Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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eAppendix 1. Inclusion and exclusion criteria

Inclusion criteria

1. Rheumatoid arthritis (RA) according to the 2010 ACR/EULAR classification criteria
2. Male or non-pregnant, non-nursing female
3. >18 years of age and <80 years of age
4. RA diagnosis after 01.01.2010.
5. Sustained remission for ≥12 months according to DAS or DAS28, with documented remission status at a minimum of 2 consecutive visits during the last 18 months.
6. DAS <1.6 and no swollen joints at inclusion.
7. Unchanged treatment with synthetic DMARDs during the previous 12 months, with a stable or reduced dose of glucocorticosteroids.
8. Subject capable of understanding and signing an informed consent form
9. Provision of written informed consent

Exclusion criteria

1. Abnormal renal function, defined as serum creatinine >142 µmol/L in female and >168 µmol/L in male, or a glomerular filtration rate <40 mL/min/1.73 m^2.
2. Abnormal liver function (defined as ASAT/ALAT >3x upper normal limit), active or recent hepatitis, cirrhosis.
3. Major co-morbidities, such as severe malignancies, severe diabetic mellitus, severe infections, uncontrollable hypertension, severe cardiovascular disease (New York Heart Association classification 3 or 4) and/or severe respiratory diseases.
4. Leukopenia and/or thrombocytopenia.
5. Inadequate birth control, pregnancy, and/or breastfeeding
6. Indications of active tuberculosis.
7. Psychiatric or mental disorders, alcohol abuse or other substance abuse, language barriers or other factors which makes adherence to the study protocol impossible.

Abbreviations:
ACR: American College of Rheumatology. ALAT: Alanine transaminase. ASAT: Aspartate transaminase. DAS: Disease Activity Score. DAS28: Disease Activity Score based on 28 joint count. DMARD: Disease-modifying antirheumatic drugs. EULAR: European League Against Rheumatism.

eAppendix 2. Summary narratives for malignancies (n=1)

A female randomized to stable conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy was diagnosed with basal cell carcinoma during the first months after inclusion. The basal cell carcinoma was removed by surgery three months after study start. At the time of surgery, she received 25 mg methotrexate weekly. Concomitant medication was ibuprofen and folic acid. The investigator considered the event not to be related to the study medication.

eAppendix 3. Additional post hoc flare analyses

Of the patients with flare, one patient in the stable group and 11 patients in the half-dose group had flare where the formal definition (a combination of Disease Activity score (DAS)>1.6, a change in DAS >0.6 and at least two swollen joints) was not met, but both the patient and the physician agreed that a clinically significant flare had occurred. After review, we had data that supported this decision in the one patient in the stable group, and in eight of eleven patients in the half-dose group.

The confirmed flares were: Five patients that had DAS >1.6 and a change of >0.6, and one swollen joint – with data showing inflammation in additional joints that were not included in the 44 joint count or by ultrasound examination, tenosynovitis, or a significant increase in C-reactive protein (CRP). One patient was no longer in DAS remission, and had four joints with newly developed ultrasound synovitis. One patient had DAS >1.6 and a change in DAS of >0.6, one swollen joint and reported fluctuating swollen joints and increasing stiffness in the last weeks. In one patient, very limited data were reported in the case report form due to logistical issues at the time of an unplanned visit, but comments from the treating physician confirmed a flare with arthritis, tendinitis and bursitis. One of the patients experienced a flare while on vacation, and thus started 10 mg of prednisone ahead of the assessment at the «flare-visit». A fulminant flare was still ongoing and reported on the visit after the first flare was recorded, with DAS>1.6, a change in DAS >0.6 and seven swollen joints, and within the follow-up period the patient had to start tumor necrosis factor inhibitor treatment.

In the remaining three patients, we did not have access to data that could confirm whether or not a clinically significant flare had occurred. In a sensitivity analysis, we repeated the main analyses with classification of these three patients as non-flares. These analyses show a flare rate of 5/78 (6%) in the stable group, and 16/77 (21%) in the half-dose group, with a risk difference of 15% (95% confidence interval of 3% to 27%), yielding the same conclusion as the main analysis.

eTable 1. Trial enrollment by study site.

