CLINICAL SCIENCE

Certolizumab pegol, abatacept, tocilizumab or active conventional treatment in early rheumatoid arthritis: 48-week clinical and radiographic results of the investigator-initiated randomised controlled NORD-STAR trial

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ABSTRACT

Background The optimal first-line treatment in early rheumatoid arthritis (RA) is debated. We compared clinical and radiographic outcomes of active conventional therapy with each of three biological treatments with different modes of action.

Methods Investigator-initiated, randomised, blinded-assessor study. Patients with treatment-naïve early RA with moderate–severe disease activity were randomised 1:1:1:1 to methotrexate combined with (1) active conventional therapy: oral prednisolone (tapered quickly, discontinued at week 36) *or* sulfasalazine, hydroxychloroquine and intra-articular glucocorticoid injections in swollen joints; (2) certolizumab pegol; (3) abatacept or (4) tocilizumab. Coprimary endpoints were week 48 Clinical Disease Activity Index (CDAI) remission (CDAI ≤2.8) and change in radiographic van der Heijde-modified Sharp Score, estimated using logistic regression and analysis of covariance, adjusted for sex, anticitrullinated protein antibody status and country. Bonferroni's and Dunnet's procedures adjusted for multiple testing (significance level: 0.025).

Results Eight hundred and twelve patients were randomised. Adjusted CDAI remission rates at week 48 were: 59.3% (abatacept), 52.3% (certolizumab), 51.9% (tocilizumab) and 39.2% (active conventional therapy). Compared with active conventional therapy, CDAI remission rates were significantly higher for abatacept (adjusted difference +20.1%, p<0.001) and certolizumab (+13.1%, p=0.021), but not for tocilizumab (+12.7%, p=0.030). Key secondary clinical outcomes were consistently better in biological groups. Radiographic progression was low, without group differences. The proportions of patients with serious adverse events were abatacept, 8.3%; certolizumab, 12.4%; tocilizumab, 9.2%; and active conventional therapy, 10.7%.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early treatment is associated with improved outcome in patients with recently diagnosed rheumatoid arthritis (RA), but the optimal first-line treatment is debated.

WHAT THIS STUDY ADDS

⇒ For the first time, three biologics with different modes of action, all in combination with methotrexate, were compared head-to-head against active conventional antirheumatic therapy with bridging glucocorticoids in a randomised clinical trial in patients with early RA.

⇒ Compared with active conventional therapy, clinical remission rates were superior for abatacept and certolizumab pegol, but not for tocilizumab.

⇒ Radiographic progression was low and similar between treatments.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings should be considered in the future management of patients with newly diagnosed RA.

Conclusions Compared with active conventional therapy, clinical remission rates were superior for abatacept and certolizumab pegol, but not for tocilizumab. Radiographic progression was low and similar between treatments.
Trial registration number NCT01491815.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which causes pain, fatigue, functional impairment and frequently progressive joint destruction.[1] Early treatment is associated with improved outcome.[2] The optimal first-line treatment of patients with early RA is debated. Several trials have shown superior outcomes in treatment-naïve patients treated with biological disease-modifying antirheumatic drugs (bDMARDs) in combination with methotrexate (MTX) compared with MTX monotherapy.[3–5] Yet, both US and European recommendations advocate conventional synthetic disease-modifying drugs (csDMARDs) as the first-line therapy, with MTX as the anchor drug.[6 7] This approach is supported by evidence suggesting that short-term addition of glucocorticoids to MTX (and/or other csDMARDs) yields results comparable with those achieved by bDMARDs.[8 9] Despite various modes of action, bDMARDs are perceived as having overall similar efficacy.[6 7] However, this is mainly based on indirect comparisons since head-to-head trials in early RA are few.[10–12]

Therefore, an investigator-initiated six-country collaboration was established to perform a randomised controlled trial, the Nordic Rheumatic Diseases Strategy Trials and Registries (NORD-STAR) study, to compare the benefits and harms of optimised conventional therapy ('active conventional therapy'), that is, MTX combined with either oral glucocorticoids or intra-articular glucocorticoids and other csDMARDs) and three different biological therapies in combination with MTX (tumor-necrosis factor inhibitor (certolizumab pegol), T-cell costimulation modulator (abatacept) and interleukin-6 inhibitor (tocilizumab)). Twenty-four week clinical results from this study have been published, showing high remission rates in all four arms, and active conventional therapy being non-inferior to certolizumab pegol and tocilizumab but not to abatacept.[13] A comparison of the ability to halt structural damage progression, which is key to the long-term joint status and disability experienced by the patient,[14 15] was not performed at 24 weeks, since the primary radiographic endpoint was at 48 weeks. Furthermore, clinical results at 48 weeks are less influenced by initial glucocorticoid bridging therapy. Thus, interdrug differences in efficacy and safety may have become more manifest at week 48 and thereby more relevant to clinical practice.

We aimed to perform a head-to-head comparison of the clinical efficacy and radiographic structural damage progression up to week 48 of active conventional therapy and each of three bDMARDs with different modes of action in combination with MTX in patients with treatment-naïve RA.

METHODS

Study design

The design of this investigator-initiated, multicentre, randomised, open-label, blinded-assessor trial (https://clinicaltrials.gov/ct2/show/NCT01491815) has been published previously.[16] Patients were randomised to one of four different treatment arms aiming at achieving remission. This report decribes the analyses regarding the initial 48 weeks of the trial, including two coprimary (one clinical and one radiographic) outcomes and secondary clinical, radiographic and safety outcomes. The trial was designed, overseen and analysed by a steering committee of academic investigators. The reporting follows the Consolidated Standards of Reporting Trials statements.[17 18] Patient representatitives were not involved in the design and conduct of this research.

Patients

Patients with early RA according to the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) 2010 classification criteria were included (table 1).[19] Key inclusion criteria were age ≥18 years; symptom duration of <24 months; moderate to severe disease activity with Disease Activity Score (28 joints) (DAS28) score of >3.2 (Disease Activity Score calculated from 28 swollen and tender joint counts, Patient Global Score and C-reactive protein (CRP)), ≥2 (of 66) swollen and ≥2 (of 68) tender joints, and rheumatoid factor or anticitrullinated protein antibody positivity (ACPA) or CRP of ≥10 mg/L. The key exclusion criterion was previous treatment with disease-modifying antirheumatic drug (DMARD) (see online supplemental appendix for details).

Randomisation and procedures

Randomisation was done 1:1:1:1, stratified by country, gender and ACPA status (see online supplemental appendix for details).

All patients started MTX on day 1 (escalated to 25 mg/week within 4 weeks) with folic acid supplementation (minimum 5 mg/week) combined with: Arm 1 (Active conventional therapy): either oral prednisolone (tapered from 20 mg/day to 5 mg/day in 9 weeks and discontinuation after 9 months (arm 1A) or enterotablets sulphasalazine (2 g/day), hydroxychloroquine (35 mg/kg/week or 200 mg/day) and intra-articular triamcinolone hexacetonide injection (or equivalent) in all swollen joints at each visit (maximally 4 joints and 80 mg/visit) (arm 1B); arm 2 (certolizumab pegol): 200 mg EOW SC (400 mg at 0, 2 and 4 weeks); arm 3 (abatacept): 125 mg/week subcutaneously; arm 4 (tocilizumab): 8 mg/kg/4 weeks intravenously or 162 mg/week subcutaneously. In arms 2–4, intra-articular glucocorticoid injections were allowed on demand up to week 12; thereafter, up to 40 mg were allowed every 12 weeks. In all arms, intraarticular glucocorticoids were prohibited in weeks 20–24 and 44–48 to minimise its influence on week 24/48 outcomes. Subjects were, as per investigator judgement, allowed to de-escalate MTX due to toxicity/intolerability, and to subsequently re-escalate up to 20 mg/week. In case of intolerability to oral MTX, subcutaneous MTX could be used. Non-steroidal anti-inflammatory drugs were allowed throughout the study.

The treatment strategy in arm one was predefined based on national recommendations for conventional RA therapy in the individual countries: arm 1A: Sweden, Norway, Iceland and Netherlands, and arm 1B: Denmark and Finland. Clinical examination included joint assessments for swelling and tenderness by independent blinded assessors. Patient reported outcomes included visual analogue scales for pain and global assessment and physical function (Health Assessment Questionnaire). These and blood samples (including CRP) were acquired at weeks 0, 4, 8, 12, 16, 24, 32, 40 and 48 (table 1).[16] Clinical Disease Activity Index (CDAI) was calculated as the sum of swollen joint count (0–28), tender joint count (0–28), Patient's Global Score of Disease Activity (0–10) and Investigator's Global Score of Disease Activity (0–10).[20]

Conventional radiographs of hands and feet were obtained at screening, week 24 and 48, and analysed for bone erosion and

Table 1 Demographics and patient characteristics at baseline (ITT population).

Parameter	Active conventional therapy (n=200)	Certolizumab pegol and MTX (n=203)	Abatacept and MTX (n=204)	Tocilizumab and MTX (n=188)*
Demographics				
Age (years)	55 (15)	55 (15)	55 (14)	52 (15)
Women, n (%)	139 (70)	139 (69)	140 (69)	129 (69)
Symptom duration (days)	195 (167)	203 (166)	212 (168)	208 (155)
Time since diagnosis (days)	13 (21)	12 (17)	16 (34)	16 (33)
Anticitrullinated peptide antibody positive, n (%)	163 (82)	166 (82)	169 (83)	153 (82)
Rheumatoid factor positive, n (%)	151 (76)	149 (73)	159 (78)	135 (72)
Baseline characteristics, clinical				
Clinical Disease Activity Index	28.7 (12.1)	27.9 (12.4)	28.6 (11.3)	26.6 (11.7)
Disease Activity Score, 28 Joints, CRP-based	5.1 (1.1)	5 (1.1)	5.1 (1)	4.9 (1)
Tender joint count, 68 joints	17 (11)	15 (10)	16 (11)	15 (10)
Swollen joint count, 66 joints	11 (7)	11 (8)	11 (7)	10 (6)
Patient's Global Assessment of Disease Activity (mm)	56.7 (23.2)	56.6 (23.7)	60.4 (23.6)	57.4 (22.6)
Physician's Global Assessment of Disease Activity (0–100 mm)	48.8 (19.2)	49.3 (19.2)	51.7 (18.7)	49.7 (18.1)
Patient's Assessment of Pain (0–100 mm)	56 (24.2)	55.7 (24.7)	59.3 (24.2)	55.3 (23)
HAQ score (0–3)	1.1 (0.6)	1 (0.6)	1.1 (0.6)	1.1 (0.5)
Baseline characteristics, radiography				
Radiographic score, total (0–448)	6.3 (8.2)	5.9 (7.6)	5.8 (9.8)	4.2 (6.7)
Radiographic score, total (0–448), median (IQR)	4 (1.0–8.5)	3 (1–8)	3 (1–6)	2 (0.5–5.0)
Radiographic score, erosion (0–280)	2.96 (4.45)	2.97 (4.58)	2.43 (4.64)	2.03 (4.33)
Radiographic score, erosion (0–280), median (IQR)	1 (0–4)	1 (0–4)	1 (0–2.5)	0.5 (0–2)
Radiographic score, JSN (0–168)	3.36 (4.49)	2.96 (3.64)	3.39 (5.85)	2.2 (3.04)
Radiographic score, JSN (0–168), median (IQR)	2 (0–5)	2 (0–4.25)	2 (0–4)	1 (0–3)

Values are mean (SD), if not otherwise indicated.
Radiographic status: as assessed by van der Heijde-modified Sharp Score.
*Seventeen Finnish patients randomised to arm 4 (Tocilizumab+MTX), but not receiving it due to unavailability, are not included. They were excluded from the ITT population to allow a fair analysis of the efficacy of Tocilizumab. Robustness analyses showed comparable results.
CRP, C reactive protein; HAQ, Health Assessment Questionnaire; ITT, intention to treat; JSN, joint space narrowing; MTX, methotrexate; n, number of patients.

joint space narrowing (JSN) using the van der Heijde-modified Sharp Score (vdHSS), with known chronology, by two experienced, independent readers, blinded to all clinical data.[21] A total vdHSS (range 0–448) was calculated by adding erosion (0–280) and JSN (0–168) scores. The average of readers' scores was used. In case of reader discrepancies in mean change in the total vdHSS from baseline to week 48 (Δtotal-vdHSSw0–w48) of ≥2, a final score was reached by reader consensus.

Outcomes

The two coprimary outcomes were clinical remission at week 48 (primary clinical outcome, defined as remission (CDAI ≤2.8); dichotomous outcome)[20] and the change in radiographic score from baseline to week 48 (Δtotal-vdHSSw0–w48; primary radiographic outcome, continuous outcome)[21] (online supplemental file 2, statistical analysis plan (SAP)). The coprimary outcomes were CDAI remission at week 24 and the aforementioned Δtotal-vdHSSw0–w48. The 24-week clinical results, but no radiographic results, have been published previously.[13] For the 48 week analysis, the CDAI remission rate at week 48 was added as a coprimary outcome, prior to any analyses (online supplemental file 2, SAP).

Key secondary clinical outcomes were ACR/EULAR Boolean remission, DAS28 remission, Simplified Disease Activity Index remission and EULAR good response at week 48.[20 22 23] Key secondary radiographic outcomes were no radiographic progression (ΔvdHSS from baseline to 48 weeks <1), changes from baseline to week 48 in vdHSS erosion scores and vdHSS JSN score and changes from baseline to week 24 and from week 24 to week 48 in total vdHSS. Other secondary clinical and radiographic outcomes are presented in online supplemental file 2 (SAP) and online supplemental appendix table S1–S7.

Safety outcomes were the numbers and percentages of patients with serious and non-serious adverse events for each treatment arm. Predefined adverse events of special interest are defined in table 2. All safety events were MedDRA V.22.0 coded.

Statistical analysis

Assuming remission rates in active conventional therapy, certolizumab pegol, abatacept and tocilizumab arms of 12%, 22%, 22% and 26%, respectively, 724–832 patients had to be randomised to reach 85%–90% power for rejecting the null hypothesis of no treatment difference[3 24–28] (see Hetland *et al*[13] for details).

This part of the trial was designed to establish the superiority of at least one of the biological treatments compared with active conventional therapy at 48 weeks on (1) achieving CDAI remission and (2) preventing progression in the radiographic van der Heijde-modified Sharp Score. Thus, there were six separate null hypotheses to be tested. To adjust for multiplicity, each of the two outcome families were tested against an overall significance level of 0.025. Superiority was claimed if any of the six hypotheses were rejected on the 0.025 level using adjusted p values according to Dunnet's method when having a common comparator.[29]

The primary analysis population was the intention-to-treat population, defined as all randomised patients except 17 Finnish patients, for whom allocated treatment (tocilizumab) was not available (see online supplemental file 2) (SAP)). Primary and

Table 2 Adverse events in the safety population*

Parameters†	Active conventional therapy (n=197)	Certolizumab pegol and MTX (n=202)	Abatacept and MTX (n=204)	Tocilizumab and MTX (n=184)
Summary of adverse events				
Adverse events	(784) 174 (88.3%)	(736)181 (89.6%)	(735) 175 (85.8%)	(886) 178 (96.7%)
Serious adverse events	(23) 21 (10.7%)	(28) 25 (12.4%)	(21) 17 (8.3%)	(20) 17 (9.2%)
Deaths		(2) 2 (1.0%)‡		
Adverse events of special interest§				
Infections	(153) 93 (47.2%)	(157) 94 (46.5%)	(181) 99 (48.5%)	(201) 107 (58.2%)
Cardiovascular disease	(4) 4 (2%)	(9) 8 (4%)	(16)12 (5.9%)	(7) 7 (3.8%)
Cataract	(6) 3 (1.5%)		(3) 2 (1%)	(1) 1 (0.5%)
Deep vein thrombosis		(1) 1 (0.5%)		
Demyelinating disease		(1) 1 (0.5%)		
Diabetes mellitus	(3) 2 (1%)			
Herpes zoster	(5) 5 (2.5%)	(3) 2 (1%)	(1) 1 (0.5%)	(1) 1 (0.5%)
Malignancy	(3) 3 (1.5%)	(5) 5 (2.5%)	(3) 3 (1.5%)	(6) 6 (3.3%)
Osteoporosis	(3) 3 (1.5%)	(3) 3 (1.5%)		(1) 1 (0.5%)
Weight gain	(3) 3 (1.5%)		(1) 1 (0.5%)	(2) 2 (1.1%)
Early terminations due to lack of efficacy/adverse events	22 (11.1%)/2 (1.0%)	7 (3.5%)/16 (7.9%)	7 (3.4%)/5 (2.4%)	1 (0.5%)/20 (10.8%)

Values are (number of events), number of patients (percentage of patients in that arm who experienced at least one event).
*Adverse events are summarised by the safety population and by actual treatment (not as randomised). Thus, the 17 Finnish patients randomised to arm 4 (tocilizumab) but not receiving it due to unavailability are not included.
†(Events) number of patients (percentage of patients in that arm). Patients could have more than one category of events.
‡Patient 1: sudden death in a woman in her 70s. A lump in the breast was discovered at the screening visit; later, breast cancer was diagnosed. She terminated early in the trial on study approximately on day 40, had mastectomy 5 days later and died suddenly approximately 9 weeks later. The events were assessed as not related to the study drug by the investigator. Patient 2: This patient had dyspnoea as an adverse event that started just before the week 24 visit. She was hospitalised on approximately day 200 due to 'severe lung infection, bilateral pulmonary infiltrates, respiratory insufficiency, suspicion of interstitial pneumonitis, admitted to intensive department with large oxygen requirement', and she died approximately 2 weeks thereafter. The event was assessed as probably related to study drug by the investigator.
§There were no events coded as tuberculosis. Osteoporosis events were reported shortly after baseline, for example, based on baseline dual-energy x-ray absorptiometry (DXA) scan.
MTX, methotrexate.

secondary dichotomous outcomes were analysed using a logistic regression model, adjusted for stratification factors in the randomisation (sex, ACPA status and country). We imputed missing remission status with worst case (non-remission).

The primary and other continuous radiographic outcomes were analysed using analysis of covariance, adjusted for baseline score and the stratification factors in the randomisation. Missing data were imputed in a hierarchical way.

Other continuous secondary outcomes were analysed using generalised linear mixed gamma (CRP), negative binomial (joint counts) or normal models (other), all with random intercept adjusted for baseline characteristics and value.

One author (ICO) performed analyses; details are found in online supplemental file 2 (SAP).

The funding sources had no role in study design, collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit for publication.

RESULTS

Nine hundred and three patients were assessed for eligibility at 29 sites from 3 December 2012 to 11 December 2018, whereof 812 underwent randomisation and 625 completed week 48 visit (last patient on 12 November 2019; online supplemental figure S1, patient disposition). Patient characteristics were well balanced (table 1). The patients (68.8%women, 81.9% ACPA positive, mean age 54.3 years) had early disease, with mean time since diagnosis of 14 days and mean symptom duration of 204 days.

The primary clinical outcome, the adjusted CDAI remission rates at week 48, were 39.2% for active conventional therapy, 59.3% for abatacept, 52.3% for certolizumab pegol and 51.9% for tocilizumab (table 3 and figure 1A). The null hypotheses were formally rejected for active conventional therapy versus abatacept (adjusted difference +20.1%, adjusted p<0.001) and active conventional therapy versus certolizumab pegol (+13.1%, p=0.021), but not for active conventional therapy versus tocilizumab (+12.7%, p=0.030), given that the cut-off for statistical significance was 0.025. As shown in figure 2A, adjusted CDAI remission rates over time in the active conventional therapy arm after week 24 gradually separated from the three bDMARD arms, with no clear and consistent separation between bDMARD arms.

The primary radiographic outcome, the adjusted estimated Δtotal-vdHSSw0–w48, was 0.45 for active conventional therapy, 0.62 for abatacept, 0.47 for certolizumab pegol and 0.50 for tocilizumab, that is, consistently low (figure 1B). No statistically significant differences in Δtotal-vdHSSw0–w48 were found between groups (table 3). Figure 2B presents a cumulative probability plot of the radiographic progression.

Key secondary clinical outcomes were consistently numerically better in bDMARD groups compared with active conventional therapy for all remission criteria, with the abatacept group being numerically the best (table 3). All key secondary radiographic outcomes were comparable across treatment groups (table 3).

Results of other secondary clinical and radiographic outcomes can be found in table 3 and online supplemental tables S1–S7). The course over time of selected outcomes is depicted in online supplemental figures S2–S14.

The smallest detectable difference (SDC) in Δtotal-vdHSSw0–w48 was 1.43. The proportion of patients showing progression above SDC (Δtotal-vdHSSw0–w48 >SDC), reflecting progression above measurement error, in active conventional therapy,

Table 3 Primary and secondary outcomes at week 48 (ITT population)

	Active conventional therapy (n=200)	Certolizumab pegol and MTX (n=203)	ABA and MTX (n=204)	Tocilizumab and MTX (n=188)*
Estimated adjusted outcome (ITT population)†				
Coprimary outcomes				
CDAI remission, week 48	39.2% (32.5 to 45.9)	52.3% (45.5 to 59.1)	59.3% (52.6 to 66)	51.9% (44.9 to 59.0)
Radiographic progression, total weeks 0–48	0.45 (0.31 to 0.59)	0.47 (0.33 to 0.61)	0.62 (0.48 to 0.76)	0.5 (0.36 to 0.64)
Key secondary outcomes				
ACR/EULAR Boolean remission, week 48	31.6% (25.3 to 38.0)	46.3% (39.5 to 53.1)	51.0% (44.2 to 57.8)	44.6% (37.6 to 51.6)
DAS28 remission, week 48	53.7% (46.9 to 60.6)	66.6% (60.1 to 73.0)	71.1% (65 to 77.3)	68.2% (61.6 to 74.7)
SDAI remission, week 48	38.1% (31.5 to 44.8)	52.8% (45.9 to 59.6)	57.8% (51.1 to 64.6)	53.5% (46.5 to 60.6)
EULAR good response, week 48	66.4% (59.9 to 72.9)	74.6% (68.7 to 80.6)	77.7% (72.0 to 83.4)	69.3% (62.8 to 75.9)
Radiographic progression, total ≤0.5, weeks 0–48	78.0% (72.3 to 83.8)	81.3% (75.9 to 86.7)	74.5% (68.5 to 80.5)	80.3% (74.6 to 86.0)
Radiographic progression, erosion, weeks 0–48	0.31 (0.21 to 0.4)	0.33 (0.23 to 0.42)	0.41 (0.31 to 0.5)	0.35 (0.25 to 0.45)
Radiographic progression, JSN, weeks 0–48	0.14 (0.05 to 0.23)	0.14 (0.05 to 0.23)	0.22 (0.13 to 0.31)	0.15 (0.06 to 0.24)
Estimated adjusted treatment difference (ITT population)†‡				
Coprimary outcomes				
CDAI remission, week 48	Reference	13.1% (3.5 to 22.6)§	20.1% (10.6 to 29.5)¶	12.7% (3 to 22.5)
ΔvdHSS total, weeks 0–48	Reference	0.02 (–0.17 to 0.22)	0.17 (–0.02 to 0.37)	0.05 (–0.15 to 0.25)
Key secondary outcomes				
ACR/EULAR Boolean remission, week 48	Reference	14.7% (5.4 to 23.9)	19.4% (10.1 to 28.7)	13% (3.5 to 22.4)
DAS28 remission, week 48	Reference	12.9% (3.5 to 22.2)	17.4% (8.2 to 26.6)	14.4% (5 to 23.9)
SDAI remission, week 48	Reference	14.6% (5.1 to 24.1)	19.7% (10.2 to 29.1)	15.4% (5.7 to 25.1)
EULAR good response, week 48	Reference	8.2% (–0.6 to 17.1)	11.3% (2.7 to 20.0)	2.9% (–6.3 to 12.2)
Radiographic progression, total progression ≤0.5, weeks 0–48	Reference	–3.3% (–11.1 to 4.6)	3.5% (–4.7 to 11.8)	–2.2% (–10.3 to 5.9)
Radiographic progression, erosion, weeks 0–48	Reference	0.02 (–0.12 to 0.16)	0.1 (–0.04 to 0.24)	0.04 (–0.1 to 0.19)
Radiographic progression, JSN, weeks 0–48	Reference	0 (–0.13 to 0.13)	0.08 (–0.05 to 0.21)	0.01 (–0.12 to 0.14)
Secondary clinical outcomes				
CDAI low disease activity, week 48	Reference	6.2% (–2.5 to 14.9)	11.3% (2.9 to 19.7)	3.1% (–5.8 to 12.1)
DAS28 low disease activity, week 48	Reference	8.7% (–0.1 to 17.5)	13.8% (5.3 to 22.3)	7.6% (–1.4 to 16.5)
ACR20 response, week 48	Reference	1.3% (–7.5 to 10.0)	8.3% (0 to 16.7)	0.9% (–8 to 9.9)
ACR50 response, week 48	Reference	9.4% (0.2 to 18.5)	13.4% (4.5 to 22.4)	3.4% (–6.2 to 13.0)
ACR70 response, week 48	Reference	14.5% (4.9 to 24.1)	13.7% (4.1 to 23.3)	9.1% (–0.8 to 18.9)
DAS28, week 48	Reference	–0.34 (–0.54 to –0.15)	–0.33 (–0.52 to –0.14)	–0.51 (–0.71 to –0.31)
CDAI, week 48	Reference	–1.41 (–2.78 to –0.03)	–1.93 (–3.28 to –0.58)	–1.75 (–3.16 to –0.33)
SDAI, week 48	Reference	–1.66 (–3.08 to –0.24)	–2.01 (–3.41 to –0.62)	–2.03 (–3.49 to –0.57)
Patient's Global Assessment of Disease Activity, 0–100 mm, week 48	Reference	–4.29 (–8.45 to –0.12)	–4.95 (–9.05 to –0.84)	–4.2 (–8.48 to 0.08)
Physician's Global Assessment of Disease Activity, 0–100 mm, week 48	Reference	–3.98 (–6.38 to –1.57)	–4.95 (–7.31 to –2.59)	–4.76 (–7.23 to –2.29)
Patient's Assessment of Pain, 0–100 mm, week 48	Reference	–5.41 (–9.41 to –1.41)	–6.03 (–9.98 to –2.09)	–5.95 (–10.07 to –1.82)
HAQ score, week 48	Reference	–0.03 (–0.11 to 0.04)	–0.04 (–0.11 to 0.04)	–0.08 (–0.16 to 0)
Serum C reactive protein, week 48	Reference	–1.93 (–2.74 to –1.12)	–0.78 (–1.67 to 0.1)	–2.96 (–3.72 to –2.21)
Erythrocyte sedimentation rate, week 48	Reference	–2.24 (–4.51 to 0.02)	–0.65 (–3.01 to 1.71)	–10.47 (–12.32 to –8.62)

Results are based on the ITT population; 17 Finnish patients allocated to tocilizumab and MTX group excluded.
Radiographic progression: as assessed by the vdHSS.
*Since they could not receive tocilizumab because the drug was not available in the Finnish part of the study.
†Clinical variables: For dichotomous variables, values are estimated adjusted marginal difference in proportions against active conventional therapy with 95% confidence limits. Confidence limits are calculated from the logistic regression model by the delta method. Missing data are imputed using worst outcome (non-responder imputation). For continuous variables, values are adjusted marginal differences at 48 weeks with 95% confidence limits using longitudinal mixed models.
‡Radiographic scores, values are estimated adjusted marginal mean change from baseline or estimated difference against active conventional therapy with 95% confidence limits from the ANCOVA model. Missing data are imputed using intrapolation or extrapolation.
§Superiority of bDMARD compared with active conventional therapy was demonstrated; p=0.021
¶Superiority of bDMARD compared with active conventional therapy was demonstrated; p<0.001.
ABA, abatacept; ACR, American College of Rheumatology; ANCOVA, analysis of covariance; bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score (28 joints, four variables, C reactive protein); EULAR, European Alliance of Associations for Rheumatology; ITT, intention to treat; JSN, joint space narrowing; MTX, methotrexate; n, number of patients; SDAI, Simplified Disease Activity Index; vdHSS, van der Heijde-modified Sharp Score.

abatacept, certolizumab pegol and tocilizumab groups were similar: 14.5%, 16.2%, 12.8% and 13.3%, respectively. Proportions of patients showing rapid radiographic progression (Δtotal-vdHSSw0–w48>5) were 0%, 1%, 0% and 0%, respectively.

Results of prespecified robustness analyses of the primary and key secondary efficacy outcomes were consistent with those of the primary analyses (online supplemental tables S8–S23). Corticosteroid use was mandatory in arm 1. In arm 1A, prednisolone was reduced from 20 mg to 5 mg in 9 weeks, was stable (5 mg) through week 32, and thereafter reduced and stopped at week 36.

In the certolizumab pegol, abatacept and tocilizumab arms, the cumulative doses of intra-articular triamcinolone hexacetonide equivalents from week 0 to week 48 were median 18 (0–49) mg, median 20 (IQR 0–60) mg and median 0 (IQR 0–40) mg, respectively, while it was median 70 (IQR 50–103) mg in arm 1B and median 0 (IQR 0–18 mg) in arm 1A (arm 1A received oral prednisolone; see previous discussion). The median cumulative dose

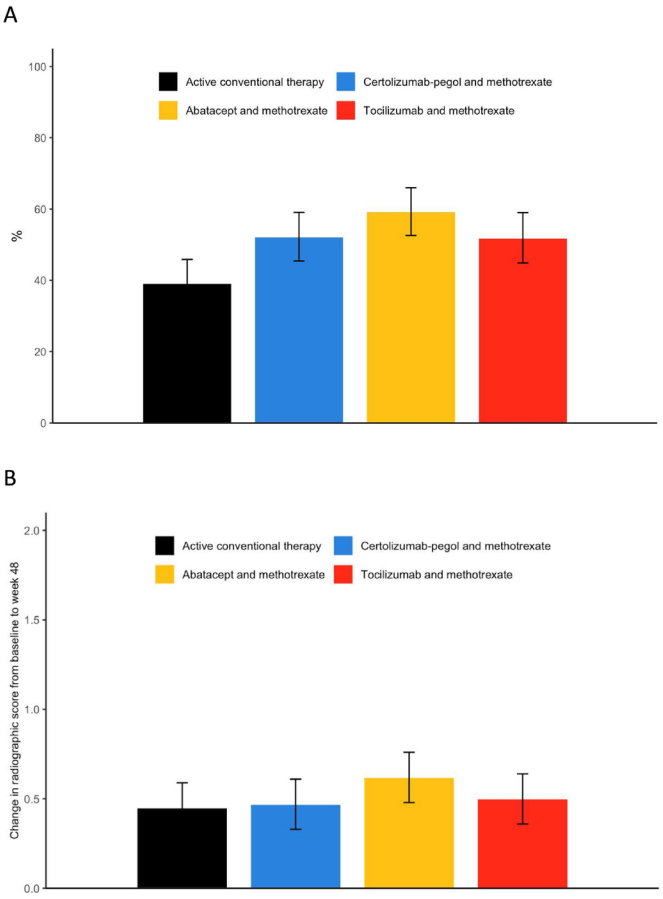

Figure 1 Plots of the co-primary outcomes: (A) clinical remission at week 48 (adjusted Clinical Disease Activity Index remission rates at week 48) and (B) radiographic progression from baseline to week 48 (adjusted change in van der Heijde-modified total Sharp Score from baseline to week 48) for the four different treatment arms. Ninety-five per cent CIs are shown.

