Efficacy of biological disease-modifying antirheumatic drugs - a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis

Supplementary material

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1 Literature search

The literature search was performed by a librarian with expertise in the field (SD). Title and abstract review of the main search was done independently by two of the authors (JLN and KTM). Discrepancies were resolved by discussion. Data were extracted and checked by both authors (JLN and KTM).

1.1 Medline search terms and limits

1 arthritis/ or arthritis, rheumatoid/ or caplan syndrome/ or felty syndrome/ or rheumatoid nodule/

2 rheumatoid arthritis.tw.

3 (early adj2 arthritis).tw.

4 inflammatory arthritis.tw.

5 or/1-4 [RA]

6 Biological Therapy/

7 biologic*.tw.

8 (bio-logic* or bio logic*).tw.

9 biosimilar*.tw.

10 (bio-similar* or bio similar*).tw.

11 infliximab.tw.

12 remicade.tw.

13 etanercept.tw.

14 enbrel.tw.

15 adalimumab.tw.

16 humira.tw.

17 abatacept.tw.

18 orencia.tw.

19 rituximab.tw.

20 mabthera.tw.

21 anakinra.tw.

22 kineret.tw.

23 tocilizumab.tw.

24 roactemra.tw.

25 golimumab.tw.

26 simponi.tw.

27 certolizumab.tw.

28 cimzia.tw.

29 sarilumab.tw.

30 secukinumab.tw.

31 sirukumab.tw.

32 ixekizumab.tw.

33 mavrilimumab.tw.

34 ustekinumab.tw.

35 guselkumab.tw.

36 (CT P13 or CT-P13).tw.

37 Inflectra.tw.

38 Remsima.tw.

39 SB2.tw.

40 SB4.tw.

41 Benepali.tw.

42 BOW015.tw.

43 HD203.tw.

44 (ABP 501 or ABP-501).tw.

45 SB5.tw.

46 ("BCD 020" or BCD-020).tw.

47 ("CHS 0214" or CHS-0214).tw.

48 GP2013.tw.

49 or/6-48 [Biological therapy]

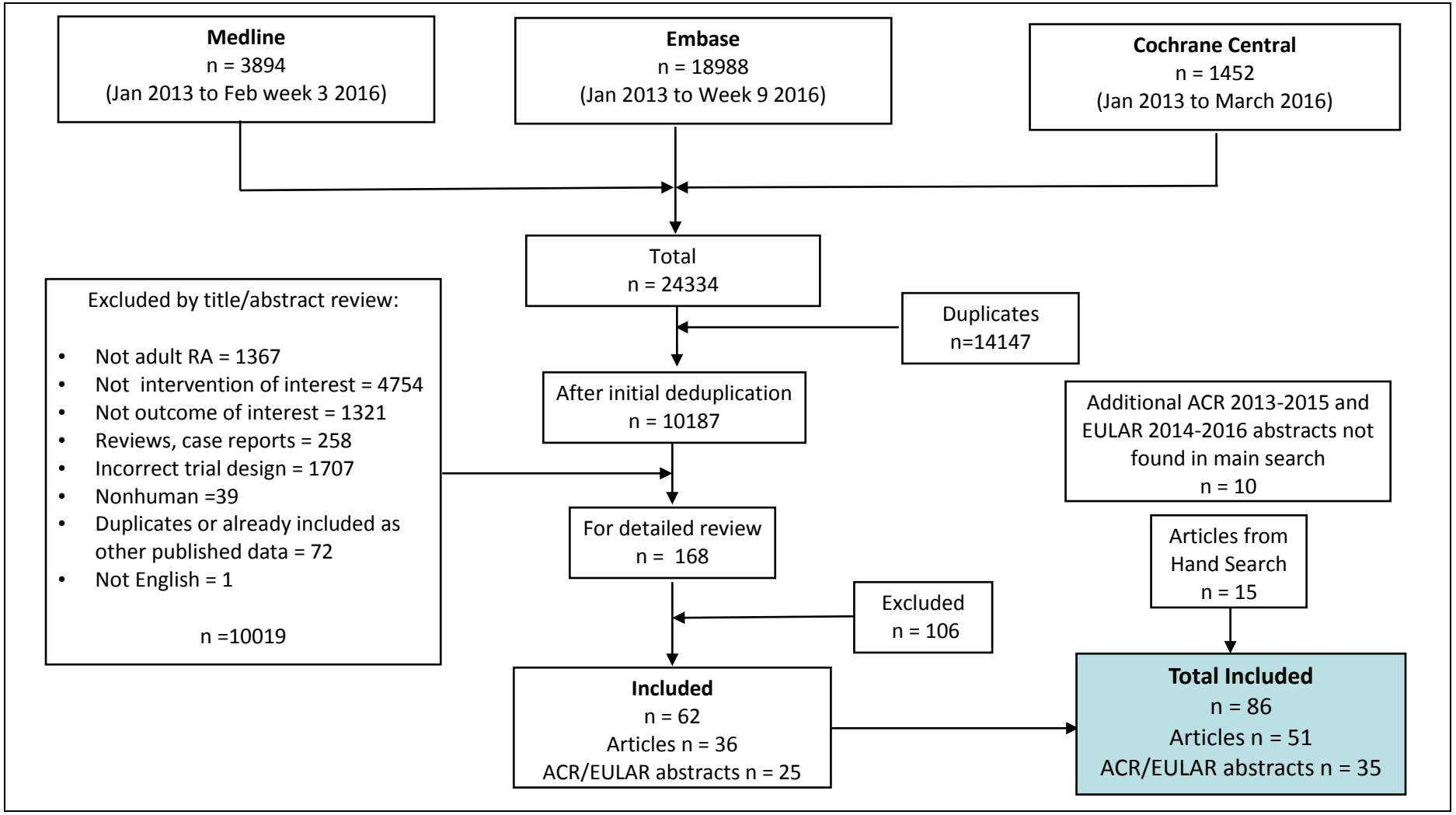
50 5 and 49 [RA and Biological therapy]

51 limit 50 to english language

52 limit 51 to yr="2013 -Current"

1.2 Search strategy

Figure 1. Seach strategy flow chart



1.3 Study selection criteria

The study selection criteria were as follows: (1) randomised controlled trials (RCTs) (double-blind for RCTs evaluating biological disease modifying anthrheumaticdrugs (bDMARDs) or bsDMARDs vs. conventional synthetic DMARDs (csDMARDs); open-label studies were included for strategy-type trials [1]); (2) patients with rheumatoid arthritis (RA) (1987 American College of Rheumatology (ACR)[2] or 2010 ACR/European League Against Rheumatism (EULAR) classification criteria[3]) or undifferentiated arthritis (UA); (3) studies on bDMARDs or bsDMARDs in phase 3 or 4 (or if unavailable, phase 2) development or targeted synthetic DMARDs (tsDMARDs)in comparison with a bDMARD; (4) ≥6 months' duration; (5) ≥50 patients; (6) publications in English. Published SLRs and meta-analyses were included if relevant.

The main reasons for exclusion were (1) articles not related to the search topic (2) review articles and case reports (3) non-randomised studies (4) studies of less than 6 months duration and (5) duplicate articles obtained from search.

Where abstracts were found and full papers subsequently (until July 2016) obtained, the published articles were selected unless abstracts provided additional study data. Only results from this search and not those from the 2010 and 2013 systematic literature reviews (SLRs)[4, 5] have been included. Results for all studies are included here in the supplementary material - including RCTs which were included in the 2013 SLR in abstract form. In the main manuscript only results from new studies have been discussed (i.e. those previously cited including those included abstract form in the 2010 and 2013 SLRs have not been reviewed in the main paper).

1.4 Baseline data and outcome measures for data extraction

Baseline demographic characteristics, disease duration, treatment allocation (dose and duration) concomitant treatments (DMARDs, corticosteroids, and non-steroidal anti-inflammatory drugs), follow-up duration and outcomes were extracted for each trial. Efficacy outcomes obtained included: those relating to signs and symptoms (including ACR and EULAR responses), radiographic outcomes, physical function (Health Assessment Questionnaire Disability Index (HAQ-DI)),[6] quality of life measures (Physical Component Score (PCS) and Mental Component Score (MCS) of the Short Form-36)[7] and fatigue (FACIT score [8, 9] and fatigue visual analogue scale [FAS]).

The following nomenclature, which differentiates between conventional synthetic (cs) and targeted synthetic (ts) DMARDs as well as biological originator (bo) and biosimilar (bs) DMARDs, has been used where appropriate.[10]

The Cochrane risk of bias assessment tool for RevMan version 5.1 was used to assess the quality of published studies.[11] Efficacy data are tabulated within the following sections (1) Comparisons of existing bDMARD +/-csDMARD vs csDMARD, (2) existing bDMARD +/-csDMARD vs bDMARD monotherapy, (3) head to head bDMARD studies, (4) bDMARD strategy-type studies, (5) bDMARD switching studies in TNFi IR, (6) bDMARD stopping, (7) bDMARD dose reduction or interval spacing, (8) existing bDMARDs vs new tsDMARD, (9) new bDMARD, (10) bsDMARDs and (11) safety outcomes from new bDMARD and bsDMARD RCTs. Data from RCTs that included a treatment arm with MTX monotherapy and the addition of a bDMARD at a later timepoint have been included in the section on strategy trials.