	Site	University function	Community/ regional hospital[a]	Number of patients enrolled
1	Diakonhjemmet Hospital	x	x	70
2	Ålesund Hospital		x	30
3	Revmatismesykehuset		x	14
4	Haukeland University Hospital	x	x	12
5	Østfold Hospital		x	9
6	University Hospital of North Norway	x	x	9
7	Drammen Hospital		x	9
8	Sørlandet Hospital		x	5
9	Helgelandssykehuset Mo i Rana		x	1
10	Martina Hansens Hospital		x	1

[a] The large majority of patients with rheumatoid arthritis in Norway receive treatment and follow-up at rheumatology departments in hospitals.

eTable 2. Response to reinstated treatment after flare

Characteristic[a]	Half-dose	Stable dosing
ACR20 response[b]	6/12 (50%)	3/3 (100%)
ACR50 response[b]	4/12 (33%)	3/3 (100%)
ACR70 response[b]	3/12 (25%)	3/3 (100%)
ACR90 response[b]	1/12 (8%)	2/3 (67%)
EULAR response: Good[c]	4/13 (31%)	3/3 (100%)
EULAR response: Moderate[c]	4/13 (31%)	0/3 (0%)
EULAR response: None[c]	5/13 (39%)	0/3 (0%)
Disease Activity Score remission	9/13 (69%)	3/3 (100%)
FDA major clinical response[d]	0/6 (0%)	0/2 (0%)

Abbreviations: ACR: American College of Rheumatology. EULAR: European Alliance of Rheumatology Associations. FDA: The U.S. Food and Drug Administration.

[a] Time to first clinical examination after a flare varied from few weeks to four months depending on the timing of the protocolized next visit.
[b] Improvement of 20%/50%/70%/90% (respectively for ACR20/50/70/90) in the number of tender and number of swollen joints, in combination with a 20%/50%/70%/90% (respectively for ACR20/50/70/90) improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure, visual analog joint pain scale, and erythrocyte sedimentation rate or C-reactive protein.
[c] A good EULAR response is a decrease in Disease Activity Score (DAS) by more than 1.2 points and resulting in a DAS of 2.4 or less. A moderate EULAR response is a decrease in DAS of more than 0.6 points and resulting in a DAS of 3.7 or less.
[d] The U.S. Food and Drug Administration major clinical response requires achieving ACR70 response at the current visit and at each visit within the previous 6 months. Results for patients with sufficient data post-flare.

eTable 3. Secondary outcomes.