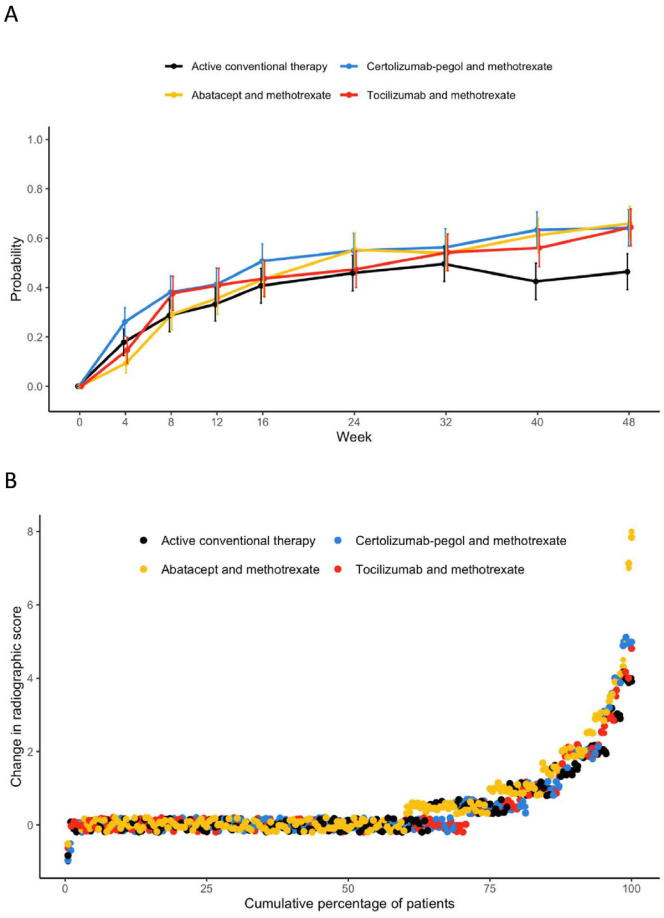

Figure 2 (A) Clinical Disease Activity Index remission rates over time (average marginal adjusted probablities). (B) Cumulative probability plot of the radiographic progression from baseline to week 48, as assessed by the Total van der Heijde-modified Sharp Score.

of intra-articular triamcinolone hexacetonide corresponded to a daily dose of 0.2 mg prednisolone in arm 1B and less than 0.1 mg in arm 1A and in the bDMARD arms (assuming 40 mg triamcinolone hexacetonide is equivalent to 50 mg prednisolone).

When split into weeks 1–24 versus weeks 25–48, doses were as follows: in arm 1B, the cumulative dose of intra-articular triamcinolone hexacetonide from week 1 to week 24 was a median of 66 (IQR 40–94) mg, while that for weeks 25–48 was only a median of 0 (IQR 0–10 mg). In arm 1A, in which oral prednisolone was administered (see previous discussion), the cumulative dose of intra-articular triamcinolone hexacetonide from week 1 to week 24 was a median of 0 (IQR 0–6) mg, while that for weeks 25–48 was a median of 0 (IQR 0–0 mg).

In the certolizumab-pegol, abatacept and tocilizumab arms, the cumulative doses of intra-articular triamcinolone hexacetonide from week 0 to week 24 were median 12 (IQR 0.0–40) mg, median 20 (IQR 0.0–52) mg and median 0.0 (IQR 0.0–40) mg, while that for weeks 25–48 was median 0 (IQR 0–0) mg for all three arms, respectively.

The percentages of patients who reported at least one adverse event in the groups receiving active conventional therapy, certolizumab pegol, abatacept and tocilizumab were 88.3%, 89.6%, 85.8% and 96.7%, respectively (table 2), while at least one serious adverse event was reported in 10.7%, 12.4%, 8.3% and 9.2%, respectively. The number of early terminations was lowest for patients treated with abatacept (n=20), compared with 38, 35 and 35 in the active conventional therapy, certolizumab pegol and tocilizumab arms, respectively (online supplemental figure S1). The numbers of patients who terminated due to lack of efficacy or adverse events were, respectively, 22 vs 2 for active conventional therapy, 7 vs 16 for certolizumab pegol, 7 vs 5 for abatacept and 1 vs 20 for tocilizumab; that is, patients on active active conventional therapy terminated almost exclusively due to lack of efficacy, while patients receiving tocilizumab almost exclusively terminated due to adverse events.

Of the prespecified adverse events of interest, infections were most frequent, being reported in 47.2%, 46.5%, 48.5% and 58.2% of patients treated with active conventional therapy, certolizumab pegol, abatacept and tocilizumab, respectively. Harms associated with glucocorticoid use (cataract, diabetes mellitus, osteoporosis and weight gain) were rare (each 0%–1.5% in all arms), and cardiovascular disease was reported in 2.0%, 4.0%, 5.9%, 3.8% of patients, respectively (see online supplemental tables S24–S29 for details).

DISCUSSION

The NORD-STAR study is the first randomised trial to demonstrate that a biological therapy (or as the case is here, two different biological therapies) given as first-line therapy is clinically superior to conventional therapy even if the latter is optimised by the inclusion of bridging glucocorticoids.

This randomised head-to-head four-arm clinical trial of patients with treatment-naïve early RA showed clinical CDAI

remission at week 48 in approximately 40% of patients treated with active conventional therapy (MTX-based with glucocorticoid bridging therapy), whereas CDAI remission rates for the biological therapies were 50%–60%. For the selective costimulation modulator abatacept and the tumour necrosis factor (TNF) inhibitor certolizumab pegol, the remission rates were statistically significantly superior to active conventional therapy, with adjusted differences of +20.1% and +13.1%, respectively. In contrast, no difference in structural progression, as assessed by serial radiographs, was seen between treatments, and progression was very low in all groups. Key secondary clinical outcomes were numerically consistently better in biological groups compared with active conventional therapy.

The primary clinical outcome in the trial was remission according to CDAI, a more stringent remission criterion than the more commonly used DAS28-based. We chose the CDAI because its algorithm does not include acute-phase reactants, which are differentially impacted by different biological treatments and could therefore bias study outcomes.

Important differences between week 48 and week 24 results were observed. Particularly, the considerable advantage of biological therapies was much more pronounced at week 48 than at week 24.[13] The CDAI remission rate in the active conventional therapy group was slightly lower at week 48 than at week 24 (39.2% vs 42.7%), probably reflecting the decreasing effect of the initial bridging glucocorticoid therapy. Nevertheless, the main reason for the increasing difference between the biological arms and the active conventional therapy was that remission rates of biological arms increased markedly (abatacept: 52.0%–59.3%; certolizumab pegol 46.5%–52.3%; tocilizumab 42.1%–51.9%).

In early RA, pain and disability are mainly related to joint inflammation, but inhibition of structural progression is important for the long-term outcome, as even minor annual differences in structural progression will over decades accumulate and cause clinically significant pain and disability.[15 30] In the current study, the radiographic progression was low in all arms, and there were no differences between active conventional therapy and biological therapies. This highlights the advantage of glucocorticoid bridging, which immediately decreases inflammation, with the aim of both improving symptoms and decreasing structural progression. In contrast, other clinical trials using MTX without glucocorticoid bridging as comparison have reported an advantage on radiographic progression of biologics in early RA.[31–33] The administered glucocorticoid dose was in all treatment arms markedly lower during weeks 25–48 than during weeks 1–24, which reflects that the need for glucocorticoid declined with the gradual onset effect of the DMARDs. Another investigator-initiated treat-to-target study found DAS remission in 61% of RA patients after 4 months of MTX and oral glucocorticoid; in non-remission patients subsequently randomised to additional conventional DMARDs versus TNF-inhibitor, higher 1-year remission rates were found in patients treated with a TNF inhibitor.[34] An open-label treat-to-target trial applying MTX plus various doses of bridging glucocorticoids found rates of DAS-28 remission (less stringent than CDAI remission) at 2 years of approximately 60%,[35] that is, overall in accordance with our data.

Biological therapies are more costly than conventional therapy. Nevertheless, using a biological therapy as first-line therapy—after demonstration of clinical superiority—may be justified by the high direct and indirect costs of poorly controlled RA.[36] The introduction of the less expensive, but equally effective and safe, biosimilar drugs adds further credence to that argument.[37–39] The cost-effectiveness should be confirmed in a dedicated analysis. Furthermore, several studies have suggested that after remission has been achieved, biologicals can often be tapered or discontinued safely.[40–42] This topic is the subject of the ongoing second part of the NORD-STAR trial.

Strengths of the study include the investigator-initiated set-up across six countries, allowing recruitment of >800 patients with early DMARD-naïve RA, with baseline characteristics typical for treatment-naïve poor-prognosis patients. The open-label design of this pragmatic trial is a limitation since it could influence certain subjective outcomes. We used blinded joint assessors to avoid bias on physician-determined outcomes. The active conventional therapy arm (arm 1) comprised two different treatment strategies based on national recommendations for conventional RA therapy in the individual countries. Analyses were adjusted for country effects, whereas the study was not powered for subgroup analyses.

No new safety signals were detected. Among prespecified events of interest, infections were common, particularly in the tocilizumab arm. An increased risk of adverse events attributable to glucocorticoid use was not found.

In conclusion, this large investigator-initiated randomised controlled trial showed a marked clinical superiority for two of the three biologicals in this study compared with active conventional therapy including MTX and glucocorticoids. We believe that the fact that two therapies (abatacept and certolizumab pegol) provide clinically and statistically significantly higher remission rates as compared with optimised conventional antirheumatic therapy with bridging glucocorticoids should be considered when the management of patients with newly diagnosed RA is decided, both in clinical practice and in treatment recommendations.

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Contributors MØ, RFvV, MLH, DCN, BG, EAH, KH-P, TU and GG designed the study and wrote the protocol. RFvV, MLH, MSH, DCN, SK, DG, NSK and EAH developed the CRFs. MØ, RFvV, AR, MLH, MSH, DCN, MTN, BG, KL, KH-P, TU, TS, GG, JLi, IG, DG, MCK, A-BA, FF, PP, TL, CG, JB, OH, DV TR, EG, MKL, EB, HL, AS, MR, AK, PL, LU, SAJ, DJS, TBL, GB, EAH and JLa contributed to the data collection and data cleaning. SK and NSK performed the data management. LMØ and PB read the radiographs. ICO wrote the statistical analysis plan, conducted the statistical analyses and made the figures. MØ wrote the manuscript with input from all authors. All authors had access to the raw dataset and vouch for the veracity of the results, and read and approved the final version of the manuscript including the decision to submit the paper. MØ, RFvV, MLH, EAH and JL are guarantors of the overall content, accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no other meeting the criteria has been omitted.

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Supplementary Appendix

Østergaard M, *et al. Ann Rheum Dis* 2023;0:1–10. doi: 10.1136/ard-2023-224116

1 List of NORD-STAR study sites

Site No.	Site	Site name	Country
01	Solna	Karolinska University Hospital, Solna	Sweden
02	Huddinge	Karolinska University Hospital, Huddinge	Sweden
03	Göteborg	Sahlgrenska University Hospital, Gothenburg	Sweden
04	Linköping	Linköping University Hospital, Linköping	Sweden
05	Västerås	Västmanlands Hospital, Västerås	Sweden
06	Lund	Skåne University Hospital, Lund	Sweden
07	Malmö	Skåne University Hospital, Malmö	Sweden
08	Uppsala	Uppsala University, Uppsala	Sweden

09	Örebro	Örebro University Hospital, Örebro	Sweden
10	Falun	Falu Hospital, Falun	Sweden
11	CFR	Academic Specialist Center, Stockholm	Sweden
21	Helsinki	Helsinki University Hospital, Helsinki	Finland
22	Tampere	Tampere University Hospital, Tampere	Finland
23	Jyväskylä	Jyväskylä Central Hospital, Jyväskylä	Finland
24	Kuopio	Kuopio University Hospital, Kuopio	Finland
41	Glostrup	Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup	Denmark
42	Silkeborg	Silkeborg University Clinic, Silkeborg	Denmark
43	Ålborg	Aalborg University Hospital, Aalborg	Denmark

44	Sønderborg	Hospital for Rheumatic Diseases, Sønderborg	Denmark
45	Odense	Odense University Hospital, Odense	Denmark
47	Århus	Aarhus University Hospital, Aarhus	Denmark
48	Svendborg	Svendborg Hospital OUH, Svendborg	Denmark
71	Oslo	Diakonhjemmet Hospital, Oslo	Norway
72	Ålesund	Ålesund Hospital, Ålesund	Norway
73	Tromsø	University Hospital of North Norway, Tromsø	Norway
74	Bergen	Haukeland University Hospital, Bergen	Norway
75	Trondheim	St Olavs Hospital University Hospital of Trondheim	Norway
81	Reade	Amsterdam Rheumatology and Immunology Center, Reade	The Netherlands

90	Reykjavik	Landspitali University Hospital, Reykjavik	Iceland

2 Supplementary Text

2.1 Randomization procedure

Randomization was done through the trial center at the Karolinska Institute. At the outset of the study, randomization lists were generated with separate lists based on the three protocol-specified stratifications: country, sex, and ACPA positivity. Thus, for each of the participating countries there were four randomization lists, one each for ACPA positive female, ACPA positive male, ACPA negative female and ACPA negative male participants. Each randomization list was generated by running an open-access internet-based random number generator set for four levels (1-2-3-4) in equal proportions (blocks of four). After a patient had consented to participation and fulfilled inclusion criteria, and without exclusion criteria, personnel at the local site dialed a dedicated randomization phone line at the Karolinska Institute, and informed trial center personnel of country, sex and ACPA status of the patient. Trial center personnel read off from the top of the appropriate list to what arm the patient was randomized and noted the patient trial number (site number and patient number) on that list. They also sent a confirmatory e-mail to the site.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria:

1. Subject is ≥18 years of age.

2. Subject has a diagnosis of RA as defined by the newly established ACR/EULAR criteria, 2010 (Appendix D). (Patients should also be classified according to the 1987-revised ACR-classification criteria, without this being an inclusion criteria) (Appendix C).
3. <24 months from arthritis symptom debut (symptom duration will be registered).
4. Subject must have DAS28 (CRP) > 3.2.
5. ≥ 2 swollen joints AND ≥ 2 tender joints (based on 66/68 joint count)
6. Subject must fulfill one of the following three criteria: RF positive OR ACPA positive OR CRP ≥10 mg/L.
7. Female subject is either not of childbearing potential (postmenopausal, surgically sterile etc.), or is of childbearing potential and practicing one of the following methods of birth control throughout the study and for 150 days after study completion:
    - Intrauterine device (IUD)
    - Contraceptives (oral, parenteral, patch) for three months prior to study drug administration)
    - A vasectomized partner
8. Female subjects of childbearing potential must have a negative pregnancy test at the Screening visit.
9. Subject is judged to be in good general health as determined by the principal investigator based upon the results of medical history, laboratory profile, physical examination, chest X-ray (CXR), and 12-lead electrocardiogram (ECG) performed at Screening.
10. Subjects must be able and willing to provide written informed consent and comply with the requirements of this study protocol.
11. Subjects must be able and willing to self-administer s.c. injections or have a qualified person available to administer s.c. injections.

2.2.2 Exclusion Criteria

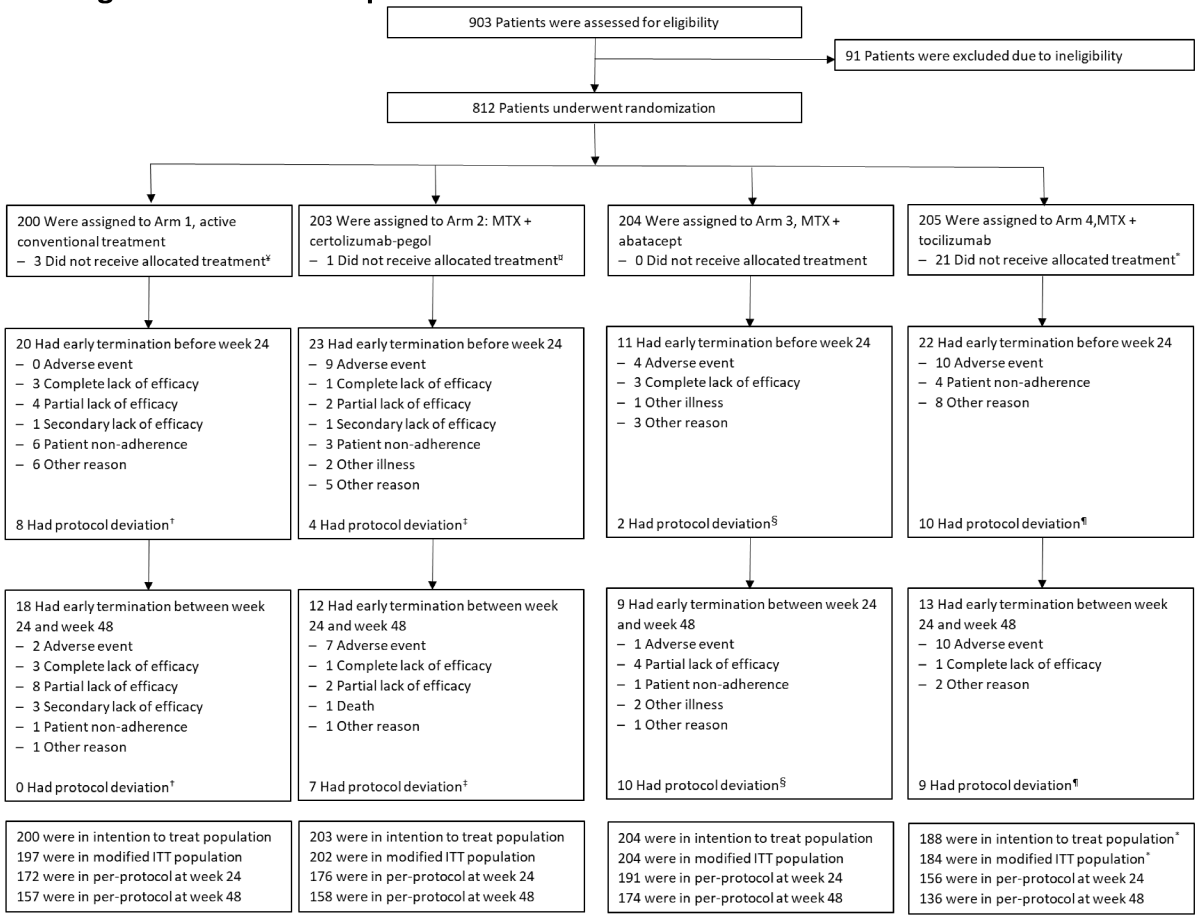
A subject will be excluded from the study if he/she meets any of the following criteria:

1. Subject has been previously treated with disease modifying antirheumatic drugs (DMARDs) for rheumatic diseases.
2. Current active inflammatory joint disease other than RA.
3. Subject has had a dose of prednisone (or equivalent) >7.5 mg/day or has had a dose change within the preceding 4 weeks.
4. Subject has been treated with intra-articular or parenteral administration of corticosteroids in the preceding 4 weeks. Inhaled corticosteroids for stable medical conditions are allowed.
5. Subject has undergone joint surgery within the preceding two months (at joints to be assessed within the study).
6. Subject has chronic arthritis diagnosed before age 17 years.
7. Subject has a history of an allergic reaction or significant sensitivity to constituents of study drugs.
8. Subject has been treated with any investigational drug within one month prior to screening visit.
9. Active infection of any kind (excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization within 4 weeks of screening.
10. Subject has a poorly controlled medical condition, such as uncontrolled diabetes, unstable heart disease, congestive heart failure, recent cerebrovascular accidents and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the study.
11. Subject has a history of clinically significant hematologic (*e.g.,* severe anemia, leukopenia, thrombocytopenia), renal or liver disease (*e.g.,* fibrosis, cirrhosis, hepatitis).
12. Subject has history of neurologic symptoms suggestive of central nervous system (CNS) demyelinating disease and/or diagnosis of central demyelinating disease.
13. Subject has history of cancer or lymphoproliferative disease. Allowable exceptions:
    a. Successfully treated cutaneous squamous cell or basal cell carcinoma
    b. Localized carcinoma in situ of the cervix
    c. Curatively treated malignancy (treatment terminated) > 5 years prior to screening

14. Subject has a history of listeriosis, histoplasmosis, untreated TB, persistent chronic infections, or recent active infections requiring hospitalization or treatment with intravenous (iv) anti-infectives within 30 days or oral anti-infectives within 14 days prior to the BL visit.
15. Subjects will be evaluated for latent TB infection with a PPD or QuantiFERON test and X-ray. Subjects with evidence for latent TB will not be enrolled but first assessed according to local guidelines.
16. Subject is known to have immune deficiency, history of Human Immunodeficiency Virus (HIV) or is otherwise severely immunocompromised.
17. Female subject who is pregnant or breast-feeding or considering becoming pregnant during the study or within 150 days after the last dose of study medication.
18. Men who are planning to father a child during the time they are included in the study
19. Subject has a history of clinically significant drug or alcohol usage in the last year.
20. Subject has a chronic widespread pain syndrome.
21. Subject is considered by the investigator, for any reason, to be an unsuitable candidate for the study.
22. Subject is unwilling to comply with the study protocol.
23. Screening clinical laboratory analyses show any of the following abnormal laboratory results:
    a. Aspartate transaminase (AST) or alanine transaminase (ALT) > 1.75 times upper limit of normal (ULN).
    b. Positive serum human chorionic gonadotropin (hCG).
    c. Positive tests for hepatitis B surface antigen (HBsAg) or hepatitis C serology indicative of current infection.
    d. Creatinine levels > 2x the ULN. If creatinine 1-2 times ULN, check GFR.
    e. Hemoglobin < 90 g/L.
    f. Absolute neutrophil count (ANC) < 1.5 $\times 10^3/\mu L$.
    g. Serum total bilirubin $\geq$ 1.5 mg/dL ($\geq$26 micromol/L).

3 Supplementary Figures

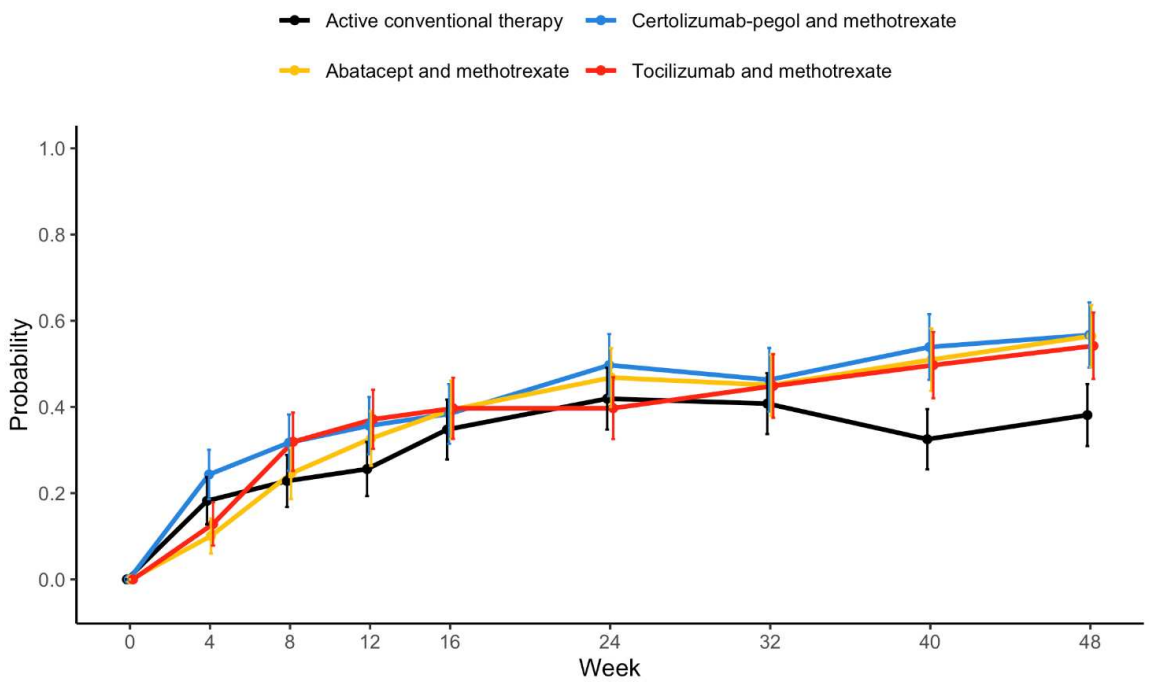
3.1 Figure S1: Patient disposition



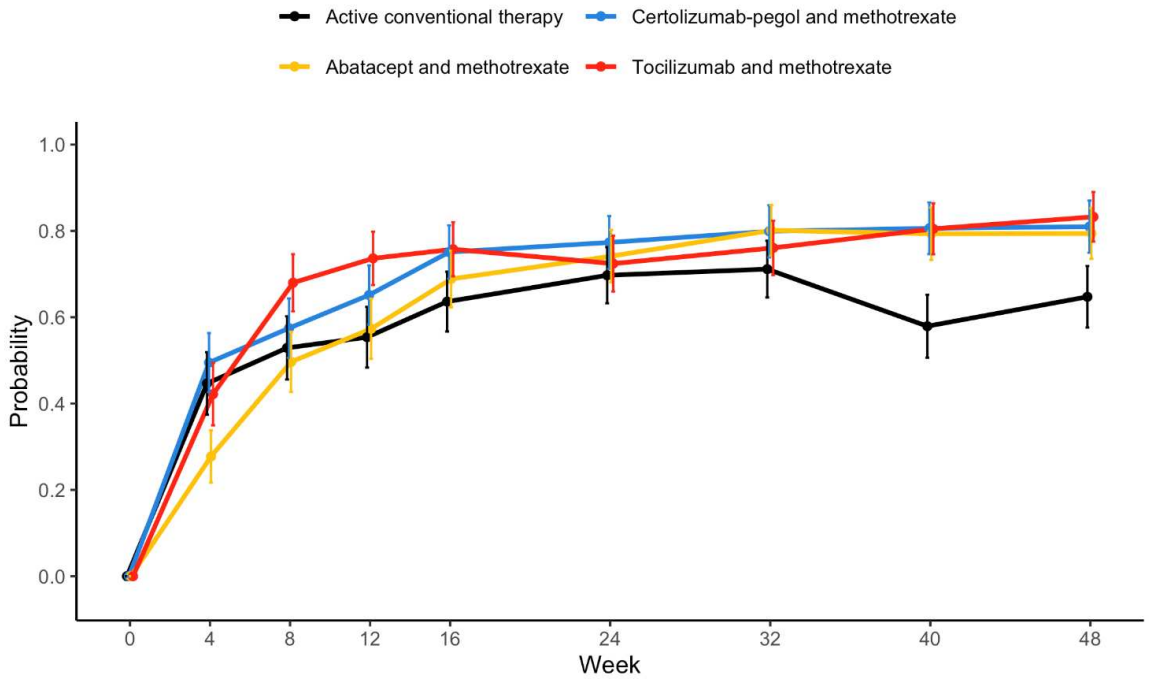
¥Two patients did not receive any glucocorticoids due to diabetes but were followed in the trial; one patient withdrew consent immediately after being allocated to Arm 1. ¤One patient was treated for latent tuberculosis and did not receive certolizumab. *At 4 Finnish sites, Helsinki, Tampere, Jyväskylä and Kuopio, 17 patients allocated to Arm 4 did not receive Tocilizumab which proved to be unavailable and were instead reallocated to Arm 1; these 17 patients were not included in the primary analysis in neither Arm 1 nor Arm 4; one patient did not receive tocilizumab as intravenous cannulation could not be performed; one patient was found to have neutropenia at baseline and did not receive tocilizumab; one patient moved abroad before receiving tocilizumab; one patient refused to have s.c. or i.v. medication. †Two patients did not receive any glucocorticoids due to diabetes but were followed in the trial; one patient received intraarticular glucocorticoids 6 days before week 24 visit; one patient received >2 mL glucocorticoids 22 days before week 24 visit; four patients received oral prednisolone >10 mg/day for >8 weeks. ‡Four patients missed more than 2 doses of certolizumab before week 24, seven patients missed more than 2 doses of certolizumab between week 24 and week 48. §Two patients missed more than 4 doses of abatacept s.c. before week 24, ten patients missed more than 4 doses of abatacept s.c. between week 24 and week 48 ¶Two patients missed more than one dose of tocilizumab i.v. before week 24, five patients missed more than one dose of tocilizumab I.v. between week 24 and week 48 ; eight patients missed more than 4 doses of tocilizumab s.c. before week 24, four patients missed more than 4 doses of tocilizumab s.c. between week 24 and week 48

3.2 Key secondary clinical outcomes over time, adjusted, ITT-population

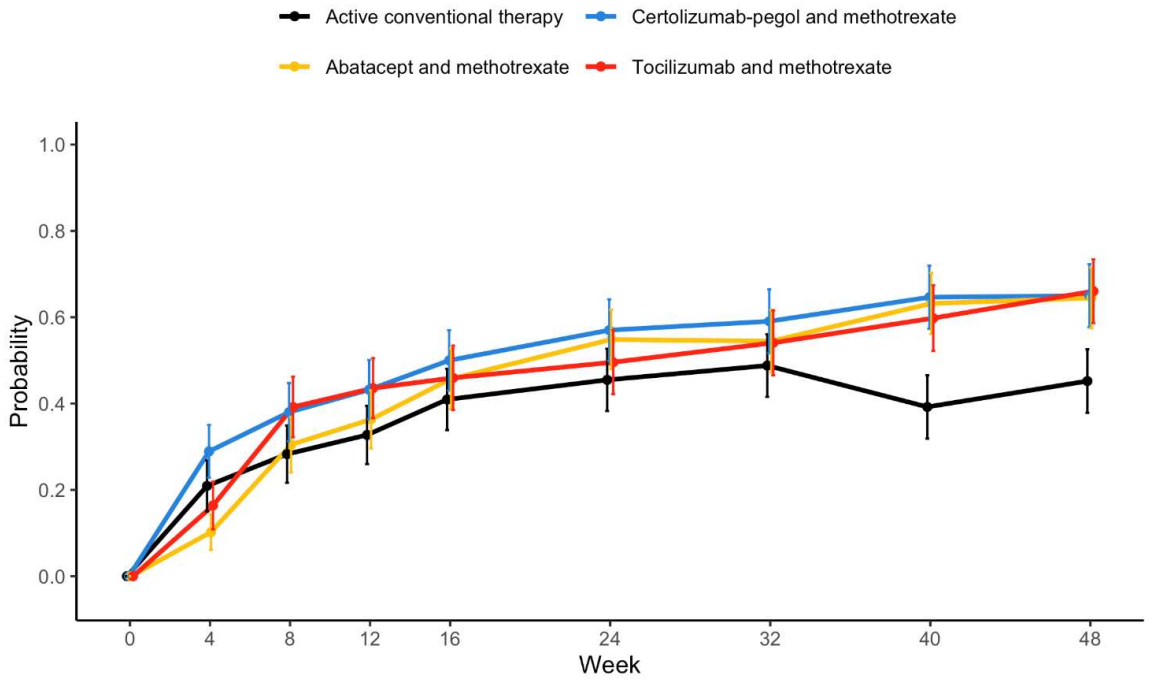
3.2.1 Figure S2: ACR/Boolean remission over time



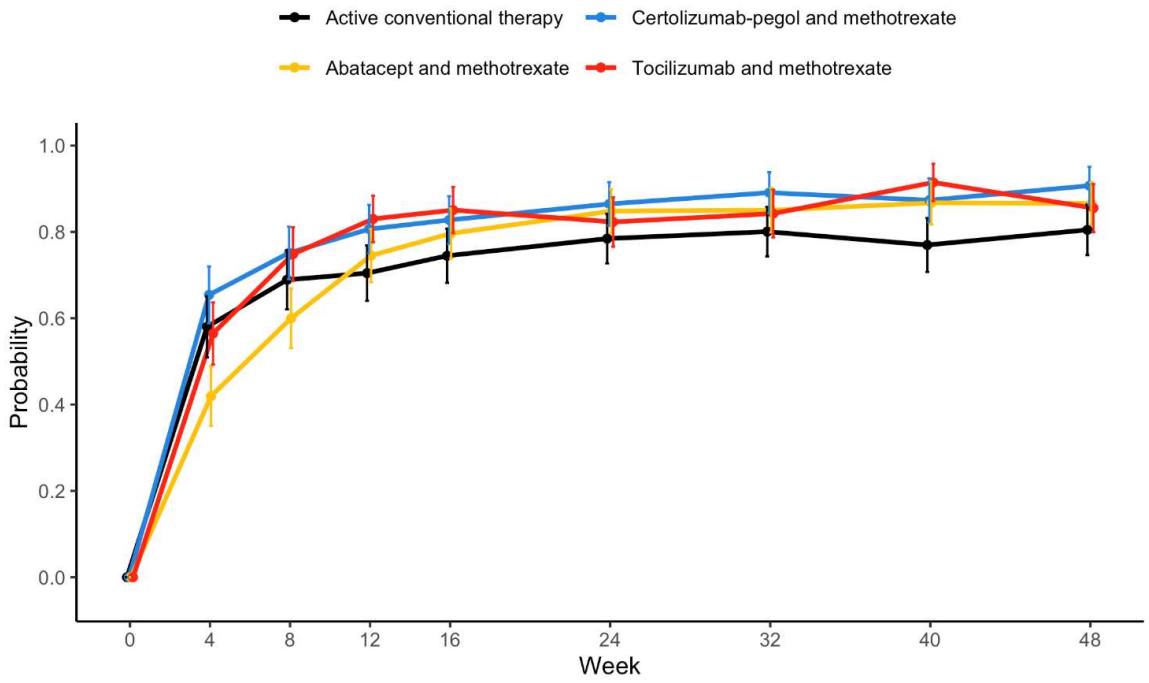
3.2.2 Figure S3: DAS28 remission over time