2 Tables of randomised controlled trials of biological DMARDs included in the systematic literature review

2.1 RCTs of biological DMARDs vs. conventional synthetic DMARDs

Table 1: Description of included RCT and baseline characteristics: Biological DMARDs in RA patients who are DMARD naïve

Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	DMARD Naïve (%)	Mean no. of previous DMARDs	On steroids (%)	On NSAIDs (%)
EULAR Emery 2015 (C-EARLY) [12] [13]	12	S	Placebo + MTX	213*	NR	NR	NR	1.7	100	NA	NR	NR
			CZP(200mg/2weeks) + MTX	655*	NR	NR	NR	1.6	100	NA	NR	NR
Weinblatt ACR 2015 (C-EARLY) [14]	12	S	Placebo + MTX	213*	51.2	NR	6.8	1.7	100	NA	NR	NR
			CZP(200mg/2weeks) + MTX	655*	50.4	NR	6.7	1.6	100	NA	NR	NR

- *CZP, certolizumab pegol; HAQ-DI, health assessment questionnaire disease index; MTX, methotrexate; NA, not applicable; NR, not recorded; S, superiority*
- ** Number of patients evaluated for baseline characteristics*

Table 2: Cochrane risk of bias assessment: Biological DMARDs in RA patients who are DMARD naïve

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Emery EULAR 2015 (C-EARLY) [12] [13]	CZP	a	a	a	a	a	a	a
Weinblatt ACR 2015 (C-EARLY) [14]	CZP	a	a	a	a	a	a	a

- *CZP, certolizumab pegol*
- *a = abstract only*

Table 3: Description of included RCTs and baseline characteristics: Biological DMARDs in RA patients who are MTX-naïve

Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	DMARD Naïve (%)	Previous DMARD excl MTX (%)	On steroids (%)	On NSAIDs (%)
Smolen 2015 (AGREE) [15]	12	S	Placebo + MTX	209*	49.2	0.59	6.3**	1.7	NR	NR	NR	NR
			ABT (10mg/kg according to weight range) + MTX	210*	49.4	0.52	6.3**	1.7	NR	NR	NR	NR
Emery 2015 (AVERT) [16]	18[†]	S	Placebo + MTX	116	49.1	0.50	5.3**	1.4	NR	NR	NR	NR
			ABT (125mg/week sc)	116	45.4	0.59	5.5**	1.4	NR	NR	NR	NR
			ABT (125mg/week sc) + MTX	119	46.4	0.58	5.5**	1.5	NR	NR	NR	NR
Furst ACR 2014, EULAR 2015 (AVERT) [17] [18]	18[†]	S	Placebo + MTX	116	NR	NR	NR	NR	NR	NR	NR	NR
			ABT (125mg/week sc)	116	NR	NR	NR	NR	NR	NR	NR	NR
			ABT (125mg/week sc) + MTX	119	NR	NR	NR	NR	NR	NR	NR	NR
Takeuchi 2014 (HOPEFUL 1) [19]	6	S	Placebo + MTX	163	54.0	0.3	6.6	1.3	46.6	53.4	30.1	NR
			ADA (40mg/2weeks) + MTX	171	54.0	0.3	6.6	1.1	56.7	43.3	33.9	NR
Scott 2016 (CARDERA-2) [20]	24[††]	S	Placebo + MTX	75	54	0.01	6.45	1.58	NR	NR	0	NR
			ANA (100mg/day) + MTX	79	56	0.01	6.37	1.49	NR	NR	0	NR
Atsumi 2016 (C-OPERA) [21]	12	S	Placebo+ MTX	157	49.0	0.36	5.5	1.1	81.5	18.5	19.7	NR
			CZP (200mg/2weeks) + MTX	159	49.4	0.33	5.4	1.0	80.5	19.5	16.4	NR
Emery 2013 (GO-BEFORE) [22]	24[‡]	S	Placebo + MTX	160	48.6	2.9	5.6**	1.5	NR	NR	NR	NR
			GLM (100mg/4weeks) + Placebo	159	48.2	4.1	5.8**	1.6	NR	NR	NR	NR
			GLM (50mg/4weeks) + MTX	159	50.9	3.5	5.7**	1.5	NR	NR	NR	NR
			GLM (100mg/4weeks) + MTX	159	50.2	3.6	5.7**	1.5	NR	NR	NR	NR
Burmester EULAR 2014 (FUNCTION) [23]	12	S	Placebo + MTX	287*	NR	NR	NR	NR	NR	NR	NR	NR
			TCZ (4mg/kg/4weeks) + MTX	288*	NR	NR	NR	NR	NR	NR	NR	NR
			TCZ (8mg/kg/4weeks) + MTX	290*	NR	NR	NR	NR	NR	NR	NR	NR
			TCZ (8mg/kg/4weeks) +	292*	NR	NR	NR	NR	NR	NR	NR	NR

			Placebo									
Burmester ACR 2014 (FUNCTION) [24]	24	S	Placebo + MTX	287*	NR	NR	NR	NR	NR	NR	NR	NR
			TCZ (4mg/kg/4weeks) + MTX	288*	NR	NR	NR	NR	NR	NR	NR	NR
			TCZ (8mg/kg/4weeks) + MTX	290*	NR	NR	NR	NR	NR	NR	NR	NR
			TCZ (8mg/kg/4weeks) + Placebo	292*	NR	NR	NR	NR	NR	NR	NR	NR
Burmester 2016 (FUNCTION) [25]	12	S	Placebo + MTX	287*	49.6	0.4	6.6	1.48	80.9	19.1	38	NR
			TCZ (4mg/kg/4weeks) + MTX	288*	51.2	0.4	6.7	1.62	81.7	18.3	37	NR
			TCZ (8mg/kg/4weeks) + MTX	290*	49.5	0.5	6.7	1.50	79.3	20.7	33	NR
			TCZ (8mg/kg/4weeks) + Placebo	292*	49.9	0.5	6.7	1.58	76.4	23.6	40	NR

- *ABT, abatacept; ADA, adalimumab; ANA anakinra; CZP, certolizumab pegol; GLM, golimumab; HAQ-DI, health assessment questionnaire disease index; MTX, methotrexate; NR, not recorded; S, superiority; TCZ, tocilizumab*
- *† Only 12 month data included in this category (before withdrawal period), †† Only 12 month data included in this category (before follow-up period), ‡ Only 12 month data included in this category (before MTX arm crossover to GLM)*
- ** Number of patients evaluated for baseline characteristics, ** DAS28 CRP*

Table 4: Cochrane risk of bias assessment: Biological DMARDs in RA patients who are MTX-naïve

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Smolen 2015 (AGREE) [15]	ABT	o	o	o	o	L	L	L
Emery 2015 (AVERT) [16]	ABT	L	L	L	L	L	L	L
Furst ACR 2014, EULAR 2015 (AVERT) [18] [17]	ABT	a	a	a	a	a	a	a
Takeuchi 2014 (HOPEFUL 1) [19]	ADA	U[1]	U[1]	L	L	L	L	L
Scott 2016 (CARDERA-2) [20]	ANA	L	L	H[2]	L	L	L	L
Atsumi 2016 (C-OPERA) [21]	CZP	L	L	L	L	L	L	L
Emery 2013 (GO-BEFORE) [22]	GLM	o	o	o	o	L	L	L

Burmester EULAR 2014 (FUNCTION) [23]	TCZ	a	a	a	a	a	a	a
Burmester ACR 2014 (FUNCTION) [24]	TCZ	a	a	a	a	a	a	a
Burmester 2016 (FUNCTION) [25]	TCZ	L	L	L	L	L	L	L

- *ABT, abatacept; ADA, adalimumab; ANA anakinra; CZP,certolizumab pegol; GLM, golimumab; MTX, methotrexate; TCZ, tocilizumab*
- *a = abstract only, o = refer to original manuscript, H= high risk; L = low risk; U = unclear risk*
- *[1]Details not recorded; [2]Open label study*

Table 5: Description of included RCTs and baseline characteristics: Biological DMARDs in RA patients who are MTX inadequate responders (MTX-IR)

Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	Baseline MTX dose (mg/week)	On steroids (%)	On NSAIDs (%)
Yamamoto 2014 (J-RAPID) [26]	6	S	Placebo + MTX	77	51.9	5.8	6.5	1.2	7.4	59.7	NR
			CZP (100mg/2weeks) + MTX	72	54.3	6.0	6.3	1.2	7.4	65.3	NR
			CZP (200mg/2weeks) + MTX	82	50.6	5.6	6.2	1.1	7.6	68.3	NR
			CZP (400mg/2weeks) + MTX	85	55.4	6.0	6.3	1.1	7.5	69.4	NR
Weinblatt 2013 (GO-FURTHER) [27]	6	S	Placebo + MTX	197	51.4	7.0	5.9**	1.6	NR	NR	NR
			GLM (2mg/kg iv) + MTX	395	51.9	6.9	6.0**	1.6	NR	NR	NR
Bingham 2014 (GO-FURTHER) [28]	6	S	Placebo + MTX	197	51.4	7.0	5.9**	1.6	NR	68.0	NR
			GLM (2mg/kg iv) + MTX	395	51.9	6.9	6.0**	1.6	NR	63.5	NR
Li ACR 2013 [29]	12[†]	S	Placebo + MTX	132	NR	NR	NR	NR	NR	NR	NR
			GLM (50mg/4weeks) + MTX	132	NR	NR	NR	NR	NR	NR	NR
Kim 2013 [30]	19[††]	S	Placebo + MTX	72	51.4	9.8*	NR	1.4	NR	NR	NR
			IFX (3mg/kg) + MTX	71	49.3	7.4*	NR	1.4	NR	NR	NR