	Half-dose	Stable dosing	Half-dose	Stable dosing	
Continuous variables [a]	**Baseline**		**Change 0-12 months**		**Adjusted difference at 12 months (95% CI)**[b]
Measures of disease activity					
Disease Activity Score[c], mean (SD)	0.8 (0.3)	0.8 (0.4)	0.2 (0.5)	0.1 (0.3)	0.0 (-0.1, 0.2)
Disease Activity Score[c], AUC			1.0 (0.4)	0.9 (0.3)	0.1 (-0.0, 0.2)
Disease Activity Score in 28 joints[d], mean (SD)	1.6 (0.6)	1.5 (0.6)	0.2 (0.8)	0.2 (0.5)	0.0 (-0.2, 0.2)
Disease Activity Score in 28 joints[d], AUC			1.8 (0.6)	1.6 (0.6)	0.1 (-0.1, 0.3)
Simplified Disease Activity Index[e], median (IQR)	0.9 (0.3,2.1)	0.8 (0.5,1.6)	1.2 (4.0)	0.6 (2.3)	0.6 (-0.4, 1.6)
Simplified Disease Activity Index[e], AUC			2.6 (2.8)	2.0 (1.8)	0.6 (-0.1, 1.3)
Clinical Disease Activity Index[f], median (IQR)	0.5 (0.1,1.7)	0.5 (0.3,1.4)	1.2 (3.8)	0.7 (2.1)	0.6 (-0.4, 1.5)
Clinical Disease Activity Index[f], AUC			2.2 (2.6)	1.7 (1.8)	0.5 (-0.1, 1.2)
Swollen-joint count[g], mean (SD)	0.0 (0.0)	0.0 (0.0)	0.3 (0.9)	0.2 (0.7)	0.1 (-0.2, 0.5)
Tender-joint count (Ritchie Articular Index)[h], median (IQR)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.3 (1.1)	0.2 (0.9)	0.2 (-0.1, 0.5)
Erythrocyte sedimentation rate, mm/hr[i], median (IQR)	7.0 (4.0,13.0)	7.0 (4.0,14.0)	0.4 (6.5)	1.1 (7.1)	-0.7 (-2.8, 1.3)
C-reactive protein, mg/dL, normal value <0.4 mg/dL[j], median (IQR)	0.2 (0.1,0.3)	0.2 (0.1,0.3)	-0.01 (0.6)	-0.07 (0.9)	0.06 (-0.1, 0.2)
Patient's global assessment[k], median (IQR)	3.0 (1.0,10.0)	3.5 (1.0,10.0)	2.3 (14.7)	3.5 (13.5)	-0.8 (-5.1, 3.5)
Physician's global assessment[k], median (IQR)	0.0 (0.0,3.0)	1.0 (0.0,4.0)	3.3 (8.1)	1.6 (6.3)	1.4 (-0.8, 3.5)
Functional outcomes					
PROMIS Physical Function[l], mean (SD)	55.6 (7.5)	56.1 (7.4)	-1.3 (5.6)	-1.5 (5.7)	0.0 (-1.6, 1.7)
EuroQol-5 Dimensions[m], median (IQR)	1.0 (0.8,1.0)	1.0 (0.8,1.0)	-0.1 (0.1)	0.0 (0.1)	0.0 (-0.1, 0.0)
Fatigue visual-analogue scale[n], median (IQR)	10.0 (2.0,29.0)	5.5 (1.0,24.0)	-1.3 (15.8)	0.0 (20.0)	-0.9 (-6.0, 4.2)
Joint pain visual-analogue scale[n], median (IQR)	4.0 (1.0,10.0)	3.0 (1.0,9.0)	2.9 (13.9)	2.7 (11.2)	0.2 (-4.0, 4.4)
SF-36 Physical Functioning[o], median (IQR)	95.0 (85.0,100.0)	95.0 (90.0,100.0)	0.2 (9.3)	-3.4 (8.5)	3.7 (1.0, 6.3)
SF-36 Bodily Pain[o], median (IQR)	90.0 (77.5,100.0)	90.0 (77.5,100.0)	-4.5 (18.7)	-5.6 (16.2)	0.1 (-5.1, 5.2)
SF-36 Role-physical[o], median (IQR)	100.0 (100.0,100.0)	100.0 (100.0,100.0)	-5.1 (35.1)	-3.2 (33.0)	-1.4 (-11.1, 8.3)
SF-36 Role-emotional[o], median (IQR)	100.0	100.0	-1.8 (32.6)	1.6 (22.8)	-3.7 (-10.5, 3.1)

eTable 3. Secondary outcomes.