3.2.3 Figure S4: SDAI remission over time

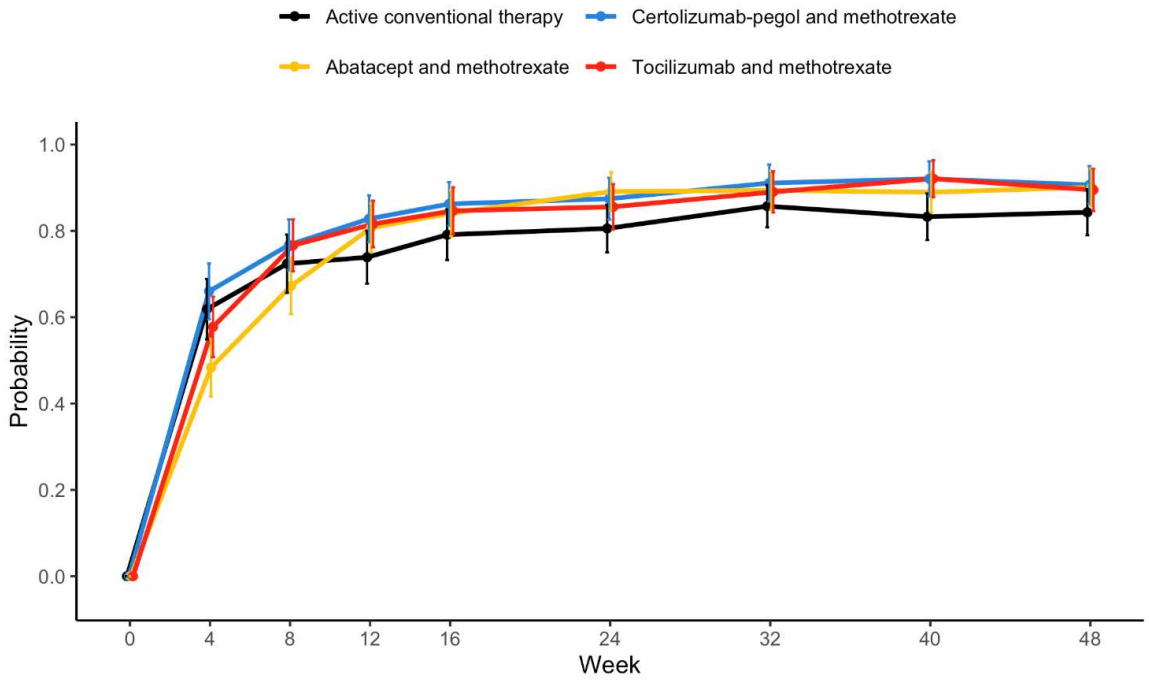


3.2.4 Figure S5: EULAR good response over time



3.3 Other secondary clinical outcomes over time, adjusted, ITT population

3.3.1 Figure S7: CDAI low disease activity over time



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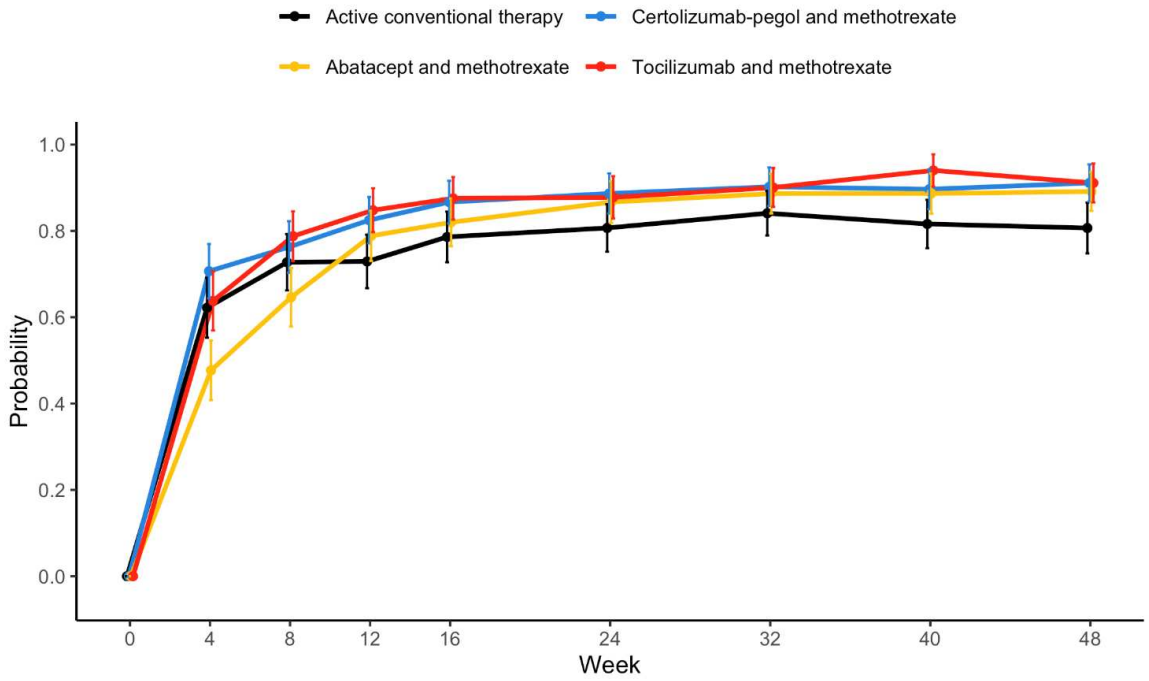
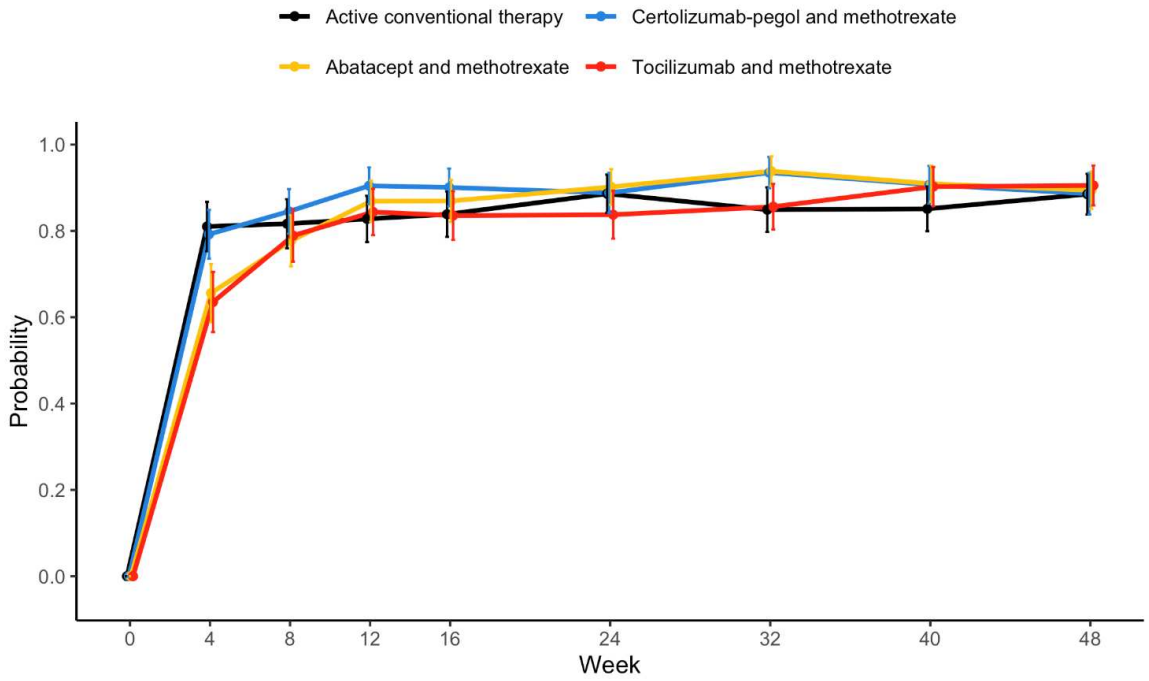
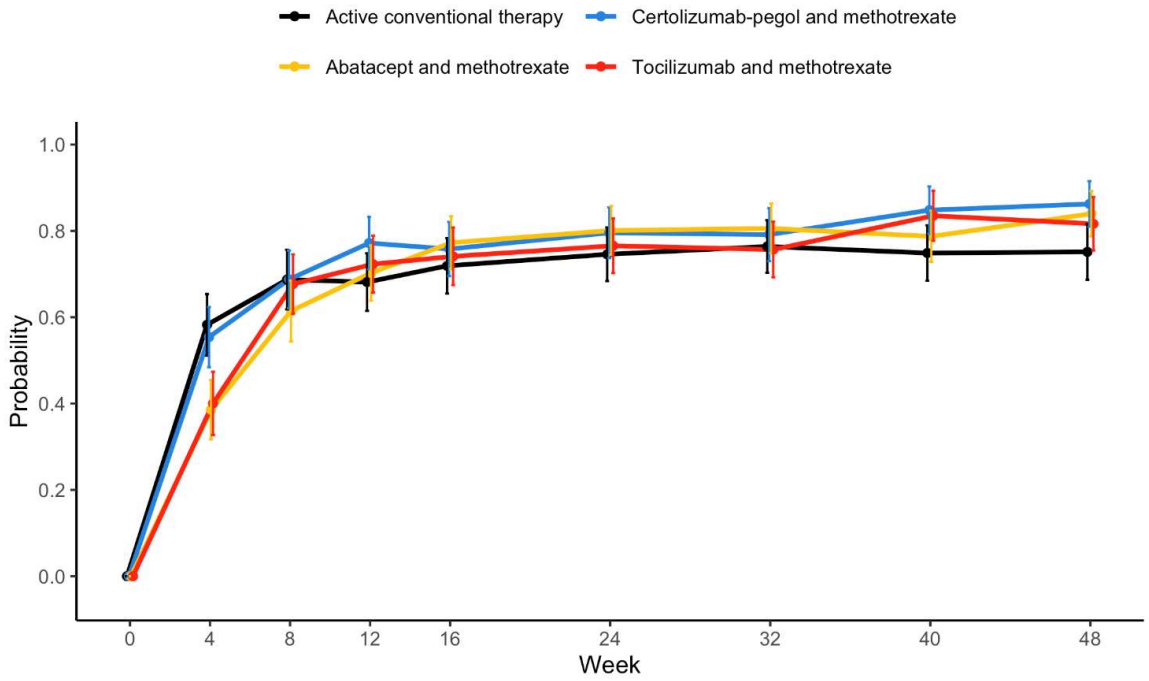
3.3.2 Figure S8: DAS28 low disease activity over time



3.3.3 Figure S10: ACR20 response over time



3.3.4 Figure S11: ACR50 response over time



3.3.5 Figure S12: ACR70 response over time

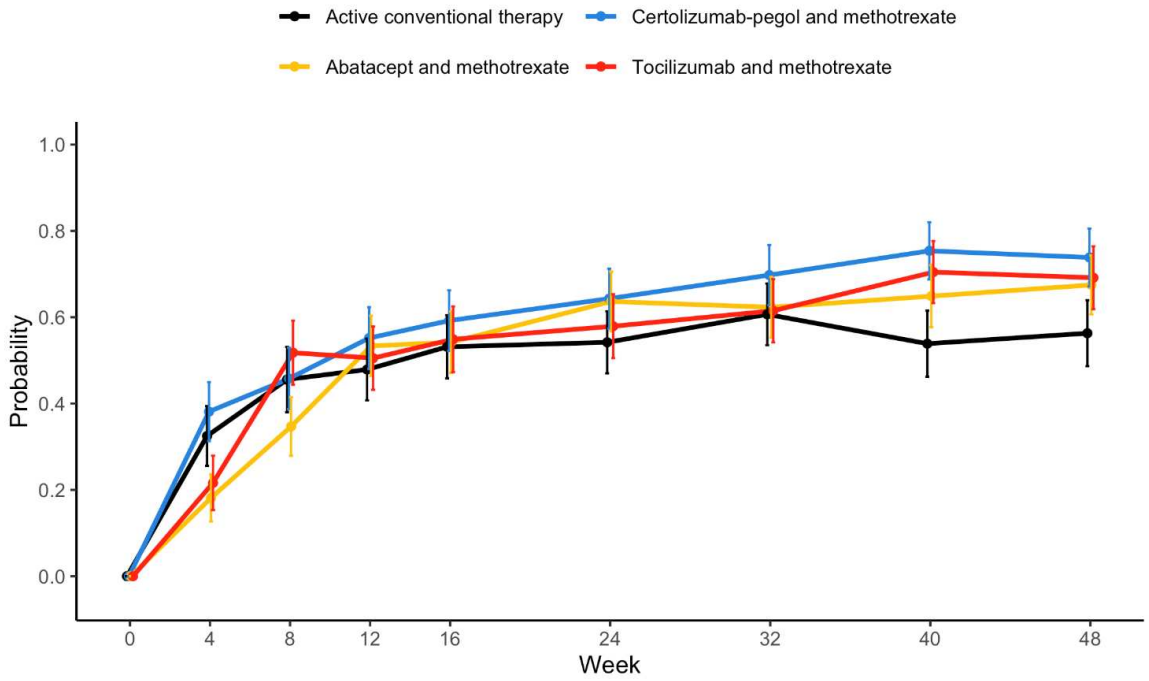


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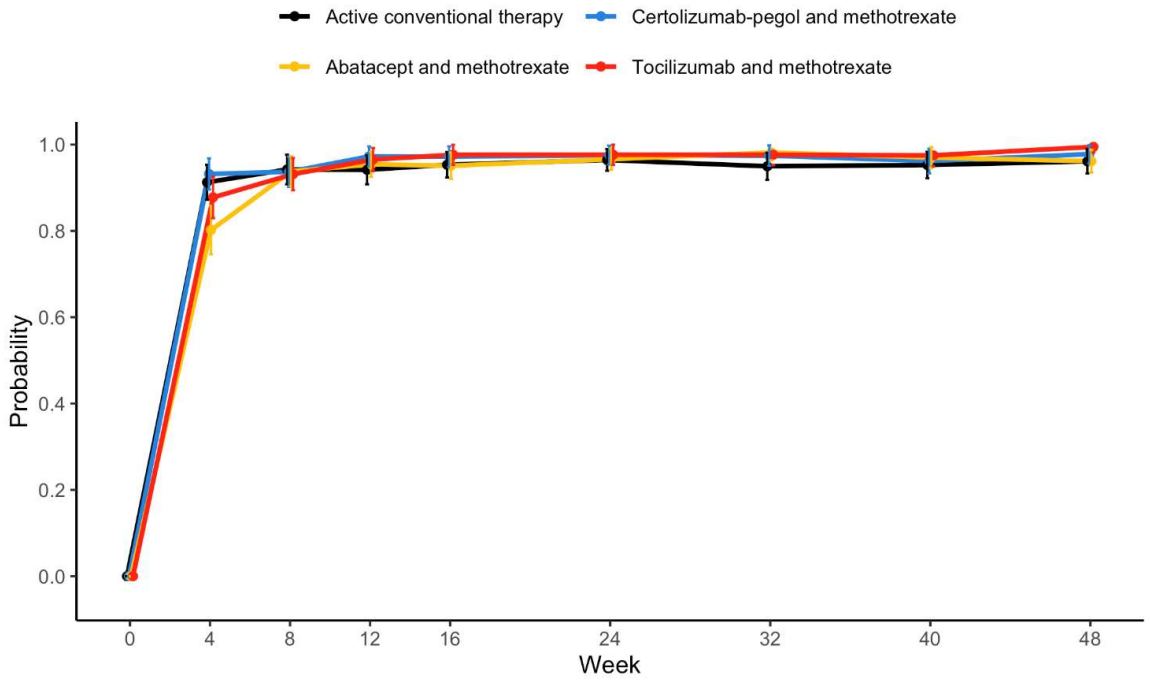
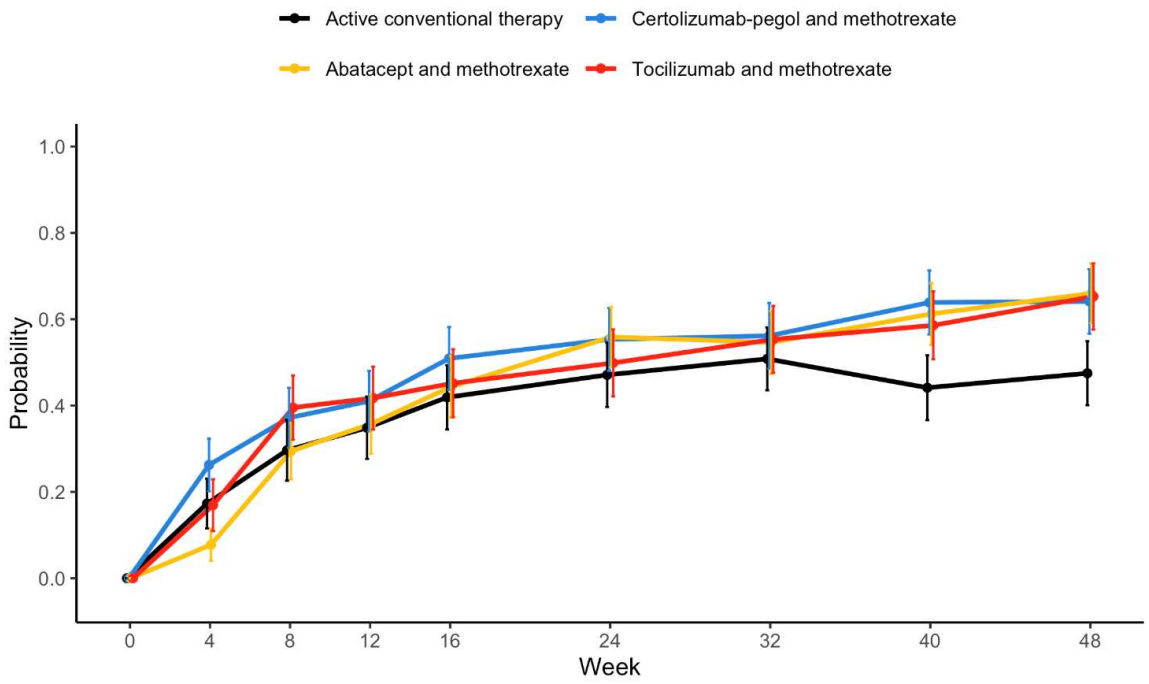
Figure S13: EULAR good/moderate response over time



3.4 Primary clinical outcome over time, adjusted, per-protocol population

3.4.1 Figure S14: CDAI remission over time



4 Supplementary tables

4.1 Other secondary outcomes: clinical dichotomous outcomes

Primary and key secondary clinical outcomes included for reference

4.1.1 Adjusted risk margins and differences using logistic regression (ITT population)

4.1.1.1 Table S1. Marginal estimated proportions, ITT population, adjusted for baseline covariates, logistic regression

Parameter	Week no.	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
CDAI remission	48	39.2% (32.5 to 45.9)	52.3% (45.5 to 59.1)	59.3% (52.6 to 66)	51.9% (44.9 to 59)
CDAI remission	24	41.7% (35.1 to 48.4)	47.3% (40.6 to 54)	51.8% (45.1 to 58.5)	42.5% (35.6 to 49.4)
ACR/EULAR Boolean remission (VAS 14)	48	31.6% (25.3 to 38)	46.3% (39.5 to 53.1)	51% (44.2 to 57.8)	44.6% (37.6 to 51.6)
ACR/EULAR Boolean remission (VAS 14)	24	38.4% (31.8 to 45)	43.4% (36.7 to 50.1)	43.6% (36.9 to 50.3)	35.7% (28.9 to 42.4)
DAS28 remission	48	53.7% (46.9 to 60.6)	66.6% (60.1 to 73)	71.1% (65 to 77.3)	68.2% (61.6 to 74.7)
DAS28 remission	24	63.5% (57 to 70)	68.1% (61.8 to 74.4)	69% (62.8 to 75.3)	64.4% (57.8 to 71.1)
SDAI remission	48	38.1% (31.5 to 44.8)	52.8% (45.9 to 59.6)	57.8% (51.1 to 64.6)	53.5% (46.5 to 60.6)
SDAI remission	24	41.2% (34.6 to 47.9)	49.3% (42.5 to 56)	50.8% (44.1 to 57.5)	44.1% (37.1 to 51)
EULAR good response	48	66.4% (59.9 to 72.9)	74.6% (68.7 to 80.6)	77.7% (72 to 83.4)	69.3% (62.8 to 75.9)
EULAR good response	24	71.5% (65.3 to 77.7)	76.6% (70.8 to 82.4)	79.6% (74 to 85.1)	72.1% (65.8 to 78.4)

EULAR good or moderate response	48	76.4% (70.6 to 82.3)	80.1% (74.6 to 85.6)	86.1% (81.3 to 90.8)	79.9% (74.2 to 85.5)
EULAR good or moderate response	24	86.5% (81.8 to 91.2)	86.5% (81.8 to 91.2)	91% (87.1 to 95)	85% (80 to 90)
CDAI low disease activity	48	68.8% (62.4 to 75.1)	75% (69.1 to 80.9)	80.1% (74.6 to 85.6)	71.9% (65.6 to 78.2)
CDAI low disease activity	24	72.4% (66.3 to 78.5)	77% (71.3 to 82.7)	81.9% (76.7 to 87.2)	74.5% (68.5 to 80.5)
DAS28 low disease activity	48	66.3% (59.8 to 72.8)	75% (69.1 to 81)	80.1% (74.6 to 85.6)	73.9% (67.7 to 80)
DAS28 low disease activity	24	72.9% (66.9 to 79)	78.5% (72.9 to 84.1)	81.4% (76.1 to 86.8)	77% (71.2 to 82.9)
ACR20 response	48	71.4% (65.2 to 77.7)	72.7% (66.6 to 78.8)	79.7% (74.2 to 85.3)	72.4% (66 to 78.7)
ACR20 response	24	79.5% (73.9 to 85)	78.1% (72.4 to 83.7)	85% (80.1 to 89.9)	73.2% (67 to 79.4)
ACR50 response	48	61.4% (54.7 to 68.2)	70.8% (64.5 to 77)	74.9% (68.9 to 80.8)	64.8% (58 to 71.6)
ACR50 response	24	66.9% (60.5 to 73.3)	69.2% (62.9 to 75.4)	74.6% (68.7 to 80.6)	66.4% (59.7 to 73)
ACR70 response	48	45.9% (39 to 52.7)	60.3% (53.6 to 67)	59.6% (52.9 to 66.3)	54.9% (47.8 to 62)
ACR70 response	24	48.8% (41.9 to 55.6)	54.3% (47.5 to 61)	58.3% (51.6 to 65)	50.7% (43.7 to 57.8)

4.1.1.2 Table S2. Marginal estimated differences, ITT population, adjusted for baseline covariates, logistic regression

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
CDAI remission	48	13.1% (3.5 to 22.6)	20.1% (10.6 to 29.5)	12.7% (3 to 22.5)
CDAI remission	24	5.5% (-3.9 to 15)	10% (0.6 to 19.5)	0.8% (-8.9 to 10.4)
ACR/EULAR Boolean remission (VAS 14)	48	14.7% (5.4 to 23.9)	19.4% (10.1 to 28.7)	13% (3.5 to 22.4)
ACR/EULAR Boolean remission (VAS 14)	24	5.1% (-4.4 to 14.5)	5.2% (-4.2 to 14.6)	-2.7% (-12.2 to 6.8)
DAS28 remission	48	12.9% (3.5 to 22.2)	17.4% (8.2 to 26.6)	14.4% (5 to 23.9)

DAS28 remission	24	4.6% (-4.5 to 13.7)	5.5% (-3.5 to 14.6)	0.9% (-8.4 to 10.3)
SDAI remission	48	14.6% (5.1 to 24.1)	19.7% (10.2 to 29.1)	15.4% (5.7 to 25.1)
SDAI remission	24	8% (-1.5 to 17.5)	9.6% (0.1 to 19)	2.8% (-6.8 to 12.5)
EULAR good response	48	8.2% (-0.6 to 17.1)	11.3% (2.7 to 20)	2.9% (-6.3 to 12.2)
EULAR good response	24	5.1% (-3.4 to 13.6)	8.1% (-0.2 to 16.4)	0.6% (-8.2 to 9.5)
EULAR good or moderate response	48	3.6% (-4.4 to 11.7)	9.6% (2.1 to 17.2)	3.5% (-4.7 to 11.6)
EULAR good or moderate response	24	0% (-6.6 to 6.7)	4.5% (-1.6 to 10.6)	-1.5% (-8.4 to 5.4)
CDAI low disease activity	48	6.2% (-2.5 to 14.9)	11.3% (2.9 to 19.7)	3.1% (-5.8 to 12.1)
CDAI low disease activity	24	4.6% (-3.8 to 12.9)	9.5% (1.4 to 17.5)	2.1% (-6.5 to 10.6)
DAS28 low disease activity	48	8.7% (-0.1 to 17.5)	13.8% (5.3 to 22.3)	7.6% (-1.4 to 16.5)
DAS28 low disease activity	24	5.6% (-2.7 to 13.8)	8.5% (0.4 to 16.6)	4.1% (-4.3 to 12.5)
ACR20 response	48	1.3% (-7.5 to 10)	8.3% (0 to 16.7)	0.9% (-8 to 9.9)
ACR20 response	24	-1.4% (-9.3 to 6.5)	5.5% (-1.9 to 12.9)	-6.3% (-14.6 to 2.1)
ACR50 response	48	9.4% (0.2 to 18.5)	13.4% (4.5 to 22.4)	3.4% (-6.2 to 13)
ACR50 response	24	2.3% (-6.7 to 11.3)	7.7% (-1 to 16.5)	-0.5% (-9.8 to 8.7)
ACR70 response	48	14.5% (4.9 to 24.1)	13.7% (4.1 to 23.3)	9.1% (-0.8 to 18.9)
ACR70 response	24	5.5% (-4.1 to 15.1)	9.5% (0 to 19.1)	2% (-7.9 to 11.8)

Footnote: Numbers are adjusted risk estimates and differences with 95% confidence intervals.

4.2 Other secondary outcomes: clinical continuous outcomes

4.2.1 Table S3. Adjusted longitudinal marginal estimates using mixed models (ITT population)

Parameter	Visit no.	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
DAS 28	24	2.31 (2.17 to 2.46)	2.07 (1.93 to 2.21)	2.14 (2 to 2.28)	2.04 (1.89 to 2.19)
DAS 28	48	2.35 (2.2 to 2.5)	1.99 (1.84 to 2.13)	2.04 (1.9 to 2.18)	1.78 (1.63 to 1.93)
CDAI	24	5.67 (4.57 to 6.77)	4.71 (3.61 to 5.8)	4.67 (3.6 to 5.73)	5.12 (3.98 to 6.26)
CDAI	48	5.65 (4.51 to 6.78)	4.37 (3.25 to 5.49)	3.99 (2.91 to 5.08)	3.66 (2.48 to 4.83)
SDAI	24	6.17 (5.02 to 7.33)	4.99 (3.85 to 6.14)	5.03 (3.91 to 6.15)	5.28 (4.07 to 6.48)
SDAI	48	6.16 (4.96 to 7.36)	4.57 (3.39 to 5.75)	4.38 (3.24 to 5.52)	3.81 (2.57 to 5.04)
Patient global by VAS	24	20.8 (17.77 to 23.82)	20.16 (17.15 to 23.17)	18.11 (15.18 to 21.05)	17.97 (14.82 to 21.11)
Patient global by VAS	48	19.96 (16.83 to 23.1)	16.01 (12.93 to 19.09)	16.45 (13.46 to 19.44)	16.14 (12.9 to 19.38)
Physician global by VAS	24	9.2 (7.36 to 11.04)	6.82 (4.99 to 8.65)	7.67 (5.89 to 9.45)	6.9 (4.99 to 8.81)
Physician global by VAS	48	9.86 (7.94 to 11.77)	6.33 (4.44 to 8.21)	5.83 (4.02 to 7.64)	5.19 (3.2 to 7.17)
Patient pain by VAS	24	18.58 (15.66 to 21.51)	16.63 (13.71 to 19.54)	14.5 (11.65 to 17.35)	14.88 (11.83 to 17.93)
Patient pain by VAS	48	18.96 (15.92 to 22)	13.82 (10.84 to 16.81)	14.39 (11.49 to 17.28)	13.25 (10.11 to 16.4)
ESR	24	12.12 (10.45 to 13.78)	12.96 (11.19 to 14.73)	14.76 (12.76 to 16.75)	3.68 (3.15 to 4.21)
ESR	48	14.07 (12.09 to 16.05)	12.4 (10.69 to 14.12)	13.89 (11.98 to 15.79)	3.75 (3.2 to 4.3)
HAQ-DI	24	0.29 (0.23 to 0.36)	0.28 (0.21 to 0.34)	0.29 (0.23 to 0.35)	0.26 (0.2 to 0.33)

HAQ-DI	48	0.32 (0.25 to 0.38)	0.27 (0.2 to 0.33)	0.29 (0.22 to 0.35)	0.24 (0.17 to 0.31)
CRP	24	4.84 (4.14 to 5.54)	3.53 (3.02 to 4.03)	3.92 (3.37 to 4.47)	2.03 (1.73 to 2.34)
CRP	48	5.22 (4.44 to 6)	3.12 (2.67 to 3.58)	4.24 (3.64 to 4.85)	2.03 (1.71 to 2.34)

4.2.2 Table S4. Adjusted longitudinal marginal differences using mixed models (ITT population)

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
DAS 28	24	-0.23 (-0.41 to -0.04)	-0.19 (-0.37 to 0)	-0.21 (-0.4 to -0.01)
DAS 28	48	-0.34 (-0.54 to -0.15)	-0.33 (-0.52 to -0.14)	-0.51 (-0.71 to -0.31)
CDAI	24	-1.08 (-2.42 to 0.26)	-1.29 (-2.61 to 0.03)	-0.29 (-1.67 to 1.08)
CDAI	48	-1.41 (-2.78 to -0.03)	-1.93 (-3.28 to -0.58)	-1.75 (-3.16 to -0.33)
SDAI	24	-1.23 (-2.62 to 0.15)	-1.38 (-2.74 to -0.02)	-0.55 (-1.97 to 0.88)
SDAI	48	-1.66 (-3.08 to -0.24)	-2.01 (-3.41 to -0.62)	-2.03 (-3.49 to -0.57)
Patient global by VAS	24	-0.95 (-5 to 3.09)	-3.96 (-7.95 to 0.04)	-2.99 (-7.14 to 1.16)
Patient global by VAS	48	-4.29 (-8.45 to -0.12)	-4.95 (-9.05 to -0.84)	-4.2 (-8.48 to 0.08)
Physician global by VAS	24	-2.74 (-5.07 to -0.41)	-2.29 (-4.58 to -0.01)	-2.23 (-4.61 to 0.14)
Physician global by VAS	48	-3.98 (-6.38 to -1.57)	-4.95 (-7.31 to -2.59)	-4.76 (-7.23 to -2.29)
Patient pain by VAS	24	-2.03 (-5.91 to 1.86)	-5.27 (-9.12 to -1.43)	-3.53 (-7.53 to 0.46)
Patient pain by VAS	48	-5.41 (-9.41 to -1.41)	-6.03 (-9.98 to -2.09)	-5.95 (-10.07 to -1.82)
ESR	24	0.35 (-1.69 to 2.4)	2.5 (0.3 to 4.7)	-8.27 (-9.81 to -6.72)
ESR	48	-2.24 (-4.51 to 0.02)	-0.65 (-3.01 to 1.71)	-10.47 (-12.32 to -8.62)
HAQ-DI	24	0 (-0.08 to 0.07)	0 (-0.08 to 0.07)	-0.03 (-0.1 to 0.05)
HAQ-DI	48	-0.03 (-0.11 to 0.04)	-0.04 (-0.11 to 0.04)	-0.08 (-0.16 to 0)
CRP	24	-1.12 (-1.89 to -0.34)	-0.72 (-1.52 to 0.07)	-2.55 (-3.24 to -1.87)