- *CZP, certolizumab pegol; GLM, golimumab; HAQ-DI, health assessment questionnaire disease index; IFX, infliximab; MTX, methotrexate; NR, not recorded*
- ** Median disease duration (years)*
- *[†] Only 6 month data included in this category (before MTX arm crossover to GLM), [††] Only 7 month data included in this category (before entension study)*
- *** DAS28 CRP*

Table 6: Cochrane risk of bias assessment: Biological DMARDs in RA patients who are MTX inadequate responders (MTX IR)

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Yamamoto 2014 (J-RAPID) [26]	CZP	L	L	L	L	L	L	L
Weinblatt 2013 (GO-FURTHER) [27]	GLM IV	L	L	L	L	L	L	L
Bingham 2014 (GO-FURTHER) [28]	GLM IV	o	o	o	o	L	L	L
Li ACR 2013 [29]	GLM	a	a	a	a	a	a	a
Kim 2013 [30]	IFX	U[1]	U[1]	L	L	L	L	L

- *CZP, certolizumab pegol; GLM, golimumab; IFX, infliximab; IV, intravenous*
- *a = abstract only, o = refer to original manuscript, H= high risk; L = low risk; U = unclear risk*
- *[1]Details not recorded*

Table 7: Description of included RCTs and baseline characteristics: Biological DMARDs in RA patients with incomplete response to conventional synthetic DMARD (not necessarily methotrexate) (mixed DMARD-IR)

Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	Previous MTX use (%)	On steroids (%)	On NSAIDs (%)
Yamamoto 2014 (HIKARI) [31]	6	S	Placebo +/- DMARD	114	55.4	5.8	6.3	1.21	100	71.1	NR
			CZP (200mg/2weeks) +/- DMARD	116	56.0	5.4	6.1	1.05	100	66.4	NR
Smolen 2015 (CERTAIN) [32]	6	S	Placebo + DMARD	98	54.0	4.7	4.5	1.0	NR	NR	NR
			CZP (200mg/2weeks) + DMARD	96	53.6	4.5	4.5	1.1	NR	NR	NR
Takeuchi 2013 [33]	12	S	Placebo + MTX	176	50.4	3.0	5.8	1.0	61.4	NR	NR
			ETN (2×10mg/week) + Placebo	192	51.5	2.9	5.7	1.2	64.1	NR	NR
			ETN (2×25mg/week) + Placebo	182	51.8	3.0	5.8	1.1	67.0	NR	NR
Behrens EULAR 2016 (AMARA)* [34]	12	S	Placebo + LEF	NR**	NR	NR	5.54	NR	NR	NR	NR
			RTX (2×1000mg) + LEF	NR**	NR	NR	5.57	NR	NR	NR	NR
Kivitz 2014 (BREVACTA) [35]	6	S	Placebo + DMARD	219	52.0	11.1	6.6	1.6	NR	NR	NR
			TCZ (162mg/2weeks sc) + DMARD	437	52.1	11.1	6.7	1.6	NR	NR	NR

- *CZP, certolizumab pegol; DMARD, disease modifying antirheumatic drug; ETN, etanercept; HAQ-DI, health assessment questionnaire disease index; LEF, leflunomide; MTX, methotrexate; RTX, rituximab; sc, subcutaneous; TCZ, tocilizumab*
- ** Incomplete response to LEF, ** Total 148 patients were randomised*

Table 8: Cochrane risk of bias assessment: Biological DMARDs in RA patients who are mixed DMARD IR

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Yamamoto 2014 (HIKARI) [31]	CZP	L	L	L	L	L	L	L
Smolen 2015 (CERTAIN) [32]	CZP	L	L	L	L	U[1]	L	L
Takeuchi 2013 [33]	ETN	L	L	L	L	L	L	L
Behrens EULAR 2016 (AMARA) [34]	RTX	a	a	a	a	a	a	a
Kivitz 2014 (BREVACTA) [35]	TCZ SC	U[2]	U[2]	L	L	L	L	L

- *CZP, certolizumab pegol; ETN, etanercept; RTX, rituximab; SC, subcutaneous; TCZ, tocilizumab*
- *a = abstract only, H= high risk; L = low risk; U = unclear risk*
- [1]*No prior data on minimal or low disease activity therefore the trial was possibly underpowered. There was still statistically signficant differences between the treatment arms but this may have affected the treatment stopping stage of the study.*
- [2]*Details not recorded*

2.2 RCTs of combination biological DMARD + MTX vs. biological DMARD monotherapy (which have not been described in section 2.1)

Table 9: Description of included RCTs and baseline characteristics: Biologic monotherapy vs. biological DMARD + MTX in RA patients who are MTX-IR

Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	Mean no. of previous DMARDs	On steroids (%)	On NSAIDs (%)
Dougados 2014 (ACT-RAY) [36]	12	S	TCZ (8mg/kg/4weeks) + Placebo	276*	53.6	8.3	6.36	1.48	1.9	50.7	NR
			TCZ (8mg/kg/4weeks) + MTX	277*	53.0	8.2	6.33	1.46	1.9	50.5	NR
Kaneko 2016 (SURPRISE) [37]	12	NI	TCZ (8mg/kg/4weeks) + Placebo	111*	56.3	3.8	5.3	1.0	NR	36.9	NR
			TCZ (8mg/kg/4weeks) + MTX	115*	55.8	3.6	5.1	1.0	NR	35.7	NR

- *HAQ-DI, health assessment questionnaire disease index; MTX, methotrexate; NI, non-inferiority; NR, not recorded; S, superiority; TCZ, tocilizumab*
- ** Baseline characteristics of randomised population*

Table 10: Cochrane risk of bias assessment: Biologic monotherapy vs. biological DMARD + MTX in RA patients who are MTX-IR

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Dougados 2014 (ACT-RAY) [36]	TCZ	o	o	o	o	L	L	L
Kaneko 2016 (SURPRISE) [37]	TCZ	L	L	H[1]	H[1]	H[2]	L	L

- *TCZ, tocilizumab*
- *a = abstract only, o = refer to original manuscript, H= high risk; L = low risk; U = unclear risk*
- *[1]open label study; [2]number of patients randomised lower than sample size calculated to prove non-inferiority*

2.3 RCTs of head to head biological DMARDs

Table 11: Description of included RCTs and baseline characteristics: Head to head biological DMARDs in RA patients who are MTX-IR

Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ	Mean no. of previous DMARDs	On steroid (%)	On NSAIDs (%)
Schiff 2014 (AMPLE) [38]	24	NI	ABT (125mg/week) + MTX	318	51.4	1.9	5.5*	1.5	NR	NR	NR
			ADA (40mg/2weeks) + MTX	328	51.0	1.7	5.5*	1.5	NR	NR	NR
Fleischmann ACR 2013 (AMPLE) [39]	24	NI	ABT (125mg/week) + MTX	318	NR	NR	NR	NR	NR	NR	NR
			ADA (40mg/2weeks) + MTX	328	NR	NR	NR	NR	NR	NR	NR
Fleischmann 2016 (AMPLE) [40]	24	NI	ABT (125mg/week) + MTX	318	51.4	1.9	5.5*	1.5	NR	NR	NR
			ADA (40mg/2weeks) + MTX	328	51.0	1.8	5.5*	1.5	NR	NR	NR

- *ADA, adalimumab; ABT, abatacept; HAQ-DI, health assessment questionnaire disease index; MTX, methotrexate; NI, non-inferiority; NR, not recorded*
- ** DAS28-CRP*

Table 12: Cochrane risk of bias assessment: Head to head biological DMARDs in RA patients who are MTX IR

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Schiff 2014 (AMPLE) [38]	ABT vs. ADA	o	o	o	o	L	L	L
Fleischmann ACR 2013 (AMPLE) [39]	ABT vs. ADA	a	a	a	a	a	a	a
Fleischmann 2016 (AMPLE) [40]	ABT vs. ADA	o	o	o	o	L	L	L

- *ADA, adalimumab; ABT, abatacept*
- *a = abstract only, o = refer to original manuscript, H= high risk; L = low risk; U = unclear risk*

2.4 Biological DMARDs strategies RCTs

Table 13: Description of included RCTs and baseline characteristics: Biological DMARDs strategies RCTs