	Half-dose	Stable dosing	Half-dose	Stable dosing	
	(100.0,100.0)	(100.0,100.0)			
SF-36 Mental health[o], median (IQR)	88.0 (80.0,92.0)	89.0 (80.0,96.0)	-1.2 (14.6)	-1.8 (15.3)	0.7 (-3.4, 4.9)
SF-36 Social Functioning[o], median (IQR)	100.0 (87.5,100.0)	100.0 (100.0,100.0)	-1.7 (15.7)	-1.7 (14.9)	0.2 (-4.2, 4.6)
SF-36 Vitality[o], median (IQR)	65.0 (55.0,75.0)	70.0 (55.0,80.0)	-0.1 (16.4)	-3.0 (13.7)	2.3 (-2.1, 6.7)
SF-36 General Health[o], median (IQR)	80.0 (70.0,85.0)	77.5 (65.0,90.0)	-0.9 (15.7)	-3.4 (13.4)	3.0 (-1.2, 7.2)
SF-36 Physical Component Summary Score[o], median (IQR)	54.3 (50.3,57.4)	55.9 (50.5,57.8)	-1.1 (7.2)	-1.9 (6.8)	0.7 (-1.3, 2.7)
SF-36 Mental Component Summary Score[o], median (IQR)	56.3 (51.4,58.8)	56.4 (52.1,59.8)	-0.4 (8.2)	-0.1 (7.7)	-0.2 (-2.3, 1.8)
RAID[p]	0.8 (0.2,1.3)	0.5 (0.1,1.2)	0.3 (1.1)	0.5 (1.1)	-0.2 (-0.6, 0.1)
Radiographic joint damage					
Total van der Heijde modified Sharp score[q], median (IQR)	4.5 (2.0,8.5)	5.0 (2.0,11.5)	0.5 (1.8)	0.3 (1.2)	0.2 (-0.3, 0.6)
van der Heijde Sharp Erosion, median (IQR)	2.0 (1.0,3.5)	2.0 (1.0,4.5)	0.4 (1.1)	0.1 (0.6)	0.3 (0.0, 0.6)
van der Heijde Sharp Joint Space Narrowing, median (IQR)	2.0 (0.5,6.0)	2.0 (0.5,8.0)	0.1 (1.0)	0.2 (0.8)	-0.1 (-0.4, 0.1)
Ultrasound outcomes[r]					
Total power Doppler signal score, median (IQR)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.1 (0.9)	0.0 (0.5)	0.1 (-0.1, 0.4)
Total grey scale score, median (IQR)	1.0 (0.0,3.0)	1.0 (0.0,2.0)	0.0 (2.8)	0.1 (1.8)	0.2 (-0.5, 0.9)
Medication					
Dose methotrexate in users, mg/week, mean (SD)	19.5 (4.3)	19.0 (4.7)	11.7 (4.3)	19.0 (4.6)	-7.3 (-8.7, -5.9)
Dose sulfasalazine in users, mg/day, mean (SD)	1563 (623)	1769 (439)	857 (244)	1792 (397)	-935 (-1243, -626)
Dose hydroxychlorochine in users, mg/day, mean (SD)	378 (67)	400 (0)	200 (0)	400 (0)	-
Dose leflunomide in users, mg/day, mean (SD)	20 (-)	20 (-)	10 (-)	20 (-)	-
Total triamcinolone hexacetonide dose (mg)	NA	NA	379	255	-
Total number of intraarticular injections	NA	NA	20	21	-
Categorized variables[a]	**Baseline**		**12 months**		**Difference at 12 months (95% CI)[b]**
Measures of disease activity					
Disease Activity Score remission[c, s]	77 (100%)	78 (100%)	63 (85%)	67 (92%)	-7% (-17%, 4%)
Disease Activity Score in 28 joints remission[d]	74 (96%)	76 (97%)	63 (84%)	67 (92%)	-8% (-18%, 3%)
Simplified Disease Activity Index remission[e]	66 (86%)	73 (94%)	55 (74%)	59 (82%)	-8% (-21%, 6%)
Clinical Disease Activity Index remission[f]	65 (84%)	74 (95%)	54 (73%)	57 (79%)	-7% (-21%, 7%)
ACR/EULAR remission[t]	50 (65%)	61 (78%)	47 (64%)	52 (71%)	-8% (-23%, 8%)

eTable 3. Secondary outcomes.