CRP	48	-1.93 (-2.74 to -1.12)	-0.78 (-1.67 to 0.1)	-2.96 (-3.72 to -2.21)

4.3 Other secondary outcomes: radiographic dichotomous outcomes

Key secondary clinical outcomes included for reference

4.3.1 Adjusted risk margins and differences using logistic regression (ITT population)

4.3.1.1 Table S4. Marginal estimated proportions, ITT population, adjusted for baseline covariates, logistic regression

Parameter	Week no.	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
Rapid radiographic progression Total	48	0% (0 to 0)	0% (0 to 0)	1% (-0.4 to 2.5)	0% (0 to 0)
Radiographic progression Total	48	22% (16.2 to 27.7)	18.7% (13.3 to 24.1)	25.5% (19.5 to 31.5)	19.7% (14 to 25.4)
Radiographic progression Total	24	12.2% (7.8 to 16.7)	14.9% (10.1 to 19.7)	17.3% (12.2 to 22.4)	13.7% (8.7 to 18.8)
Radiographic progression 24w-48w Total	48	12.1% (7.6 to 16.6)	8% (4.3 to 11.8)	9% (5.1 to 13)	10.6% (6.4 to 14.9)
Radiographic progression Erosion	48	17.5% (12.3 to 22.8)	17.3% (12.1 to 22.5)	20.1% (14.6 to 25.6)	15.4% (10.2 to 20.5)
Radiographic progression Erosion	24	8.4% (4.6 to 12.2)	12.1% (7.7 to 16.5)	13% (8.5 to 17.5)	9.1% (4.9 to 13.3)
Radiographic progression 24w-48w erosion	48	7.6% (3.9 to 11.2)	8% (4.3 to 11.7)	5.5% (2.4 to 8.6)	9.2% (5.2 to 13.2)

Radiographic progression JSN	48	6.4% (3.1 to 9.8)	6.4% (3 to 9.7)	8.3% (4.5 to 12.1)	5.4% (2.1 to 8.7)
Radiographic progression JSN	24	3.9% (1.3 to 6.5)	5.8% (2.6 to 8.9)	6.7% (3.4 to 10.1)	5.8% (2.3 to 9.2)
Radiographic progression 24w-48w JSN	48	3.5% (1 to 6.1)	1.5% (-0.2 to 3.2)	3.6% (1 to 6.1)	1% (-0.4 to 2.4)
Radiographic progression above smallest detectable change	48	14.4% (9.6 to 19.3)	12.8% (8.2 to 17.3)	16.2% (11.2 to 21.2)	13.4% (8.5 to 18.3)

4.3.1.2 Table S5. Marginal estimated differences, ITT population, adjusted for baseline covariates, logistic regression

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
Rapid radiographic progression Total	48	0% (0 to 0)	1% (-0.4 to 2.5)	0% (0 to 0)
Radiographic progression Total	48	-3.3% (-11.1 to 4.6)	3.5% (-4.7 to 11.8)	-2.2% (-10.3 to 5.9)
Radiographic progression Total	24	2.7% (-3.9 to 9.3)	5.1% (-1.7 to 11.9)	1.5% (-5.3 to 8.2)
Radiographic progression 24w-48w Total	48	-4.1% (-10 to 1.8)	-3.1% (-9.1 to 2.9)	-1.5% (-7.7 to 4.8)
Radiographic progression Erosion	48	-0.2% (-7.6 to 7.1)	2.6% (-5 to 10.2)	-2.2% (-9.5 to 5.2)
Radiographic progression Erosion	24	3.7% (-2.1 to 9.5)	4.6% (-1.3 to 10.5)	0.7% (-5 to 6.4)
Radiographic progression 24w-48w erosion	48	0.4% (-4.8 to 5.7)	-2.1% (-6.9 to 2.8)	1.6% (-3.8 to 7.1)
Radiographic progression JSN	48	-0.1% (-4.8 to 4.7)	1.9% (-3.2 to 7)	-1% (-5.7 to 3.7)
Radiographic progression JSN	24	1.9% (-2.2 to 6)	2.9% (-1.4 to 7.1)	1.9% (-2.5 to 6.3)
Radiographic progression 24w-48w JSN	48	-2% (-5.1 to 1)	0% (-3.6 to 3.6)	-2.5% (-5.4 to 0.3)
Radiographic progression above smallest detectable change	48	-1.6% (-8.3 to 5)	1.8% (-5.2 to 8.8)	-1% (-7.9 to 5.9)

Footnote: Numbers are adjusted risk estimates and differences with 95% confidence intervals.

Footnote: Smallest detectable difference (SDC) is calculated to 1.428

4.3.2 Adjusted univariate marginal estimates and differences using ANCOVA (ITT population)

4.3.2.1 Table S6. Adjusted change from baseline marginal estimates using ANCOVA (ITT population)

Parameter	Week no.	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
Change from baseline Erosion	24	0.19 (0.11 to 0.28)	0.2 (0.12 to 0.28)	0.28 (0.2 to 0.36)	0.2 (0.12 to 0.29)
Change from baseline Erosion	48	0.31 (0.21 to 0.4)	0.33 (0.23 to 0.42)	0.41 (0.31 to 0.5)	0.35 (0.25 to 0.45)
Change from W24 Erosion	48	0.15 (0.09 to 0.2)	0.15 (0.09 to 0.21)	0.15 (0.09 to 0.2)	0.17 (0.11 to 0.23)
Change from baseline Joint Space Narrowing	24	0.09 (0.01 to 0.17)	0.13 (0.04 to 0.21)	0.13 (0.05 to 0.22)	0.15 (0.06 to 0.23)
Change from baseline Joint Space Narrowing	48	0.14 (0.05 to 0.23)	0.14 (0.05 to 0.23)	0.22 (0.13 to 0.31)	0.15 (0.06 to 0.24)
Change from W24 Joint Space Narrowing	48	0.08 (0.02 to 0.13)	0.03 (-0.02 to 0.09)	0.1 (0.05 to 0.16)	0.02 (-0.04 to 0.08)
Change from baseline Total	24	0.29 (0.17 to 0.41)	0.32 (0.2 to 0.44)	0.41 (0.29 to 0.53)	0.35 (0.22 to 0.47)
Change from baseline Total	48	0.45 (0.31 to 0.59)	0.47 (0.33 to 0.61)	0.62 (0.48 to 0.76)	0.5 (0.36 to 0.64)
Change from W24 Total	48	0.22 (0.14 to 0.31)	0.19 (0.11 to 0.27)	0.24 (0.16 to 0.33)	0.19 (0.1 to 0.27)

4.3.2.2 Table S7. Estimated treatment difference in change from baseline using ANCOVA (ITT population)

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
Change from baseline Erosion	24	0 (-0.11 to 0.12)	0.09 (-0.03 to 0.2)	0.01 (-0.11 to 0.13)
Change from baseline Erosion	48	0.02 (-0.12 to 0.16)	0.1 (-0.04 to 0.24)	0.04 (-0.1 to 0.19)
Change from W24 Erosion	48	0.01 (-0.08 to 0.09)	0 (-0.08 to 0.08)	0.02 (-0.06 to 0.1)
Change from baseline Joint Space Narrowing	24	0.03 (-0.08 to 0.15)	0.04 (-0.08 to 0.16)	0.05 (-0.07 to 0.17)
Change from baseline Joint Space Narrowing	48	0 (-0.13 to 0.13)	0.08 (-0.05 to 0.21)	0.01 (-0.12 to 0.14)
Change from W24 Joint Space Narrowing	48	-0.04 (-0.13 to 0.04)	0.03 (-0.05 to 0.11)	-0.05 (-0.14 to 0.03)
Change from baseline Total	24	0.04 (-0.13 to 0.21)	0.13 (-0.04 to 0.3)	0.06 (-0.11 to 0.24)
Change from baseline Total	48	0.02 (-0.17 to 0.22)	0.17 (-0.02 to 0.37)	0.05 (-0.15 to 0.25)
Change from W24 Total	48	-0.04 (-0.15 to 0.08)	0.02 (-0.09 to 0.14)	-0.03 (-0.15 to 0.08)

4.4 Robustness analyses on primary and key secondary outcomes: dichotomous clinical outcomes

4.4.1 *Unadjusted* risk margins and differences using logistic regression (ITT population)

4.4.1.1 Table S8. Marginal estimated differences, ITT population, unadjusted, logistic regression

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
CDAI remission	48	13.2% (3.6 to 22.9)	20.3% (10.8 to 29.9)	11% (1.2 to 20.9)
ACR/EULAR Boolean remission	48	14.8% (5.4 to 24.2)	19.5% (10 to 28.9)	11.1% (1.5 to 20.7)
DAS28 remission	48	13% (3.5 to 22.5)	17.6% (8.3 to 26.8)	13% (3.4 to 22.7)
SDAI remission	48	14.7% (5.1 to 24.3)	19.8% (10.3 to 29.4)	13.6% (3.8 to 23.4)
EULAR good response	48	8.4% (-0.5 to 17.2)	11.4% (2.8 to 20.1)	2.1% (-7.2 to 11.4)

Footnote: Numbers are adjusted risk estimates and differences with 95% confidence intervals.

4.4.1.2 Table S9. ITT population, adjusted for baseline covariates, longitudinal analysis with GEE

Parameter	At	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
CDAI remission	Overall, time adjusted	12% (5.3 to 18.7)	8.2% (1.6 to 14.8)	8.3% (1.7 to 14.9)
CDAI remission	Week 48	17.8% (7.4 to 28.1)	19.6% (9.6 to 29.6)	18% (7.6 to 28.4)
ACR/EULAR Boolean remission (VAS 14)	Overall, time adjusted	10.9% (4.6 to 17.3)	8.5% (2.2 to 14.8)	8.6% (2.1 to 15)
ACR/EULAR Boolean remission (VAS 14)	Week 48	18.6% (8.1 to 29)	18.3% (8.1 to 28.5)	16.1% (5.5 to 26.6)
DAS28 remission	Overall, time adjusted	9.9% (3.6 to 16.1)	2.4% (-4.1 to 8.8)	11.4% (5.1 to 17.7)
DAS28 remission	Week 48	16.3% (6.9 to 25.6)	14.7% (5.4 to 23.9)	18.5% (9.4 to 27.7)
SDAI remission	Overall, time adjusted	14.3% (7.7 to 21)	9.7% (3.1 to 16.3)	11.3% (4.6 to 18)
SDAI remission	Week 48	19.8% (9.4 to 30.2)	19.2% (9.1 to 29.4)	20.8% (10.4 to 31.2)
EULAR good response	Overall, time adjusted	7.5% (2.5 to 12.5)	-1.7% (-7 to 3.7)	5.5% (0.3 to 10.7)
EULAR good response	Week 48	10.2% (2.9 to 17.5)	6.1% (-1.5 to 13.7)	5% (-3 to 13.1)

4.4.2 Adjusted risk margins and differences using logistic regression (PP population)

4.4.2.1 Table S10. Marginal estimated proportions, PP population, adjusted for baseline covariates, logistic regression

Parameter	Week no.	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
CDAI remission	48	44.5% (37.2 to 51.8)	59.4% (52.3 to 66.6)	63.4% (56.7 to 70.2)	58.8% (51.2 to 66.4)
ACR/EULAR Boolean remission	48	35.6% (28.6 to 42.7)	53.2% (45.9 to 60.5)	54.5% (47.5 to 61.5)	52% (44.3 to 59.7)

DAS28 remission	48	60.8% (53.6 to 68)	75.9% (69.6 to 82.2)	76.1% (70.1 to 82.1)	77.7% (71.3 to 84.1)
SDAI remission	48	43.2% (35.9 to 50.6)	60.6% (53.4 to 67.8)	61.8% (55 to 68.7)	60.8% (53.2 to 68.3)
EULAR good response	48	74.9% (68.5 to 81.4)	84.5% (79.2 to 89.9)	83.1% (77.8 to 88.4)	79.9% (73.7 to 86.1)

4.4.2.2 Table S11: Marginal estimated differences, PP population, adjusted for baseline covariates

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
CDAI remission	48	15% (4.7 to 25.2)	19% (9 to 28.9)	14.3% (3.7 to 24.9)
ACR/EULAR Boolean remission	48	17.6% (7.4 to 27.7)	18.9% (8.9 to 28.8)	16.4% (5.9 to 26.8)
DAS28 remission	48	15.1% (5.6 to 24.7)	15.3% (5.9 to 24.7)	16.9% (7.3 to 26.6)
SDAI remission	48	17.3% (7.1 to 27.6)	18.6% (8.6 to 28.6)	17.5% (7 to 28)
EULAR good response	48	9.6% (1.2 to 18)	8.2% (-0.2 to 16.5)	5% (-4 to 14)

Footnote: Numbers are adjusted risk estimates and differences with 95% confidence intervals.

4.5 Robustness analyses on primary and key secondary outcomes – continuous clinical outcomes

According to the SAP, there will be no sensitivity analyses on continuous clinical outcomes

4.6 Robustness analyses on primary and key secondary outcomes - radiographic dichotomous outcomes

4.6.1 Radiographic Dichotomous Efficacy Endpoints: Unadjusted risk margins and differences using logistic regression (ITT population)

4.6.1.1 Table S12. Marginal estimated proportions, ITT population, unadjusted, logistic regression

Parameter	Week no.	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
Rapid radiographic progression Total	48	0% (0 to 0)	0% (0 to 0)	1% (-0.4 to 2.3)	0% (0 to 0)
Radiographic progression Total	48	22% (16.3 to 27.7)	18.7% (13.4 to 24.1)	25.5% (19.5 to 31.5)	19.7% (14 to 25.4)
Radiographic progression Total	24	12.5% (7.9 to 17.1)	15.3% (10.3 to 20.2)	17.6% (12.4 to 22.9)	12.8% (8 to 17.5)
Radiographic progression 24w-48w Total	48	12% (7.5 to 16.5)	7.9% (4.2 to 11.6)	8.8% (4.9 to 12.7)	11.2% (6.7 to 15.7)
Radiographic progression Erosion	48	17.5% (12.2 to 22.8)	17.2% (12 to 22.4)	20.1% (14.6 to 25.6)	15.4% (10.3 to 20.6)
Radiographic progression Erosion	24	8.5% (4.6 to 12.4)	12.3% (7.8 to 16.8)	13.2% (8.6 to 17.9)	8.5% (4.5 to 12.5)
Radiographic progression 24w-48w erosion	48	7.5% (3.8 to 11.2)	7.9% (4.2 to 11.6)	5.4% (2.3 to 8.5)	9.6% (5.4 to 13.8)
Radiographic progression JSN	48	6.5% (3.1 to 9.9)	6.4% (3 to 9.8)	8.3% (4.5 to 12.1)	5.3% (2.1 to 8.5)
Radiographic progression JSN	24	4% (1.3 to 6.7)	5.9% (2.7 to 9.2)	6.9% (3.4 to 10.3)	5.3% (2.1 to 8.5)
Radiographic progression 24w-48w JSN	48	3.5% (1 to 6)	1.5% (-0.2 to 3.1)	3.4% (0.9 to 5.9)	1.1% (-0.4 to 2.5)

Radiographic progression above smallest detectable change	48	14.5% (9.6 to 19.4)	12.8% (8.2 to 17.4)	16.2% (11.1 to 21.2)	13.3% (8.4 to 18.2)

4.6.1.2 Table S13. Marginal estimated differences, ITT population, unadjusted, logistic regression

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
Rapid radiographic progression Total	48	0% (0 to 0)	1% (-0.4 to 2.3)	0% (0 to 0)
Radiographic progression Total	48	-3.3% (-11.1 to 4.6)	3.5% (-4.8 to 11.8)	-2.3% (-10.4 to 5.8)
Radiographic progression Total	24	2.8% (-4 to 9.5)	5.1% (-1.8 to 12.1)	0.3% (-6.3 to 6.9)
Radiographic progression 24w-48w Total	48	-4.1% (-10 to 1.7)	-3.2% (-9.1 to 2.8)	-0.8% (-7.2 to 5.5)
Radiographic progression Erosion	48	-0.3% (-7.7 to 7.1)	2.6% (-5 to 10.2)	-2.1% (-9.4 to 5.3)
Radiographic progression Erosion	24	3.8% (-2.1 to 9.8)	4.7% (-1.3 to 10.8)	0% (-5.5 to 5.6)
Radiographic progression 24w-48w erosion	48	0.4% (-4.8 to 5.6)	-2.1% (-6.9 to 2.7)	2.1% (-3.5 to 7.6)
Radiographic progression JSN	48	-0.1% (-4.9 to 4.7)	1.8% (-3.3 to 6.9)	-1.2% (-5.9 to 3.5)
Radiographic progression JSN	24	1.9% (-2.3 to 6.1)	2.9% (-1.5 to 7.3)	1.3% (-2.9 to 5.5)
Radiographic progression 24w-48w JSN	48	-2% (-5.1 to 1)	-0.1% (-3.6 to 3.5)	-2.4% (-5.4 to 0.5)
Radiographic progression above smallest detectable change	48	-1.7% (-8.4 to 5)	1.7% (-5.3 to 8.7)	-1.2% (-8.1 to 5.7)

Footnote: Numbers are adjusted risk estimates and differences with 95% confidence intervals.

Footnote: Smallest detectable difference (SDC) is calculated to 1.428

4.6.2 Radiographic Dichotomous Efficacy Endpoints - Adjusted risk margins and differences using logistic regression (PP population)

4.6.2.1 Table S14. Marginal estimated proportions, PP population, adjusted for baseline covariates, logistic regression

Parameter	Week no.	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
Rapid radiographic progression Total	48	0% (0 to 0)	0% (0 to 0)	1.1% (-0.4 to 2.6)	0% (0 to 0)
Radiographic progression Total	48	25.1% (18.6 to 31.5)	20.9% (14.9 to 26.9)	26.7% (20.4 to 32.9)	21.9% (15.4 to 28.4)
Radiographic progression Total	24	13.8% (8.7 to 18.9)	16.6% (11.2 to 22)	18.4% (13 to 23.8)	15.2% (9.4 to 21)
Radiographic progression 24w-48w Total	48	14.2% (9 to 19.4)	9.1% (4.9 to 13.4)	9.6% (5.4 to 13.8)	11.7% (6.8 to 16.6)
Radiographic progression Erosion	48	19.9% (14 to 25.9)	19.3% (13.5 to 25.1)	20.9% (15.2 to 26.7)	17.2% (11.3 to 23.1)
Radiographic progression Erosion	24	9.3% (5 to 13.6)	13.3% (8.4 to 18.2)	13.9% (9 to 18.7)	10.2% (5.3 to 15.1)
Radiographic progression 24w-48w erosion	48	8.9% (4.7 to 13.2)	9.1% (4.9 to 13.3)	5.8% (2.5 to 9.1)	10.5% (5.8 to 15.2)
Radiographic progression JSN	48	7.5% (3.6 to 11.4)	6.8% (3.1 to 10.5)	8.9% (4.9 to 12.9)	5.9% (2.2 to 9.7)
Radiographic progression JSN	24	4.5% (1.5 to 7.5)	6.1% (2.6 to 9.6)	7.1% (3.6 to 10.7)	6.4% (2.4 to 10.3)
Radiographic progression 24w-48w JSN	48	4.1% (1.2 to 7)	1.7% (-0.2 to 3.6)	3.8% (1.1 to 6.5)	0.6% (-0.6 to 1.8)
Radiographic progression above smallest detectable					

change	48	16.3% (10.8 to 21.8)	14% (9 to 19.1)	17.2% (11.9 to 22.5)	15% (9.3 to 20.6)

4.6.2.2 Table S15. Marginal estimated differences, PP population, adjusted for baseline covariates, logistic regression

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
Rapid radiographic progression Total	48	0% (0 to 0)	1.1% (-0.4 to 2.6)	0% (0 to 0)
Radiographic progression Total	48	-4.1% (-12.9 to 4.7)	1.6% (-7.4 to 10.6)	-3.2% (-12.4 to 6)
Radiographic progression Total	24	2.8% (-4.6 to 10.2)	4.6% (-2.8 to 12)	1.4% (-6.3 to 9.1)
Radiographic progression 24w-48w Total	48	-5.1% (-11.8 to 1.7)	-4.6% (-11.3 to 2.1)	-2.5% (-9.7 to 4.6)
Radiographic progression Erosion	48	-0.6% (-9 to 7.7)	1% (-7.3 to 9.3)	-2.7% (-11.1 to 5.7)
Radiographic progression Erosion	24	4% (-2.6 to 10.5)	4.5% (-1.9 to 11)	0.9% (-5.6 to 7.4)
Radiographic progression 24w-48w erosion	48	0.2% (-5.8 to 6.2)	-3.1% (-8.5 to 2.3)	1.6% (-4.8 to 7.9)
Radiographic progression JSN	48	-0.7% (-6.1 to 4.7)	1.4% (-4.2 to 7)	-1.5% (-7 to 3.9)
Radiographic progression JSN	24	1.6% (-3 to 6.2)	2.6% (-2 to 7.3)	1.9% (-3.2 to 6.9)
Radiographic progression 24w-48w JSN	48	-2.4% (-5.9 to 1.1)	-0.3% (-4.3 to 3.7)	-3.5% (-6.6 to -0.3)
Radiographic progression above smallest detectable change	48	-2.2% (-9.7 to 5.2)	0.9% (-6.7 to 8.6)	-1.3% (-9.2 to 6.6)

Footnote: Numbers are adjusted risk estimates and differences with 95% confidence intervals.

Footnote: Smallest detectable difference (SDC) is calculated to 1.428

4.7 Robustness analyses on primary and key secondary outcomes – radiographic continuous outcomes

4.7.1 Radiographic Continuous Efficacy Endpoints - Unadjusted univariate marginal estimates and differences using ANCOVA (ITT population)

4.7.1.1 Table S16. Adjusted change from baseline marginal estimates using ANCOVA (ITT population)

Parameter	Week no.	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
Change from baseline Erosion	24	0.2 (0.12 to 0.28)	0.21 (0.12 to 0.29)	0.29 (0.2 to 0.37)	0.18 (0.1 to 0.27)
Change from baseline Erosion	48	0.31 (0.21 to 0.4)	0.32 (0.23 to 0.42)	0.41 (0.31 to 0.5)	0.35 (0.25 to 0.45)
Change from W24 Erosion	48	0.14 (0.09 to 0.2)	0.15 (0.09 to 0.21)	0.14 (0.09 to 0.2)	0.17 (0.11 to 0.23)
Change from baseline Joint Space Narrowing	24	0.1 (0.02 to 0.18)	0.13 (0.05 to 0.22)	0.14 (0.06 to 0.23)	0.12 (0.03 to 0.21)
Change from baseline Joint Space Narrowing	48	0.14 (0.05 to 0.23)	0.14 (0.05 to 0.23)	0.22 (0.13 to 0.31)	0.14 (0.05 to 0.24)
Change from W24 Joint Space Narrowing	48	0.08 (0.02 to 0.13)	0.03 (-0.03 to 0.09)	0.1 (0.04 to 0.16)	0.03 (-0.03 to 0.09)
Change from baseline Total	24	0.3 (0.17 to 0.42)	0.34 (0.22 to 0.46)	0.43 (0.3 to 0.55)	0.3 (0.17 to 0.43)
Change from baseline Total	48	0.45 (0.31 to 0.59)	0.47 (0.33 to 0.61)	0.62 (0.48 to 0.76)	0.5 (0.35 to 0.64)
Change from W24 Total	48	0.22 (0.14 to 0.3)	0.18 (0.1 to 0.27)	0.24 (0.16 to 0.32)	0.2 (0.12 to 0.29)

4.7.1.2 Table S17. Estimated treatment difference in change from baseline using ANCOVA (ITT population)

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
Change from baseline Erosion	24	0.01 (-0.11 to 0.12)	0.09 (-0.03 to 0.2)	-0.02 (-0.14 to 0.1)
Change from baseline Erosion	48	0.02 (-0.12 to 0.16)	0.1 (-0.04 to 0.24)	0.05 (-0.09 to 0.19)
Change from W24 Erosion	48	0 (-0.08 to 0.09)	0 (-0.08 to 0.08)	0.03 (-0.05 to 0.11)
Change from baseline Joint Space Narrowing	24	0.03 (-0.09 to 0.15)	0.04 (-0.08 to 0.16)	0.02 (-0.1 to 0.14)
Change from baseline Joint Space Narrowing	48	0 (-0.13 to 0.13)	0.08 (-0.05 to 0.2)	0 (-0.13 to 0.13)
Change from W24 Joint Space Narrowing	48	-0.04 (-0.12 to 0.04)	0.03 (-0.06 to 0.11)	-0.05 (-0.13 to 0.04)
Change from baseline Total	24	0.04 (-0.13 to 0.22)	0.13 (-0.05 to 0.3)	0 (-0.18 to 0.18)
Change from baseline Total	48	0.02 (-0.17 to 0.22)	0.17 (-0.02 to 0.37)	0.05 (-0.15 to 0.25)
Change from W24 Total	48	-0.04 (-0.15 to 0.08)	0.02 (-0.1 to 0.14)	-0.02 (-0.14 to 0.1)

4.7.2 Radiographic Continuous Efficacy Endpoints - Adjusted estimated yearly change and treatment difference using mixed models (ITT population)

4.7.2.1 Table S18. Adjusted estimated yearly change using mixed models (ITT population)

Parameter	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
Erosion	0.37 (0.25 to 0.48)	0.4 (0.28 to 0.51)	0.44 (0.33 to 0.55)	0.4 (0.28 to 0.52)
Joint Space Narrowing	0.18 (0.07 to 0.29)	0.16 (0.06 to 0.27)	0.25 (0.15 to 0.35)	0.13 (0.02 to 0.25)
Total	0.55 (0.39 to 0.71)	0.56 (0.4 to 0.72)	0.69 (0.53 to 0.84)	0.54 (0.37 to 0.7)

4.7.2.2 Table S19. Estimated treatment difference in yearly change using mixed models (ITT population)

Parameter	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
Erosion	0.05 (-0.11 to 0.21)	0.06 (-0.1 to 0.22)	0.04 (-0.12 to 0.21)
Joint Space Narrowing	-0.01 (-0.16 to 0.14)	0.07 (-0.07 to 0.22)	-0.04 (-0.19 to 0.12)
Total	0.04 (-0.19 to 0.27)	0.14 (-0.09 to 0.36)	0.01 (-0.23 to 0.24)

4.7.3 Radiographic Continuous Efficacy Endpoints - Adjusted univariate marginal estimates and differences using ANCOVA (PP population)

4.7.3.1 Table S20. Adjusted change from baseline marginal estimates using ANCOVA (pp population)

Parameter	Week no.	Active conventional therapy	Certolizumab-pegol and methotrexate	Abatacept and methotrexate	Tocilizumab and methotrexate
Change from baseline Erosion	24	0.22 (0.12 to 0.31)	0.22 (0.13 to 0.32)	0.3 (0.21 to 0.39)	0.22 (0.12 to 0.32)
Change from baseline Erosion	48	0.35 (0.24 to 0.46)	0.37 (0.26 to 0.48)	0.43 (0.33 to 0.54)	0.39 (0.27 to 0.5)
Change from W24 Erosion	48	0.17 (0.1 to 0.23)	0.17 (0.11 to 0.24)	0.15 (0.09 to 0.22)	0.19 (0.12 to 0.25)
Change from baseline Joint Space Narrowing	24	0.11 (0.01 to 0.2)	0.14 (0.05 to 0.23)	0.14 (0.05 to 0.23)	0.17 (0.07 to 0.27)
Change from baseline Joint Space Narrowing	48	0.16 (0.06 to 0.26)	0.15 (0.05 to 0.26)	0.24 (0.14 to 0.33)	0.17 (0.06 to 0.28)
Change from W24 Joint Space Narrowing	48	0.09 (0.02 to 0.16)	0.04 (-0.03 to 0.1)	0.11 (0.05 to 0.17)	0.02 (-0.05 to 0.09)
Change from baseline Total	24	0.32 (0.19 to 0.46)	0.37 (0.23 to 0.5)	0.44 (0.31 to 0.57)	0.38 (0.24 to 0.53)

Change from baseline Total	48	0.51 (0.35 to 0.66)	0.53 (0.38 to 0.68)	0.67 (0.52 to 0.81)	0.55 (0.39 to 0.72)
Change from W24 Total	48	0.26 (0.16 to 0.35)	0.22 (0.12 to 0.31)	0.26 (0.17 to 0.35)	0.21 (0.11 to 0.31)

4.7.3.2 Table S21. Estimated treatment difference in change from baseline using ANCOVA (pp population)

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
Change from baseline Erosion	24	0.01 (-0.12 to 0.14)	0.08 (-0.05 to 0.21)	0 (-0.13 to 0.14)
Change from baseline Erosion	48	0.02 (-0.13 to 0.18)	0.09 (-0.06 to 0.24)	0.04 (-0.12 to 0.2)
Change from W24 Erosion	48	0.01 (-0.09 to 0.1)	-0.01 (-0.1 to 0.08)	0.02 (-0.08 to 0.11)
Change from baseline Joint Space Narrowing	24	0.03 (-0.1 to 0.17)	0.04 (-0.09 to 0.17)	0.06 (-0.08 to 0.2)
Change from baseline Joint Space Narrowing	48	-0.01 (-0.15 to 0.14)	0.08 (-0.07 to 0.22)	0.01 (-0.14 to 0.16)
Change from W24 Joint Space Narrowing	48	-0.05 (-0.14 to 0.04)	0.02 (-0.07 to 0.11)	-0.07 (-0.16 to 0.03)
Change from baseline Total	24	0.04 (-0.15 to 0.23)	0.12 (-0.07 to 0.31)	0.06 (-0.14 to 0.26)
Change from baseline Total	48	0.02 (-0.2 to 0.24)	0.16 (-0.06 to 0.37)	0.04 (-0.18 to 0.27)
Change from W24 Total	48	-0.04 (-0.17 to 0.09)	0 (-0.13 to 0.13)	-0.05 (-0.19 to 0.09)

4.8 Robustness analyses: 17 Finnish patients included.

4.8.1 Seventeen Finnish patients included in arm 4 (TCZ + MTX).

4.8.1.1 Table S22. Primary and secondary dichotomous efficacy endpoints, strict ITT population, adjusted for baseline covariates

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
CDAI remission	48	12.2% (2.7 to 21.6)	19.8% (10.5 to 29.1)	11.8% (2.4 to 21.2)
ACR/EULAR Boolean remission	48	13.5% (4.3 to 22.7)	19.1% (10 to 28.3)	12.1% (3 to 21.3)

DAS28 remission	48	11.6% (2.3 to 20.8)	16.7% (7.7 to 25.7)	12.8% (3.6 to 22)
SDAI remission	48	13.4% (4.1 to 22.8)	19.3% (10.1 to 28.6)	14% (4.7 to 23.3)
EULAR good response	48	7.8% (-1 to 16.7)	11% (2.4 to 19.7)	3.2% (-5.9 to 12.2)

Footnote: Numbers are adjusted risk differences with 95% confidence intervals.

