted in compliance with the protocol, GCP and all other applicable regulatory requirements. The trial is monitored by the local Danish GCP units for Aarhus, Aalborg and Odense University Hospitals. If the trial is completed before time or suspended, the BIODOPT trial group will inform the local Ethics Committee and the reason for the termination/suspension will be notified. After the end of this trial, the investigators will inform the participants about the results and conclusions of the trial.

13.2 Recruitment procedures

Participants will be recruited at a routine visit at the four Rheumatology outpatient clinics or upon request for participation by a letter, see below. In the outpatient clinics, information material for physicians regarding this trial and referral of possible participant to the investigator will be found (Informationsmateriale til læger på reumatologisk afdeling).When a potential participant has expressed interest in the trial, the investigator is notified and will contact the possible participant as soon as possible to arrange a visit in the outpatient clinic within 7 days for further information. The potential participant receives the Participant Information per e-boks or mail before the scheduled visit in the outpatient clinic. A possible participant can also be recruited upon request for participation by a letter per e-boks or mail (Brev til mulige forsøgsdeltagere). The possible participant will also receive the Participant Information with the letter. The possible participant is requested to contact his/her Rheumatology outpatient clinic if he/she wishes to participate in the trial. If the investigator has not heard from the possible participant within 1 month, the investigator will contact the possible participant by telephone and provide oral information about the trial. If the patient wishes to participate in the trial, a visit in the outpatient clinic is scheduled within 7 days.

At baseline, the informed consent is received as described below, see section 13.2. Informed consent, and the participant is included, randomised and examined as described in this protocol before the first dose reduction of the biological therapy. The patients will be treated and monitored according to the procedures specified in this protocol by the investigators during this trial. If during this trial circumstances is detected, that require further investigation and/or treatment for the individual patient, the patient will be informed if permission is given on the informed consent form.
All participants are given the name and telephone number to the trial nurse and local investigator in case of any questions. In addition, the participants receive the pamphlets "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt" and "Før du beslutter dig" from the Danish National Ethics Committee.

13.3. Informed consent

At the scheduled visit in the outpatient clinic, the potential participant will be given verbal and written information about the trial by the investigator before inclusion. The investigators must provide complete and sufficient verbal and written information, in uninterrupted surroundings, about the trial including potential harms to the participant and answer any questions concerning the trial. The potential participant is informed about participation being voluntary and of his/her right to at least 24 hours to reflection before the informed consent is given. In addition, the participant is informed about his/her right to bring a relative or friend to receive information about the trial and to discuss any questions. The participants is also informed of their right to withdraw consent at any time without a specific reason. The participant is asked to fill out the informed consent form and a separate consent form regarding storage of extra biological material in the Danish Rheumatology Biobank for later analysis if he/she wishes to participate in the trial. If the participant wishes to participate in the trial, fulfil the inclusion criteria and none of the exclusion criteria and has signed the two informed consents, he/she is included in the trial. The informed consent will be signed and dated by the participant and the investigator who administered the informed consent. A copy of the informed consent form will be given to the participant and the original will be placed in the trial master file (TMF). In the source documents (e.g. the patient's medical record), it is stated that the informed consent was obtained prior to any trial-related procedures and that the participant received a signed copy.

14. CONFIDENTIALITY

In this trial, information regarding previous medical history and treatment will be passed on from the participant and/or his/her medical record. This information is used together with other source data to identify possible prognostic factors for successful tapering of the biological therapy. All trial-related information will be stored securely at the trial sites. All trial-related data will be identified by a coded ID number to maintain participant confidentiality, however, this does not apply for records that contain names or other personal identifiers, such as informed consent forms, which will be stored with the TMF in locked file cabinets in areas with limited access, thus away from trial records identified by ID number. The code for the ID numbers is stored safely in another locked file cabinet in areas with limited access away from all other trial-related data. Access to the e-CRF in this trial (REDCap) will be excluded to the research personnel at the trial site, however the sponsor-investigator and the coordinating investigator will have access to e-CRF for all trial sites. The REDCap database meets current data security requirements because of data logging, which create an audit trail as explained in section 9.21. Data management. All trial-related data may under no circumstances be made available to a third party with the exception of authorized representatives of the relevant health or regulatory authorities, e.g. the Ethics Committee and/or the Danish Medicines Agency, as well as the trial monitor, e.g. GCP units. This trial will comply with The Danish laws regarding patient confidentiality (Lov om behandling af personoplysninger og Sundhedsloven) and is reported to the Danish Data Protection Agency through the Regions joint notification system (Regionernes fælles paraply-anmeldelse). Data will be destroyed 15 years after the end of this trial. The local Ethics Committee will receive information within 90 days after completion of this trial and a report 1 year after the end of the trial.

15. MONITORING

This trial is conducted in accordance with the protocol, the ICH-GCP guideline and applicable regulations and legislations in this area. The ethical principles from the Declaration of Helsinki will be followed. Applicable procedures for quality control and quality assurance will be followed in this trial. The sponsor-investigator SK are responsible for monitoring the trial after the GCP principles. This trial is submitted to the Danish Data Protection Agency, the Danish Medicines Agency and the local Ethics Committee and are monitored by the local Danish GCP units at Aarhus, Aalborg and Odense University Hospitals.

This trial uses an electronic e-CRF in REDCap. Investigators at each trial site will review and update the e-CRF to accuracy with date and signature when this is requested. The e-CRF and source documents are available to research personnel in the BIODOPT trial at the respective trial site, so they can enter data in the e-CRF as needed. The investigators will ensure that all source data will be available for monitoring, auditing and inspection by the GCP unit, the Danish Medicines Agency and other health authorities. All original informed consent forms, copies of all e-CRFs and detailed records of medical disposition will be stored safely and destroyed after 15 years.

16. COMPENSATION AND INSURANCE

Trial participants will not be financially reimbursed in this trial. The general insurance of patients and the "Lov om klage- og erstatningsadgang inden for sundhedsvæsnet" apply to all participants. The participants will be informed of this at baseline by vocal and written information provided by the investigator.

Research personnel including investigators will not be financially reimbursed for enrolling participants in this trial. The members of the BIODOPT trial group are covered by the statutory insurance of the hospital.

17. PROTOCOL AMENDMENTS

Any modifications to the protocol, which may affect the conduct of the trial, potential benefit of the patient or may affect patient safety, including changes of trial objectives, trial design, patient population, sample size, trial procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendment must be agreed upon by the BIODOPT trial group, approved by the local Ethics Committee prior to implementation and notified to the Danish Medicines Agency in accordance with applicable regulations. Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the trial is conducted. These administrative changes will be agreed upon by the BIODOPT trial group and will be documented in a memorandum. The local Ethics Committee may be notified of administrative changes at the discretion of the BIODOPT trial group.

18. DECLARATION OF INTEREST

None of the investigators has conflict of interest regarding the conduct of this trial. The trial is partly funded by donations from the Danish Regions (Regionernes Medicinpulje) and the Health Science

Research Fund of the Region of Northern Jutland (Region Nordjyllands Sundhedsvidenskabelige Forskningsfond) and the Department of Rheumatology at Aalborg University Hospital, see section 20. Budget. Pharmaceutical companies are not involved in this trial and do not provide financial support.