	Half-dose	Stable dosing	Half-dose	Stable dosing	
No swollen joints	77 (100%)	78 (100%)	63 (85%)	66 (90%)	-6% (-16%, 5%)
Imaging outcomes					
No radiographic progression 0-12 months, defined as vdHSS ≥ 1.0 units/year			47 (63%)	58 (79%)	-18% (-33%, -2%)
No radiographic progression 0-12 months, defined as vdHSS ≥ 0.5 units/year			36 (48%)	41 (56%)	-8% (-24%, 8%)
No radiographic progression 0-12 months defined as vdHSS ≥ 2.0 units/year			61 (81%)	68 (93%)	-12% (-22%, -1%)
No radiographic progression 0-12 months defined as vdHSS ≥ 5.0 units/year			74 (99%)	72 (99%)	0% (-4%, 4%)
No power Doppler signal in any joint	71 (92%)	72 (94%)[u]	65 (90%)	65 (93%)	-3% (-12%, 7%)
Medication					
Methotrexate monotherapy	65 (84%)	61 (78%)	67 (87%)	62 (80%)	8% (-4%, 19%)
Methotrexate monotherapy p.o.	51 (66%)	51 (65%)	53 (69%)	51 (65%)	3% (-11%, 18%)
Methotrexate monotherapy s.c.	14 (18%)	10 (13%)	14 (18%)	11 (14%)	4% (-8%, 16%)
Sulfasalazine monotherapy	0 (0%)	1 (1%)	0 (0%)	1 (1%)	-
Leflunomide monotherapy	0 (0%)	1 (1%)	0 (0%)	1 (1%)	-
Hydroxychloroquine monotherapy	1 (1%)	0 (0%)	1 (1%)	0 (0%)	-
Methotrexate/sulfasalazine	2 (3%)	2 (3%)	2 (3%)	2 (3%)	-
Methotrexate/ leflunomide	1 (1%)	0 (0%)	1 (1%)	0 (0%)	-
Methotrexate/hydroxychloroquine	2 (3%)	3 (4%)	1 (1%)	3 (4%)	-
Methotrexate/sulfasalazine/hydroxychloroquine	6 (8%)	10 (13%)	5 (7%)	9 (12%)	-
Biologic treatment	-	-	1 (1%)	1 (1%)	-
Patients with any intraarticular glucocorticoid injections 0-12 months	-	-	11 (15%)	10 (14%)	1% (-10%, 12%)
Any prednisolone use over 12 months – no. (%)	-	-	13 (17%)	4 (5%)	12% (2%, 21%)

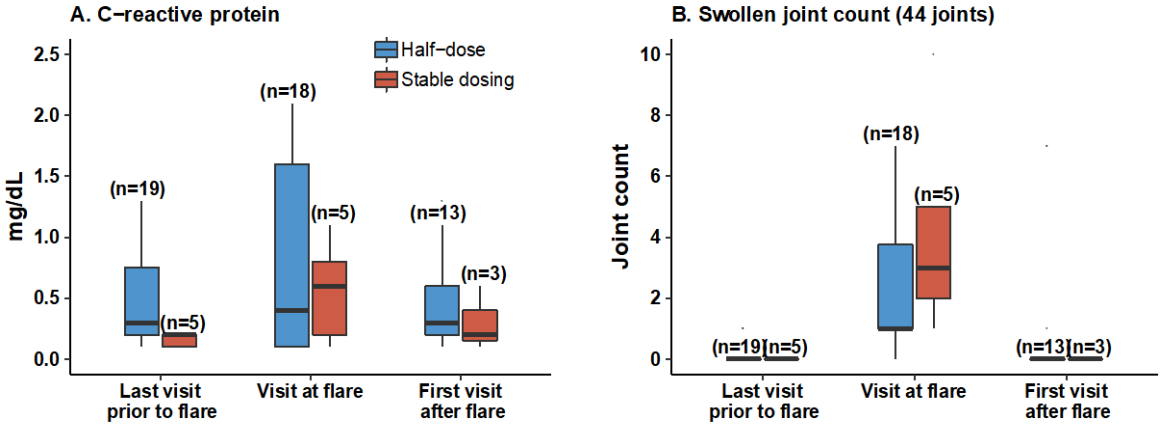
Abbrevations: ACR: American College of Rheumatology, AUC: Area under the curve. EQ-5D: EuroQol-5 Dimensions. EULAR: European Alliance of Associations for Rheumatology. IQR: Interquartile range. P.O: Per os. PROMIS: Patient-reported Outcomes Measurement Information Score. RAID: Rheumatoid Arthritis Index of Disease. S.c.: Subcutaneous. SD: Standard deviation. SF-36: 36-item Short Form Health Survey. vdHSS: van der Heijde modified Sharp score.

[a] Analyzed in the primary analysis population, defined as all randomized patients meeting the study entry criteria, and with no protocol deviations affecting the treatment efficacy (defined as failure to follow the treatment regimen or withdrawal from the study).