4.8.2 Seventeen Finnish patients included in arm 1 (ACT)

4.8.2.1 Table S23. Primary and secondary dichotomous efficacy endpoints, Finnish as treated population, adjusted for baseline covariates

Parameter	Week no.	(CZP + MTX) vs ACT	(ABA + MTX) vs ACT	(TCZ + MTX) vs ACT
CDAI remission	48	10.8% (1.5 to 20.1)	18.4% (9.3 to 27.6)	9.7% (0.2 to 19.2)
ACR/EULAR Boolean remission	48	12.1% (3 to 21.1)	17.7% (8.6 to 26.7)	10.1% (0.8 to 19.4)
DAS28 remission	48	11.1% (2 to 20.2)	16.2% (7.3 to 25)	12.4% (3.2 to 21.7)
SDAI remission	48	12% (2.8 to 21.3)	17.9% (8.8 to 27)	12% (2.6 to 21.5)
EULAR good response	48	7.5% (-1.2 to 16.2)	10.7% (2.2 to 19.2)	2.6% (-6.5 to 11.7)

Footnote: Numbers are adjusted risk differences with 95% confidence intervals.

4.9 Safety tables

4.9.1 Table S24. Summary of Adverse Events

Parameter	ACT (N=197)	CZP + MTX (N=202)	ABA + MTX (N=204)	TCZ + MTX (N=184)
Number of AEs	[784] 174 (88.3%)	[736] 181 (89.6%)	[735] 175 (85.8%)	[886] 178 (96.7%)
Number of patients with any AEs?	174 (88.3%)	181 (89.6%)	175 (85.8%)	178 (96.7%)
Number of patients with one AE	27 (13.7%)	36 (17.8%)	27 (13.2%)	12 (6.5%)
Number of patients with two AE	29 (14.7%)	30 (14.9%)	26 (12.7%)	29 (15.8%)

Number of patients with three or more AEs	118 (59.9%)	115 (56.9%)	122 (59.8%)	137 (74.5%)
Number of SAEs	[23] 21 (10.7%)	[28] 25 (12.4%)	[21] 17 (8.3%)	[20] 17 (9.2%)
Number of patients with any SAEs?	21 (10.7%)	25 (12.4%)	17 (8.3%)	17 (9.2%)

4.9.2 Table S25: Adverse Events by System Organ Class and Preferred term

System Organ Class	Preferred Term	ACT (N=197)	CZP + MTX (N=202)	ABA + MTX (N=204)	TCZ + MTX (N=184)
Blood and lymphatic system disorders	#Total	[9] 7 (3.6%)	[14] 10 (5%)	[7] 5 (2.5%)	[45] 32 (17.4%)
	Anaemia	[3] 3 (1.5%)	[2] 2 (1%)	[2] 1 (0.5%)	[1] 1 (0.5%)
	Bone marrow failure		[1] 1 (0.5%)		
	Eosinophilia				[1] 1 (0.5%)
	Hilar lymphadenopathy				[1] 1 (0.5%)
	Increased tendency to bruise		[1] 1 (0.5%)		[1] 1 (0.5%)
	Leukopenia	[4] 2 (1%)	[3] 2 (1%)	[3] 2 (1%)	[11] 6 (3.3%)
	Lymphadenitis		[2] 2 (1%)		
	Lymphadenopathy		[1] 1 (0.5%)		
	Neutropenia	[2] 2 (1%)	[2] 2 (1%)	[2] 2 (1%)	[26] 20 (10.9%)
	Spontaneous haematoma		[2] 1 (0.5%)		

	Thrombocytopenia				[4] 4 (2.2%)
Cardiac disorders	#Total	[4] 4 (2%)	[9] 8 (4%)	[16] 12 (5.9%)	[7] 7 (3.8%)
	Angina pectoris		[1] 1 (0.5%)		[1] 1 (0.5%)
	Arrhythmia			[2] 2 (1%)	
	Atrial fibrillation	[2] 2 (1%)	[2] 2 (1%)	[3] 3 (1.5%)	
	Cardiac failure		[1] 1 (0.5%)		[1] 1 (0.5%)
	Cardiac flutter			[1] 1 (0.5%)	
	Extrasystoles			[1] 1 (0.5%)	
	Palpitations	[1] 1 (0.5%)	[3] 3 (1.5%)	[6] 6 (2.9%)	[4] 4 (2.2%)
	Pericarditis			[2] 2 (1%)	
	Tachycardia	[1] 1 (0.5%)	[2] 2 (1%)	[1] 1 (0.5%)	[1] 1 (0.5%)
Congenital, familial and genetic disorders	#Total	[1] 1 (0.5%)			[1] 1 (0.5%)
	Diverticulitis Meckel's	[1] 1 (0.5%)			
	Fibrous dysplasia of jaw				[1] 1 (0.5%)
Ear and labyrinth disorders	#Total	[4] 4 (2%)	[7] 6 (3%)	[8] 8 (3.9%)	[3] 2 (1.1%)
	Ear discomfort	[2] 2 (1%)	[1] 1 (0.5%)		
	Ear pain			[1] 1 (0.5%)	

	Excessive cerumen production		[1] 1 (0.5%)		
	Hypoacusis			[1] 1 (0.5%)	
	Tinnitus	[1] 1 (0.5%)	[4] 3 (1.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Vertigo	[1] 1 (0.5%)	[1] 1 (0.5%)	[4] 4 (2%)	
	Vertigo positional			[1] 1 (0.5%)	[2] 1 (0.5%)
Endocrine disorders	#Total	[1] 1 (0.5%)		[2] 2 (1%)	
	Cushingoid	[1] 1 (0.5%)			
	Hyperparathyroidism			[1] 1 (0.5%)	
	Hyperthyroidism			[1] 1 (0.5%)	
Eye disorders	#Total	[19] 16 (8.1%)	[9] 9 (4.5%)	[8] 8 (3.9%)	[10] 8 (4.3%)
	Blepharitis				[1] 1 (0.5%)
	Cataract	[2] 2 (1%)			[1] 1 (0.5%)
	Conjunctival haemorrhage			[1] 1 (0.5%)	
	Dry eye	[3] 3 (1.5%)	[1] 1 (0.5%)	[2] 2 (1%)	[2] 2 (1.1%)
	Erythema of eyelid	[1] 1 (0.5%)			
	Eye disorder			[1] 1 (0.5%)	
	Eye haemorrhage	[2] 2 (1%)			

	Eye inflammation		[1] 1 (0.5%)		[1] 1 (0.5%)
	Eye irritation	[1] 1 (0.5%)	[3] 3 (1.5%)		[2] 2 (1.1%)
	Eye pain	[1] 1 (0.5%)			[1] 1 (0.5%)
	Eye swelling	[1] 1 (0.5%)			
	Keratitis				[1] 1 (0.5%)
	Lacrimation increased			[2] 2 (1%)	
	Ocular hyperaemia	[1] 1 (0.5%)			[1] 1 (0.5%)
	Retinal detachment		[1] 1 (0.5%)		
	Ulcerative keratitis			[1] 1 (0.5%)	
	Vision blurred	[5] 5 (2.5%)	[1] 1 (0.5%)		
	Visual impairment	[2] 2 (1%)	[1] 1 (0.5%)	[1] 1 (0.5%)	
	Vitreous floaters		[1] 1 (0.5%)		
Gastrointestinal disorders	#Total	[188] 105 (53.3%)	[134] 89 (44.1%)	[166] 98 (48%)	[157] 90 (48.9%)
	Abdominal discomfort	[6] 6 (3%)	[4] 4 (2%)	[3] 2 (1%)	[1] 1 (0.5%)
	Abdominal distension	[3] 3 (1.5%)	[3] 3 (1.5%)	[2] 2 (1%)	[1] 1 (0.5%)
	Abdominal pain	[2] 2 (1%)	[2] 2 (1%)	[10] 8 (3.9%)	[5] 5 (2.7%)
	Abdominal pain lower				[1] 1 (0.5%)

Abdominal pain upper	[12] 10 (5.1%)	[7] 6 (3%)	[4] 4 (2%)	[3] 3 (1.6%)
Abdominal tenderness		[2] 2 (1%)		
Anal fistula	[1] 1 (0.5%)			
Anal haemorrhage				[1] 1 (0.5%)
Angular cheilitis	[1] 1 (0.5%)	[1] 1 (0.5%)		[3] 3 (1.6%)
Aphthous ulcer		[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
Cheilitis		[1] 1 (0.5%)		[4] 4 (2.2%)
Constipation	[1] 1 (0.5%)	[3] 3 (1.5%)	[2] 2 (1%)	[2] 2 (1.1%)
Defaecation disorder			[1] 1 (0.5%)	
Diarrhoea	[17] 16 (8.1%)	[11] 9 (4.5%)	[12] 12 (5.9%)	[15] 13 (7.1%)
Diarrhoea haemorrhagic			[1] 1 (0.5%)	
Diverticulum				[1] 1 (0.5%)
Diverticulum intestinal	[1] 1 (0.5%)			
Dry mouth	[3] 3 (1.5%)	[1] 1 (0.5%)	[2] 2 (1%)	[4] 4 (2.2%)
Duodenal ulcer			[1] 1 (0.5%)	
Dyspepsia	[13] 11 (5.6%)	[4] 4 (2%)	[4] 4 (2%)	[4] 4 (2.2%)

Dysphagia		[1] 1 (0.5%)		
Enterocolitis		[1] 1 (0.5%)		
Epigastric discomfort	[1] 1 (0.5%)			
Flatulence	[2] 2 (1%)			[3] 3 (1.6%)
Food poisoning	[1] 1 (0.5%)			
Frequent bowel movements		[1] 1 (0.5%)		
Gastric ulcer	[1] 1 (0.5%)		[1] 1 (0.5%)	
Gastritis	[2] 2 (1%)	[3] 3 (1.5%)	[1] 1 (0.5%)	[2] 2 (1.1%)
Gastrointestinal haemorrhage				[1] 1 (0.5%)
Gastrooesophageal reflux disease	[3] 3 (1.5%)		[2] 2 (1%)	
Glossodynia		[1] 1 (0.5%)		
Haematochezia	[1] 1 (0.5%)			[1] 1 (0.5%)
Haemorrhoidal haemorrhage		[1] 1 (0.5%)	[1] 1 (0.5%)	
Inguinal hernia				[1] 1 (0.5%)
Lip blister			[1] 1 (0.5%)	[1] 1 (0.5%)
Lip dry			[1] 1 (0.5%)	
Lip ulceration		[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)

Mouth haemorrhage		[1] 1 (0.5%)		
Mouth ulceration	[9] 8 (4.1%)	[9] 9 (4.5%)	[8] 7 (3.4%)	[13] 10 (5.4%)
Nausea	[96] 71 (36%)	[64] 55 (27.2%)	[85] 70 (34.3%)	[66] 51 (27.7%)
Oral mucosal blistering	[1] 1 (0.5%)	[2] 2 (1%)	[10] 8 (3.9%)	[11] 9 (4.9%)
Oral mucosal hypertrophy		[1] 1 (0.5%)		
Pancreatic cyst			[1] 1 (0.5%)	
Paraesthesia oral	[2] 2 (1%)		[1] 1 (0.5%)	[2] 2 (1.1%)
Periodontal disease				[1] 1 (0.5%)
Proctitis				[1] 1 (0.5%)
Rectal discharge	[1] 1 (0.5%)			
Salivary hypersecretion	[1] 1 (0.5%)		[1] 1 (0.5%)	
Stomatitis		[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
Swollen tongue			[1] 1 (0.5%)	
Tongue blistering		[1] 1 (0.5%)		
Tongue discomfort		[1] 1 (0.5%)		
Tongue pruritus		[1] 1 (0.5%)		

	Tooth loss				[1] 1 (0.5%)
	Toothache		[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Vomiting	[7] 7 (3.6%)	[3] 3 (1.5%)	[6] 6 (2.9%)	[4] 4 (2.2%)
General disorders and administration site conditions	#Total	[47] 33 (16.8%)	[64] 50 (24.8%)	[38] 32 (15.7%)	[41] 35 (19%)
	Asthenia		[1] 1 (0.5%)	[1] 1 (0.5%)	
	Chest discomfort		[4] 3 (1.5%)		[4] 4 (2.2%)
	Chest pain	[4] 3 (1.5%)	[3] 2 (1%)	[1] 1 (0.5%)	[3] 3 (1.6%)
	Chills			[1] 1 (0.5%)	
	Chronic fatigue syndrome		[1] 1 (0.5%)		
	Death		[1] 1 (0.5%)		
	Discomfort	[1] 1 (0.5%)	[1] 1 (0.5%)		
	Face oedema			[1] 1 (0.5%)	[1] 1 (0.5%)
	Fat necrosis	[1] 1 (0.5%)			
	Fatigue	[22] 19 (9.6%)	[17] 17 (8.4%)	[16] 15 (7.4%)	[11] 10 (5.4%)
	Feeling cold			[1] 1 (0.5%)	
	Gait disturbance			[1] 1 (0.5%)	
	General physical health deterioration		[1] 1 (0.5%)		

Hunger		[1] 1 (0.5%)		
Impaired healing				[1] 1 (0.5%)
Influenza like illness		[2] 2 (1%)	[2] 2 (1%)	[4] 4 (2.2%)
Infusion site swelling				[1] 1 (0.5%)
Injection site bruising		[2] 1 (0.5%)		
Injection site erythema		[2] 2 (1%)	[1] 1 (0.5%)	
Injection site irritation				[2] 2 (1.1%)
Injection site joint pain				[1] 1 (0.5%)
Injection site rash				[1] 1 (0.5%)
Injection site reaction		[3] 3 (1.5%)		[4] 3 (1.6%)
Malaise	[3] 2 (1%)	[6] 6 (3%)	[3] 3 (1.5%)	[1] 1 (0.5%)
Mucosal inflammation		[1] 1 (0.5%)		
Nodule		[1] 1 (0.5%)		
Oedema	[2] 2 (1%)	[1] 1 (0.5%)		
Oedema peripheral	[2] 2 (1%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1.1%)
Pain	[1] 1 (0.5%)		[2] 2 (1%)	
Peripheral swelling	[2] 2 (1%)		[1] 1 (0.5%)	

	Prolapse		[1] 1 (0.5%)		
	Pyrexia	[9] 8 (4.1%)	[13] 10 (5%)	[6] 6 (2.9%)	[2] 2 (1.1%)
	Sudden death		[1] 1 (0.5%)		
	Swelling				[1] 1 (0.5%)
	Tenderness				[1] 1 (0.5%)
	Thirst				[1] 1 (0.5%)
Hepatobiliary disorders	#Total	[1] 1 (0.5%)	[4] 2 (1%)		[2] 2 (1.1%)
	Biliary colic		[3] 2 (1%)		
	Cholecystitis		[1] 1 (0.5%)		
	Cholelithiasis				[1] 1 (0.5%)
	Drug-induced liver injury	[1] 1 (0.5%)			
	Jaundice				[1] 1 (0.5%)
Immune system disorders	#Total	[4] 4 (2%)	[3] 3 (1.5%)	[2] 2 (1%)	[2] 2 (1.1%)
	Anaphylactic reaction		[1] 1 (0.5%)		
	Hypersensitivity	[4] 4 (2%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Sarcoidosis		[1] 1 (0.5%)		[1] 1 (0.5%)
	Seasonal allergy			[1] 1 (0.5%)	

Infections and infestations	#Total	[153] 93 (47.2%)	[157] 94 (46.5%)	[181] 99 (48.5%)	[201] 107 (58.2%)
	Anal abscess	[1] 1 (0.5%)	[2] 1 (0.5%)		
	Appendicitis			[1] 1 (0.5%)	
	Borrelia infection	[2] 2 (1%)	[3] 3 (1.5%)	[3] 3 (1.5%)	[2] 2 (1.1%)
	Bronchitis	[2] 2 (1%)	[5] 3 (1.5%)	[1] 1 (0.5%)	[8] 8 (4.3%)
	Campylobacter gastroenteritis	[2] 2 (1%)			
	Conjunctivitis	[4] 2 (1%)	[1] 1 (0.5%)	[2] 2 (1%)	
	Conjunctivitis bacterial	[1] 1 (0.5%)			
	Cystitis	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1.1%)
	Dermatophytosis			[1] 1 (0.5%)	
	Diverticulitis	[1] 1 (0.5%)			
	Ear infection		[1] 1 (0.5%)		
	Epididymitis	[1] 1 (0.5%)			
	Erysipelas	[1] 1 (0.5%)			
	Escherichia urinary tract infection				[1] 1 (0.5%)
	Eye infection	[1] 1 (0.5%)	[1] 1 (0.5%)	[3] 3 (1.5%)	[2] 2 (1.1%)
	Folliculitis		[1] 1 (0.5%)		

Fungal skin infection				[2] 2 (1.1%)
Furuncle			[1] 1 (0.5%)	[3] 2 (1.1%)
Gastroenteritis	[4] 4 (2%)	[2] 2 (1%)	[4] 4 (2%)	[6] 6 (3.3%)
Gastroenteritis shigella		[1] 1 (0.5%)		
Gastroenteritis viral	[3] 3 (1.5%)	[2] 2 (1%)	[1] 1 (0.5%)	[3] 2 (1.1%)
Genital herpes	[1] 1 (0.5%)	[1] 1 (0.5%)	[5] 1 (0.5%)	[1] 1 (0.5%)
Genital infection fungal			[1] 1 (0.5%)	[2] 2 (1.1%)
Gingival abscess			[1] 1 (0.5%)	
Gingivitis		[2] 2 (1%)	[1] 1 (0.5%)	
Helicobacter gastritis	[1] 1 (0.5%)			
Helicobacter infection	[1] 1 (0.5%)		[1] 1 (0.5%)	
Herpes simplex		[5] 3 (1.5%)	[6] 3 (1.5%)	[6] 3 (1.6%)
Herpes virus infection		[2] 2 (1%)	[1] 1 (0.5%)	
Herpes zoster	[5] 5 (2.5%)	[3] 2 (1%)	[1] 1 (0.5%)	[1] 1 (0.5%)
Hordeolum	[1] 1 (0.5%)			
Impetigo	[1] 1 (0.5%)			
Infected bite		[1] 1 (0.5%)		[1] 1 (0.5%)

Infected skin ulcer	[1] 1 (0.5%)			
Infection	[2] 2 (1%)	[1] 1 (0.5%)		[1] 1 (0.5%)
Influenza	[5] 5 (2.5%)	[9] 9 (4.5%)	[17] 13 (6.4%)	[5] 5 (2.7%)
Latent tuberculosis				[1] 1 (0.5%)
Localised infection		[1] 1 (0.5%)	[1] 1 (0.5%)	[3] 3 (1.6%)
Lower respiratory tract infection	[1] 1 (0.5%)			
Lung infection			[1] 1 (0.5%)	
Mastitis			[1] 1 (0.5%)	
Nail bed infection				[2] 1 (0.5%)
Nasopharyngitis	[48] 35 (17.8%)	[38] 29 (14.4%)	[52] 38 (18.6%)	[61] 45 (24.5%)
Nipple infection				[2] 1 (0.5%)
Onychomycosis	[1] 1 (0.5%)			
Oral fungal infection	[1] 1 (0.5%)			
Oral herpes	[1] 1 (0.5%)	[2] 2 (1%)	[3] 2 (1%)	[3] 3 (1.6%)
Otitis media			[3] 2 (1%)	
Paronychia			[2] 1 (0.5%)	[1] 1 (0.5%)
Parotid abscess				[1] 1 (0.5%)

Parotitis		[1] 1 (0.5%)		
Periodontitis	[1] 1 (0.5%)			
Pharyngitis		[3] 3 (1.5%)	[1] 1 (0.5%)	[8] 8 (4.3%)
Pharyngitis streptococcal				[1] 1 (0.5%)
Pneumocystis jirovecii pneumonia		[1] 1 (0.5%)		
Pneumonia	[7] 6 (3%)	[11] 10 (5%)	[3] 3 (1.5%)	[2] 2 (1.1%)
Postoperative wound infection	[1] 1 (0.5%)			[1] 1 (0.5%)
Pulpitis dental	[1] 1 (0.5%)			
Rash pustular				[1] 1 (0.5%)
Respiratory syncytial virus infection	[1] 1 (0.5%)			
Respiratory tract infection	[2] 2 (1%)	[2] 2 (1%)	[6] 6 (2.9%)	[4] 4 (2.2%)
Rhinitis	[1] 1 (0.5%)		[1] 1 (0.5%)	[2] 2 (1.1%)
Root canal infection		[1] 1 (0.5%)		
Sebaceous gland infection	[1] 1 (0.5%)			
Sinusitis		[6] 5 (2.5%)	[3] 3 (1.5%)	[2] 2 (1.1%)
Skin infection	[1] 1 (0.5%)	[1] 1 (0.5%)		
Soft tissue infection		[1] 1 (0.5%)		

Streptococcal infection		[3] 2 (1%)		
Subcutaneous abscess				[3] 2 (1.1%)
Tinea versicolour	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1%)	[1] 1 (0.5%)
Tonsillitis	[1] 1 (0.5%)	[3] 3 (1.5%)	[2] 2 (1%)	[3] 3 (1.6%)
Tooth abscess	[1] 1 (0.5%)			
Tooth infection	[2] 2 (1%)	[2] 2 (1%)	[3] 3 (1.5%)	[5] 5 (2.7%)
Tracheitis				[1] 1 (0.5%)
Upper respiratory tract infection	[26] 19 (9.6%)	[26] 21 (10.4%)	[24] 20 (9.8%)	[34] 26 (14.1%)
Urinary tract infection	[8] 6 (3%)	[7] 6 (3%)	[14] 11 (5.4%)	[9] 7 (3.8%)
Urinary tract infection bacterial	[4] 2 (1%)		[1] 1 (0.5%)	
Varicella				[1] 1 (0.5%)
Vestibular neuronitis			[1] 1 (0.5%)	
Viral diarrhoea				[1] 1 (0.5%)
Viral infection			[2] 2 (1%)	[1] 1 (0.5%)
Viral upper respiratory tract infection			[1] 1 (0.5%)	
Vulvovaginal candidiasis			[1] 1 (0.5%)	
Vulvovaginal mycotic infection		[2] 1 (0.5%)	[1] 1 (0.5%)	

	Wound infection		[1] 1 (0.5%)		[1] 1 (0.5%)
Injury, poisoning and procedural complications	#Total	[28] 23 (11.7%)	[25] 22 (10.9%)	[16] 16 (7.8%)	[30] 21 (11.4%)
	Animal bite	[1] 1 (0.5%)			[2] 1 (0.5%)
	Ankle fracture			[1] 1 (0.5%)	
	Arthropod bite	[1] 1 (0.5%)			[2] 2 (1.1%)
	Arthropod sting	[1] 1 (0.5%)	[1] 1 (0.5%)		
	Bite	[1] 1 (0.5%)			
	Concussion	[2] 2 (1%)	[1] 1 (0.5%)		
	Contusion	[2] 2 (1%)	[2] 2 (1%)	[1] 1 (0.5%)	[2] 2 (1.1%)
	Epicondylitis		[1] 1 (0.5%)		
	Fall	[6] 5 (2.5%)	[3] 3 (1.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Foot fracture	[3] 2 (1%)		[2] 2 (1%)	
	Hip fracture			[1] 1 (0.5%)	
	Humerus fracture				[1] 1 (0.5%)
	Iliotibial band syndrome	[1] 1 (0.5%)			
	Incorrect dosage administered			[1] 1 (0.5%)	
	Incorrect dose administered		[1] 1 (0.5%)		

Infusion related reaction				[1] 1 (0.5%)
Joint dislocation		[1] 1 (0.5%)		
Joint injury	[1] 1 (0.5%)			
Ligament sprain	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1%)	[1] 1 (0.5%)
Limb injury		[3] 3 (1.5%)	[2] 2 (1%)	[3] 3 (1.6%)
Lower limb fracture		[1] 1 (0.5%)		
Nail injury				[1] 1 (0.5%)
Patella fracture		[1] 1 (0.5%)		
Post procedural inflammation	[1] 1 (0.5%)			
Post-traumatic pain				[1] 1 (0.5%)
Procedural pain				[1] 1 (0.5%)
Product use complaint	[1] 1 (0.5%)			
Radius fracture				[1] 1 (0.5%)
Rib fracture			[2] 2 (1%)	
Road traffic accident				[2] 2 (1.1%)
Skin abrasion				[3] 2 (1.1%)
Skin wound	[1] 1 (0.5%)	[3] 3 (1.5%)		[3] 3 (1.6%)

	Spinal fracture	[1] 1 (0.5%)			
	Stress fracture	[1] 1 (0.5%)			
	Sunburn		[1] 1 (0.5%)		
	Tendon rupture				[2] 1 (0.5%)
	Thermal burn		[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Toxicity to various agents				[1] 1 (0.5%)
	Traumatic haematoma	[2] 2 (1%)	[2] 2 (1%)		
	Upper limb fracture		[1] 1 (0.5%)		
	Wound			[1] 1 (0.5%)	[1] 1 (0.5%)
	Wrist fracture	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	
Investigations	#Total	[47] 37 (18.8%)	[67] 47 (23.3%)	[78] 49 (24%)	[120] 74 (40.2%)
	Alanine aminotransferase increased	[17] 14 (7.1%)	[35] 29 (14.4%)	[42] 28 (13.7%)	[55] 39 (21.2%)
	Angiocardiogram				[1] 1 (0.5%)
	Aspartate aminotransferase increased		[1] 1 (0.5%)	[2] 2 (1%)	[2] 2 (1.1%)
	Biopsy lung				[1] 1 (0.5%)
	Biopsy prostate			[1] 1 (0.5%)	
	Blood alkaline phosphatase increased			[2] 2 (1%)	

Blood bilirubin increased			[1] 1 (0.5%)	[3] 3 (1.6%)
Blood calcium increased			[1] 1 (0.5%)	
Blood cholesterol increased				[2] 2 (1.1%)
Blood creatinine decreased				[1] 1 (0.5%)
Blood creatinine increased	[1] 1 (0.5%)		[1] 1 (0.5%)	[2] 2 (1.1%)
Blood glucose increased	[1] 1 (0.5%)			
Blood iron decreased	[1] 1 (0.5%)		[1] 1 (0.5%)	
Blood lactate dehydrogenase increased			[1] 1 (0.5%)	
Blood parathyroid hormone increased			[1] 1 (0.5%)	
Blood pressure decreased		[1] 1 (0.5%)		
Blood pressure increased	[1] 1 (0.5%)	[3] 3 (1.5%)		[1] 1 (0.5%)
Blood thyroid stimulating hormone decreased	[1] 1 (0.5%)	[1] 1 (0.5%)		
Blood triglycerides increased				[1] 1 (0.5%)
C-reactive protein increased	[1] 1 (0.5%)	[2] 2 (1%)		
Calcium ionised increased			[1] 1 (0.5%)	
Cardiac murmur		[1] 1 (0.5%)		
Chest X-ray abnormal			[2] 2 (1%)	

Culture positive			[1] 1 (0.5%)	
Gamma-glutamyltransferase increased	[1] 1 (0.5%)			
Haemoglobin decreased	[3] 3 (1.5%)	[2] 2 (1%)	[1] 1 (0.5%)	[1] 1 (0.5%)
Hepatic enzyme increased	[9] 9 (4.6%)	[13] 12 (5.9%)	[7] 7 (3.4%)	[23] 17 (9.2%)
Investigation		[1] 1 (0.5%)		
Lipids increased			[1] 1 (0.5%)	[2] 2 (1.1%)
Mean cell volume increased				[1] 1 (0.5%)
Neutrophil count decreased			[1] 1 (0.5%)	[1] 1 (0.5%)
Platelet count decreased	[1] 1 (0.5%)		[1] 1 (0.5%)	[2] 2 (1.1%)
Platelet count increased		[1] 1 (0.5%)		
Prostatic specific antigen increased			[1] 1 (0.5%)	
Red blood cell sedimentation rate increased	[1] 1 (0.5%)	[1] 1 (0.5%)		
Scan myocardial perfusion				[1] 1 (0.5%)
Smear cervix				[1] 1 (0.5%)
Smear cervix abnormal		[1] 1 (0.5%)		
Transaminases increased	[4] 3 (1.5%)	[2] 2 (1%)	[5] 5 (2.5%)	[9] 8 (4.3%)

	Urine analysis abnormal	[2] 2 (1%)			
	Weight decreased		[1] 1 (0.5%)		[3] 3 (1.6%)
	Weight increased	[3] 3 (1.5%)		[1] 1 (0.5%)	[2] 2 (1.1%)
	White blood cell count decreased			[2] 2 (1%)	[5] 5 (2.7%)
	White blood cell count increased		[1] 1 (0.5%)		
	White blood cells urine positive			[1] 1 (0.5%)	
Metabolism and nutrition disorders	#Total	[6] 5 (2.5%)	[3] 3 (1.5%)	[6] 6 (2.9%)	[8] 7 (3.8%)
	Decreased appetite	[3] 3 (1.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1.1%)
	Diabetes mellitus inadequate control	[2] 1 (0.5%)			
	Fluid retention		[1] 1 (0.5%)	[1] 1 (0.5%)	
	Hypercalcaemia			[1] 1 (0.5%)	
	Hypercholesterolaemia				[2] 2 (1.1%)
	Hyperlipidaemia		[1] 1 (0.5%)		[1] 1 (0.5%)
	Hypertriglyceridaemia				[1] 1 (0.5%)
	Hypokalaemia			[1] 1 (0.5%)	
	Increased appetite			[1] 1 (0.5%)	
	Type 2 diabetes mellitus	[1] 1 (0.5%)			

	Vitamin B12 deficiency				[2] 2 (1.1%)
	Vitamin D deficiency			[1] 1 (0.5%)	
Musculoskeletal and connective tissue disorders	#Total	[54] 35 (17.8%)	[35] 28 (13.9%)	[45] 33 (16.2%)	[29] 23 (12.5%)
	Arthralgia	[4] 4 (2%)		[3] 3 (1.5%)	[4] 3 (1.6%)
	Arthritis	[1] 1 (0.5%)			
	Arthropathy		[1] 1 (0.5%)		
	Back pain	[5] 4 (2%)	[5] 5 (2.5%)	[9] 8 (3.9%)	[4] 4 (2.2%)
	Bursitis	[2] 2 (1%)	[1] 1 (0.5%)		
	Enthesopathy			[1] 1 (0.5%)	
	Exostosis	[1] 1 (0.5%)			[1] 1 (0.5%)
	Groin pain			[1] 1 (0.5%)	[1] 1 (0.5%)
	Intervertebral disc compression	[1] 1 (0.5%)			
	Intervertebral disc protrusion		[1] 1 (0.5%)		
	Joint lock		[1] 1 (0.5%)		
	Joint swelling	[1] 1 (0.5%)			[1] 1 (0.5%)
	Muscle spasms	[3] 3 (1.5%)	[4] 3 (1.5%)	[6] 6 (2.9%)	[7] 6 (3.3%)
	Muscle twitching	[1] 1 (0.5%)		[1] 1 (0.5%)	

Muscular weakness			[1] 1 (0.5%)	
Musculoskeletal pain	[4] 4 (2%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
Musculoskeletal stiffness	[1] 1 (0.5%)	[1] 1 (0.5%)	[4] 4 (2%)	
Myalgia	[7] 7 (3.6%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1.1%)
Neck pain		[3] 3 (1.5%)	[4] 4 (2%)	
Osteitis		[3] 2 (1%)	[1] 1 (0.5%)	
Osteoarthritis	[1] 1 (0.5%)		[1] 1 (0.5%)	[1] 1 (0.5%)
Osteopenia	[2] 2 (1%)		[1] 1 (0.5%)	
Osteoporosis	[3] 3 (1.5%)	[3] 3 (1.5%)		[1] 1 (0.5%)
Pain in extremity	[2] 2 (1%)	[3] 3 (1.5%)	[4] 4 (2%)	[2] 2 (1.1%)
Pain in jaw	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
Rheumatoid arthritis	[8] 5 (2.5%)		[1] 1 (0.5%)	[1] 1 (0.5%)
Rheumatoid nodule		[1] 1 (0.5%)		
Rotator cuff syndrome	[1] 1 (0.5%)		[1] 1 (0.5%)	
Spondylitis			[1] 1 (0.5%)	
Synovial cyst	[1] 1 (0.5%)	[1] 1 (0.5%)		[1] 1 (0.5%)
Tendon discomfort	[3] 2 (1%)			