19. DISSEMINATION POLICY

19.1. Dissemination from the coordinating investigator to the sponsor

Throughout the trial period, the PhD student and coordinating investigator LU is required to keep the sponsor-investigator (SK) verbally as well as written informed of the conduct of this trial including all SAE and SAR.

19.2. Dissemination to health and regulatory authorities

Once a year during the trial period the coordinating investigator (LU) will report a summary of SAEs and SARs together with a report on participants' safety to the local Ethics Committee and the Danish Medicines Agency.

19.3. Dissemination of trial results

All results of this trial will be reported; preferably in English-language peer reviewed medical journals as well as presented at international congresses. Both negative, inconclusive and positive research results will be reported regardless of publication in a medical journal or not. Members of the BIODOPT trial group will be co-authors of all publications from the BIODOPT trial. Line Uhrenholt will be first author, Annette Schlemmer, Ellen-Margrethe Hauge and Robin Christensen will be co-authors and Salome Kristensen will be last author. Other authors will be dependent on the contributions. The site investigator will be qualified as co-authors of the main publication if 10 patients complete the trial, if 20 patients complete the trial the site will be qualified for 2 co-authorships on the main publication. The entire team of researchers will be mentioned in the author list as "and the BIODOPT trial group". Spin-off projects must be approved by the BIODOPT trial group in advance and will be co-authored by the BIODOPT trial group, the spin-off project group and others that have contributed markedly. In case of dispute, the BIODOPT trial group will resolve authorship issues. The Vancouver rules for authorship will be followed.

20. BUDGET

This trial is investigator-initiated and partly funded by donations from the Danish Regions (Regionernes Medicinpulje) (2.821.500 dkr.) and from the Health Science Research Fund of the Region of Northern Jutland (80.000 dkr.) and the Department of Rheumatology Aalborg University Hospital (322.875 dkr). The funding source had no role in the design of this trial and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. Coordinating investigator (LU) will seek additional funding for the expenses of the trial from private foundations. Upon receipt of funds, the amount is paid to a research account belonging to the Rheumatology Department at Aalborg University Hospital with reference to the title of the PhD-project. The BIODOPT trial group will use excess funding for future research within the same participant area.
Pharmaceutical companies are not involved in the trial and do not provide financial support. However, the Musculoskeletal Statistics Unit at Parker Institute, Bispebjerg and Frederiksberg Hospital, is supported by core grant OCAY-13-309 from the Oak Foundation.

Budget:

Budget for the BIODOPT-trial	Cost
Pay for PhD student LU for 6 months – the Rheumatology Department Aalborg University Hospital	322.875 dkr.
Pay for PhD student LU for 24 months – the Danish Regions	1.291.500 dkr.
Pay for PhD student LU for 1,5 months – Health Science Research Fund of the Region of Northern Jutland	80.000 dkr.
Pay for PhD student LU for 4,5 months – not financed yet	257.292 dkr.
Bio analysts – the Danish Regions	210.000 dkr.
Research nurse – the Rheumatology Department Aalborg Univeristy Hospital	349.600 dkr.
Blood tests: drug-level and anti-drug-antibody – the Danish Regions	800.000 dkr.
Blood tests: cytokins – the Danish Regions	400.000 dkr.
Publication expenses – the Danish Regions	20.000 dkr.
Statistical assistance, creation of "window" in DANBIO – the Danish Regions	100.000 dkr.
Sum	**3.831.267 dkr.**

21. TIME SCHEDULE

The screening period will start after relevant authorities approve this protocol. The screening period is scheduled to start November 2017 and last 1 year. The dose optimisation period is 12 months long starting from the participant's baseline. Follow up will be 5 years as described in this protocol.

22. FEASIBILITY OF THE TRIAL

The necessary facilities and expertise for implementation of this trial is present at the four Rheumatology Departments. Blood sampling are carried out by the Clinical Biochemistry Department associated with the four Rheumatology Departments, some blood samples are stored in the Danish Rheumatology Biobank as described in this protocol. The visits in this trial is part of the participants' usual outpatient control. The participants are registered in DANBIO at each visit as done at usual outpatient visits. Each visit in the outpatient clinic lasts approximately 1 hour. The patient receives the appointment for his/her next visit in the rheumatology outpatient clinic by electronic mail (e-boks)/by mail as usual. PhD Student LU is the coordinating investigator and responsible for the practical implementation of the trial, which is expected to be included in a PhD thesis.

23. INVESTIGATORS AND SPONSORS AGREEMENT

I have read this protocol and agree that the trial is ethical. I agree to conduct the trial as outlined and in accordance with all applicable regulations and guidelines. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Date, name and signature from Principal Investigator and sponsor Salome Kristensen

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Date, name and signature from Coordinating Investigator Line Uhrenholt

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Date, name and signature from Principal Investigator at trial site

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25. List of appendix'

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Appendix 2: ASDAS

Appendix 3: DAPSA

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Statistical Analysis Plan for the Randomised Controlled Trial:

Dose reduction and discontinuation of biological therapy in patients with inflammatory arthritis: *Primary results from the 18 months randomised, open label, parallel-group, multi-centre trial*

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Section 1: Administrative Information

Title and trial registration

Statistical analysis plan (SAP) for the randomised controlled trial entitled "*Dose reduction and discontinuation of biological therapy in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: An 18 months randomised, open label, parallel-group, multi-centre trial*".

Trial registration: EudraCT number: 2017-001970-41.

SAP version

Version 1.0

September 14th, 2021

Protocol version

This document has been written based on information contained in the study protocol version 10, dated September 5th, 2019.

SAP revisions

None.

Roles and responsibility

LU and RC designed and wrote this SAP in accordance to the SPIRIT/CONSORT and SAP statement for randomised trials (1–3). LU and RC are responsible for analysis of the trial results according to the SAP.

Signatures

Line Uhrenholt 14/9-21

MD, PhD Student, Coordinating investigator Line Uhrenholt Date

Sept. 14/2021

Professor, MSc, PhD, Senior Biostatistician, Robin Christensen Date

Section 2: Introduction

Background and rationale

BIODOPT was designed as a pragmatic, multicentre, randomised controlled, open-label, parallel-group trial, assessing the impact of tapering biological disease-modifying anti-rheumatic drugs (bDMARDs) in patients with inflammatory arthritis (i.e. rheumatoid arthritis [RA], psoriatic arthritis [PsA], and axial spondyloarthritis [axSpA]) in sustained remission or low disease activity (LDA). Traditionally, standard dose of bDMARDs are maintained lifelong after sustained remission/LDA are reached; however, recent studies indicate that a significant proportion successfully can taper bDMARDs while maintaining a stable low disease activity (4).

Aims

The trial aims to assess whether a disease activity-guided tapering strategy for bDMARDs will enable a significant dose reduction while maintaining disease activity compared with usual care.

Objectives

Primary outcome

There are two co-primary efficacy endpoints:

- 1A Superiority: The proportion of patients who at 18 months are reduced to 50% or less of their baseline dose of bDMARD
- 1B Equivalence: Disease activity assessed 18 months from baseline.