Patient group	Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	On steroids (%)
DMARD naïve	Heimans 2013/ 2014 (IMPROVED) [41] [42]	12	S	Early remission (MTX)	387	52	0.33	3.0[§]	1.0	0.0
				Arm1 (Predonisone + SSZ + HCQ + MTX)	83	48/49	0.42	3.6[§]	1.4	0.0
				Arm2 (ADA 40mg/2weeks + MTX)	78	51	0.40	3.6[§]	1.4	0.0
				Outside protocol treatment	50	54	0.35	3.6[§]	1.3	0.0
	Hørslev-Petersen 2014 (OPERA) [43]	12	S	Placebo + DMARD	91	54.2[#]	0.23[#]	5.6[#]**	NR	0.0
				ADA (40mg/2weeks) + DMARD	89	56.2[#]	0.24[#]	5.5[#]**	NR	0.0
	Hørslev-Petersen 2016 (OPERA) [44]	24	S	Placebo + DMARD	91	NR	NR	5.6[#]**	1.00[#]	0.0
				ADA (40mg/2weeks) + DMARD	89	NR	NR	5.5[#]**	1.13[#]	0.0
	Nam 2014 (EMPIRE) [45]	18	S	Placebo + MTX	55	48.38	0.67[#]	4.17**	1.00	NR
				ETN (50mg/week) + MTX	55	47.91	0.50[#]	4.10**	1.01	NR
	Markusse 2016 (Best) [46]	120	S	Sequential Monotherapy	126	54	0.44[#]	4.5	1.4	NR
				Step-up Combination therapy	121	54	0.50[#]	4.5	1.4	NR
				Initial Combination Therapy With Prednisone	133	55	0.44[#]	4.4	1.4	NR
				Initial Combination Therapy With IFX	128	54	0.44[#]	4.3	1.4	NR
	Nam 2014 (IDEA) [47]	18	S	IV MP (250mg) + MTX	57	52.9	0.10[#]	3.56[§]	1.339	0
				IFX (3mg/kg) + MTX	55	53.7	0.10[#]	4.05[§]	1.426	0
	Bijlsma 2016 (U-ACT-EARLY) [48]	24	S	MTX + Placebo	108	53.5	0.07	5.1	1.1	0
				TCZ (8mg/kg/4weeks) + Placebo	103	55.0	0.07	5.3	1.3	0
				TCZ (8mg/kg/4weeks) + MTX	106	53.0	0.07	5.2	1.1	0
MTX naïve	Emery 2013 (GO-BEFORE) [22]	24	S	Placebo + MTX → GLM (100mg/4weeks)	160	48.6	2.9	5.6**	1.5	NR
				GLM (100mg/4weeks) + Placebo	159	48.2	4.1	5.8**	1.6	NR
				GLM (50mg/4weeks) + MTX	159	50.9	3.5	5.7**	1.5	NR
				GLM (100mg/4weeks) + MTX	159	50.2	3.6	5.7**	1.5	NR
MTX IR	Li ACR 2013 [29]	12	S	Placebo + MTX→ GLM (50mg/4weeks)	132	NR	NR	NR	NR	NR
				GLM (50mg/4weeks) + MTX	132	NR	NR	NR	NR	NR
	Weinblatt ACR 2013 (GO-	24	S	Placebo + MTX → GLM (2mg/kg iv) + MTX	197	NR	NR	NR	NR	NR

	FURTHER) [49]			GLM (2mg/kg iv) + MTX	395	NR	NR	NR	NR	NR
	Weinblatt 2014 (GO-FURTHER) [50]	12	S	Placebo + MTX → GLM (2mg/kg iv) + MTX	197	51.4	7.0	5.9**	1.6	NR
				GLM (2mg/kg iv) + MTX	395	51.9	6.9	6.0**	1.6	NR
	Scott 2015 (TACIT) [51]	12	NI	DMARD combinations strategy	104*	58	4.4[#]	6.2	1.8	NR
				TNFi strategy	101*	57	5.9[#]	6.3	1.9	NR
Mixed DMARD IR	Takeuchi 2013 (GO-MONO) [52]	6	S	Placebo → GLM (50mg/4weeks)	105*	52.4	9.2	5.9	1.0	NR
				GLM (50mg/4weeks)	101*	52.9	8.1	5.8	1.1	NR
				GLM (100mg/4weeks)	102*	51.6	9.4	6.0	1.0	NR

- *ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GLM, golimumab; HAQ-DI, health assessment questionnaire disease index; HCQ, hydroxychloroquine; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; NI, non-inferiority; NR, not recorded; S, superiority; SSZ, sulphasalazine; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor*
- [#] *Median*, [§] *DAS44, ** DAS28-CRP*
- ** Baseline characteristics of randomised population*

Table 14: Cochrane risk of bias assessment: Biological DMARDs strategies RCTs

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Heimans 2013 (IMPROVED) [41]	ADA	o	o	o	o	L	L	L
Heimans 2014 (IMPROVED) [42]	ADA	L	L	H[1]	L	L	L	L
Hørslev-Petersen 2014 (OPERA) [43]	ADA	U[2]	U[2]	L	L	L	L	L
Hørslev-Petersen 2016 (OPERA) [44]	ADA	o	o	o	o	L	L	L
Nam 2014 (EMPIRE)[45]	ETN	L	L	L	L	L	L	L
Markusse 2016 (Best) [46]	IFX	o	o	o	o	H[3]	L	L
Nam 2014 (IDEA) [47]	IFX	L	L	L	L	L	L	L
Bijlsma 2016 (U-ACT-EARLY) [48]	TCZ	L	L	L	L	L	H[4]	L
Emery 2013 (GO-BEFORE) [22]	GLM	o	o	o	o	L	L	L
Li ACR 2013 [29]	GLM	a	a	a	a	a	a	a

Weinblatt ACR 2013 (GO-FURTHER) [49]	GLM IV	a	a	a	a	a	a	a
Weinblatt 2014 (GO-FURTHER) [50]	GLM IV	L	L	L	L	L	L	L
Scott 2015 (TACIT) [51]	TNFi	L	L	H[5]	H[5]	L	H[6]	L
Takeuchi 2013 (GO-MONO) [52]	GLM	U[2]	U[2]	L	L	L	L	L

- *ADA, adalimumab; GLM, golimumab; IFX, infliximab; IV, intravenous; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor*
- *a = abstract only, o = refer to original manuscript, H= high risk; L = low risk; U = unclear risk*
- *[1]single blind study; [2]details not recorded; [3] 38% patient dropout by year 10 – data analysed by multiple imputation to overcome this; completer analysis to be interpreted with caution; [4] DAS28 (a measure which includes an acute phase reactant) used as the primary outcome may bias results towards more favourable outcome for the TCZ groups; [5]open label study; [6]Large non-inferiority margin, limiting interpretablility*

2.5 Biological DMARDs switching RCTs

Table 15: Description of included RCTs and baseline characteristics: Biological DMARDs switching between bDMARDs RCTs

Patient group	Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	On steroids (%)
TNFi IR	Manders 2015 (DREAM) [53]	12	NI	ABT	43	56.16	6.56*	4.74	1.46	11.6
				RTX	46	57.09	7.60*	4.87	1.39	8.7
				TNFi	50	55.81	5.64*	4.92	1.37	10.0
	Gottenberg ACR 2013 (ROC) [54]	6	NR	2nd non-TNFi (ABT, RTX, TCZ)	146	58.2	10.0*	5.2	1.3	54.8
				2nd TNFi (ADA, CZP, ETN, IFX)	145	55.9	10.5*	5.0	1.3	51.0
	Gottenberg ACR 2015 (ROC) [55]	12	NR	2nd non-TNFi (ABT, RTX, TCZ)	146	NR	NR	NR	NR	NR
				2nd TNFi (ADA, CZP, ETN, IFX)	146	NR	NR	NR	NR	NR

- *ABT, abatacept; ADA, adalimumab; CZP,certolizumab pegol; ETN, etanercept; HAQ-DI, health assessment questionnaire disease index; IFX, infliximab; NI, non-inferiority; NR, not recorded; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TNFi IR, tumour necrosis factor inhibitor incomplete responder*
- ** Median disease duration (years)*

Table 16: Cochrane risk of bias assessment: Biological DMARDs switching between bDMARDs RCTs

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Manders 2015 (DREAM) [53]	ABT vs. RTX vs. TNFi	L	L	H[1]	H[1]	L	L	L
Gottenberg ACR 2015 (ROC) [55]	2nd non-TNFi vs. 2nd TNFi	a	a	H[1]	H[1]	a	a	a
Gottenberg ACR 2013 (ROC) [54]	2nd non-TNFi vs. 2nd TNFi	a	a	H[1]	H[1]	a	a	a

- *ABT, abatacept; RTX, rituximab; TNFi, tumour necrosis factor inhibitor*
- *a = abstract only, o = refer to original manuscript, H= high risk; L = low risk; U = unclear risk*
- *[1]open label study*

2.6 RCTs addressing biological DMARD stopping

Table 17: Description of included RCTs and baseline characteristics: RCTs addressing Biological DMARD stopping