	Tendon disorder	[1] 1 (0.5%)			
	Tendonitis		[3] 3 (1.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Torticollis			[1] 1 (0.5%)	
	Trismus		[1] 1 (0.5%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	#Total	[3] 3 (1.5%)	[5] 5 (2.5%)	[3] 3 (1.5%)	[6] 6 (3.3%)
	Anal cancer				[1] 1 (0.5%)
	Basal cell carcinoma		[1] 1 (0.5%)	[1] 1 (0.5%)	
	Breast cancer		[1] 1 (0.5%)		
	Colon adenoma				[1] 1 (0.5%)
	Ependymoma	[1] 1 (0.5%)			
	Lentigo maligna				[1] 1 (0.5%)
	Malignant melanoma			[1] 1 (0.5%)	[1] 1 (0.5%)
	Monoclonal gammopathy			[1] 1 (0.5%)	
	Neoplasm progression	[1] 1 (0.5%)			
	Oesophageal carcinoma		[1] 1 (0.5%)		
	Papillary thyroid cancer				[1] 1 (0.5%)
	Prostate cancer	[1] 1 (0.5%)	[1] 1 (0.5%)		[1] 1 (0.5%)

	Seborrhoeic keratosis		[1] 1 (0.5%)		
Nervous system disorders	#Total	[65] 41 (20.8%)	[58] 39 (19.3%)	[45] 37 (18.1%)	[37] 29 (15.8%)
	Anosmia				[1] 1 (0.5%)
	Balance disorder	[1] 1 (0.5%)		[1] 1 (0.5%)	[1] 1 (0.5%)
	Burning sensation		[1] 1 (0.5%)		
	Carotid artery dissection		[1] 1 (0.5%)		
	Carpal tunnel syndrome		[2] 2 (1%)		[1] 1 (0.5%)
	Cerebral infarction	[1] 1 (0.5%)			
	Cerebrovascular accident		[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Dementia			[1] 1 (0.5%)	
	Depressed level of consciousness		[2] 1 (0.5%)		
	Dizziness	[15] 12 (6.1%)	[16] 12 (5.9%)	[8] 8 (3.9%)	[8] 7 (3.8%)
	Dizziness postural		[1] 1 (0.5%)		
	Dysgeusia	[4] 4 (2%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Facial paralysis	[1] 1 (0.5%)			
	Head discomfort			[1] 1 (0.5%)	[1] 1 (0.5%)

Headache	[28] 17 (8.6%)	[20] 19 (9.4%)	[21] 17 (8.3%)	[13] 12 (6.5%)
Hypoaesthesia		[4] 4 (2%)	[3] 3 (1.5%)	
Lethargy		[1] 1 (0.5%)		
Loss of proprioception				[1] 1 (0.5%)
Memory impairment				[1] 1 (0.5%)
Migraine	[4] 4 (2%)		[1] 1 (0.5%)	[1] 1 (0.5%)
Migraine with aura				[1] 1 (0.5%)
Morton's neuralgia			[1] 1 (0.5%)	
Multiple sclerosis		[1] 1 (0.5%)		
Muscle contractions involuntary		[1] 1 (0.5%)		
Neuralgia	[1] 1 (0.5%)			
Neurological symptom			[1] 1 (0.5%)	
Paraesthesia	[1] 1 (0.5%)		[2] 2 (1%)	[2] 2 (1.1%)
Poor quality sleep	[1] 1 (0.5%)			
Presyncope	[1] 1 (0.5%)			[1] 1 (0.5%)
Sciatica	[2] 2 (1%)			
Syncope	[1] 1 (0.5%)	[5] 2 (1%)		[1] 1 (0.5%)

	Taste disorder	[1] 1 (0.5%)		[1] 1 (0.5%)	[1] 1 (0.5%)
	Tension headache			[1] 1 (0.5%)	
	Transient global amnesia		[1] 1 (0.5%)		
	Tremor	[3] 3 (1.5%)		[1] 1 (0.5%)	[1] 1 (0.5%)
Pregnancy, puerperium and perinatal conditions	#Total			[1] 1 (0.5%)	[5] 2 (1.1%)
	Abortion spontaneous				[2] 2 (1.1%)
	Pregnancy			[1] 1 (0.5%)	[3] 2 (1.1%)
Product issues	#Total	[1] 1 (0.5%)			
	Needle issue	[1] 1 (0.5%)			
Psychiatric disorders	#Total	[18] 17 (8.6%)	[15] 15 (7.4%)	[7] 6 (2.9%)	[11] 11 (6%)
	Adjustment disorder with mixed anxiety and depressed mood			[1] 1 (0.5%)	
	Agitation	[2] 2 (1%)			
	Anxiety		[5] 5 (2.5%)	[1] 1 (0.5%)	
	Confusional state	[1] 1 (0.5%)			
	Depressed mood		[3] 3 (1.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Depression	[2] 2 (1%)			[3] 3 (1.6%)

	Emotional distress				[1] 1 (0.5%)
	Insomnia	[8] 8 (4.1%)	[3] 3 (1.5%)		[3] 3 (1.6%)
	Mental fatigue		[1] 1 (0.5%)		
	Mood altered	[2] 2 (1%)			
	Mood swings	[1] 1 (0.5%)			
	Nervousness				[1] 1 (0.5%)
	Nightmare			[1] 1 (0.5%)	
	Panic attack			[1] 1 (0.5%)	[1] 1 (0.5%)
	Psychiatric symptom		[1] 1 (0.5%)		
	Psychotic disorder	[1] 1 (0.5%)			
	Sleep disorder		[2] 2 (1%)	[2] 2 (1%)	
	Stress				[1] 1 (0.5%)
	Terminal insomnia	[1] 1 (0.5%)			
Renal and urinary disorders	#Total	[5] 5 (2.5%)	[1] 1 (0.5%)	[4] 4 (2%)	[3] 3 (1.6%)
	Chromaturia	[1] 1 (0.5%)			
	Dysuria	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1.1%)
	Haematuria	[3] 3 (1.5%)		[1] 1 (0.5%)	[1] 1 (0.5%)

	Renal mass			[1] 1 (0.5%)	
	Urinary incontinence			[1] 1 (0.5%)	
Reproductive system and breast disorders	#Total	[6] 6 (3%)	[6] 5 (2.5%)	[7] 6 (2.9%)	[4] 4 (2.2%)
	Balanoposthitis		[1] 1 (0.5%)		
	Benign prostatic hyperplasia	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	
	Breast mass				[1] 1 (0.5%)
	Erectile dysfunction			[1] 1 (0.5%)	
	Genital blister	[1] 1 (0.5%)			
	Genital swelling				[1] 1 (0.5%)
	Hypomenorrhoea			[1] 1 (0.5%)	
	Menorrhagia				[1] 1 (0.5%)
	Menstrual discomfort	[1] 1 (0.5%)			
	Menstrual disorder		[1] 1 (0.5%)		
	Metrorrhagia		[1] 1 (0.5%)	[1] 1 (0.5%)	
	Ovarian cyst	[1] 1 (0.5%)			
	Prostatic disorder		[1] 1 (0.5%)		
	Uterine polyp			[1] 1 (0.5%)	

	Vaginal cyst			[1] 1 (0.5%)	
	Vaginal discharge		[1] 1 (0.5%)		
	Vaginal haemorrhage	[2] 2 (1%)			
	Vulvovaginal dryness			[1] 1 (0.5%)	
	Vulvovaginal pruritus				[1] 1 (0.5%)
Respiratory, thoracic and mediastinal disorders	#Total	[28] 23 (11.7%)	[40] 33 (16.3%)	[30] 25 (12.3%)	[45] 35 (19%)
	Alveolitis		[1] 1 (0.5%)		
	Asthma	[1] 1 (0.5%)	[1] 1 (0.5%)		
	Bronchitis chronic			[1] 1 (0.5%)	
	Chronic obstructive pulmonary disease				[2] 1 (0.5%)
	Cough	[8] 8 (4.1%)	[10] 10 (5%)	[9] 9 (4.4%)	[10] 10 (5.4%)
	Dysphonia		[2] 1 (0.5%)		[1] 1 (0.5%)
	Dyspnoea	[7] 7 (3.6%)	[6] 6 (3%)	[5] 5 (2.5%)	[3] 3 (1.6%)
	Dyspnoea exertional		[1] 1 (0.5%)		
	Epistaxis	[3] 3 (1.5%)	[3] 3 (1.5%)	[1] 1 (0.5%)	[2] 2 (1.1%)
	Hyperactive pharyngeal reflex			[1] 1 (0.5%)	

Hypersensitivity pneumonitis		[1] 1 (0.5%)		[1] 1 (0.5%)
Increased viscosity of upper respiratory secretion		[1] 1 (0.5%)		
Interstitial lung disease		[2] 2 (1%)		[1] 1 (0.5%)
Nasal congestion			[2] 2 (1%)	[3] 3 (1.6%)
Nasal discomfort	[3] 3 (1.5%)			[4] 3 (1.6%)
Nasal septum ulceration		[1] 1 (0.5%)		
Nasal ulcer				[3] 3 (1.6%)
Oropharyngeal pain		[5] 5 (2.5%)	[4] 4 (2%)	[7] 5 (2.7%)
Painful respiration			[1] 1 (0.5%)	
Pneumonitis	[1] 1 (0.5%)			
Productive cough	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1.1%)
Pulmonary embolism	[2] 2 (1%)			[1] 1 (0.5%)
Pulmonary fibrosis		[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
Respiratory disorder		[1] 1 (0.5%)		
Respiratory failure		[1] 1 (0.5%)		
Respiratory tract haemorrhage	[1] 1 (0.5%)			
Respiratory tract irritation		[1] 1 (0.5%)		

	Rhinitis allergic			[1] 1 (0.5%)	[1] 1 (0.5%)
	Sneezing			[1] 1 (0.5%)	
	Snoring		[1] 1 (0.5%)		
	Throat irritation	[1] 1 (0.5%)			
	Throat lesion				[2] 2 (1.1%)
	Throat tightness			[2] 2 (1%)	
	Tonsillar hypertrophy				[1] 1 (0.5%)
Skin and subcutaneous tissue disorders	#Total	[69] 48 (24.4%)	[65] 47 (23.3%)	[42] 34 (16.7%)	[93] 62 (33.7%)
	Acne	[1] 1 (0.5%)	[2] 2 (1%)	[1] 1 (0.5%)	
	Actinic keratosis	[1] 1 (0.5%)			
	Alopecia	[16] 15 (7.6%)	[13] 13 (6.4%)	[10] 10 (4.9%)	[18] 18 (9.8%)
	Blister		[5] 2 (1%)	[3] 3 (1.5%)	[7] 5 (2.7%)
	Dermatitis	[2] 2 (1%)	[2] 2 (1%)		
	Dermatitis allergic			[1] 1 (0.5%)	
	Dermatitis psoriasiform			[1] 1 (0.5%)	
	Dry skin	[1] 1 (0.5%)			[2] 2 (1.1%)
	Ecchymosis	[1] 1 (0.5%)			[1] 1 (0.5%)

Eczema	[1] 1 (0.5%)			[3] 3 (1.6%)
Erythema	[4] 4 (2%)	[2] 2 (1%)	[2] 2 (1%)	[3] 3 (1.6%)
Guttate psoriasis		[1] 1 (0.5%)		
Hair colour changes		[1] 1 (0.5%)		
Hyperhidrosis	[3] 3 (1.5%)	[2] 2 (1%)		[1] 1 (0.5%)
Ingrowing nail				[1] 1 (0.5%)
Melanoderma	[1] 1 (0.5%)			
Nail disorder	[1] 1 (0.5%)			
Night sweats	[2] 2 (1%)	[1] 1 (0.5%)		[1] 1 (0.5%)
Pain of skin	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	
Palmar erythema			[1] 1 (0.5%)	
Perioral dermatitis		[2] 2 (1%)		
Photosensitivity reaction	[1] 1 (0.5%)			[3] 3 (1.6%)
Pityriasis lichenoides et varioliformis acuta		[1] 1 (0.5%)		
Pruritus	[3] 3 (1.5%)	[2] 2 (1%)	[2] 1 (0.5%)	[9] 8 (4.3%)
Psoriasis	[1] 1 (0.5%)			
Purpura		[1] 1 (0.5%)		[1] 1 (0.5%)

	Rash	[16] 13 (6.6%)	[21] 17 (8.4%)	[17] 15 (7.4%)	[26] 22 (12%)
	Rash erythematous	[1] 1 (0.5%)	[1] 1 (0.5%)		[2] 1 (0.5%)
	Rash macular	[1] 1 (0.5%)			
	Rash papular		[1] 1 (0.5%)		
	Rash pruritic	[1] 1 (0.5%)			[5] 3 (1.6%)
	Sebaceous gland disorder				[1] 1 (0.5%)
	Sensitive skin		[1] 1 (0.5%)		
	Skin atrophy		[1] 1 (0.5%)		
	Skin discolouration				[1] 1 (0.5%)
	Skin fissures		[1] 1 (0.5%)		
	Skin hyperpigmentation				[1] 1 (0.5%)
	Skin lesion	[2] 2 (1%)		[1] 1 (0.5%)	[3] 2 (1.1%)
	Skin ulcer	[1] 1 (0.5%)			[1] 1 (0.5%)
	Solar dermatitis			[1] 1 (0.5%)	[1] 1 (0.5%)
	Urticaria	[6] 5 (2.5%)	[3] 3 (1.5%)	[1] 1 (0.5%)	[2] 1 (0.5%)
	Vasculitic rash	[1] 1 (0.5%)			
Social circumstances	#Total	[1] 1 (0.5%)			[1] 1 (0.5%)

	Physical abuse				[1] 1 (0.5%)
	Stress at work	[1] 1 (0.5%)			
Surgical and medical procedures	#Total	[12] 10 (5.1%)	[2] 2 (1%)	[12] 11 (5.4%)	[13] 12 (6.5%)
	Breast prosthesis removal			[1] 1 (0.5%)	
	Bunion operation			[1] 1 (0.5%)	
	Carpal tunnel decompression				[1] 1 (0.5%)
	Cataract operation	[4] 3 (1.5%)		[3] 2 (1%)	
	Dental care			[1] 1 (0.5%)	[1] 1 (0.5%)
	Dental implantation	[1] 1 (0.5%)			
	Dental operation				[1] 1 (0.5%)
	Endodontic procedure				[2] 2 (1.1%)
	Hysterectomy	[1] 1 (0.5%)			
	Inguinal hernia repair			[1] 1 (0.5%)	
	Joint surgery	[1] 1 (0.5%)			
	Knee arthroplasty	[1] 1 (0.5%)			
	Knee operation				[1] 1 (0.5%)
	Limb operation				[1] 1 (0.5%)

	Lipoma excision	[1] 1 (0.5%)	[1] 1 (0.5%)		
	Meniscus operation				[1] 1 (0.5%)
	Parathyroidectomy	[1] 1 (0.5%)			
	Post procedural drainage				[1] 1 (0.5%)
	Radical mastectomy		[1] 1 (0.5%)		
	Rehabilitation therapy	[1] 1 (0.5%)		[3] 3 (1.5%)	[1] 1 (0.5%)
	Rheumatoid nodule removal			[1] 1 (0.5%)	
	Thyroidectomy	[1] 1 (0.5%)			
	Toe operation			[1] 1 (0.5%)	
	Tooth extraction				[2] 2 (1.1%)
	Wisdom teeth removal				[1] 1 (0.5%)
Vascular disorders	#Total	[10] 9 (4.6%)	[13] 13 (6.4%)	[11] 11 (5.4%)	[12] 12 (6.5%)
	Aortic aneurysm	[1] 1 (0.5%)			
	Deep vein thrombosis		[1] 1 (0.5%)		
	Flushing	[1] 1 (0.5%)	[2] 2 (1%)		
	Haematoma		[2] 2 (1%)	[1] 1 (0.5%)	[2] 2 (1.1%)
	Hot flush	[4] 3 (1.5%)		[2] 2 (1%)	[2] 2 (1.1%)

	Hypertension	[4] 4 (2%)	[7] 7 (3.5%)	[5] 5 (2.5%)	[7] 7 (3.8%)
	Hypotension			[1] 1 (0.5%)	
	Poor peripheral circulation				[1] 1 (0.5%)
	Thrombophlebitis		[1] 1 (0.5%)	[1] 1 (0.5%)	
	Vasculitis			[1] 1 (0.5%)	
NA	#Total	[23] 23 (11.7%)	[21] 21 (10.4%)	[29] 29 (14.2%)	[6] 6 (3.3%)

4.9.3 Table S26. Adverse Events of Special Interest by System Organ Class and Preferred term

System Organ Class	Preferred Term	ACT (N=197)	CZP + MTX (N=202)	ABA + MTX (N=204)	TCZ + MTX (N=184)
Cardiac disorders	Angina pectoris		[1] 1 (0.5%)		[1] 1 (0.5%)
	Arrhythmia			[2] 2 (1%)	
	Atrial fibrillation	[2] 2 (1%)	[2] 2 (1%)	[3] 3 (1.5%)	
	Cardiac failure		[1] 1 (0.5%)		[1] 1 (0.5%)
	Cardiac flutter			[1] 1 (0.5%)	
	Extrasystoles			[1] 1 (0.5%)	
	Palpitations	[1] 1 (0.5%)	[3] 3 (1.5%)	[6] 6 (2.9%)	[4] 4 (2.2%)
	Pericarditis			[2] 2 (1%)	
	Tachycardia	[1] 1 (0.5%)	[2] 2 (1%)	[1] 1 (0.5%)	[1] 1 (0.5%)

Eye disorders	Cataract	[2] 2 (1%)			[1] 1 (0.5%)
Infections and infestations	Anal abscess	[1] 1 (0.5%)	[2] 1 (0.5%)		
	Appendicitis			[1] 1 (0.5%)	
	Borrelia infection	[2] 2 (1%)	[3] 3 (1.5%)	[3] 3 (1.5%)	[2] 2 (1.1%)
	Bronchitis	[2] 2 (1%)	[5] 3 (1.5%)	[1] 1 (0.5%)	[8] 8 (4.3%)
	Campylobacter gastroenteritis	[2] 2 (1%)			
	Conjunctivitis	[4] 2 (1%)	[1] 1 (0.5%)	[2] 2 (1%)	
	Conjunctivitis bacterial	[1] 1 (0.5%)			
	Cystitis	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1.1%)
	Dermatophytosis			[1] 1 (0.5%)	
	Diverticulitis	[1] 1 (0.5%)			
	Ear infection		[1] 1 (0.5%)		
	Epididymitis	[1] 1 (0.5%)			
	Erysipelas	[1] 1 (0.5%)			
	Escherichia urinary tract infection				[1] 1 (0.5%)
	Eye infection	[1] 1 (0.5%)	[1] 1 (0.5%)	[3] 3 (1.5%)	[2] 2 (1.1%)
	Folliculitis		[1] 1 (0.5%)		

Fungal skin infection				[2] 2 (1.1%)
Furuncle			[1] 1 (0.5%)	[3] 2 (1.1%)
Gastroenteritis	[4] 4 (2%)	[2] 2 (1%)	[4] 4 (2%)	[6] 6 (3.3%)
Gastroenteritis shigella		[1] 1 (0.5%)		
Gastroenteritis viral	[3] 3 (1.5%)	[2] 2 (1%)	[1] 1 (0.5%)	[3] 2 (1.1%)
Genital herpes	[1] 1 (0.5%)	[1] 1 (0.5%)	[5] 1 (0.5%)	[1] 1 (0.5%)
Genital infection fungal			[1] 1 (0.5%)	[2] 2 (1.1%)
Gingival abscess			[1] 1 (0.5%)	
Gingivitis		[2] 2 (1%)	[1] 1 (0.5%)	
Helicobacter gastritis	[1] 1 (0.5%)			
Helicobacter infection	[1] 1 (0.5%)		[1] 1 (0.5%)	
Herpes simplex		[5] 3 (1.5%)	[6] 3 (1.5%)	[6] 3 (1.6%)
Herpes virus infection		[2] 2 (1%)	[1] 1 (0.5%)	
Herpes zoster	[5] 5 (2.5%)	[3] 2 (1%)	[1] 1 (0.5%)	[1] 1 (0.5%)
Hordeolum	[1] 1 (0.5%)			
Impetigo	[1] 1 (0.5%)			
Infected bite		[1] 1 (0.5%)		[1] 1 (0.5%)

Infected skin ulcer	[1] 1 (0.5%)			
Infection	[2] 2 (1%)	[1] 1 (0.5%)		[1] 1 (0.5%)
Influenza	[5] 5 (2.5%)	[9] 9 (4.5%)	[17] 13 (6.4%)	[5] 5 (2.7%)
Latent tuberculosis				[1] 1 (0.5%)
Localised infection		[1] 1 (0.5%)	[1] 1 (0.5%)	[3] 3 (1.6%)
Lower respiratory tract infection	[1] 1 (0.5%)			
Lung infection			[1] 1 (0.5%)	
Mastitis			[1] 1 (0.5%)	
Nail bed infection				[2] 1 (0.5%)
Nasopharyngitis	[48] 35 (17.8%)	[38] 29 (14.4%)	[52] 38 (18.6%)	[61] 45 (24.5%)
Nipple infection				[2] 1 (0.5%)
Onychomycosis	[1] 1 (0.5%)			
Oral fungal infection	[1] 1 (0.5%)			
Oral herpes	[1] 1 (0.5%)	[2] 2 (1%)	[3] 2 (1%)	[3] 3 (1.6%)
Otitis media			[3] 2 (1%)	
Paronychia			[2] 1 (0.5%)	[1] 1 (0.5%)
Parotid abscess				[1] 1 (0.5%)

Parotitis		[1] 1 (0.5%)		
Periodontitis	[1] 1 (0.5%)			
Pharyngitis		[3] 3 (1.5%)	[1] 1 (0.5%)	[8] 8 (4.3%)
Pharyngitis streptococcal				[1] 1 (0.5%)
Pneumocystis jirovecii pneumonia		[1] 1 (0.5%)		
Pneumonia	[7] 6 (3%)	[11] 10 (5%)	[3] 3 (1.5%)	[2] 2 (1.1%)
Postoperative wound infection	[1] 1 (0.5%)			[1] 1 (0.5%)
Pulpitis dental	[1] 1 (0.5%)			
Rash pustular				[1] 1 (0.5%)
Respiratory syncytial virus infection	[1] 1 (0.5%)			
Respiratory tract infection	[2] 2 (1%)	[2] 2 (1%)	[6] 6 (2.9%)	[4] 4 (2.2%)
Rhinitis	[1] 1 (0.5%)		[1] 1 (0.5%)	[2] 2 (1.1%)
Root canal infection		[1] 1 (0.5%)		
Sebaceous gland infection	[1] 1 (0.5%)			
Sinusitis		[6] 5 (2.5%)	[3] 3 (1.5%)	[2] 2 (1.1%)
Skin infection	[1] 1 (0.5%)	[1] 1 (0.5%)		

Soft tissue infection		[1] 1 (0.5%)		
Streptococcal infection		[3] 2 (1%)		
Subcutaneous abscess				[3] 2 (1.1%)
Tinea versicolour	[1] 1 (0.5%)	[1] 1 (0.5%)	[2] 2 (1%)	[1] 1 (0.5%)
Tonsillitis	[1] 1 (0.5%)	[3] 3 (1.5%)	[2] 2 (1%)	[3] 3 (1.6%)
Tooth abscess	[1] 1 (0.5%)			
Tooth infection	[2] 2 (1%)	[2] 2 (1%)	[3] 3 (1.5%)	[5] 5 (2.7%)
Tracheitis				[1] 1 (0.5%)
Upper respiratory tract infection	[26] 19 (9.6%)	[26] 21 (10.4%)	[24] 20 (9.8%)	[34] 26 (14.1%)
Urinary tract infection	[8] 6 (3%)	[7] 6 (3%)	[14] 11 (5.4%)	[9] 7 (3.8%)
Urinary tract infection bacterial	[4] 2 (1%)		[1] 1 (0.5%)	
Varicella				[1] 1 (0.5%)
Vestibular neuronitis			[1] 1 (0.5%)	
Viral diarrhoea				[1] 1 (0.5%)
Viral infection			[2] 2 (1%)	[1] 1 (0.5%)
Viral upper respiratory tract infection			[1] 1 (0.5%)	

	Vulvovaginal candidiasis			[1] 1 (0.5%)	
	Vulvovaginal mycotic infection		[2] 1 (0.5%)	[1] 1 (0.5%)	
	Wound infection		[1] 1 (0.5%)		[1] 1 (0.5%)
Investigations	Weight increased	[3] 3 (1.5%)		[1] 1 (0.5%)	[2] 2 (1.1%)
Metabolism and nutrition disorders	Diabetes mellitus inadequate control	[2] 1 (0.5%)			
	Type 2 diabetes mellitus	[1] 1 (0.5%)			
Musculoskeletal and connective tissue disorders	Osteoporosis	[3] 3 (1.5%)	[3] 3 (1.5%)		[1] 1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Anal cancer				[1] 1 (0.5%)
	Basal cell carcinoma		[1] 1 (0.5%)	[1] 1 (0.5%)	
	Breast cancer		[1] 1 (0.5%)		
	Colon adenoma				[1] 1 (0.5%)
	Ependymoma	[1] 1 (0.5%)			
	Lentigo maligna				[1] 1 (0.5%)
	Malignant melanoma			[1] 1 (0.5%)	[1] 1 (0.5%)
	Monoclonal gammopathy			[1] 1 (0.5%)	
	Neoplasm progression	[1] 1 (0.5%)			

	Oesophageal carcinoma		[1] 1 (0.5%)		
	Papillary thyroid cancer				[1] 1 (0.5%)
	Prostate cancer	[1] 1 (0.5%)	[1] 1 (0.5%)		[1] 1 (0.5%)
	Seborrhoeic keratosis		[1] 1 (0.5%)		
Nervous system disorders	Multiple sclerosis		[1] 1 (0.5%)		
Surgical and medical procedures	Cataract operation	[4] 3 (1.5%)		[3] 2 (1%)	
Vascular disorders	Deep vein thrombosis		[1] 1 (0.5%)		

4.9.4 Table S27. Serious Adverse Events by System Organ Class and Preferred term

System Organ Class	Preferred Term	ACT (N=197)	CZP + MTX (N=202)	ABA + MTX (N=204)	TCZ + MTX (N=184)
Blood and lymphatic system disorders	#Total	[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)	
	Anaemia	[1] 1 (0.5%)		[1] 1 (0.5%)	
	Bone marrow failure		[1] 1 (0.5%)		
Cardiac disorders	#Total	[1] 1 (0.5%)		[2] 2 (1%)	
	Atrial fibrillation	[1] 1 (0.5%)		[1] 1 (0.5%)	
	Pericarditis			[1] 1 (0.5%)	

Congenital, familial and genetic disorders	#Total	[1] 1 (0.5%)			
	Diverticulitis Meckel's	[1] 1 (0.5%)			
Eye disorders	#Total		[1] 1 (0.5%)		
	Retinal detachment		[1] 1 (0.5%)		
Gastrointestinal disorders	#Total		[1] 1 (0.5%)	[2] 2 (1%)	
	Diarrhoea haemorrhagic			[1] 1 (0.5%)	
	Enterocolitis		[1] 1 (0.5%)		
	Haemorrhoidal haemorrhage			[1] 1 (0.5%)	
General disorders and administration site conditions	#Total		[4] 4 (2%)		
	Chest pain		[1] 1 (0.5%)		
	Death		[1] 1 (0.5%)		
	Pyrexia		[1] 1 (0.5%)		
	Sudden death		[1] 1 (0.5%)		
Hepatobiliary disorders	#Total		[1] 1 (0.5%)		
	Cholecystitis		[1] 1 (0.5%)		
Immune system disorders	#Total		[2] 2 (1%)		[1] 1 (0.5%)

	Anaphylactic reaction		[1] 1 (0.5%)		
	Sarcoidosis		[1] 1 (0.5%)		[1] 1 (0.5%)
Infections and infestations	#Total	[6] 6 (3%)	[4] 4 (2%)	[2] 2 (1%)	[3] 3 (1.6%)
	Anal abscess	[1] 1 (0.5%)			
	Appendicitis			[1] 1 (0.5%)	
	Cystitis				[1] 1 (0.5%)
	Epididymitis	[1] 1 (0.5%)			
	Helicobacter gastritis	[1] 1 (0.5%)			
	Oral herpes			[1] 1 (0.5%)	
	Parotitis		[1] 1 (0.5%)		
	Pneumocystis jirovecii pneumonia		[1] 1 (0.5%)		
	Pneumonia	[1] 1 (0.5%)	[2] 2 (1%)		[1] 1 (0.5%)
	Respiratory syncytial virus infection	[1] 1 (0.5%)			
	Tracheitis				[1] 1 (0.5%)
	Upper respiratory tract infection	[1] 1 (0.5%)			

Injury, poisoning and procedural complications	#Total	[1] 1 (0.5%)	[2] 2 (1%)	[2] 2 (1%)	[1] 1 (0.5%)
	Concussion		[1] 1 (0.5%)		
	Foot fracture			[1] 1 (0.5%)	
	Hip fracture			[1] 1 (0.5%)	
	Lower limb fracture		[1] 1 (0.5%)		
	Spinal fracture	[1] 1 (0.5%)			
	Tendon rupture				[1] 1 (0.5%)
Metabolism and nutrition disorders	#Total			[1] 1 (0.5%)	
	Hypokalaemia			[1] 1 (0.5%)	
Musculoskeletal and connective tissue disorders	#Total	[2] 2 (1%)			[1] 1 (0.5%)
	Arthralgia				[1] 1 (0.5%)
	Arthritis	[1] 1 (0.5%)			
	Rheumatoid arthritis	[1] 1 (0.5%)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	#Total	[2] 2 (1%)	[3] 3 (1.5%)	[2] 2 (1%)	[4] 4 (2.2%)
	Anal cancer				[1] 1 (0.5%)

	Basal cell carcinoma			[1] 1 (0.5%)	
	Breast cancer		[1] 1 (0.5%)		
	Ependymoma	[1] 1 (0.5%)			
	Lentigo maligna				[1] 1 (0.5%)
	Malignant melanoma			[1] 1 (0.5%)	
	Oesophageal carcinoma		[1] 1 (0.5%)		
	Papillary thyroid cancer				[1] 1 (0.5%)
	Prostate cancer	[1] 1 (0.5%)	[1] 1 (0.5%)		[1] 1 (0.5%)
Nervous system disorders	#Total	[3] 3 (1.5%)	[3] 3 (1.5%)	[4] 4 (2%)	[1] 1 (0.5%)
	Carotid artery dissection		[1] 1 (0.5%)		
	Cerebral infarction	[1] 1 (0.5%)			
	Cerebrovascular accident		[1] 1 (0.5%)	[1] 1 (0.5%)	[1] 1 (0.5%)
	Dizziness	[1] 1 (0.5%)		[1] 1 (0.5%)	
	Facial paralysis	[1] 1 (0.5%)			
	Migraine			[1] 1 (0.5%)	

	Multiple sclerosis		[1] 1 (0.5%)		
	Paraesthesia			[1] 1 (0.5%)	
Pregnancy, puerperium and perinatal conditions	#Total				[4] 2 (1.1%)
	Abortion spontaneous				[2] 2 (1.1%)
	Pregnancy				[2] 1 (0.5%)
Psychiatric disorders	#Total	[1] 1 (0.5%)		[1] 1 (0.5%)	
	Anxiety			[1] 1 (0.5%)	
	Psychotic disorder	[1] 1 (0.5%)			
Reproductive system and breast disorders	#Total		[1] 1 (0.5%)	[1] 1 (0.5%)	
	Prostatic disorder		[1] 1 (0.5%)		
	Uterine polyp			[1] 1 (0.5%)	
Respiratory, thoracic and mediastinal disorders	#Total	[2] 2 (1%)	[2] 2 (1%)		[4] 3 (1.6%)
	Chronic obstructive pulmonary disease				[1] 1 (0.5%)
	Hypersensitivity pneumonitis		[1] 1 (0.5%)		[1] 1 (0.5%)
	Interstitial lung disease				[1] 1 (0.5%)
	Pulmonary embolism	[2] 2 (1%)			[1] 1 (0.5%)