The primary objective is met if a statistically significant reduction in dose of biologics is demonstrated compared to control (i.e. superior) while maintaining a comparable (i.e. equivalent) disease state.

Secondary outcomes

Key secondary endpoints are:

- Proportion of patients in remission at 18 months
- Proportion of patients in LDA at 18 months

Additional supportive secondary endpoints are applicable to all patients: Changes from baseline to month 18 for the following:

- Pain Visual Analog Scale (VAS),
- Fatigue VAS,

- Patient global health VAS,
- Health Assessment Questionnaire Disability Index (HAQ-DI),
- Short Form Health Survey 36 (SF-36) physical component summary (PCS),
- Short Form Health Survey 36 (SF-36) mental component summary (MCS),
- Physician global health VAS,
- Joint count: swollen joints,
- Joint count: tender joints,
- C-reactive protein (CRP)

Exploratory outcomes:

All of the above, analysed according to their assessments at month 4, 8, and 12

RA patients (only):

- Disease Activity Score28crp (DAS28crp),
- Clinical Disease Activity Index (CDAI), and
- Simplified Disease Activity Index (SDAI)

PsA patients (only):

- DAS28crp,
- Disease Activity in Psoriatic Arthritis (DAPSA),
- Minimal disease activity criteria (MDA),
- Psoriasis Area Severity Index (PASI),
- Modified Nail Psoriasis Severity Index (mNAPSI),
- Enthesitis score by Spondyloarthritis Research Consortium Canada enthesitis score (SPARCC), and
- Dactylitis by number of affected fingers/toes

AxSpA patients (only):

- Ankylosing Spondylitis Disease Activity Score (ASDAS),
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),
- Bath Ankylosing Spondylitis Functional Index (BASFI),
- Bath Ankylosing Spondylitis Metrology Index (BASMI),
- PASI,
- mNAPSI,

- SPARCC, and
- Dactylitis status.

Protocol amendments

Protocol amendments with dates of report to the relevant authorities are summarised below.

Amendment number	Amendment date	Description of amendment
1	June 12th 2018	The Department of Rheumatology, South West Jutland, Esbjerg, was added as study site (but the site never included any patients)
2	September 24th 2018	The biosimilar drugs Imraldi and Amgevita (adalimumab) was added as approved study drugs as all patients treated with adalimumab per national guideline had to switch to biosimilar adalimumab in the form of Imraldi or Amgevita.
3	March 8th 2019	The biosimilar drug Zessly (infliximab) was added as approved study drug as all patients treated with infliximab per national guideline had to switch to biosimilar infliximab in the form of Zessly.
4	September 5th 2019	The Department of Rheumatology, Silkeborg Regional Hospital, was added as study site
5	November 30th 2020	The biosimilar drugs Erelzi (etanercept) and Hyrimoz (adalimumab) was added as approved study drugs as all patients treated with etanercept or adalimumab per national guideline had to switch to biosimilar Erelzi or Hyrimoz, respectively.
6	March 20th 2020	Suspension of patient enrolment due to the national implication of the COVID-19 pandemic to the Danish health care system
7	April 2nd 2020	The inclusion period was closed 1 month before scheduled due to the continued national COVID-19 implication to the Danish health care system.

Section 3: Study Methods

Trial design

BIODOPT was designed as a pragmatic, multicentre, randomised controlled, open-label, parallel-group trial of 18 months duration. Eligible patients were diagnosed with RA, PsA or axSpA treated with bDMARDs while maintaining remission/LDA during the past 12 months. Patients were randomised in a ratio of 2:1 to either disease activity-guided tapering of bDMARDs (experimental intervention group) or continuation of bDMARDs as usual care (comparator/control group).

Randomisation

The randomisation sequence was computer-generated before start of the enrolment period by the senior biostatistician with no clinical involvement in the trial (RC). Patients were allocated in ratio 2:1 in permuted blocks of 3 to 6 stratified by trial site (Aalborg, Aarhus, Odense, or Silkeborg), diagnosis (RA, axSpA or PsA) and repeated biologics failure (currently on biological agent number 3 or higher). The randomisation sequences (24 mutually independent strata in total) were generated using SAS statistical software (version 9.4; SAS Proc Plan).

The allocation sequence was concealed in a password-protected computer file only accessible to RC and the independent data manager (JHW). JHW entered the randomisation sequence into the electronic case report form (e-CRF) in the Research Electronic Data Capture (REDCap) platform. REDCap provided consecutive screening numbers with concealed group allocation (depending on the specific combination of strata's).

Power and sample size considerations

The sample size calculation was performed in accordance with the DELTA^2 guideline for reporting sample size calculations in randomised controlled trials (5).

Primary efficacy endpoint 1A: Based on data from the DRESS-RA trial (6), it was assumed that 30% in the experimental intervention group and 5% in the comparator control group would meet the primary endpoint 1A. Using Pearson's Chi-square statistic with a two-sided significance level of 0.05 and an allocation ratio of 2:1, a sample size of 180 patients (appr. 120 *vs* 60 in each group) yielded a very high statistical power of 0.992 (99%) if the proportion of patients reduced to 50% or less of their baseline dose of bDMARD were 30% and 5% as suggested above.

Primary efficacy endpoint 1B: Members of the BIODOPT trial group defined an equivalence margin of ± 0.5 DAS28crp points for patients with RA or PsA and ±0.5 ASDAS points for

patients with axSpA. The margins were based on "less than half of the effect" that would be considered a clinically relevant reduction in disease activity i.e. ΔDAS28crp > 1.2 or ΔASDAS > 1.1. Two one-sided test analysis was applied for additive equivalence of two-sample normal means with bounds ±0.5 for the mean difference, an allocation ratio of 2:1 and a significance level of 0.05 when assuming a mean difference of 0 and a common standard deviation of 1.0. Thus, a sample size of 180 patients (appr. 120 *vs* 60 in each group) was required to obtain a power of 0.868 (87%).

Framework

The primary efficacy 1A will be tested in terms of the expected superiority, while endpoint 1B will be interpreted based on its comparability between groups (i.e. equivalence: sufficiently narrow confidence intervals).

Statistical interim analyses and stopping guidance

No interim analyses are performed during this trial.

Timing of final analysis

Final analysis will be performed collectively and published in one paper (expected submission date January 2022).

Timing of outcome assessments

A detailed overview of all study procedures for each diagnosis (i.e. RA, PsA or axSpA) are presented in the trial protocol, Table 1A-1C on page 35-37.

Section 4: Statistical Principles

Confidence intervals and *P* values

Level of statistical significance and use of confidence intervals

All applicable statistical tests and 95% confidence intervals (95%CI) will be 2-sided and performed using a 5% significance level as indicative of a possible difference between groups.

For the primary efficacy endpoint 1A (i.e. reduction of bDMARD dose to 50% or less of baseline dose), a statistically, significant difference between the intervention groups is required to demonstrate superiority for tapering bDMARDs compared to continuous use. To confirm equivalence for primary efficacy endpoint 1B (i.e. comparable disease activity after 18 months), the 95%CI around the mean difference in disease activity must be within ±0.5 DAS28crp/ASDAS points (i.e. the equivalence margins).