Patient group	Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean DAS28*	Mean baseline HAQ-DI	Mean HAQ-DI*
DMARD naïve	Hørslev-Petersen 2016 (OPERA) [44]	12+12	S	Placebo + DMARD	91	NR	NR	5.6#**	NR	1.00**	NR
				ADA (40mg/2weeks) + DMARD	89	NR	NR	5.5#**	NR	1.13**	NR
	Bingham EULAR 2016 (C-EARLY)[8] [56]	12+12	S	CZP (200mg/2weeks) + MTX → Placebo + MTX	79	NR	NR	NR	NR	NR	0.33
				CZP (200mg/2weeks) + MTX → CZP (200mg/4weeks) + MTX	126	NR	NR	NR	NR	NR	0.33
				CZP (200mg/2weeks) + MTX → CZP (200mg/2weeks) + MTX	84	NR	NR	NR	NR	NR	0.32
	Nam 2014 (EMPIRE)‼ [45]	12+6	S	Placebo + MTX → MTX	55	48.38	0.67**	4.17#	NR	1.00	NR
				ETN (50mg/week) + MTX → MTX	55	47.91	0.50**	4.10#	NR	1.01	NR
	Markusse 2016 (Best)¶ [46]	120	S	Sequential monotherapy	126	54	0.44**	4.5	NR	1.4	NR
				Step-up combination therapy	121	54	0.50**	4.5	NR	1.4	NR
				Initial combination therapy with prednisone	133	55	0.44**	4.4	NR	1.4	NR
				Initial combination therapy with IFX	128	54	0.44**	4.3	NR	1.4	NR
	Nam 2014 (IDEA)※ [47]	18	S	IV MP (250mg) + MTX	57	52.9	0.10**	3.56§	NR	1.339	NR
				IFX (3mg/kg) + MTX	55	53.7	0.10**	4.05§	NR	1.426	NR
MTX naïve	Furst ACR 2014 (AVERT) [17]	12+6	S	MTX → no treatment	116	NR	NR	NR	NR	NR	NR
				ABT (125mg/week sc) → no treatment	116	NR	NR	NR	NR	NR	NR
				ABT (125mg/week sc) + MTX → no treatment	119	NR	NR	NR	NR	NR	NR
	Furst EULAR 2015 (AVERT) [18]	12+6	S	MTX → no treatment	116	NR	NR	NR	NR	NR	NR
				ABT (125mg/week sc) → no treatment	116	NR	NR	NR	NR	NR	NR
				ABT (125mg/week sc) + MTX → no treatment	119	NR	NR	NR	NR	NR	NR

	Emery 2015 (AVERT) [16]	12+6	S	MTX → no treatment	116	49.1	0.50	5.3[#]	NR	1.4	NR
				ABT (125mg/week sc) → no treatment	116	45.4	0.59	5.5[#]	NR	1.4	NR
				ABT (125mg/week sc) + MTX → no treatment	119	46.4	0.58	5.5[#]	NR	1.5	NR
	Smolen 2014 (OPTIMA) [57]	6+12	S	MTX monotherapy	112	48.5	0.33	5·5[#]	2.2[#]	1.4	0.3
				ADA continuation (40mg/2weeks) + MTX	105	49.5	0.33	5·7[#]	2.0[#]	1.4	0.4
				ADA withdrawal + MTX	102	50.1	0.33	5·9[#]	2.2[#]	1.6	0.3
				ADA carry-on	259	50.4	0.33	6·2[#]	4.2[#]	1.7	1.0
				ADA rescue	348	50.7	0.34	6·1[#]	4.5[#]	1.7	1.1
	Emery 2014 (PRIZE) [8] [58]	12+9+6	S	ETN (50mg/week) + MTX → Placebo → no treatment	65[†]/32[¥]	50.9[†]/51.4[¥]	0.29[†]/0.23[¥]	5.9[†]/5.7[¥]	NR	1.2[†]/1.1[¥]	NR
				ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65[†]/46[¥]	47.7[†]/46.8[¥]	0.28[†]/0.30[¥]	5.7[†]/5.9[¥]	NR	1.1[†]/1.2[¥]	NR
				ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63[†]/53[¥]	49.6[†]/48.9[¥]	0.24[†]/0.25[¥]	5.9[†]/5.9[¥]	NR	1.2[†]/1.2[¥]	NR
	Wiland 2016 (PRIZE) [8] [59]	12+9+6	S	ETN (50mg/week) + MTX → Placebo → no treatment	65	NR	NR	NR	NR	NR	NR
				ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65	NR	NR	NR	NR	NR	NR
				ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63	NR	NR	NR	NR	NR	NR
MTX IR	Furst 2015 (DOSEFLEX) [60]	4+4	S	CZP (200mg/2weeks) + MTX → Placebo + MTX	69	51.5	6.5	6.4	NR	1.42	NR
				CZP (200mg/2weeks) + MTX → CZP (200mg/2weeks) + MTX	70	55.6	5.9	6.4	NR	1.57	NR
				CZP (200mg/2weeks) + MTX → CZP (400mg/week) + MTX	70	53.1	6.4	6.2	NR	1.41	NR
	Yamanaka 2016 (ENCOURAGE) [61]	12+12	S	ETN (2×25mg/week) + MTX → MTX	34[‡]	53.9*	2.4*	NR	1.8	NR	0.1
				ETN (2×25mg/week) + MTX → ETN (2×25mg/week) + MTX	33[‡]	49.8*	1.9*	NR	1.7	NR	0.1
	Huizinga 2015	12+12	S	TCZ (8mg/kg/4weeks) + Placebo	276*	53.6	8.3	6.36	NR	1.48	NR

	(ACT-RAY)∬ [62]			TCZ (8mg/kg/4weeks) + MTX	277*	53.0	8.2	6.33	NR	1.46	NR
Mixed DMARD IR	van Vollenhoven 2016 (DOSERA) [8] [63]	2+12	S	ETN (50mg/week) + MTX → Placebo + MTX	23	56.1	12.3	4.8	1.9	NR	0.13**
				ETN (50mg/week) + MTX → ETN (25mg/week) + MTX	27	59.6	16.6	5.2	1.9	NR	0.38**
				ETN (50mg/week) + MTX → ETN (50mg/week) + MTX	23	53.8	11.5	4.9	1.9	NR	0.25**

- *ABT, abatacept; ADA, adalimumab; CZP, certolizumab pegol; DMARD, disease modifying antirheumatic drug; ETN, etanercept; HAQ-DI, health assessment questionnaire disease index; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; S, superiority; TCZ, tocilizumab; NR, not recorded*
- **At randomisation, † The population of double-blind phase, ¥ The population of treatment-withdrawal phase, ‡ Number of patients evaluated for efficacy; # DAS28 CRP, § DAS44, ** median*
- *[8] Studies also addressing bDMARD dose reduction*
- *‼ Efficacy data included under strategy study section as csDMARDs allowed between 12 and 18 months when ETN/placebo was withdrawn*
- *¶ The medication dosage could be tapered if DAS calculations determined every 3 mo were 2.4 or less for at least 6 mo consecutively.*
- *※ IFX infusions were withdrawn if patients taking IFX were in sustained remission (DAS44<1.6) for 6 months at all consecutive visits.*
- *∬ Between weeks 52 and 104, patients in sustained clinical remission, discontinued TCZ and were assessed every 4 weeks for 1 year. If sustained remission was maintained, added*
- *csDMARDs, then MTX/PBO, were discontinued.*

Table 18: Cochrane risk of bias assessment: RCTs addressing Biological DMARD stopping

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Hørslev-Petersen 2016 (OPERA) [43]	ADA	o	o	o	o	L	L	L
Bingham EULAR 2016 (C-EARLY) [8] [56]	CZP	a	a	a	a	a	a	a
Nam 2014 (EMPIRE) [45]	ETN	L	L	L	L	L	L	L
Markusse 2016 (Best) [46]	IFX	o	o	o	o	H[1]	L	L
Nam 2014 (IDEA) [47]	IFX	L	L	L	L	L	L	L
Furst ACR 2014 (AVERT) [17]	ABT	a	a	a	a	a	a	a
Furst EULAR 2015 (AVERT) [18]	ABT	a	a	a	a	a	a	a
Emery 2015 (AVERT) [16]	ABT	L	L	L	L	L	L	L
Smolen 2014 (OPTIMA) [57]	ADA	L	L	L	L	L	L	L
Emery 2014 (PRIZE) [8] [58]	ETN	U[2]	U[2]	L	L	L	L	L
Wiland 2016 (PRIZE) [8] [59]	ETN	a	a	a	a	a	a	a
Furst 2015 (DOSEFLEX) [60]	CZP	U[2]	U[2]	L	L	L	L	L
Yamanaka 2016 (ENCOURAGE) [61]	ETN	U[2]	U[2]	H[3]	H[3]	H[4]	L	L
Huizinga 2015 (ACT-RAY) [62]	TCZ	o	o	H[5]	H[5]	L	L	L
van Vollenhoven 2016 (DOSERA) [8] [63]	ETN	U[2]	U[2]	L	L	L	L	L

- *ABT, abatacept; ADA, adalimumab; CZP, certolizumab pegol; ETN, etanercept; IFX, infliximab; TCZ, tocilizumab*
- *a = abstract only, o = refer to original manuscript, H= high risk; L = low risk; U = unclear risk*
- *[8] Studies also addressing bDMARD dose reduction*
- *[1]38% patient dropout by year 10 – data analysed by multiple imputation to overcome this; completer analysis to be interpreted with caution; [2]details not recorded; [3]open label study; [4] approximately one third in each group not included in final analysis due to withdrawal of consent or protocol violations; [5]open label from week 52*