	Respiratory disorder		[1] 1 (0.5%)		
Skin and subcutaneous tissue disorders	#Total		[2] 2 (1%)		
	Dermatitis		[1] 1 (0.5%)		
	Pityriasis lichenoides et varioliformis acuta		[1] 1 (0.5%)		
Surgical and medical procedures	#Total	[3] 3 (1.5%)	[1] 1 (0.5%)	[3] 3 (1.5%)	[1] 1 (0.5%)
	Parathyroidectomy	[1] 1 (0.5%)			
	Radical mastectomy		[1] 1 (0.5%)		
	Rehabilitation therapy	[1] 1 (0.5%)		[3] 3 (1.5%)	[1] 1 (0.5%)
	Thyroidectomy	[1] 1 (0.5%)			

4.9.5 Table S28. Serious Adverse Events of Special Interest by System Organ Class and Preferred term

System Organ Class	Preferred Term	ACT (N=197)	CZP + MTX (N=202)	ABA + MTX (N=204)	TCZ + MTX (N=184)
Cardiac disorders	Atrial fibrillation	[1] 1 (0.5%)		[1] 1 (0.5%)	
	Pericarditis			[1] 1 (0.5%)	
Infections and infestations	Anal abscess	[1] 1 (0.5%)			

	Appendicitis			[1] 1 (0.5%)	
	Cystitis				[1] 1 (0.5%)
	Epididymitis	[1] 1 (0.5%)			
	Helicobacter gastritis	[1] 1 (0.5%)			
	Oral herpes			[1] 1 (0.5%)	
	Parotitis		[1] 1 (0.5%)		
	Pneumocystis jirovecii pneumonia		[1] 1 (0.5%)		
	Pneumonia	[1] 1 (0.5%)	[2] 2 (1%)		[1] 1 (0.5%)
	Respiratory syncytial virus infection	[1] 1 (0.5%)			
	Tracheitis				[1] 1 (0.5%)
	Upper respiratory tract infection	[1] 1 (0.5%)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Anal cancer				[1] 1 (0.5%)
	Basal cell carcinoma			[1] 1 (0.5%)	
	Breast cancer		[1] 1 (0.5%)		
	Ependymoma	[1] 1 (0.5%)			

	Lentigo maligna				[1] 1 (0.5%)
	Malignant melanoma			[1] 1 (0.5%)	
	Oesophageal carcinoma		[1] 1 (0.5%)		
	Papillary thyroid cancer				[1] 1 (0.5%)
	Prostate cancer	[1] 1 (0.5%)	[1] 1 (0.5%)		[1] 1 (0.5%)
Nervous system disorders	Multiple sclerosis		[1] 1 (0.5%)		

4.9.6 Table S29. Most common adverse events (more than 2 percent) by Preferred Term

Preferred Term	ACT (N=197)	CZP + MTX (N=202)	ABA + MTX (N=204)	TCZ + MTX (N=184)
Nausea	[96] 71 (36%)	[64] 55 (27.2%)	[85] 70 (34.3%)	[66] 51 (27.7%)
Nasopharyngitis	[48] 35 (17.8%)	[38] 29 (14.4%)	[52] 38 (18.6%)	[61] 45 (24.5%)
Alanine aminotransferase increased	[17] 14 (7.1%)	[35] 29 (14.4%)	[42] 28 (13.7%)	[55] 39 (21.2%)
Upper respiratory tract infection	[26] 19 (9.6%)	[26] 21 (10.4%)	[24] 20 (9.8%)	[34] 26 (14.1%)
Rash	[16] 13 (6.6%)	[21] 17 (8.4%)	[17] 15 (7.4%)	[26] 22 (12%)
Headache	[28] 17 (8.6%)	[20] 19 (9.4%)	[21] 17 (8.3%)	[13] 12 (6.5%)
Fatigue	[22] 19 (9.6%)	[17] 17 (8.4%)	[16] 15 (7.4%)	[11] 10 (5.4%)
Alopecia	[16] 15 (7.6%)	[13] 13 (6.4%)	[10] 10 (4.9%)	[18] 18 (9.8%)

Diarrhoea	[17] 16 (8.1%)	[11] 9 (4.5%)	[12] 12 (5.9%)	[15] 13 (7.1%)
Hepatic enzyme increased	[9] 9 (4.6%)	[13] 12 (5.9%)	[7] 7 (3.4%)	[23] 17 (9.2%)
Dizziness	[15] 12 (6.1%)	[16] 12 (5.9%)	[8] 8 (3.9%)	[8] 7 (3.8%)
Cough	[8] 8 (4.1%)	[10] 10 (5%)	[9] 9 (4.4%)	[10] 10 (5.4%)
Mouth ulceration	[9] 8 (4.1%)	[9] 9 (4.5%)	[8] 7 (3.4%)	[13] 10 (5.4%)
Influenza	[5] 5 (2.5%)	[9] 9 (4.5%)	[17] 13 (6.4%)	[5] 5 (2.7%)
Urinary tract infection	[8] 6 (3%)	[7] 6 (3%)	[14] 11 (5.4%)	[9] 7 (3.8%)
Neutropenia	[2] 2 (1%)	[2] 2 (1%)	[2] 2 (1%)	[26] 20 (10.9%)
Pyrexia	[9] 8 (4.1%)	[13] 10 (5%)	[6] 6 (2.9%)	[2] 2 (1.1%)
Abdominal pain upper	[12] 10 (5.1%)	[7] 6 (3%)	[4] 4 (2%)	[3] 3 (1.6%)
Dyspepsia	[13] 11 (5.6%)	[4] 4 (2%)	[4] 4 (2%)	[4] 4 (2.2%)
Hypertension	[4] 4 (2%)	[7] 7 (3.5%)	[5] 5 (2.5%)	[7] 7 (3.8%)
Pneumonia	[7] 6 (3%)	[11] 10 (5%)	[3] 3 (1.5%)	[2] 2 (1.1%)
Back pain	[5] 4 (2%)	[5] 5 (2.5%)	[9] 8 (3.9%)	[4] 4 (2.2%)
Dyspnoea	[7] 7 (3.6%)	[6] 6 (3%)	[5] 5 (2.5%)	[3] 3 (1.6%)
Oral mucosal blistering	[1] 1 (0.5%)	[2] 2 (1%)	[10] 8 (3.9%)	[11] 9 (4.9%)
Vomiting	[7] 7 (3.6%)	[3] 3 (1.5%)	[6] 6 (2.9%)	[4] 4 (2.2%)
Transaminases increased	[4] 3 (1.5%)	[2] 2 (1%)	[5] 5 (2.5%)	[9] 8 (4.3%)
Muscle spasms	[3] 3 (1.5%)	[4] 3 (1.5%)	[6] 6 (2.9%)	[7] 6 (3.3%)
Abdominal pain	[2] 2 (1%)	[2] 2 (1%)	[10] 8 (3.9%)	[5] 5 (2.7%)
Gastroenteritis	[4] 4 (2%)	[2] 2 (1%)	[4] 4 (2%)	[6] 6 (3.3%)

High Level Term	ACT (N=197)	CZP + MTX (N=202)	ABA + MTX (N=204)	TCZ + MTX (N=184)
Nausea and vomiting symptoms	[103] 75 (38.1%)	[67] 58 (28.7%)	[91] 74 (36.3%)	[70] 53 (28.8%)
Upper respiratory tract infections	[76] 54 (27.4%)	[76] 55 (27.2%)	[83] 55 (27%)	[111] 72 (39.1%)
Liver function analyses	[31] 26 (13.2%)	[51] 39 (19.3%)	[57] 39 (19.1%)	[92] 63 (34.2%)
Asthenic conditions	[25] 20 (10.2%)	[25] 24 (11.9%)	[20] 18 (8.8%)	[12] 11 (6%)
Rashes, eruptions and exanthems NEC	[18] 14 (7.1%)	[23] 19 (9.4%)	[17] 15 (7.4%)	[28] 23 (12.5%)
Headaches NEC	[28] 17 (8.6%)	[20] 19 (9.4%)	[22] 18 (8.8%)	[13] 12 (6.5%)
Alopecias	[16] 15 (7.6%)	[13] 13 (6.4%)	[10] 10 (4.9%)	[18] 18 (9.8%)
Diarrhoea (excl infective)	[17] 16 (8.1%)	[11] 9 (4.5%)	[13] 13 (6.4%)	[15] 13 (7.1%)
Neurological signs and symptoms NEC	[16] 13 (6.6%)	[17] 13 (6.4%)	[10] 10 (4.9%)	[10] 9 (4.9%)
Gastrointestinal and abdominal pains (excl oral and throat)	[14] 12 (6.1%)	[11] 10 (5%)	[14] 12 (5.9%)	[9] 9 (4.9%)
Stomatitis and ulceration	[9] 8 (4.1%)	[12] 12 (5.9%)	[11] 10 (4.9%)	[16] 13 (7.1%)
Coughing and associated symptoms	[9] 9 (4.6%)	[11] 11 (5.4%)	[10] 10 (4.9%)	[12] 12 (6.5%)
Musculoskeletal and connective tissue pain and discomfort	[11] 9 (4.6%)	[12] 11 (5.4%)	[18] 14 (6.9%)	[7] 6 (3.3%)
Lower respiratory tract and lung infections	[10] 9 (4.6%)	[16] 13 (6.4%)	[5] 5 (2.5%)	[10] 10 (5.4%)
Urinary tract infections	[9] 7 (3.6%)	[8] 7 (3.5%)	[15] 12 (5.9%)	[11] 9 (4.9%)
Herpes viral infections	[7] 7 (3.6%)	[13] 9 (4.5%)	[16] 7 (3.4%)	[12] 9 (4.9%)
Influenza viral infections	[5] 5 (2.5%)	[9] 9 (4.5%)	[17] 13 (6.4%)	[5] 5 (2.7%)
Infections NEC	[5] 5 (2.5%)	[6] 6 (3%)	[7] 7 (3.4%)	[11] 10 (5.4%)
Upper respiratory tract signs and symptoms	[4] 4 (2%)	[9] 8 (4%)	[7] 6 (2.9%)	[14] 9 (4.9%)

Neutropenias	[2] 2 (1%)	[2] 2 (1%)	[2] 2 (1%)	[26] 20 (10.9%)
Febrile disorders	[9] 8 (4.1%)	[13] 10 (5%)	[6] 6 (2.9%)	[2] 2 (1.1%)
Dyspeptic signs and symptoms	[14] 12 (6.1%)	[4] 4 (2%)	[4] 4 (2%)	[4] 4 (2.2%)
Non-site specific injuries NEC	[12] 9 (4.6%)	[6] 5 (2.5%)	[2] 2 (1%)	[9] 7 (3.8%)
Vascular hypertensive disorders NEC	[4] 4 (2%)	[7] 7 (3.5%)	[5] 5 (2.5%)	[7] 7 (3.8%)
Pain and discomfort NEC	[6] 5 (2.5%)	[8] 6 (3%)	[3] 3 (1.5%)	[8] 8 (4.3%)
Breathing abnormalities	[7] 7 (3.6%)	[7] 7 (3.5%)	[5] 5 (2.5%)	[3] 3 (1.6%)
Dental and oral soft tissue infections	[5] 5 (2.5%)	[6] 6 (3%)	[5] 4 (2%)	[6] 6 (3.3%)
Oral soft tissue signs and symptoms	[1] 1 (0.5%)	[2] 2 (1%)	[10] 8 (3.9%)	[11] 9 (4.9%)
Abdominal and gastrointestinal infections	[6] 6 (3%)	[4] 3 (1.5%)	[5] 5 (2.5%)	[6] 6 (3.3%)
Muscle related signs and symptoms NEC	[4] 4 (2%)	[4] 3 (1.5%)	[7] 7 (3.4%)	[7] 6 (3.3%)
Pruritus NEC	[4] 4 (2%)	[2] 2 (1%)	[2] 1 (0.5%)	[14] 11 (6%)
Skin injuries NEC	[3] 3 (1.5%)	[5] 5 (2.5%)	[1] 1 (0.5%)	[9] 8 (4.3%)

High Level Term Group Term	ACT (N=197)	CZP + MTX (N=202)	ABA + MTX (N=204)	TCZ + MTX (N=184)
Infections - pathogen unspecified	[122] 77 (39.1%)	[122] 82 (40.6%)	[131] 82 (40.2%)	[166] 98 (53.3%)
Gastrointestinal signs and symptoms	[142] 88 (44.7%)	[90] 67 (33.2%)	[114] 84 (41.2%)	[88] 61 (33.2%)
Hepatobiliary investigations	[31] 26 (13.2%)	[51] 39 (19.3%)	[57] 39 (19.1%)	[92] 63 (34.2%)
Epidermal and dermal conditions	[35] 27 (13.7%)	[41] 33 (16.3%)	[30] 25 (12.3%)	[65] 41 (22.3%)
General system disorders NEC	[37] 28 (14.2%)	[41] 35 (17.3%)	[31] 27 (13.2%)	[29] 26 (14.1%)
Oral soft tissue conditions	[13] 12 (6.1%)	[18] 16 (7.9%)	[23] 19 (9.3%)	[37] 30 (16.3%)

Viral infectious disorders	[16] 16 (8.1%)	[24] 20 (9.9%)	[38] 23 (11.3%)	[22] 15 (8.2%)
Skin appendage conditions	[23] 22 (11.2%)	[19] 19 (9.4%)	[11] 11 (5.4%)	[22] 22 (12%)
Neurological disorders NEC	[25] 21 (10.7%)	[31] 19 (9.4%)	[19] 17 (8.3%)	[17] 14 (7.6%)
Headaches	[32] 18 (9.1%)	[20] 19 (9.4%)	[23] 19 (9.3%)	[15] 14 (7.6%)
Gastrointestinal motility and defaecation conditions	[21] 20 (10.2%)	[15] 13 (6.4%)	[18] 16 (7.8%)	[17] 15 (8.2%)
Respiratory disorders NEC	[17] 14 (7.1%)	[21] 19 (9.4%)	[15] 13 (6.4%)	[15] 15 (8.2%)
Injuries NEC	[19] 15 (7.6%)	[17] 15 (7.4%)	[7] 7 (3.4%)	[24] 16 (8.7%)
Musculoskeletal and connective tissue disorders NEC	[12] 10 (5.1%)	[13] 12 (5.9%)	[23] 17 (8.3%)	[8] 7 (3.8%)
White blood cell disorders	[6] 4 (2%)	[5] 4 (2%)	[5] 4 (2%)	[38] 27 (14.7%)
Muscle disorders	[11] 10 (5.1%)	[6] 4 (2%)	[10] 10 (4.9%)	[9] 8 (4.3%)
Joint disorders	[16] 13 (6.6%)	[3] 3 (1.5%)	[7] 7 (3.4%)	[7] 5 (2.7%)
Respiratory tract signs and symptoms	[4] 4 (2%)	[9] 8 (4%)	[8] 7 (3.4%)	[14] 9 (4.9%)
Body temperature conditions	[9] 8 (4.1%)	[13] 10 (5%)	[6] 6 (2.9%)	[2] 2 (1.1%)
Bacterial infectious disorders	[12] 9 (4.6%)	[7] 6 (3%)	[6] 6 (2.9%)	[7] 5 (2.7%)
Vascular hypertensive disorders	[4] 4 (2%)	[7] 7 (3.5%)	[5] 5 (2.5%)	[7] 7 (3.8%)
Bone and joint injuries	[7] 6 (3%)	[5] 5 (2.5%)	[7] 7 (3.4%)	[2] 2 (1.1%)
Sleep disorders and disturbances	[9] 9 (4.6%)	[5] 5 (2.5%)	[3] 3 (1.5%)	[3] 3 (1.6%)
Upper respiratory tract disorders (excl infections)	[3] 3 (1.5%)	[4] 3 (1.5%)	[5] 5 (2.5%)	[10] 9 (4.9%)
Bone disorders (excl congenital and fractures)	[7] 7 (3.6%)	[7] 6 (3%)	[3] 3 (1.5%)	[3] 3 (1.6%)
Haematology investigations (incl blood groups)	[5] 4 (2%)	[5] 4 (2%)	[5] 3 (1.5%)	[10] 7 (3.8%)

5 SUPPLEMENTARY DOCUMENTS (IN SEPARATE FILES)

5.1 The signed SAP version 1.0

5.2 CONSORT checklist

STATISTICAL ANALYSIS PLAN for the NORD-STAR trial

Administrative information:

Sponsor name	Ronald van Vollenhoven, The Karolinska Institute
Sponsor address	Stockholm, Sweden
EudraCT number / REC no	2011-004720-35
Trial title	A multicenter, randomized, open-label, blinded-assessor, phase 4 study in patients with early rheumatoid arthritis to compare active conventional therapy versus three biologic treatments, and two de-escalation strategies in patients who respond to treatment.
Trial ID	NORD-STAR
Trial registration number	NCT01491815

SAP and protocol version:

SAP version and date:	This SAP is version 1.0, dated 18 May, 2021
Protocol version	This document has been written based on information contained in the study protocol version 7.0 December 2013

SAP revision history:

Protocol version	SAP version	Section number changed	Description and reason for change	Date changed
7.0	1.0	NA	Final version relating to the first study period from screening to week 24	02 Sep 2019
7.0	1.1	NA	First updated version relating to the data from screening to week 48	26 June 2020

Østergaard M, *et al. Ann Rheum Dis* 2023;0:1–10. doi: 10.1136/ard-2023-224116

[5.0]	[3.0]	[No changes required]	[SAP reviewed against protocol amendments]	[7 May 2018]

STATISTICAL ANALYSIS PLAN for the NORD-STAR trial

SIGNATURE PAGE

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19 MAY 2021

Signature

Date (dd/mmm/yyyy)

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18/May/2021

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18/May/2021

Signature

Date (dd/mmm/yyyy)

Østergaard M, *et al. Ann Rheum Dis* 2023;0:1–10. doi: 10.1136/ard-2023-224116

STATISTICAL ANALYSIS PLAN for the NORD-STAR trial

ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical/Therapeutic/Chemical
BMI	Body Mass Index
BPM	Beats Per Minute
CI	Confidence Interval
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class

Østergaard M, *et al. Ann Rheum Dis* 2023;0:1–10. doi: 10.1136/ard-2023-224116

STATISTICAL ANALYSIS PLAN for the NORD-STAR trial

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN for the NORD-STAR trial

1 Introduction

1.1 Background and rationale

This is the Statistical Analysis Plan (SAP) describing the statistical analyses of the NORD-STAR trial until 48 weeks of the first treatment period (TP1). This analysis plan should be seen as a part of the trial protocol, detailing all analyses to be undertaken for this time period. If there are inconsistencies between this SAP and the protocol, the SAP will be the governing document.

Further background and rationale is described below and in the latest version of the protocol, version 8.0 dated 10 February 2020.

Rheumatoid arthritis (RA) is a common inflammatory disorder with a reported prevalence of approximately 1% of the population. It is characterized by a progressive inflammatory synovitis with joint swelling and tenderness. Over time, structural joint damage evidenced by radiographic progression occurs and joint function diminishes. The most significant factor that has a great impact on prognosis of RA is pharmacologic intervention. A delay in starting a disease-modifying anti-rheumatic drug (DMARD) therapy has a significant negative impact. Patients treated early have a significant reduction of radiographic progression. Patients with more aggressive diseases seemed to benefit most from early DMARD initiation. MTX, given at 15 mg or more/weekly and folic acid; 5-15 mg/weekly, has remained the anchor drug for treatment of RA. In some countries initial combination therapy is preferred. Glucocorticoids are part of the early standard treatment in RA patients and widely used as add-on therapy to conventional DMARDs because of their effectiveness in controlling inflammation as well as reducing radiographic damages for a low cost. However, they also have adverse effects when used long-time, among others: negative effect on glucose and bone metabolism, increased risk for infection, osteoporosis, skin atrophy, osteonecrosis, cataract, hypertension, etc. Consequently, they are not recommended for long time use, but short time use of moderate-to-high dose glucocorticoids provides rapid initial control of active synovitis in early RA. Most rheumatologists recommend the use of biological DMARD after a trial of at least one or two conventional DMARDs in patients who continue having active synovitis. A recent recommendation suggests the use of biologics even in patients who have not yet failed non-biological DMARDs in case the patient has high disease activity and negative prognostic markers. Clinical data from the initial 24 weeks of the trial is covered in a previous SAP and has recently been analysed (Hetland et al, ACR abstract 2019)

1.2 Trial Objectives

1.2.1 Primary Objective

The objective of this part or the trial is to assess and compare radiographic and clinical outcomes after 48 weekes of active conventional therapy (ACT) versus each of three biological therapies (1) certolizumab-pegol, (2) abatacept and (3) tocilicumab.

The overall objective of the part of the NORDSTAR study covered by this SAP is, in RA patients treated with active conventional therapy (ACT) versus each of three different biologic therapies (certolizumab-pegol, abatacept and tocilicumab), to assess and compare the radiographic progression from baseline to the 48-week follow-up as well to assess and compare the proportion of subjects who achieve remission at the 48 week follow-up.

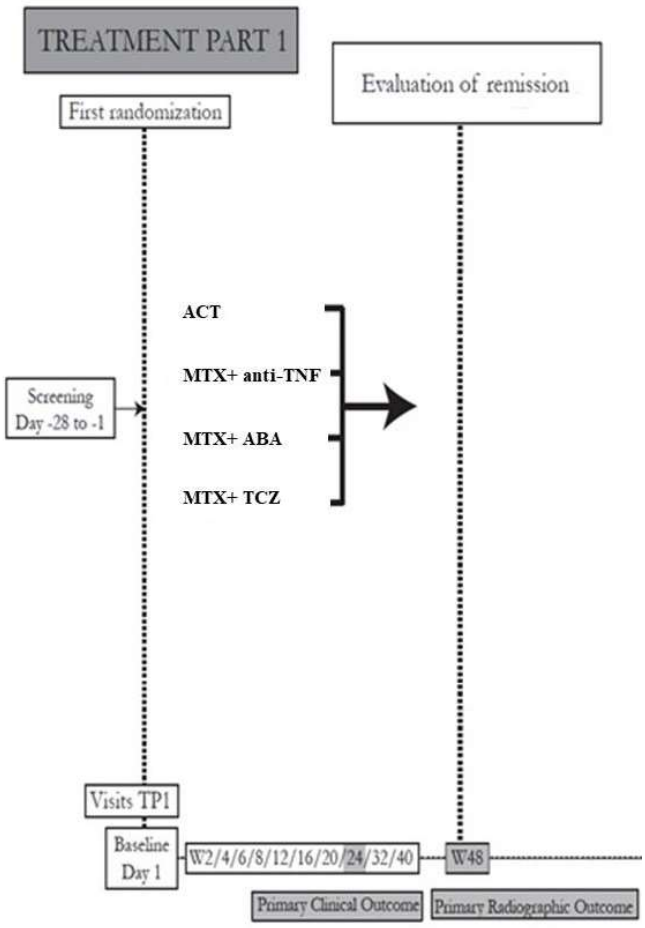
1.2.1 Secondary and Exploratory Objectives

Secondary and exploratory objectives are to assess radiographic progression and achievement of remission at other available time points, as well as differences in outcomes related to treatment response, disease activity, patient reported outcomes including quality of life, and safety ((serious) adverse events).

2 Trial Methods

2.1 Trial Design

This SAP describes the 48 week clinical and radiographic outcome in a 160 week, multicenter, randomized, open-label, blinded-assessor, double-treatment period study designed to compare the safety and efficacy of active conventional therapy (ACT; 1A: MTX+Prednisolone; 1B: MTX + sulphasalazine (SSZ) + hydroxochloroquine (HCQ)+ intraarticular glucocorticoids) and three biologic treatments (MTX+certolizumab; MTX+abatacept; MTX+tocilizumab) in subjects with early RA. (Figure 1).



After 8th of May 2014 tocilizumab was no longer available in Finland, and patients randomised to tocilizumab were treated with ACT.

2.2 Randomisation

All screening laboratory results were reviewed by the investigator prior to randomization. Subjects who met the selection criteria proceeded to randomization.

Randomization has been done through the trial center at the Karolinska Institute. There, at the outset of the study, randomization lists were generated with separate lists based on the three protocol-specified stratifications: by country, sex, and ACPA positivity. Thus, for each of the participating countries there were four randomization lists, one each for ACPA positive female, ACPA positive male, ACPA negative female and ACPA negative male participants. Each randomization list was generated by running an open-access internet-based random number generator set for four levels (1-2-3-4) in equal proportions (blocks of four). For practical reasons lists were generated of length 200 for Sweden and 100 for all other countries. Participating sites were provided with a dedicated telephone number in Stockholm, manned by site personnel at all business hours. After a patient had consented to participation and fulfilled inclusion criteria, and without exclusions, personnel at the local site dialed the randomization phone line, and informed trial center personnel of country, sex and ACPA status of the patient. Trial center personnel read off from the top of the appropriate list to what arm the patient was randomized, and noted the patient trial number (site number and patient number) on that list. They also sent a confirmatory e-mail to the site.

2.3 Sample size

The sample size calculation as described in the protocol was done for the whole trial.

Under the assumption that the true remission rates in the treatment arms are 0.12 in the ACT arm, 0.22 in the certulizumab-pegol arm, 0.22 in the abatacept arm and 0.26 in the tocilizumab, 724 patients must be randomised to reach 85% power to reject the null hypothesis that the remission rates are equal in the four treatment arms using the standard chi-square test. With 90% power, 832 patients have to be randomised.

2.4 Statistical Framework

2.4.1 Hypothesis Tests

This part of the trial is designed to establish the superiority of at least one of the biologic treatments compared to active conventional treatment on (1) avoiding progression in the radiographic Sharp-van der Heijde Score from randomisation to 48 weeks and (2) achieving CDAI remission at 48 weeks. Thus, there are six separate null hypotheses to be tested in this trial.

$H_0^{rx,c}$: The progression in the radiographic Sharp van der Heijde score from randomisation to 48 weeks is equal when receiving certulizumab-pegol compared to active conventional therapy

$H_0^{rx,a}$: The progression in the radiographic Sharp van der Heijde score from randomisation to 48 weeks is equal when receiving abatacept compared to active conventional therapy

$H_0^{rx,t}$: The progression in the radiographic Sharp van der Heijde score from randomisation to 48 weeks is equal when receiving tocilizumab compared to active conventional therapy

$H_0^{cdai,c}$: The probability of achieving CDAI remission at 48 weeks is equal when receiving certulizumab-pegol compared to active conventional therapy

$H_0^{cdai,a}$: The probability of achieving CDAI remission at 48 weeks is equal when receiving abatacept compared to active conventional therapy

$H_0^{cdai,t}$: The probability of achieving CDAI remission at 48 weeks is equal when receiving tocilizumab compared to active conventional therapy

These hypotheses will be tested adjusting for multiplicity by testing the null hypotheses regarding CDAI remission and radiographic outcome separately and adjusting for multiplicity by Dunnett's procedure within each outcome family.

There will be no other hypotheses tested, and all other efficacy and safety analyses will be regarded as supportive or exploratory.

2.4.2 Decision Rule

Each of the two outcome families (CDAI remission and Sharp-van der Heijde) will be tested to an overall significance level of 0.025. If any of the six hypotheses are rejected on the 0.025 level using adjusted p-values according to Dunnet's method when you have a common comparator (according to expression (5) in Hothorn, Bretz and Westfall (2008)), a difference is claimed either in favour of active conventional therapy or the corresponding biological therapy dependent on the direction of the contrast measure.

2.5 Statistical Interim Analyses and Stopping Guidance

There have been no interim analyses in this trial.

2.6 Timing of Final Analysis

The main analysis for this part of the trial is planned when all patients have concluded 48 ± 1 week of treatment, all data up to 48 weeks have been entered, verified and validated and the primary database has been locked.

The last patient entered the study in December 2018 and the last patient's week 48 visit (LPLV) was performed in December 2019. A soft lock of the database for the first 48 weeks of treatment is planned to be performed in Q2 20201. The hard lock target date is Q4 2020.

Prior to DBL a final determination is made that the data have achieved minimal quality standards. Each country develops a procedure for the national level of data cleansing and data management. It has been established that Study sites have been regularly monitored and that the three Data Centers have well-established internal routines for QC.

After solving of queries the national databases are exported to Zitelab for additional QC in accordance with a written procedure. Test analysis will be performed by the statistician with random allocation of patients to the different treatment arms to detect any outliers and errors in the database. Continuous variables will be visualized in histograms for the same purpose. Mock datasets (i.e. all variables, soft-locked) will be sent to the statistician to allow him to initiate the writing of code.

This SAP has been reviewed by an independent statistician for quality control before final approval.

Unresolved issues regarding the softlocked dataset will be discussed and decided upon by the Steering Committee. Thereafter, the final, locked and merged dataset will be delivered to the statistician from Zitelab.

2.7 Timing of Outcome Assessments

For all clinically planned measures, visits should occur within a window of the scheduled visit. Visits outside visit window is regarded a protocol deviation. The target day and visits window is defined in the protocol as:

Visit Label	**Target Day**	**Definition (Day window)**
Screening	-1	-28 to -1 day
V1. Baseline	Day 1 (Randomization)	Day 1
V2 Week 2	15	Target day ± 3 days
V3 Week 4	29	Target day ± 3 days
V4 Week 6	43	Target day ± 3 days
V5 Week 8	57	Target day ± 3 days
V6 Week 12	85	Target day ± 14 days
V7 Week 16	113	Target day ± 14 days
V8 Week 20	141	Target day ± 14 days
V9 Week 24	169	Target day ± 7 days
V10 Week 32	225	Target day ± 30 days
V11 Week 40	281	Target day ± 30 days
V12 Last study visit* Week 48	337	Target day ± 7 days

*The last study visit is defined as the visit following the last visit with randomised treatment, and where there is a study end statement.

For analysis and tabulation purposes, we define study time points as

Time Point Label	**Target Day**	**Definition (Day window)**
TP1. Baseline	Day 1 (Randomisation)	Information up to randomisation
TP2 Week 2	15	Day 2 to 21
TP3 Week 4	29	Day 22 to 35
TP4 Week 6	43	Day 36 to 49
TP5 Week 8	57	50 to 70
TP6 Week 12	85	71 to 98
TP7 Week 16	113	99 to 126
TP8 Week 20	141	127 to 154
TP9 Week 24	169	155 to 196
TP10 Week 32	225	197 to 252
TP11 Week 40	281	253 to 308
TP12 Last study visit* Week 48	337	309 to 364

If more than one visit fall into the same time point interval, information on all visits will be used in the analyses.

3 Statistical Principles

3.1 Confidence Intervals and p-values

All calculated p-values will be two-sided and compared to a 5% family wise error rate. All efficacy estimates will be presented with two-sided confidence intervals. When the efficacy estimates relates to one of the pre-specified null hypotheses as defined in section 2.4.1, adjusted confidence intervals will be used when applicable. Otherwise, unadjusted 95% confidence intervals will be presented.

3.2 Adherence and Protocol Deviations

3.2.1 Adherence to Allocated Treatment

3.2.2 Protocol Deviations

The following are pre-defined major protocol deviations regarded to affect the efficacy of the intervention:

1. Patient withdrew from study (Early termination visit before TP1-w48)
2. Randomized study medication (RSM) was permanently stopped before TP1-w48
3. RSM was interrupted for 12 weeks or more between TP1-Day1 and TP1-w24 or between TP1-w24 and TP1-w48
4. DMARD therapy was added – except SSZ/HCQ added in arm 1 (Sweden, Norway, The Netherlands or Iceland).
5. For Sweden, Norway, The Netherlands and Iceland:
   5.1: Prednisolone (or equivalent) >10 mg/day and/or greater than baseline dose is given for >8 weeks
   5.2: Prednisolone (or equivalent) > 10 mg/day and/or greater than baseline dose is given from week 20 to 24 or from week 44 to 48
   5.3: Prednisolone (or equivalent) > 10 mg/day and/or greater than baseline dose is given on any day during the week prior to the week 24 visit or on any day during the week prior to the week 48 visit
6. For Denmark and Finland:
   6.1: Any oral prednisolone
7. For all countries:
   7.1: IA injection of triamcinolonehexacetonid (Lederspan) or equivalent >4 mL or > 4 joints at one visit after week 4
   7.2: IA injection of triamcinolonehexacetonid (Lederspan) or equivalent >2 mL from week 20 to 24 or from week 44 to 48
   7.3: Any IA injection of triamcinolonehexacetonid (Lederspan) or equivalent during the week prior to the week 24 visit or during the week prior to the week 48 visit.