Rationale for any adjustment for multiplicity

The primary objective in the BIODOPT trial is a composite primary endpoint requiring two co-primary efficacy endpoints to be met. Two steps will be applied for evaluation of the primary objective. In step 1, superiority of primary efficacy endpoint 1A will be evaluated i.e. significantly more patients (higher proportion) in the experimental intervention group reduce bDMARDs dose to 50% or less of their baseline dose compared to the control comparator group ($P < 0.05$). If and only if, statistically significant superiority in primary efficacy endpoint 1A is indicated, then, equivalence in disease activity i.e. primary efficacy endpoint 1B will be evaluated in step 2. Equivalence for primary efficacy endpoint 1B will be judged as likely if the 95%CI for the between-group difference in disease activity (DAS28crp/ASDAS) lies within: ±0.5 disease activity points.

Because of the multitude of secondary endpoints, multiplicity of efficacy evidence from these will be taken into consideration (7). Therefore, a hierarchical order will be applied in the evaluation of the key and supportive secondary outcomes to preserve the overall type-1 error rate at a two-sided alpha level of approximately 0.05(8).

Adherence and protocol deviations

Acceptable adherence to the trial protocol is defined as participants who complete visit month 18. Possible withdrawal from assigned intervention or withdrawal from treatment including concomitant

csDMARD or NSAIDs will be tracked by research personnel in the e-CRF in REDCap and summarised by treatment arm. Furthermore, missing variables will be summarised by number per intervention group corresponding to the intention-to-treat population.

Pre-defined major protocol violations that might occur are:

- Enrolled patients not fulfilling study eligibility criteria
- Visit month 18 not performed due to e.g. withdrawal or loss to follow-up

A summary of major protocol deviations and violations by number and percentage in each intervention group will be provided together with details of the type of violation. The intention-to-treat (ITT) population data set will be used as the denominator to calculate the percentages. No formal statistical tests will be performed.

Analysis populations

The primary and secondary outcomes will be analysed according to the ITT population i.e. all randomised participants with available outcome data independent of protocol deviations (9). ITT analyses with single-step replacement of missing data as well as "*per protocol*" analyses will be performed for the purpose of sensitivity, in order to explore the robustness of the overall study findings.

Section 5: Trial Population

Screening data

The screening period started on May 17th, 2018, and was suspended on March 13th, 2020, due to the implication of the COVID-19 pandemic on the Danish health care activities. On April 2nd, 2020, the screening period was closed as the national suspension had not yet been lifted; moreover, due to a lower enrolment rate than expected the screening period had already been prolonged one additional year and was therefore scheduled to end in May 2020.

The following screening data will be registered and presented:

- Length of the screening period
- Number of patients screened
- Number of patients enrolled and randomised
- Number of screened patients not enrolled
- Reason for non-enrolment

Eligibility

Eligibility criteria are described in detail in the trial protocol. The number of ineligible patients randomised, if any, will be reported, with reasons for ineligibility. A CONSORT flow diagram (**Outline Figure 1**, presented below) will illustrate participant enrolment including reasons for non-enrolment.

Recruitment

The use of a CONSORT flow diagram provides an overview of the number of patients screened, eligible, randomised, receiving the allocated intervention, withdrawing consent/discontinued/lost to follow-up and included in primary analysis. Any reason for exclusion with number of patients will be reported.

Withdrawal/follow-up

Withdrawal will be classified as:

- Withdraw from the trial but allow use of data collected to date
- Withdraw from the trial and withdraw consent for use of data collected to date
- Lost to follow-up

Numbers and reasons for any withdrawals, exclusions or loss to follow-up will be summarised by intervention group and presented in the CONSORT flow diagram.

Baseline patient characteristics

Outline Table 1, illustrated below, gives an overview of baseline characteristics of enrolled and randomised participants. Categorical data will be summarised by numbers and percentages and continuous data will be summarised by mean and SD if data are normally distributed and median and IQR if data are skewed; Also the range (minimum and maximum, respectively) will be summarised for continuous data. Formal tests for statistical significance will not be performed; however, apparent imbalances will be noted and, if necessary, will be evaluated based on standardised differences rather than *P*-values from erroneous null-hypotheses.

Section 6: Analysis

Outcome definitions

Primary endpoint

There are two co-primary efficacy endpoints:

- 1A Superiority: The proportion of patients who at 18 months are reduced to 50% or less of their inclusion dose of bDMARD (i.e. abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or tocilizumab).
- 1B Equivalence: Disease activity assessed with DAS28crp for patients with RA and PsA, and with ASDAScrp for patients with axSpA 18 months from baseline.

The primary outcome is only met if a statistically significant reduction in biologics is demonstrated (i.e. superiority) while maintaining a comparable (i.e. equivalent) disease state.

Secondary outcomes

Key secondary endpoints are:

- Proportion of patients in remission (defined as DAS28crp < 2.6 or ASDAScrp < 1.3) in each intervention group at 18 months
- Proportion of patients in LDA (defined as DAS28crp < 3.2 or ASDAScrp < 2.1) in each intervention group at 18 months

Supportive secondary endpoints are:

- Changes from baseline to month 18 for the following:
    - Pain VAS
    - Fatigue VAS
    - Patient Global Health VAS
    - HAQ-DI
    - SF-36 PCS
    - SF-36 MCS
    - Physician Global Health VAS
    - Swollen joint count
    - Tender joint count
    - CRP

Other exploratory outcomes are (stratified by condition):

- All of the above, reported according to their assessments at month 4, 8, and 12
- RA: DAS28crp, CDAI, and SDAI
- PsA: DAS28crp, DAPSA, MDA, PASI, mNAPSI, enthesitis score by SPARCC, and dactylitis by number
- AxSpA: ASDAS, BASDAI, BASFI, BASMI, PASI, mNAPSI, SPARCC, dactylitis by number

Analysis methods

All analyses will be performed in accordance with this pre-specified SAP (3,10) and reported in accordance with the recommendations of the EQUATOR network (11); i.e. the appropriate CONSORT statement (1,2).

All outcome measures will be analysed based on the ITT population (12), including all randomised participants with available data at baseline (i.e. modified ITT population) (13). Missing data for continuous outcome variables will be handled indirectly, statistically modelled using repeated-measures linear mixed-effects models (see below). These models will be valid if data are '*Missing at Random*' (MAR) (14). Contrasts between groups will be estimated based on the least squares means and the corresponding standard errors derived from the full model with repeated-measures analysis (0, 4, 8, 12, and 18 months from baseline); with the important contrast between groups corresponding to 18 months from baseline. The model will include group (i.e. tapering *vs* continuation), diagnosis (RA, PsA, *or*, axSpA), bDMARD failure history (<3 previous bDMARDs, *or* ≥3 previous bDMARDs), centre status (Aalborg, Aarhus, Odense, *or* Silkeborg), and time point (0, 4, 8, 12, and 18 months from baseline) as class (fixed effect) factors, while the baseline value of the relevant variable will be included as a covariate to reduce the random variation. Categorical outcomes for dichotomous endpoints (including responder status and harms) will be analysed with logistic regression (excluding repeated measures) with the same fixed effect factors and covariates as for the continuous outcome measures. In the main analyses, missing data for the dichotomous outcomes will be analysed based on the conservative assumption that the trial was a failure (e.g. patients *were not able* to reduce their biologics to 50% or less of their baseline dose; or *did not* sustain low disease activity/remission).