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2.7 RCTs addressing biological DMARD dose reduction[8]

Table 19: Description of included RCTs and baseline characteristics: RCTs addressing Biological DMARD dose reduction

Patient group	Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean DAS28*	Mean baseline HAQ-DI	Mean HAQ-DI*
MTX naïve	Westhovens 2015 (AGREE) [64]	12+12	S	ABT (10mg/kg) + MTX → ABT (5mg/kg) + MTX	50*	51.1*	2.4*	NR	2.1[#]	NR	0.6
				ABT (10mg/kg) + MTX → ABT (10mg/kg) + MTX	58*	50.1*	2.2*	NR	2.1[#]	NR	0.5
Mixed DMARD IR	Fautrel 2016 (STRASS) [65]	18	E	M-arm (Maintenance)	73	56.4	11.0	1.7	NR	0.4	NR
				S-arm (ADA or ETN Injection spacing[‡])	64	54.3	8.3	1.9	NR	0.5	NR
	van Herwaarden 2015 (DRESS) [66]	18	NI	Usual care	59	58	10**	2.5	NR	NR	NR
				Dose reduction (ADA or ETN)[∴]	121	59	10**	2.5	NR	NR	NR
	Galloway EULAR 2015 (OPTTIRA) [67]	6	NR	Control	50	NR	NR	NR	NR	NR	NR
				33% Taper (Tapering ADA or ETN doses)	48	NR	NR	NR	NR	NR	NR
				66% Taper (Tapering ADA or ETN doses)	38	NR	NR	NR	NR	NR	NR
TNFi IR	Mariette 2014 (SMART) [68]	6+18	NI	RTX 1000mgx2 + MTX →RTX 1000mgx1 + MTX	70	55	11**	5.8[#]	NR	1.7	NR
				RTX 1000mgx2 + MTX →RTX 2000mgx1 + MTX	73	57	12**	5.8[#]	NR	1.8	NR

- *ABT, abatacept; ADA, adalimumab; E, equivalence; ETN, etanercept; HAQ-DI, health assessment questionnaire disease index; MTX, methotrexate; NI, noninferiority; S, superiority; SSZ, sulphasalazine; NR, not recorded*
- ** At randomisation, ** median, [#]DAS28 CRP*
- *[8] Bingham EULAR 2016 (C-EARLY) [56]; Emery 2014 (PRIZE) [58]; van Vollenhoven 2016 (DOSERA) [63]; Wiland 2016 (PRIZE) [59] = studies addressing bDMARD dose reduction and stopping; see section 2.6 'Biological DMARD RCTs addressing biological DMARD stopping' for details*
- *[‡] Injections spacing by 50% every 3 months up to complete stop, [∴] Stepwise increase the injection interval every three months, until flare of disease activity or discontinuation*

Table 20: Cochrane risk of bias assessment: RCTs addressing Biological DMARD dose reduction

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Westhovens 2015 (AGREE) [64]	ABT	U[1]	U[1]	L	L	U[1]	L	L
Fautrel 2016 (STRASS) [65]	ADA & ETN	L	L	H[2]	L	H[3]	L	L
van Herwaarden 2015 (DRESS) [66]	ADA & ETN	L	L	H[4]	H[4]	L	U[5]	L
Galloway EULAR 2015 (OPTTIRA) [67]	ADA & ETN	a	a	a	a	a	a	a
Mariette 2014 (SMART) [68]	RTX	L	L	H[4]	H[4]	L	L	L

- *ABT, abatacept; ADA, adalimumab; bDMARD, biological disease modifying antirheumatic drug; ETN, etanercept; RTX, rituximab*
- *a = abstract only, o = refer to original manuscript, H= high risk; L = low risk; U = unclear risk*
- *[1] details not recorded; [1]power calculation not performed for dose reduction substudy; [2]single blind study; [3]underpowered due to lack of funding and recruitment difficulties; [4]open label study*
- *[5]change in primary endpoint from difference in cumulative incidence of all flares to cumulative incidence of major flares during study but before outcomes available; based on clinical judgement. Of note non-inferiority margin of 20% also based on clinical judgement so power calculation probably not affected by change in choice of primary endpoint.*

2.8 RCTs comparing a biological and targeted synthetic DMARD

Table 21: Description of included RCTs and baseline characteristics: RCTs comparing a Biological and targeted synthetic DMARD

Patient group	Study	Study duration (months)	Study design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	On steroids (%)
MTX-IR	Taylor ACR 2015 (RA-BEAM) [69]	6	S	Placebo + MTX	488	NR	NR	NR	NR	NR
				Baricitinib (4mg/day) + MTX	487	NR	NR	NR	NR	NR
				ADA (40mg/2weeks) + MTX	330	NR	NR	NR	NR	NR

- *ADA, adalimumab; HAQ-DI, health assessment questionnaire disease index; MTX, methotrexate; MTX IR, methotrexate incomplete responder; NR, not recorded*

Table 22: Cochrane risk of bias assessment: RCT that included both Biological and targeted synthetic DMARDs

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Taylor ACR 2015 (RA-BEAM) [69]	ADA vs. Baricitinib	a	a	a	a	a	a	a

- *ADA, adalimumab; a = abstract only*

2.9 RCTs of new biological DMARDs

Table 23: Description of included RCTs and baseline characteristics: RCTs of new Biological DMARDs

Patient group	Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	On steroids (%)
MTX-IR	Strand ACR 2014 (MOBILITY) [70]	12	S	Placebo + MTX	398	NR	NR	NR	NR	NR
				Sarilumab (150mg/2weeks) + MTX	400	NR	NR	NR	NR	NR
				Sarilumab (200mg/2weeks) + MTX	399	NR	NR	NR	NR	NR
	Genovese 2015 (MOBILITY) [71]	12	S	Placebo + MTX	398	50.9	9.1	5.9[#]	1.6	63.3
				Sarilumab (150mg/2weeks) + MTX	400	50.1	9.5	6.0[#]	1.6	66.8
				Sarilumab (200mg/2weeks) + MTX	399	50.8	8.6	6.0[#]	1.7	64.7

	Genovese ACR 2015 (MOBILITY) [72]	12	S	Placebo + MTX	398	NR	NR	NR	NR	NR
				Sarilumab (150mg/2weeks) + MTX	400	NR	NR	NR	NR	NR
				Sarilumab (200mg/2weeks) + MTX	399	NR	NR	NR	NR	NR
	Weinblatt 2015 [73]	6	S	MTX + Placebo	61	51.4	6.4	6.1[#]	1.6	NR
				ADA (40mg/2weeks) + MTX	59	52.8	6.1	6.3[#]	1.9	NR
				Clazakizumab (100mg/4weeks) + Placebo	60	55.0	7.4	5.9[#]	1.6	NR
				Clazakizumab (200mg/4weeks) + Placebo	59	50.0	5.0	6.1[#]	1.7	NR
				Clazakizumab (25mg/4weeks) + MTX	59	47.4	5.0	5.7[#]	1.5	NR
				Clazakizumab (100mg/4weeks) + MTX	60	49.9	5.6	5.8[#]	1.5	NR
				Clazakizumab (200mg/4weeks) + MTX	60	46.4	6.0	5.8[#]	1.4	NR
	Burmester ACR 2014 [74]	6	S	Placebo + MTX	81	NR	NR	NR	NR	NR
				Mavrilimumab (30mg/2weeks) + MTX	81	NR	NR	NR	NR	NR
				Mavrilimumab (100mg/2weeks) + MTX	85	NR	NR	NR	NR	NR
				Mavrilimumab (150mg/2weeks) + MTX	79	NR	NR	NR	NR	NR
	Burmester EULAR 2015 [75]	6	S	Placebo + MTX	81	NR	NR	NR	NR	NR
				Mavrilimumab (30mg/2weeks) + MTX	81	NR	NR	NR	NR	NR
				Mavrilimumab (100mg/2weeks) + MTX	85	NR	NR	NR	NR	NR
				Mavrilimumab (150mg/2weeks) + MTX	79	NR	NR	NR	NR	NR
	Smolen EULAR 2015 [76]	6	S	Placebo + MTX	55	NR	NR	NR	NR	NR
				Ustekinumab (90mg/8weeks) + MTX	55	NR	NR	NR	NR	NR
				Ustekinumab (90mg/12weeks) + MTX	55	NR	NR	NR	NR	NR
				Guselkumab (50mg/8weeks) + MTX	55	NR	NR	NR	NR	NR
				Guselkumab (200mg/8weeks) + MTX	54	NR	NR	NR	NR	NR
	Smolen 2015 [77]	12	S	Placebo + MTX	349	52.9	7.1	5.7[#]	1.5	NR
				Tabalumab (90mg/2weeks) + MTX	347	52.8	6.7	5.6[#]	1.5	NR
				Tabalumab (120mg/4weeks) + MTX	345	53.7	6.8	5.7[#]	1.6	NR
Mixed DMARD IR	Thorne EULAR 2016 [78]	12	S	Placebo, Bio-naïve	360	NR	NR	NR	NR	NR
				Placebo, Bio-experienced	196	NR	NR	NR	NR	NR
				Sirukumab (50mg/4weeks), Bio-naïve	382	NR	NR	NR	NR	NR
				Sirukumab (50mg/4weeks), Bio-experienced	175	NR	NR	NR	NR	NR