[b] Mean difference at 12 months in patients with visit 4 data, values in half dose group – values in stable group. Adjusted for baseline.
[c] The Disease Activity Score for 44-joint counts (DAS) ranges from 0 to 10, with higher scores indicating more disease activity, remission defined as a DAS value <1.6 [1].
[d] The Disease Activity Score for 28-joint counts with Erythrocyte sedimentation rate (DAS28 ESR) ranges from 0 to 10 with higher scores indicating more disease activity, remission defined as a DAS28 value <2.6[2].
[e] The Simplified Disease Activity Index (SDAI) ranges from 0 to 86, with higher scores indicating more disease activity, remission defined as a SDAI value ≤3.3[3,4].
[f] The Clinical Disease Activity Index (CDAI) ranges from 0 to 76, with higher scores indicating more disease activity, CDAI remission defined as a CDAI value ≤2.8[4,5].
[g] The swollen-joint count is the number of swollen joints out of 44 joints assessed.
[h] The tender joint count is performed by the Ritchie articular index[6] assessing tenderness of 26 joint regions, the index ranges from 0 to 3 for individual measures and the sum 0 to 78 overall, with higher scores indicating more tenderness.
[I] At time of baseline visit, normal values might be subject to laboratory.
[j] At time of baseline visit, normal values might be subject to laboratory. To convert C-reactive protein to mg/L (SI unit), multiply by 10
[k] The patient's and physician's global assessments are self-reported and physician-reported, respectively, overall assessments of disease with use of a visual analogue scale that ranges from 0 to 100 mm, with higher scores indicating more severe disease.
[l] Patient-reported Outcomes Measurement Information Score (PROMIS)[7] 20-item short form range from 0 to 100, with scores lower than 50 indicating disability worse than average.
[m] EuroQol-5 Dimensions (EQ-5D)[8,9], UK weighted; Range from 1 (best possible health), through 0 (death) to -0.59 (worse than death).
[n] Fatigue and joint pain is self-reported with use of a visual analogue scale that ranges from 0 to 100 mm, with higher scores indicating more severe fatigue.
[o] The 36-item Short Form Health Survey (SF-36) ranges from 0 to 100[10].
[p] The Rheumatoid Arthritis Index of Disease (RAID) is calculated based on seven numerical rating scales (NRS) questions. Each NRS is assessed as a number between 0 and 10. The seven NRS correspond to pain, function, fatigue, sleep, emotional wellbeing, physical wellbeing and coping/self-efficacy.
[q] Total van der Heijde modified Sharp score[11] is a score of erosions and joint space narrowing based on radiographs of hands and feet, with range from 0 to 448 (with higher scores indicating greater joint damage), and quantifies erosions on a scale from 0 to 280 and joint-space narrowing on a scale from 0 to 168.
[r] Ultrasound examination was performed using 0-3 semi quantitative scoring systems[12] for both grey-scale and power Doppler in each of the following 32 joints; metacarpophalangeal joints (MCP) 1-5, radiocarpal joint, intercarpal joint, distal radioulnar joint, elbow, knee, talocrural joint and metatarsophalangeal joints (MTP) 1-5 bilaterally. Ranges from 0 to 192 for total ultrasound score, and from 0 to 96 for grey-scale and power Doppler ultrasound score.
[s] At screening visit.
[t] ACR/EULAR Boolean remission[13] is defined as tender joint count ≤1, swollen-joint count ≤1, C-reactive protein ≤1mg/dL and patient's global assessment ≤10.
[u] The denominator are 77 as ultrasound examination was missing in one patient at baseline.

eFigure. Disease activity during flare[a].

Panel A: C-reactive protein (mg/dL) at the visit before a flare occurred, at the flare visit and the visit after a flare occurred. Panel B: 44 swollen joint count at the visit before a flare occurred, at the flare visit and the visit after a flare occurred. Boxes mark first and third quartiles, the band inside the box is the second quartile (the median), while the whiskers indicate the highest and lowest values within 1.5 x the interquartile range. Dots denote individual patients (outliers).



[a] Analyzed in those who flared in the primary analysis population, defined as all randomized patients meeting the study entry criteria, and with no protocol deviations affecting the treatment efficacy (defined as failure to follow the treatment regimen or withdrawal from the study).

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