To assess the adequacy of the linear models describing the observed data—and checking assumptions for the systematic and the random parts of the models—we will use the predicted

values and the residuals; i.e., the residuals have to be approximately normally distributed (around 0) and be independent of the predicted values.

The cumulative incidence of patients having flares will be visualized for the two trial arms in a Kaplan-Meier time-to-event (survival) curve presented with hazard ratio using Cox proportional-hazards model. All analyses will be performed using commercially available statistical software (SAS, version 9.4; SAS Institute Inc and/or STATA, version 16).

Missing data

For the main analyses, simplistic imputation techniques will be used to handle missing data for dichotomous outcomes (assuming trial failure), while continuous outcomes will be handled indirectly via the mixed-effects model framework.

Regarding prevention and treatment of missing data in clinical trials, robustness is a relatively new concept (15); a concept that we will apply to assess the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis. Robustness implies that the treatment effect and primary conclusion of the trial are not substantially affected when analyses are carried out based on alternative assumptions or analytic approaches (15). Since lost to follow-up and missing data for various reasons is difficult to avoid in randomised (pragmatic) trials like the BIODOPT trial, we will apply the following analysis framework suggested by White et al. (16).

Missing data related to the ITT approach depend on making plausible assumptions about the missingness of the data and including all participants in subsequent sensitivity analyses (steps: 1 to 4):

1. We will: Attempt to follow up all randomised participants, even if they withdraw from allocated treatment.

2. We will: Perform the primary analyses of all observed data that are valid under a plausible assumption about the missingness of the data (i.e., Model-based: using repeated-measures linear mixed-effects models, assuming that data are '*Missing at Random*' [MAR]).

3. Perform sensitivity analyses to explore the effect of departures from the assumption made in the primary (#2) analyses (i.e., a non-responder-imputation: using the value at baseline to replace missing data will correspond to a non-responder imputation; these models will potentially be informative even if data are '*Missing Not At Random*' [MNAR]).

4. Account for all randomised participants, at least in the sensitivity analyses (covered by #2 and supported by #3 above, plus the corresponding analyses based on the *per protocol* population).

The interpretation of the corresponding statistical measures of uncertainty of the treatment effect and treatment comparisons will involve consideration of the potential contribution of bias to the *P*-value, 95% CI, and of the inference in general.

Additional analyses

Stratified (subgroup) analyses on the primary endpoint(s) will be performed to explore potentially relevant effect modifiers among the baseline measures (17):

- Site: Aalborg, Aarhus, Odense or Silkeborg
- Diagnosis: RA, PsA or axSpA
- Repeated biologics failure: <3 or ≥ 3
- Sex: female or male
- Age: < median age or ≥ median age
- bDMARD drug mode of action: TNFi, IL6-inhibitor or t-cell-co-stimulation blocker
- Remission status: remission or LDA

Harms and adverse events

Number and percentage of adverse events (AE) including flare and infectious adverse events will be reported as well as serious adverse events (SAE) such as serious infections, cardiovascular events, malignancies, and deaths as illustrates in **Outline Table 3**. The type AE, severity and relationship to study drugs will be reported. Moreover, number and percentage of patients in each intervention group who prematurely discontinue their study drug due to any AE will also be reported.

Thus, safety and harm summaries will be reported by trial arm including an estimate of the between group difference which will be analysed using Chi-square test/Fisher's exact test (depending on large/small sample).

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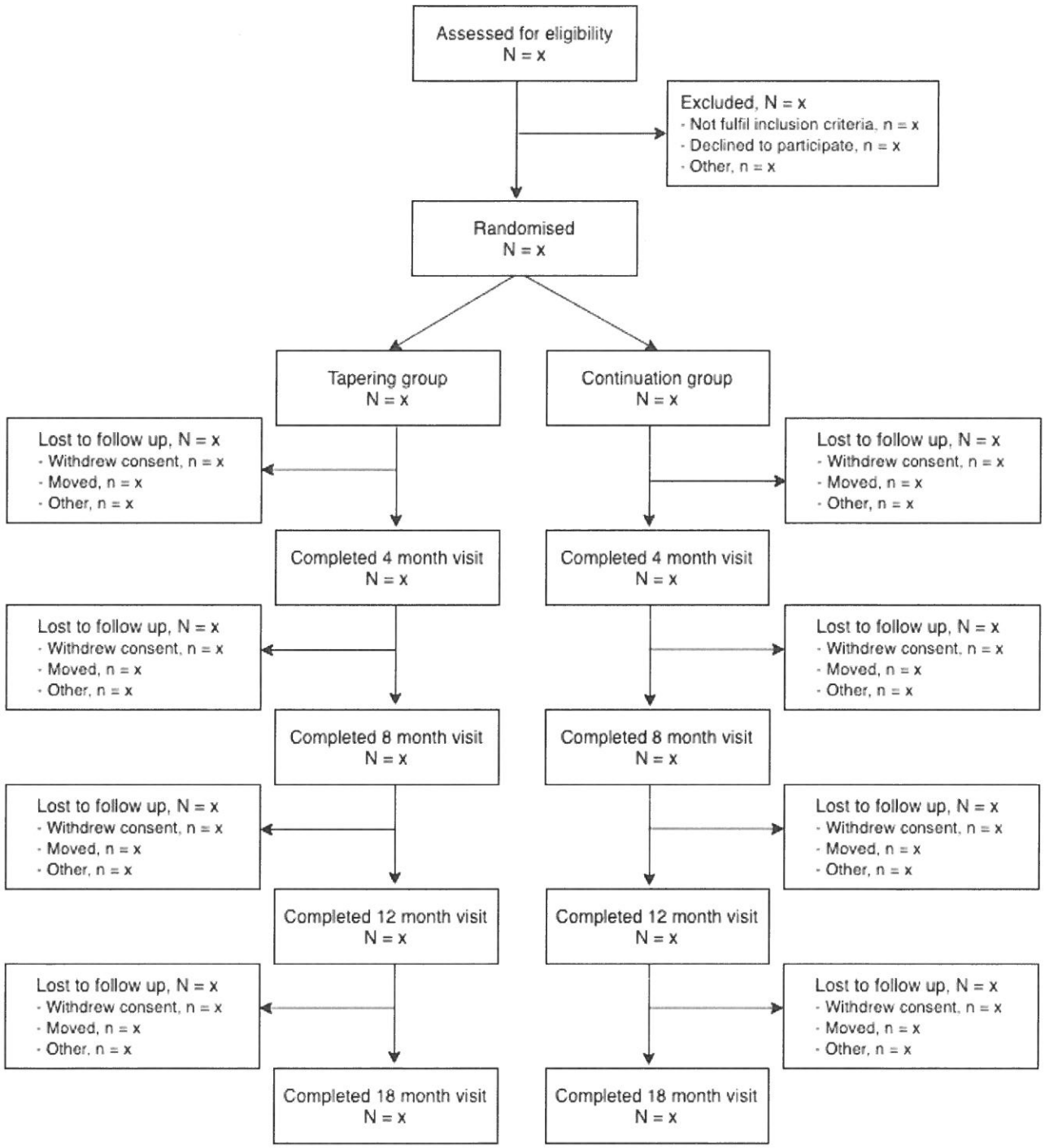
Section 7: Manuscript outline