				Sirukumab (100mg/2weeks), Bio-naïve	345	NR	NR	NR	NR	NR
				Sirukumab (100mg/2weeks), Bio-experienced	212	NR	NR	NR	NR	NR
	Thorne EULAR 2016 [79]	12	S	Placebo	556	NR	NR	NR	NR	NR
				Sirukumab (50mg/4weeks)	557	NR	NR	NR	NR	NR
				Sirukumab (100mg/2weeks)	557	NR	NR	NR	NR	NR
	Karpouzas EULAR 2016 [80]	12	S	Placebo	556	NR	NR	NR	NR	NR
				Sirukumab (50mg/4weeks)	557	NR	NR	NR	NR	NR
				Sirukumab (100mg/2weeks)	557	NR	NR	NR	NR	NR
	Genovese 2015 (FLEX-O) [81]	6	S	Placebo + DMARD	251	51.0	5.8	5.3[#]	1.4	44
				Tabalumab (90mg/2weeks) + DMARD	374	50.6	5.7	5.3[#]	1.4	45
				Tabalumab (120mg/4weeks) + DMARD	379	52.4	6.2	5.3[#]	1.4	45
TNFi-IR	Fleischmann ACR 2015 (TARGET) [82]	6	S	Placebo + DMARD	181	NR	NR	NR	NR	NR
				Sarilumab (150mg/2weeks) + DMARD	181	NR	NR	NR	NR	NR
				Sarilumab (200mg/2weeks) + DMARD	184	NR	NR	NR	NR	NR
	Strand ACR 2015 (TARGET) [83]	6	S	Placebo + DMARD	181	NR	NR	NR	NR	NR
				Sarilumab (150mg/2weeks) + DMARD	181	NR	NR	NR	NR	NR
				Sarilumab (200mg/2weeks) + DMARD	184	NR	NR	NR	NR	NR
	Schiff 2015 (FLEX V) [84]	6	S	Placebo + DMARD	155	54.0	8.7	5.89[#]	1.66	55.5
				Tabalumab (90mg/2weeks) + DMARD	148	51.3	7.9	5.88[#]	1.68	57.4
				Tabalumab (120mg/4weeks) + DMARD	153	54.2	8.1	5.84[#]	1.67	53.6

- *ADA, adalimumab; DMARD, disease modifying antirheumatic drug; DMARD IR, disease modifying antirheumatic drug incomplete responder; HAQ-DI, health assessment questionnaire disease index; MTX, methotrexate; MTX IR, methotrexate incomplete responder; NR, not recorded; TNFi IR, tumour necrosis factor inhibitor incomplete responder*
- *[#] DAS28 CRP*

Table 24: Cochrane risk of bias assessment: RCTs of new Biological DMARDs

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Strand ACR 2014 (MOBILITY) [70]	Sarilumab	a	a	a	a	a	a	a
Genovese 2015 (MOBILITY) [71]	Sarilumab	L	L	L	L	L	L	L
Genovese ACR 2015 (MOBILITY) [72]	Sarilumab	a	a	a	a	a	a	a
Weinblatt 2015 [73]	Clazakizumab vs. ADA	U[1]	U[1]	L	L	L	L	L
Burmester ACR 2014 [74]	Mavrilimumab	a	a	a	a	a	a	a
Burmester EULAR 2015 [75]	Mavrilimumab	a	a	a	a	a	a	a
Smolen EULAR 2015 [76]	Ustekinumab vs. Guselkumab	a	a	a	a	a	a	a
Smolen 2015 [77]	Tabalumab	U[1]	U[1]	L	L	L	L	L
Thorne EULAR 2016 [78]	Sirukumab	a	a	a	a	a	a	a
Thorne EULAR 2016 [79]	Sirukumab	a	a	a	a	a	a	a
Karpouzas EULAR 2016 [80]	Sirukumab	a	a	a	a	a	a	a
Genovese 2015 (FLEX-O) [81]	Tabalumab	U[1]	U[1]	L	L	L	L	L
Fleischmann ACR 2015 (TARGET) [82]	Sarilumab	a	a	a	a	a	a	a
Strand ACR 2015 (TARGET) [83]	Sarilumab	a	a	a	a	a	a	a
Schiff 2015 (FLEX V) [84]	Tabalumab	L	L	L	L	L	L	L

- *ADA, adalimumab*
- *a = abstract only, H= high risk; L = low risk; U = unclear risk*
- *[1]details not recorded*

2.10 RCTs of biosimilar DMARDs

Table 25: Description of included RCTs and baseline characteristics: RCTs of new Biological and Biosimilar DMARDs

Patient group	Study	Study duration (months)	Trial design	Interventions	No. of patients	Mean age (years)	Mean disease duration (years)	Mean baseline DAS28	Mean baseline HAQ-DI	On steroids (%)
MTX IR	Matsumoto ACR 2015 [85]	6	E	ABP 501 (40mg/2weeks) + MTX	264	NR	NR	NR	NR	NR
				ADA (40mg/2weeks) + MTX	262	NR	NR	NR	NR	NR
	Cohen EULAR 2016 [86]	6	E	ABP 501 (40mg/2weeks) + MTX	264	NR	NR	NR	NR	NR
				ADA (40mg/2weeks) + MTX	262	NR	NR	NR	NR	NR
	Weinblatt ACR 2015 [87]	6	E	SB5 (40mg/2weeks) + MTX	271	NR	NR	NR	NR	NR
				ADA (40mg/2weeks) + MTX	273	NR	NR	NR	NR	NR
	Kay EULAR 2016 [88]	6	E	SB5 (40mg/2weeks) + MTX	269*	NR	NR	NR	NR	NR
				ADA (40mg/2weeks) + MTX	273*	NR	NR	NR	NR	NR
	Weinblatt EULAR 2016 [89]	6+6	E	SB5 (40mg/2weeks) + MTX → SB5 (40mg/2weeks) + MTX	254	NR	NR	NR	NR	NR
				ADA (40mg/2weeks) + MTX → SB5 (40mg/2weeks) + MTX	125	NR	NR	NR	NR	NR
				ADA (40mg/2weeks) + MTX → ADA (40mg/2weeks) + MTX	127	NR	NR	NR	NR	NR
	Bae 2016 (HERA) [90]	12	E	HD203 (50mg/week) + MTX	115*	51.0	7.19	NR	1.1	86.96
				ETN (50mg/week) + MTX	118*	51.3	8.05	NR	1.1	91.53
	Emery 2015 [91]	6	E	SB4 (50mg/week) + MTX	299	52.1	6.0	6.5	1.49	NR
				ETN (50mg/week) + MTX	297	51.6	6.2	6.5	1.50	NR
	Vencovsky ACR 2015 [92]	12	E	SB4 (50mg/week) + MTX	299	NR	NR	NR	NR	NR
				ETN (50mg/week) + MTX	297	NR	NR	NR	NR	NR
	Choe 2015 [93]	6	E	SB2 (3mg/kg) + MTX	291	51.6	6.3	6.5	1.5	NR
				IFX (3mg/kg) + MTX	293	52.6	6.6	6.5	1.5	NR
	Choe ACR 2015 [94]	12	E	SB2 (3mg/kg) + MTX	291	NR	NR	NR	NR	NR
				IFX (3mg/kg) + MTX	293	NR	NR	NR	NR	NR
	Takeuchi 2015 [95]	12	E	CT-P13 (3mg/kg) + MTX	50*	54.5	7.1	5.929	1.03	36.0
				IFX (3mg/kg) + MTX	51*	53.8	8.0	6.104	1.12	47.1
Mixed DMARD IR	Yoo ACR 2013 [96]	12+12	E	CT-P13 (3mg/kg) + MTX → CT-P13 (3mg/kg) + MTX	151	NR	NR	NR	NR	NR
				IFX (3mg/kg) + MTX → CT-P13 (3mg/kg) + MTX	142	NR	NR	NR	NR	NR

TNFi IR	Eremeeva EULAR 2016 [97]	6	E	BCD-020 (2×1000mg) + MTX RTX (2×1000mg) + MTX	NR** NR**	NR NR	NR NR	NR NR	NR NR	NR NR

- *ADA, adalimumab; ETN, etanercept; HAQ-DI, health assessment questionnaire disease index; IFX, infliximab; MTX, methotrexate; MTX IR, methotrexate incomplete responder; NR, not recorded; RTX, rituximab; TNFi IR, tumour necrosis factor inhibitor incomplete responder*
- ** Number of patients evaluated for baseline characteristics, ** Total 160 patients were randomised; 159 patients were evaluated for baseline characteristics*