The following deviations are defined as minor; deviations that exceed those mentioned here are regarded as major protocol deviations:

1. Methotrexate: up to four missed doses between TP1-Day1 and TP1-w24 and up to four missed doses between TP1-w24 and TP1-w48. Deviations from the scheduled dosing regimen are allowed when medically indicated
2. Certolizumab-pegol: up to two missed doses between TP1-Day1 and TP1-w24 and up to two missed doses between TP1-w24 and TP1-w48. A single mistakenly administered extra dose is allowed, but NOT later than the week 20 visit or 4 weeks prior to the week 48 visit;
3. Abatacept SC: up to four missed doses between TP1-Day1 and TP1-w24 and up to four missed doses between TP1-w24 and TP1-w48. A single mistakenly administered extra dose (but NOT later than the week 20 visit or 4 weeks prior to the week 48 visit)
4. Abatacept IV: up to one missed dose between TP1-Day1 and TP1-w24 and up to one missed dose between TP1-w24 and TP1-w48
5. Tocilizumab SC: up to four missed doses between TP1-Day1 and TP1-w24 and up to four missed doses between TP1-w24 and TP1-w48. A single mistakenly administered extra dose (but NOT later than the week 20 visit or 4 weeks prior to the week 48 visit)

6. Tocilizumab IV: up to one missed dose between TP1-Day1 and TP1-w24 and up to one missed dose between TP1-w24 and TP1-w482.

The number (and percentage) of patients with major and minor protocol deviations will be summarised by treatment group with details of type of deviation provided. The patients that are included in the ITT analysis data set will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

3.3 Analysis Populations

The Enrolled set will include all patients who have provided informed consent and have been included into the study data base.

The Intention to Treat (ITT) population will be defined as all patients randomly assigned to a treatment group except 17 patients from Finland for whom the allocated treatment (tocilizumab) was not available.

The as-treated population will be defined as all randomized patients who received at least one dose of randomized study medication (i.e, at least one dose of MTX in combination with at least one dose of prednisolone or at least one intra-articular injections of corticosteroid (arm 1A and 1B, respectively)), at least one dose of certolizumab-pegol (arm 2), at least one dose of abatacept (arm 3), or at least one dose of tocilizumab (arm 4). Thus, patients who received only MTX (and no glucocorticoid) are not included in the as-treated population).

The Safety Analysis Set will be identical to the as-treated population.

The Per Protocol Analysis Set (PPS) will include all randomised patients meeting the study eligibility criteria and with no major protocol deviations affecting the treatment efficacy as defined in section 3.2.2.

The ITT population will be regarded as the primary analysis population. All results based on the as-treated and PP populations are considered sensitivity or robustness analyses.

4 Trial Population

4.1 Screening Data, Eligibility and Recruitment

The total number of screened patients and reasons for not entering the trial will be summarised and tabulated.

A CONSORT flow diagram (appendix A) will be used to summarise the number of patients who were:

- assessed for eligibility at screening
- eligible at screening
- ineligible at screening*
- eligible and randomised
- eligible but not randomised*

- received the randomised allocation
- did not receive the randomised allocation*
- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.

4.2 Withdrawal/Follow-up

The status of eligible and randomised patients at trial end will be tabulated by treatment group according to

- completed intervention and assessments
- completed assessments but not intervention
- withdrew consent
- lost to follow-up

Time from randomisation to treatment discontinuation and time from randomisation to withdrawal/lost to follow-up will be presented graphically using the Kaplan-Meier estimator.

4.3 Baseline Patient Characteristics

The patient demographics and baseline characteristics to be summarised include age in years, gender, Body Mass Index (BMI), smoking status, symptom duration, disease duration, RF/ACPA status, Tender Joint Count (TJC), Swollen Joint Count, Clinical Disease Activity Index (CDAI) , Disease activity Score in 28 joints (DAS28), Patient's Global Assessment of disease activity (PGA), Physician's Global assessment of Disease Activity (PhGA), pain on a Visual Analogue Scale (VAS), questionnaires and radiographic damage score.

Patient demographics and baseline characteristics will be summarised by randomised treatment arm and overall using descriptive statistics (N, mean, standard deviation, median, 25/75 percentiles, minimum, and maximum) for continuous variables, and number and percentages of patients for categorical variables. There will be no statistical analysis of treatment difference. Any clinically important imbalance between the treatment groups will be noted.

5 Analysis

5.1 Outcome Definitions

5.1.1 General Definitions and Derived Variables

5.1.1.1 Body Mass Index

Body Mass Index (BMI) = Body weight in kilograms divided by the square of the height in meters.

5.1.1.2 Change from baseline

Change from baseline (Δ) = time-point value - baseline value.

% change from baseline (%Δ) = [(time-point value – baseline value) / baseline value] *100%

5.1.1.3 Joint Counts

The Tender Joint Count of 68 joints (TJC68) is the number of joints with pain in 68 joints (temporomandibulars (TMJs), sternoclaviculars (SCs), acromioclaviculars (ACs), shoulder, elbows, wrists, metacarpophalangeals (MCPs), finger proximal interphalangeals (finger PIPs), distal interphalangeals (DIPs), hips, knees, ankles, tarsi, metatarsophangeals (MTPs) and toe proximal interphalangeals (toe PIPs)).

The Swollen Joint Count of 66 joints (SJC66) is the number of joints with swelling in 66 joints. The joints are the same as for TJC68 except hips.

The Tender and Swollen Joint Counts of 28 joints (TJC28/SJC28) are based on the following joints: shoulders, elbows, wrists, MCP, finger PIPs and knees.

5.1.1.4 Sharp van der Heijde Score

The Sharp van der Heijde Score (vdHSS) is a score of erosion and joint space narrowing (JSN) based on radiographs of hands and feet. The score for erosion ranges from 0 to 160 in the hands and from 0 to 120 in the feet (erosion total 280). The score for JSN ranges from 0 to 120 in the hands and from 0 to 48 in the feet (JSN total 168). The total vdHSS score is the sum of scores of erosion and JSN, the maximum score is 448.

Each radiograph has been read twice by two independent readers. Consensus reads was elicited by a difference in change in Total Sharp van der Heijde score (Total SvdH score) from 0-48 weeks >= 2 between readers. Cases selected for consensus reads was read by the two readers together, and a final assessment was made (joint by joint level).

The final joint score used for analysis will be the consensus read if available or the mean of the two joint scores if no consensus read is needed.

Table 5.1 Overview of vdHSS

Area	Joints	Erosion left	Erosion right	JSN left	JSN right

Hand	Metacarpophalangeal (MCP)				
	- First (MCP1)	0-5	0-5	0-4	0-4
	- Second (MCP2)	0-5	0-5	0-4	0-4
	- Third (MCP3)	0-5	0-5	0-4	0-4
	- Fourth (MCP4)	0-5	0-5	0-4	0-4
	- Fifth (MCP5)	0-5	0-5	0-4	0-4
	Proximal interphalangeal (IP/PIP)				
	- First (IP1)	0-5	0-5	NA	NA
	- Second (PIP2)	0-5	0-5	0-4	0-4
	- Third (PIP3)	0-5	0-5	0-4	0-4
	- Fourth (PIP4)	0-5	0-5	0-4	0-4
	- Fifth (PIP5)	0-5	0-5	0-4	0-4
	Carpometacarpal (CMC)				
	- Third (CMC3)	NA	NA	0-4	0-4
	- Fourth (CMC4)	NA	NA	0-4	0-4
	- Fifth (CMC5)	NA	NA	0-4	0-4
Wrist	First metacarpal base (MCB)	0-5	0-5	NA	NA
	Radius bone	0-5	0-5	NA	NA
	Ulna bone	0-5	0-5	NA	NA
	Trapezium/trapezoid (multangular)	0-5	0-5	NA	NA
	Navicula	0-5	0-5	NA	NA
	Capitatum naviculare	0-5	0-5	0-4	0-4
	Multangular navicular	NA	NA	0-4	0-4
	radiocarpal	NA	NA	0-4	0-4
Foot	Metatarsophalangeal (MTP)				
	- First (MTP1)	0-10	0-10	0-4	0-4

- Second (MTP2)	0-10	0-10	0-4	0-4
- Third (MTP3)	0-10	0-10	0-4	0-4
- Fourth (MTP4)	0-10	0-10	0-4	0-4
- Fifth (MTP5)	0-10	0-10	0-4	0-4
Interphalangeal (IP)	0-10	0-10	0-4	0-4

Rules for handling of missing data /data imputation

Hierarchical rules for imputation:

1. If some or all *data from one of three timepoints are missing*: Impute by Linear interpolation/extrapolation on the lowest possible level (i.e per joint)
2. If some or all *data from two of three timepoints are missing* only one time point is available: Use last observation carried forwards (LOCF) or First observation carried backwards (FOCB)
3. If data from *some joints within a hand or foot are missing from all time points*: Use the mean of neighboring joints.
4. If *data from one entire foot or one entire hand are missing at all time points*: Use the score from the contralateral foot or hand for the missing foot/hand.
5. If *data from two feet are missing at all timepoints*: Use scores of the two hands and normalize to the total score range for both hands and feet of the Total SvdH score (0-448)/JSN score (0-168) and erosion score (0-280). (Range erosion score both hands 160, range JSN score two hands 120).
6. If *data from two hands are missing at all timepoints*: Use scores from the two feet and normalize to the total score range for both hands and feet of the Total SvdH score (448)/JSN score (168) and erosion score (280)

5.1.1.5 CDAI

The Clinical Disease Activity Index (CDAI) includes TCJ28, SJC28, Patient's Global Assessment of disease activity on a VAS 0-100 mm (PGA), in addition to the treating Physician's Global Assessment of disease activity on a VAS 0-100 mm (PhGA).

The CDAI is calculated as follows:

CDAI=TCJ28 + SJC28 + PGA/10 + PhGA/10

According to CDAI, the following cut-points are used:

High disease activity: CDAI > 22.0

Moderate disease activity: 22.0 ≥ CDAI>10.0

Low disease activity: 10.0 ≥ CDAI > 2.8

In remission: CDAI ≤ 2.8

5.1.1.6 SDAI

The Simplified Disease Activity Index (SDAI) includes TCJ28, SJC28, PGA, PhGA and C-reactive protein (CRP) in mg/L.

The SDAI is calculated as follows:

SDAI=TCJ28 + SJC28 + PGA/10 + PhGA/10 + CRP/10

According to SDAI, the following cut-points are used:

High disease activity: SDAI> 26.0

Moderate disease activity: 26.0 ≥ SDAI>11.0

Low disease activity: 11.0 ≥ SDAI > 3.3

In remission: SDAI ≤ 3.3

5.1.1.7 DAS28-CRP

The 28-joint Disease Activity Score (DAS28) includes TJC28, SJC28, CRP and PGA.

The DAS28-CRP is calculated as follows:

DAS28 = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*Ln(CRP+1) + 0.014*PGA + 0.96

If any of the components are missing, then the DAS28 is missing.

According to DAS28, the following cut-points are used:

High disease activity: DAS28 > 5.1

Moderate disease activity: 5.1 ≥ DAS28>3.2

Low disease activity: 3.2 ≥ DAS28 ≥ 2.6

In remission: DAS28 < 2.6

5.1.1.8 ACR/EULAR remission

The patient must satisfy all of the following in order to achieve ACR/EULAR remission:

- TJC68 ≤ 1
- SJC66 ≤ 1
- CRP ≤ 1

- PGA ≤ 14

5.1.1.9 HAQ-DI

The Stanford Health Assessment Questionnaire was introduced in the 1980s and is now widely used in evaluation of physical function in patients with RA. The disability index of this instrument includes questions concerning the ability of patients to perform 20 activities of daily living and is most commonly referred to as the HAQ questionnaire, and sometimes as the HAQ disability index (HAQ-DI).

According to Maska, L., Anderson, J. and Michaud, K. (2011), Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). Arthritis Care Res, 63: S4-S13. doi:10.1002/acr.20620:

"Eight categories, reviewing a total of 20 specific functions evaluate patient difficulty with activities of daily living over the past week. Categories include dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and errands and chores. Also identified are specific aids or devices utilized for assistance, as well as help needed from another person (aids/help).

There are 41 total items: 20 4-point Likert-scale questions assessing specific activities of daily living, 13 additional questions assessing use of assistive devices, and 8 additional questions assessing help received from another.

Twenty specific activities are assessed on a 4-point Likert scale where 0 = without difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do. The 20 activities are grouped into 8 functional categories with each category given a single score equal to the maximum value of their component activities (0, 1, 2, or 3).

There are 3 steps to scoring the HAQ (with aids/help): 1) identify the highest subcategory score from each of the 8 categories. Adjust for use of aids/help by increasing the category score from 0 or 1 to a 2 if use of aids/help for that category (utilize table of companion aids/help for HAQ categories). If the category score is already a 2 or 3, no adjustment is made; 2) sum the category scores; and 3) divide the final sum by the number of categories answered to obtain the final HAQ score rounded to the nearest value evenly divisible by 0.125. Requires a minimum of 6 categories answered; if less, do not score."

5.1.1.10 ACR response

An ACR20 response is defined if the following criteria are fulfilled:

- 20% improvement in TJC68, AND
- 20% improvement in SJC66, AND
- 20% improvement in at least 3 of 5 other core set items

The other core set items consist of:

- PhGA
- PGA
- Patient's Global Assessment of Pain on a VAS 0-100 mm

- HAQ-DI
- ESR/hsCRP

ACR50, ACR70 and ACR90 are defined in a similar manner with 50%, 70% and 90% improvement, respectively. High sensitivity CRP (hsCRP) will be used as primary measure of inflammation, while ESR will be used if hsCRP is not available. All improvements will be % change from baseline.

5.1.1.11 EULAR response

The European League Against Rheumatism (EULAR) response rates will be calculated. A EULAR response is defined by the state and change in DAS and DAS28, and categorized into good, moderate and none using the following definitions:

Table 5.2 EULAR DAS28 response

	Change from baseline in DAS28		
DAS28 at time-point	ΔDAS28 ≤ - 1.2	-1.2 < DAS28 < -0.6	DAS28 ≥ 0.6
DAS28 ≤ 3.2	Good	Moderate	None
3.2 < DAS28 ≤ 5.1	Moderate	Moderate	None
DAS28 > 5.1	Moderate	None	None

5.1.1.12 SF-36

The SF-36 is a multi-purpose, short-form health survey with 36 questions. The SF-36 will be scored according to RAND 36-Item Health Survey 1.0 (http://www.rand.org/health/surveys_tools/mos/mos_core_36item_scoring.html) to form eight measures scores 0-100: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. In addition, composite scores for physical and mental health summary measures are calculated according to the New England Medical Centre scoring instructions.(Ware, Kosinski, & Keller, 1994) The composite scores are computed according to the 1998 US general population means and standard deviations.

5.1.1.13 EQ-5D

EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D index values are calculated according to the EQ-5D UK Time Trade-Off (TTO) value set.

5.1.1.14 WPAI

Worker productivity is generally subdivided into 2 components: absenteeism and presenteeism. The worker productivity in this study is based on the Work Productivity and Activity Impairment Questionnaire: Rheumatoid arthritis V2.0 (WPAI:RA).

The WPAI yields four types of scores:

1. Absenteeism (work time missed)
2. Presenteeism (impairment at work / reduced on-the-job effectiveness)
3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)
4. Activity Impairment

The scores are based on the following questions:

Q1= currently employed

Q2 = hours missed due to specified problem

Q3 = hours missed other reasons

Q4 = hours actually worked

Q5 = degree problem affected productivity while working

Q6 = degree problem affected regular activities

Scores:

Multiply scores by 100 to express in percentages.

Percent work time missed due to RA (Absenteeism): $\frac{Q2}{Q2+Q4}$

Percent impairment while working due to RA (Presenteeism): $\frac{Q5}{10}$

Percent overall work impairment due to RA (Work productivity loss):

$$\frac{Q2}{(Q2+Q4)} + \left[1 - \frac{Q2}{Q2+Q4}\right] \cdot \frac{Q5}{10}$$

Percent activity impairment due to problem: $\frac{Q6}{10}$

5.1.2 Primary Outcome Definition

The primary radiographic outcome is the change in total van der Heijde-modified Sharp Score from baseline to week 48 (ΔvdHSS). The primary radiographic outcome is continuous.

The primary clinical outcome is the occurrence of CDAI remission at week 48. The primary clinical outcome is dichotomous.

5.1.3 Secondary Outcomes Definitions

Group	Endpoint	Assessment time	Type
Key Radiology	No radiographic progression (ΔvdHSS at 48 weeks ≤ 0.5)	At 48 weeks	Dichotomous
	ΔErosion score	0 to 48 weeks	Continuous Δ
	ΔJSN	0 to 48 weeks	Continuous Δ
	ΔvdHSS	0 to 24 weeks 24 to 48 weeks	Continuous Δ
Key Clinical	ACR/EULAR Boolean remission	At 48 weeks	Dichotomous
	DAS28 remission	At 48 weeks	Dichotomous
	SDAI remission	At 48 weeks	Dichotomous
	EULAR good response	At 48 weeks	Dichotomous
Other Radiology	Radiographic progression above smallest detectable change (ΔvdHSS at 48 weeks > SDC*)	At 48 weeks	Dichotomous
	Rapid radiographic progression (ΔvdHSS at 48 weeks > 5)	At 48 weeks	Dichotomous
	ΔErosion score	0 to 24 weeks 24 to 48 weeks	Continuous Δ
	ΔJSN	0 to 24 weeks 24 to 48 weeks	Continuous Δ

	No Radiographic progression (ΔvdHSS at 24 weeks ≤ 0.5)	At 24 weeks	Dichotomous
	Radiographic progression (ΔvdHSS between 24 and 48 weeks > 0.5)	At 48 weeks	Dichotomous
	Erosion progression (ΔErosion at 48 weeks > 0.5)	At 48 weeks	Dichotomous
	Erosion progression (ΔErosion at 24 weeks > 0.5)	At 24 weeks	Dichotomous
	No erosion progression (ΔErosion between 24 and 48 weeks ≤ 0.5)	At 48 weeks	Dichotomous
	Joint space narrowing progression (ΔJSN at 48 weeks > 0.5)	At 48 weeks	Dichotomous
	No joint space narrowing progression (ΔJSN at 24 weeks ≤ 0.5)	At 24 weeks	Dichotomous
	No joint space narrowing progression (ΔJSN between 24 and 48 weeks ≤ 0.5)	At 48 weeks	Dichotomous

Other Clinical	CDAI remission	All post-baseline visits, except 48 weeks	Dichotomous
	ACR/EULAR Boolean remission	All post-baseline visits, except 48 weeks	Dichotomous
	DAS28 remission	All post-baseline visits, except 48 weeks	Dichotomous
	SDAI remission	All post-baseline visits, except 48 weeks	Dichotomous
	EULAR good response	All post-baseline visits, except 48 weeks	Dichotomous
	CDAI Low disease activity	All post-baseline visits, except 48 weeks	Dichotomous
	DAS28 Low disease activity	All post-baseline visits	Dichotomous
	ACR20 response	All post-baseline visits	Dichotomous
	ACR50 response	All post-baseline visits	Dichotomous
	ACR70 response	All post-baseline visits	Dichotomous
	EULAR Good or moderate response	All post-baseline visits	Dichotomous
	ΔDAS28	All post-baseline visits	Continuous Δ
	ΔSDAI	All post-baseline visits	Continuous Δ
	ΔCDAI	All post-baseline visits	Continuous Δ
	ΔSJC66	All post-baseline visits	Continuous Δ

	ΔSJC28	All post-baseline visits	Continuous Δ
	ΔTJC68	All post-baseline visits	Continuous Δ
	ΔHAQ-DI	All post-baseline visits	Continuous Δ
	Morning stiffness	All post-baseline visits	Dichotomous
	ΔPGA	All post-baseline visits	Continuous Δ
	ΔPhGA	All post-baseline visits	Continuous Δ
	ΔJointPain	All post-baseline visits	Continuous Δ
	ΔESR	All post-baseline visits	Continuous Δ
	ΔCRP	All post-baseline visits	Continuous Δ

Smallest detectable change (SDC): SDC= 1.966 $SD_{\Delta vdHSSw0\text{-}w48}/(\sqrt{2}\ x\ \sqrt{k})$, where k is the number of readers (k=2) For this method one firstly calculates the differences between the change-scores obtained in the repeated reading session (i.e the change in score between baseline and follow-up for reader 1 is subtracted from the change in score between baseline and follow-up for reader 2). Secondly, the SD of these differences is calculated. This SDD(CHANGE-SCORES) reflects the measurement error of the difference between two change-scores that is, the measurement error when discriminating between two change-scores. (Bruynesteen et al, Ann Rheum Dis 2005; 64: 179–182).

5.1.4 Patient reported outcome measures

Group	Endpoint	Assessment time	Type
SF-36	ΔPhysical functioning	All post-baseline visits	Continuous Δ
	ΔBodily pain	All post-baseline visits	Continuous Δ
	ΔRole limitations due to physical health problems	All post-baseline visits	Continuous Δ
	ΔRole limitations due to personal or emotional problems	All post-baseline visits	Continuous Δ

	ΔEmotional well-being	All post-baseline visits	Continuous Δ
	ΔSocial functioning	All post-baseline visits	Continuous Δ
	ΔEnergy/fatigue	All post-baseline visits	Continuous Δ
	ΔGeneral health perception	All post-baseline visits	Continuous Δ
	ΔPhysical health composite score	All post-baseline visits	Continuous Δ
	ΔMental health composite score	All post-baseline visits	Continuous Δ
RAID	ΔRAID total score	All post-baseline visits	Continuous Δ
EQ5D	ΔEQ5D index value	All post-baseline visits	Continuous Δ
WPAI	ΔAbsenteeism	All post-baseline visits	Continuous Δ
	ΔPresenteeism	All post-baseline visits	Continuous Δ
	ΔWork productivity loss	All post-baseline visits	Continuous Δ
	ΔActivity impairment	All post-baseline visits	Continuous Δ
PASS	Patient Acceptable Symptom State	All post-baseline visits	Dichotomous
FACIT Fatigue	FACIT-Fatigue subscale score	All post-baseline visits	Continuous Δ

5.1.5 Safety outcome definitions

5.1.5.1 Treatment emerging adverse events

Treatment emerging adverse events (TEAEs) are defined as AEs with a start date on or after the randomization date.

5.1.5.2 Past disease and concomitant disease

Past disease/condition

A disease/condition is considered as past disease/condition if it is not ongoing at screening visit.

Concomitant disease

A disease/condition is considered as concomitant disease/condition if it is ongoing at screening visit.

Previous and Concomitant medications

- previous medication (start date < date of randomisation);
- concomitant medication (start date ≥ date of randomisation);

In case of missing or incomplete dates/times not directly allowing allocation to any of the two categories of medications, a worst-case allocation was performed according to the available parts of the start and the end dates. The medication was allocated to the first category allowed by the available data, according to the following order:

- concomitant medication;
- previous medication.

5.2 Analysis Methods

5.2.1 Primary Outcome

5.2.1.1 Primary Analysis

The change in total van der Heijde-modified Sharp score from baseline to week 48 will be analysed using analysis of covariance (ANCOVA), adjusted for baseline score and the stratification factor in the randomisation (gender, anti-CCP status and country) .

The occurrence of CDAI remission at 48 weeks will be analysed using logistic regression, adjusted for the stratification factors in the randomisation (gender, anti-CCP status and country).

The primary analyses will be performed on the ITT population as defined in section 3.3.

5.2.1.2 Summary Measures

Descriptive statistics will include cumulative probability plots, and number and percentage by treatment group. Descriptive statistics will be based on non-imputed data, thus the number of evaluable outcome measurements at the time of primary interest (48 weeks) will also be presented.

The primary radiographic effect estimates will be the adjusted difference in mean ΔvdHSS between ACT and each of the three biologic treatments. Each effect estimate together with the 95% confidence interval and p-value of the null hypothesis test will be presented, adjusted for multiplicity by the Dunnett's procedure.

The primary clinical effect estimate will be the adjusted risk difference in CDAI remission between ACT and each of the three biologic treatments, computed from the logistic regression effect estimate using the delta method. The adjusted relative risk will also be reported together with the p-value of the null-hypothesis test of no treatment difference from the logistic regression. P-values and confidence intervals will be adjusted for multiplicity by the Dunnett's procedure.

5.2.1.3 Assumption Checks and Alternative Analyses

The ANCOVA model will be checked for deviations from the normal assumption by plotting the residuals both against the fitted values and the quantiles against quantiles. Blinded analyses have revealed an expected deviation from the normality assumption. However, we assume the sample size is sufficient for the model to provide unbiased estimates according to the central limit theorem.

A robustness analysis will be undertaken where the adjusted p-values will be calculated based on normal scores i.e. that the values of ΔvdHSS will be transformed to the corresponding quantile according to the normal distribution. The same ANCOVA model will be used, and p-values will be adjusted according to the Dunnett's method.

The logistic regression relies on few assumptions, and there will be no assumption checks for the primary analysis of CDAI remission.

5.2.1.4 Missing Data

For the primary radiographic outcome missing observations will be imputed as described in section 5.1.1.4

For the primary clinical outcome, missing data will be imputed with worst outcome which is no response. From the blinded review, it is known that the majority of missing data for this outcome is lack of response to the allocated treatment. Thus, a non-response imputation is the only clinically relevant method.

5.2.1.5 Sensitivity Analyses

For both primary endpoints, the following robustness analyses will be performed:

- unadjusted analyses on the ITT population
- adjusted on the PP population
- longitudinal analyses based on mixed models

Details will be given in the corresponding section for dichotomous and radiographic outcomes.

5.2.1.6 Subgroup Analyses

There will be no subgroup analyses in this part of the trial.

5.2.2 Dichotomous Secondary Outcomes at 48 weeks

Dichotomous secondary outcomes at 48 weeks will be analysed similar to the primary clinical CDAI remission outcome. There will be no adjustments for multiplicity in the secondary outcome analyses.

5.2.2.1 Main Analysis

Dichotomous secondary outcomes will be analysed using logistic regression, adjusted for the stratification factors in the randomisation (gender, anti-CCP status and country).

The main analysis will be performed on the ITT population.

5.2.2.2 Summary Measures

Summary measures will include descriptive numbers and percentages in addition to adjusted risk differences. Effect measures will be presented with unadjusted 95% confidence limits, but without

p-values. The adjusted risk differences and corresponding 95% confidence intervals will be based on the averaged predictive margins and the delta method.

5.2.2.3 Assumption Checks

There will be no assumptions checks.

5.2.2.4 Missing Data

Missing data will be imputed by worst outcome.

5.2.2.5 Sensitivity Analyses

There will be no sensitivity analyses.

5.2.2.6 Subgroup Analyses

There will be no subgroup analyses.

5.2.1 Longitudinal Analyses of Dichotomous Secondary Outcomes

Dichotomous secondary outcomes for all visits post baseline will be analysed using a repeated measures methodology. There will be no adjustments for multiplicity.

5.2.1.1 Main Analysis

Dichotomous secondary outcomes will be analysed using repeated measures logistic regression, adjusted for the stratification factors in the randomisation (gender, anti-CCP status and country). Within-patient dependencies will be handled by estimating the variance-covariance matrix using generalized estimating equations.

This analysis will be performed on the ITT population.

5.2.1.2 Summary Measures

Summary measures will include descriptive numbers and percentages in addition to adjusted risks and risk differences. Effect measures will be presented with unadjusted 95% confidence limits, but without p-values. Plots with the adjusted risks and confidence limits by treatment will be presented. The adjusted risk differences and corresponding 95% confidence intervals will be based on the averaged predictive margins and the delta method.

5.2.1.3 Assumption Checks

There will be no assumptions checks.

5.2.1.4 Missing Data

Missing data will be imputed by worst outcome.

5.2.1.5 Sensitivity Analyses

The following sensitivity analysis will be performed:

- unadjusted analyses on the ITT population
- adjusted on the PP population

5.2.1.6 Subgroup Analyses

There will be no subgroup analyses.

5.2.2 Continuous Secondary Radiographic Outcomes

Continuous secondary radiographic outcomes will be analysed similar to the primary radiographic outcome. There will be no adjustments for multiplicity in the secondary outcome analyses.

5.2.2.1 Main Analysis

Secondary continuous radiographic outcomes will be analysed using ANCOVA, adjusted for the stratification factors in the randomisation (gender, anti-CCP status and country) and baseline value.

This analysis will be performed on the ITT population.

5.2.2.2 Summary Measures

Summary measures will include cumulative probability plots and adjusted difference in adjusted mean between ACT and each of the three biologic treatments. Effect measures will be presented with unadjusted 95% confidence limits, but without p-values. The adjusted estimates and corresponding 95% confidence intervals will be based on the averaged predictive margins and the delta method.

5.2.2.3 Assumption Checks

There will be no assumptions checks.

5.2.2.4 Missing Data

All missing observations will be imputed as described in section 5.1.1.4. A sensitivity analysis on un-imputed data will be performed using mixed models with random intercept and random slope as described in the next section.

5.2.2.5 Sensitivity Analyses

The following sensitivity analysis will be performed:

- unadjusted analyses on the ITT population
- adjusted on the PP population

In addition, sensitivity analyses will be performed using mixed models with time by treatment as fixed covariates, and random intercept and random slope as random covariates. This analysis will be done on non-imputed data. The structure of the covariance matrix will be set to unrestricted. The summary measure from this model will be the difference in average yearly radiographic slope (deterioriation) between the treatment groups.

5.2.2.6 Subgroup Analyses

There will be no subgroup analyses.

5.2.3 Continuous Secondary Outcomes

5.2.3.1 Main Analysis

Secondary continuous longitudinal outcomes other than radiographic outcomes will be analysed using generalized linear mixed model with random intercept, adjusted for the stratification factors in the randomisation (gender, anti-CCP status and country). For skewed variables (CRP and ESR) we will

use a gamma model, for count variables (joint counts) we will use a negative binomial model. For all other variables we will use the normal model.

5.2.3.2 Summary Measures

Summary measures will include estimated marginal means and corresponding unadjusted 95% confidence limits, both by treatment group and time, and by treatment difference and time. The adjusted estimates and corresponding 95% confidence intervals will be based on the averaged predictive margins and the delta method.

5.2.3.3 Assumption Checks

The residuals will be checked in models without treatment term

5.2.3.4 Missing Data

Missing data will be handled within the longitudinal mixed model framework.

5.2.3.5 Sensitivity Analyses

There will be no sensitivity analyses.

5.2.3.6 Subgroup Analyses

There will be no subgroup analyses.

5.2.4 Additional Analyses

None.

6 Safety Analyses

General safety evaluations will be based on the incidence, intensity, and type of adverse events (AEs) Safety variables will be tabulated and presented for all patients in the safety set.

6.1 Adverse Events

Adverse events will be coded using MedDRA, version 22.0. The investigator records the maximum intensity of each AE using the levels mild, moderate and severe. For tabulations, only treatment emerging adverse events (TEAEs) will be presented. TEAEs are defined as AEs with a start date on or after date of first randomised treatment. Any AEs prior to treatment will be listed but not tabulated.

The number (%) of subjects with any TEAEs, with 1, 2 or > 3 TEAEs, with treatment related TEAEs, with treatment emerging serious AEs (TESAE) and TEAEs of special interest will be summarised by treatment group. TEAEs of special interest are infections, cardiovascular diseases, cataracts, demyelinating diseases, diabetes mellitus, herpes zosters, malignancies, osteoporosis, and weight gain. The number of events and number (%) of subjects with adverse events by system organ class (SOC) and preferred term (PT) will be summarised by treatment group, overall, for serious AEs and for AEs of special interest. In addition, a summary table of AEs reported by >= 2% of all patients will be presented by SOC and PT.

7 Statistical Software

All statistical analyses will be done in Stata v16 (StataCorp. 2020. *Stata Statistical Software: Release 16*. College Station, TX, USA), and R version 4.03 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/)

8 References

8.1 Literature References

8.2 Reference to Data Handling Plan

8.3 Reference to the Trial Master File and Statistical Documentation

8.4 Reference to other Standard Operating Procedures or Documents