The manuscript outline will include the following documents:

- Outline Figure 1: Flow diagram of participant recruitment and trial profile
- Outline Table 1: Baseline demographics and disease characteristics in the ITT population.
- Outline Figure 2: Mock-up (simulated data visualisation) of disease activity during the study period by diagnosis. Values will be Least Squares Means with Standard Errors.
- Outline Table 2: Comparison between groups at 18 months based on the ITT population using repeated-measures linear mixed-effects models
- Outline Figure 3: Mock-up (simulated data visualisation) of flares by trial arm visualised by a Kaplan Meier cumulative incidence curve.
- Outline Table 3: Safety and harm summary (data analysed "as observed" based on the original ITT population)
- Outline Appendix 1: The BIODOPT trial protocol, version 10, September 5th 2019
- Outline Appendix 2: The statistical analysis plan, version 1.0
- Outline Appendix Table 1: Baseline demographics and disease characteristics by diagnosis
- Outline Appendix Table 2: Comparison between groups at 18 months based on the ITT population using non-responder imputation (Baseline Observation Carried Forward)
- Outline Appendix Table 3: Comparison between groups at 18 months based on the *per protocol* population (i.e. no missing data)
- Outline Appendix Table 4: Descriptive results reported by diagnosis

Outline Figure 1: Flow diagram of patient recruitment



Outline Table 1: Baseline demographics and disease characteristics in the ITT population.

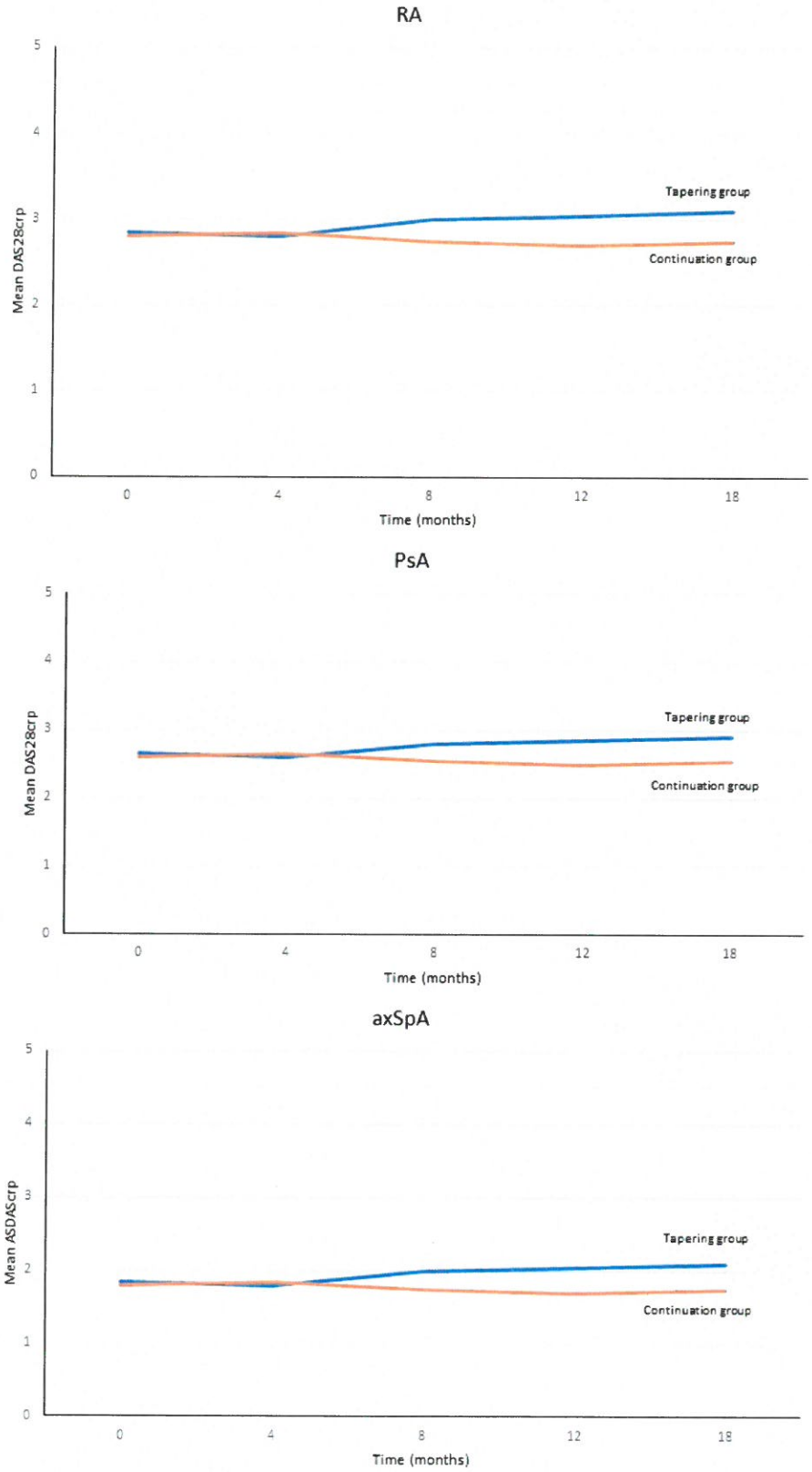
Variable	Tapering group (*N*=?)	Continuation group (*N*=?)	All (N = ?)
General characteristics			
Female, n (%)			
Age (years)			
Smoking, n (%)			
Body Mass Index (kg/m^2)			
Arthritis characteristics:			
Diagnosis:			
- RA, n (%)			
- PsA, n (%)			
- axSpA, n (%)			
Disease duration from arthritis diagnosis			
Disease activity measures:			
HAQ-DI (score: 0-3)			
Pain VAS (score: 0-100 mm)			
Fatigue VAS (score: 0-100 mm)			
Patient global health VAS (score: 0-100 mm)			
Short Form-36:			
Physical component summary (score 0-100)			
Mental component summary (score: 0-100)			
Physician global health VAS (score: 0-100 mm)			
Tender joint count (0-68)			
Swollen joint count (0-66)			
CRP (mg/L)			
In remission[1], n (%)			
Arthritis treatment characteristics			
csDMARDs, n (%)			
Combination csDMARDs, n (%)			
MTX, n (%)			
Duration of current bDMARDs (months)			
Current bDMARD therapy:			
TNF-α inhibitor, n (%)			
IL-6 inhibitor, n (%)			
T-cell co-stimulation blocker, n (%)			
Repeated bDMARD failure history (≥ 3 bDMARDs), n (%)			

Values are means and standard deviation (SD) unless otherwise stated.

n: number, kg: kilogram, m^2: square metre, RA: rheumatoid arthritis, PsA: psoriatic arthritis, axSpA: axial spondyloarthritis, HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analog Scale, CRP: C-reactive protein, mg: milligram, L:litre, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, MTX: methotrexate, bDMARD: biologic disease-modifying antirheumatic drug, TNF: Tumor necrosis factor, IL: Interleukin

[1]: Evaluated as Disease Activity Score (DAS)28crp < 2.6 for RA and PsA and Ankylosing Spondylitis Disease Activity Score (ASDAS)crp < 1.3 for axSpA.

Outline Figure 2: Mock-up (simulated data visualisation) of disease activity during the study period by diagnosis. Values are Least Squares Means with Standard Errors.



Outline Table 2: Comparison between groups at 18 months based on the ITT population using repeated-measures linear mixed-effects models

Outcome	Tapering group N =	Continuation group N =	Difference between groups, (95%CI)	*P*-value
Primary outcome:				
bDMARDs reduced to 50% or less[1], n (%)				
Disease activity score[2]				
Secondary outcomes:				
In remission[3], n (%)				
In low disease activity[4], n (%)				
HAQ-DI (score: 0-3)[5]				
Pain VAS (score: 0-100)[5]				
Fatigue VAS (score: 0-100)[5]				
Patient Global Health VAS (score: 0-100)[5]				
Short Form-36 PCS (score: 0-100)[5]				
Short Form-36 MCS (score: 0-100)[5]				
Physician Global Health VAS (score: 0-100)[5]				
Tender joint count (score: 0-68)[5]				
Swollen joint count (score: 0-66)[5]				
CRP (mg/L)[5]				

N: number, CI: confidence interval, VAS: Visual Analog Scale, PCS: physical component summary, MCS: mental component summary, CRP: C-reactive protein, mg: milligram, L:litre.

*Dichotomous outcomes are analysed based on logistic regression analyses (18 months from baseline), missing data are imputed as trial failures.

[1]: Compared to baseline bDMARD dose

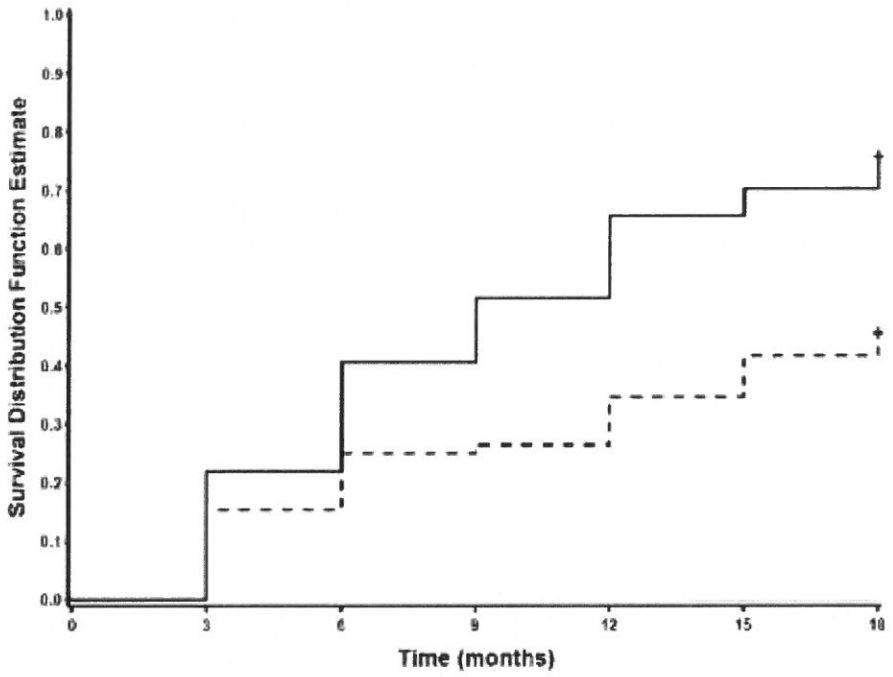
[2]: Assessed by Disease Activity Score (DAS)28crp for RA and PsA and Ankylosing Spondylitis Disease Activity Score (ASDAS)crp for axSpA

[3]: Evaluated as DAS28crp < 2.6 for RA and PsA and ASDAScrp < 1.3 for axSpA.

[4]: Evaluated as DAS28crp < 3.2 for RA and PsA and ASDAScrp < 2.1 for axSpA.

[5]: Change from baseline

Outline Figure 3 Mock-up (simulated data visualisation (18)) of flare by trial arm visualised by a Kaplan Meier cumulative incidence curve.



Outline Table 3: Safety and harm summary (data analysed "as observed" based on the original ITT population)

	Tapering group N =	Continuation group N =	Difference, (95%CI)
Flare:			
Fulfil flare criteria, n (%)			
Flare according to rheumatologist in patients not fulfilling the flare criteria, n (%)			
bDMARDs dose escalation rescue therapy, n (%)			
Glucocorticoid rescue therapy, n (%)			
Non-reversable flare after rescue therapy, n (%)			
Switched to another biologic due to flare, n (%)			
Non-reversable flare after switch, n (%)			
Adverse events of particular interest:			
Infections, n (%)			
Uveitis, n (%)			
Psoriasis skin flare, n (%)			
Psoriasis nail flare, n (%)			
Flare in symptoms of IBD, n (%)			
Discontinued study drug due to any AE, n (%)			
Serious adverse events:			
Serious infections, n (%)			
Cardiovascular events, n (%)			
Malignancy, n (%)			
Death, n (%)			

N: number, CI: confidence interval, bDMARD: biologic disease-modifying antirheumatic drug, IBD: inflammatory bowel disease, AE: adverse event.

Outline Appendix Table 1: Baseline demographics and disease characteristics by diagnosis

Variable	Tapering group	Continuation group	All
RA:			
Female, n (%)			
Age (years)			
Disease duration from arthritis diagnosis			
RF positive, n (%)			
ACPA positive, n (%)			
Erosive, n (%)			
DAS28crp (0.96-9.4)			
CDAI (score 0-76)			
SDAI (score: 0-86)			
Concomitant csDMARDs, n (%)			
Concomitant MTX, n (%)			
MTX dose, mg/week			
PsA:			
Female, n (%)			
Age (years)			
Disease duration from arthritis diagnosis			
SPARCC Enthesitis Index (score: 0-16)			
Dactylitis by number (0-20)			
PASI (score: 0-72)			
mNAPSI (score: 0-130)			
Erosive, n (%)			
DAS28crp (0.96-9.4)			
DAPSA (score: 0-164)			
In MDA, n (%)			
Concomitant csDMARDs, n (%)			
Concomitant MTX, n (%)			
MTX dose, mg/week			
axSpA:			
Female, n (%)			
Age (years)			
Disease duration from arthritis diagnosis			
Ankylosing spondylitis, n (%)			
HLA-B27 positive, n (%)			
BASFI (score: 0-100)			
SPARCC Enthesitis Index (score: 0-16)			
Dactylitis by number (0-20)			
PASI (score: 0-72)			
mNAPSI (score: 0-130)			
BASDAI (score: 0-100)			
ASDAS (score: 0.6-∞)			
BASMI (score: 0-100)			
Concomitant NSAIDs, n (%)			

Values are means and standard deviation (SD) unless otherwise stated.

RA: rheumatoid arthritis, n: number, RF: Rheumatoid Factor, ACPA: Anti-Citrullinated Peptide Antibodies, DAS28crp: Disease Activity Score 28crp, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, PsA: psoriatic arthritis, SPARCC: Spondyloarthritis Research Consortium of Canada, PASI: Psoriasis Area Severity Index, mNAPSI: modified Nail Psoriasis Severity Index, DAPSA: Disease Activity index for PSoriatic Arthritis, MDA: Minimal Disease Activity in PsA, axSpA: axial spondyloarthritis, HLA-B27: Human leukocyte antigen subtype B27, BASFI: Bath Ankylosing Spondylitis Functional Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASMI: Bath Ankylosing Spondylitis Metrology Index NSAIDs: Non-steroidal anti-inflammatory drugs.

Outline Appendix Table 2: Comparison between groups at 18 months based on the ITT population using non-responder imputation (Baseline Observation Carried Forward)

Outcome	Tapering group N =	Continuation group N =	Difference between groups, (95%CI)	*P*-value
Primary outcome:				
bDMARDs reduced to 50% or less[1], n (%)				
Disease activity score2				
Secondary outcomes:				
In remission[3], n (%)				
In low disease activity[4], n (%)				
HAQ-DI (score: 0-3)[5]				
Pain VAS (score: 0-100)[5]				
Fatigue VAS (score: 0-100)[5]				
Patient Global Health VAS (score: 0-100)[5]				
Short Form-36 PCS (score: 0-100)[5]				
Short Form-36 MCS (score: 0-100)[5]				
Physician Global Health VAS (score: 0-100)[5]				
Tender joint count (score: 0-68)[5]				
Swollen joint count (score: 0-66)[5]				
CRP (mg/L)[5]				

N: number, CI: confidence interval, VAS: Visual Analog Scale, PCS: physical component summary, MCS: mental component summary, CRP: C-reactive protein, mg: milligram, L:litre.

*Dichotomous outcomes are analysed based on logistic regression analyses (18 months from baseline), missing data are imputed as trial failures.

[1]: Compared to baseline bDMARD dose

[2]: Assessed by Disease Activity Score (DAS)28crp for RA and PsA and Ankylosing Spondylitis Disease Activity Score (ASDAS)crp for axSpA

[3]: Evaluated as DAS28crp < 2.6 for RA and PsA and ASDAScrp < 1.3 for axSpA.

[4]: Evaluated as DAS28crp < 3.2 for RA and PsA and ASDAScrp < 2.1 for axSpA.

[5]: Change from baseline

Outline Appendix Table 3: Comparison between groups at 18 months based on the *per protocol* population (i.e. no missing data)

Outcome	Tapering group N =	Continuation group N =	Difference between groups, (95%CI)	*P*-value
Primary outcome:				
bDMARDs reduced to 50% or less[1], n (%)				
Disease activity score[2]				
Secondary outcomes:				
In remission[3], n (%)				
In low disease activity[4], n (%)				
HAQ-DI (score: 0-3)[5]				
Pain VAS (score: 0-100)[5]				
Fatigue VAS (score: 0-100)[5]				
Patient Global Health VAS (score: 0-100)[5]				
Short Form-36 PCS (score: 0-100)[5]				
Short Form-36 MCS (score: 0-100)[5]				
Physician Global Health VAS (score: 0-100)[5]				
Tender joint count (score: 0-68)[5]				
Swollen joint count (score: 0-66)[5]				
CRP (mg/L)[5]				

N: number, CI: confidence interval, VAS: Visual Analog Scale, PCS: physical component summary, MCS: mental component summary, CRP: C-reactive protein, mg: milligram, L:litre.

*Dichotomous outcomes are analysed based on logistic regression analyses (18 months from baseline), missing data are imputed as trial failures.

[1]: Compared to baseline bDMARD dose

[2]: Assessed by Disease Activity Score (DAS)28crp for RA and PsA and Ankylosing Spondylitis Disease Activity Score (ASDAS)crp for axSpA

[3]: Evaluated as DAS28crp < 2.6 for RA and PsA and ASDAScrp < 1.3 for axSpA.

[4]: Evaluated as DAS28crp < 3.2 for RA and PsA and ASDAScrp < 2.1 for axSpA.

[5]: Change from baseline

Outline Appendix Table 4: Descriptive results reported by diagnosis

Outcome	Tapering group N =	Continuation group N =
RA disease specific outcomes		
HAQ-DI (score: 0-3)[1]		
Pain VAS (score 0-100)[1]		
Patient Global Health VAS (score 0-100)[1]		
Tender joint count (0-68)[1]		
Swollen joint count (0-66)[1]		
Physician Global Health VAS (score 0-100)[1]		
CRP (mg/L)[1]		
DAS28crp (score: 0.96-9.4)[1]		
CDAI (score 0-76)[1]		
SDAI (score: 0-86)[1]		
PsA disease specific outcomes		
HAQ-DI (score: 0-3)[1]		
Pain VAS (score 0-100)[1]		
Patient Global Health VAS (score 0-100)[1]		
Tender joint count (0-68)[1]		
Swollen joint count (0-66)[1]		
Physician Global Health VAS (score 0-100)[1]		
CRP (mg/L)[1]		
SPARCC Enthesitis Index (score: 0-16)[1]		
Dactylitis by number (0-20)[1]		
PASI (score: 0-72)[1]		
mNAPSI (score: 0-130)[1]		
DAS28crp (score: 0.96-9.4)[1]		
DAPSA (score: 0-164)[1]		
In MDA, n (%)[1]		
axSpA disease specific outcomes		
HAQ-DI (score: 0-3)[1]		
Pain VAS (score 0-100)[1]		
Patient Global Health VAS (score 0-100)[1]		
Backpain i.e. BASDAI question 2 (score: 0-100)[1]		
Morning stiffness i.e. BASDAI question 5 (score: 0-100)[1]		
Peripheral pain/swelling i.e. BASDAI question 3 (score: 0-100)[1]		
Tender joint count (0-68)[1]		
Swollen joint count (0-66)[1]		
Physician Global Health VAS (score 0-100)[1]		
CRP (mg/L)[1]		
SPARCC Enthesitis Index (score: 0-16)[1]		
Dactylitis by number (0-20)[1]		
PASI (score: 0-72)[1]		
mNAPSI (score: 0-130)[1]		
ASDAS (score: 0.6-∞)[1]		
BASDAI (score 0-100)[1]		

N: number, CI: confidence interval, RA: rheumatoid arthritis, HAQ-DI: Health Assessment Questionnaire Disability Index, VAS: Visual Analog Scale, CRP: C-Reactive Protein, mg: milligram, L: litre, DAS28crp: Disease Activity Score 28crp, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, PsA: psoriatic arthritis, SPARCC: Spondyloarthritis Research Consortium of Canada, PASI: Psoriasis Area Severity Index, mNAPSI: modified Nail Psoriasis Severity Index, DAPSA: Disease Activity index for PSoriatic Arthritis, MDA: Minimal Disease Activity in PsA, axSpA: axial spondyloarthritis, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index.

[1]: Change from baseline