Table 26: Cochrane risk of bias assessment: RCTs of Biosimilar DMARDs

Study	Biological DMARD	ROB1: Random sequence generation	ROB2: Allocation concealment	ROB3: Blinding of participants and personnel	ROB4: Blinding of outcome assessment	ROB5: Incomplete outcome data	ROB6: Other bias	ROB7: Selective reporting
Matsumoto ACR 2015 [85]	ABP 501 vs. ADA	a	a	a	a	a	a	a
Cohen EULAR 2016 [86]	ABP 501 vs. ADA	a	a	a	a	a	a	a
Weinblatt ACR 2015 [87]	SB5 vs. ADA	a	a	a	a	a	a	a
Kay EULAR 2016 [88]	SB5 vs. ADA	a	a	a	a	a	a	a
Weinblatt EULAR 2016 [89]	SB5 vs. ADA	a	a	a	a	a	a	a
Bae 2016 (HERA) [90]	HD203 vs. ETN	L	L	L	L	L	L	L
Emery 2015 [91]	SB4 vs. ETN	U[1]	U[1]	L	L	L	L	L
Vencovsky ACR 2015 [92]	SB4 vs. ETN	a	a	a	a	a	a	a
Choe 2015 [93]	SB2 vs. IFX	L	L	L	L	L	L	L
Choe ACR 2015 [94]	SB2 vs. IFX	a	a	a	a	a	a	a
Takeuchi 2015 [95]	CT-P13 vs. IFX	U[1]	U[1]	L	L	L	L	L
Yoo ACR 2013 [96]	CT-P13 vs. IFX	a	a	a	a	a	a	a
Eremeeva EULAR 2016 [97]	BCD-020 vs. RTX	a	a	a	a	a	a	a

- *ADA, adalimumab; ETN, etanercept; IFX, infliximab; RTX, rituximab; a = abstract only, H= high risk; L = low risk; U = unclear risk; [1]details not recorded*

3 Tables of efficacy outcome measures

3.1 Outcome measures of combination biological DMARD +/- conventional synthetic DMARDs vs. conventional synthetic DMARDs

3.1.1 Signs and symptoms

3.1.1.1 ACR responses

Table 27: DMARD-Naïve: Combination Biological DMARD +MTX vs. MTX – ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
CZP	Weinblatt ACR 2015 (C-EARLY) [14]	Placebo + MTX	213	12			53.1	referent		
		CZP (200mg/2weeks) + MTX	655				62.3	0.023		

- *CZP, certolizumab pegol; MTX, methotrexate*

Table 28: MTX-Naïve: Combination Biological DMARD +/- MTX vs. MTX – ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
ABT	Emery 2015 (AVERT) [16]	Placebo + MTX	116	12	63.8		46.6		34.5	
		ABT (125mg/week sc)	116		65.5		53.4		38.8	
		ABT (125mg/week sc) + MTX	119		74.8		63.0		52.1	
ADA	Takeuchi 2014 (HOPEFUL 1) [19]	Placebo + MTX	163	6	56.4	referent	38.7	referent	22.7	referent
		ADA (40mg/2weeks) + MTX	171		75.4	<0.001	64.3	<0.001	47.4	<0.001
ANA	Scott 2016 (CARDERA-2) [20]	Placebo + MTX	75	12		referent		referent		referent
		ANA (100mg/day) + MTX	79			0.55		0.86		0.45
CZP	Atsumi 2016 (C-OPERA) [21]	Placebo+ MTX	157	12	68.8	referent	51.6	referent	34.4	referent
		CZP (200mg/2weeks) + MTX	159		78.6	0.055	73.0	<0.001	57.2	<0.001
GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX	160	12	51.9	referent	35.6	referent	21.9	referent
		GLM (100mg/4weeks) + Placebo	159		53.5	0.78	38.4	0.61	22.0	0.97

		GLM (50mg/4weeks) + MTX	159		59.7	0.16	42.1	0.24	28.3	0.19
		GLM (100mg/4weeks) + MTX	159		66.7	0.007	48.4	0.021	31.4	0.054
TCZ	Burmester ACR 2014/	Placebo + MTX	287	12	58.5*	referent**	41.5*	referent	29.3*	referent**
	2016 (FUNCTION)	TCZ (4mg/kg/4weeks) + MTX	288		65.3*	0.1511**	54.9*	0.0045	37.8*	0.0315**
	[24] [25]	TCZ (8mg/kg/4weeks) + MTX	290		67.9*	0.0118**	56.2*	0.0003	43.4*	0.0003**
		TCZ (8mg/kg/4weeks) + Placebo	292		65.4*	0.1406**	50.7*	0.0358	37.0*	0.0630**

- *ABT, abatacept; ADA, adalimumab; ANA anakinra; CZP,certolizumab pegol; GLM, golimumab; TCZ, tocilizumab; MTX, methotrexate*
- ** from Burmester ACR 2014; ** from Burmester 2016*

Table 29: MTX-IR: Combination Biological DMARD +/- MTX vs. MTX – ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
CZP	Yamamoto 2014 (J-	Placebo + MTX	77	6	24.7	referent	16.9	referent	1.3	referent
	RAPID) [26]	CZP (100mg/2weeks) + MTX	72		61.1	<0.0001	44.4	<0.001	26.4	<0.01
		CZP (200mg/2weeks) + MTX	82		73.2	<0.0001	54.9	<0.0001	29.3	<0.001
		CZP (400mg/2weeks) + MTX	85		71.8	<0.0001	54.1	<0.0001	30.6	<0.001
GLM	Weinblatt 2013 (GO-	Placebo + MTX	197	6			13.2	referent		
	FURTHER) [27]	GLM (2mg/kg iv) + MTX	395				34.9	<0.001		
GLM	Li ACR 2013 [29]	Placebo + MTX	132	6	15.9	referent				
		GLM (50mg/4weeks) + MTX	132		42.4	<0.001				
		Placebo + MTX	132	12	56.8	referent				
		GLM (50mg/4weeks) + MTX	132		69.7	NS				
IFX	Kim 2013 [30]	Placebo + MTX	72	7	30.6	referent				
		IFX (3mg/kg) + MTX	71		50.7	0.014				

- *CZP,certolizumab pegol; GLM, golimumab; IFX, infliximab; MTX, methotrexate; NS, not significant*

Table 30: Mixed DMARD-IR : Combination Biological DMARD +/- conventional synthetic DMARD vs. conventional synthetic DMARD/ placebo – ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
CZP	Smolen 2015 (CERTAIN) [32]	Placebo + DMARD	98	6	15.3		7.1		3.1	
		CZP (200mg/2weeks) + DMARD	96		36.5		20.8		9.4	
	Yamamoto 2014 (HIKARI) [31]	Placebo	114	6	11.4	referent	6.1	referent	0.9	referent
		CZP (200mg/2weeks)	116		63.8	<0.0001	46.6	<0.0001	25.9	<0.0005
ETN	Takeuchi 2013 [33]	MTX	176	12	62.5	referent	36.9	referent	15.9	referent
		ETN (2×10mg/week)	192		75.9*	<0.01	59.4	<0.0001	33.9	<0.0001
		ETN (2×25mg/week)	182		78.6	<0.001	62.1	<0.0001	36.3	<0.0001
TCZ	Kivitz 2014 (BREVACTA) [35]	Placebo + DMARDs	219	6	31.5	referent	12	referent	6	referent
		TCZ (162mg/2weeks sc) + DMARD	437		60.9	<0.0001	40	<0.0001	20	<0.0001
RTX	Behrens EULAR 2016 (AMARA)* [34]	Placebo + LEF	NR	6	27.6	referent	14.9	referent		
		RTX (2×1000mg) + LEF	NR		46.2	<0.05	27.0	NS		

- *CZP,certolizumab pegol; DMARD, disease modifying antirheumatic drug; ETN, etanercept; MTX, methotrexate; LEF, leflunomide; NS, not significant; RTX, rituximab; TCZ, tocilizumab*
- ** denominator = 191*

3.1.1.2 DAS28 remission and low disease activity

Table 31: DMARD-Naïve: Combination Biological DMARD + MTX vs. MTX - DAS28 remission and Low disease activity

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 remission (DAS28 <2.6) (%)	p	LDAS (DAS28 <3.2) (%)	p
CZP	Weinblatt ACR 2015 (C-EARLY) [14]	Placebo + MTX	213	12	15.0	referent	28.6	referent
		CZP (200mg/2weeks) + MTX	655		28.9	<0.001	43.8	<0.001

- *CZP, certolizumab pegol; MTX, methotrexate*

Table 32: MTX Naïve: Combination Biological DMARD +/- MTX vs. MTX - DAS 28 remission and Low disease activity

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 remission (DAS28 <2.6) (%)	p	LDAS (DAS28 <3.2) (%)	p
ABT	Smolen 2015 (AGREE) [15]	Placebo + MTX	209	12	27.3		43.1	
		ABT (10mg/kg) + MTX	210		47.6		63.3	
ADA	Takeuchi 2014 (HOPEFUL 1) [19]	Placebo + MTX	163	6	14.7	referent	24.5	referent
		ADA (40mg/2weeks) + MTX	171		31.0	<0.001	44.5	<0.001
CZP	Atsumi 2016 (C-OPERA) [21]	Placebo+ MTX	157	12	36.9	referent		
		CZP (200mg/2weeks) + MTX	159		57.2	<0.001		
GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX	160	12	35.0	referent		
		GLM (100mg/4weeks) + Placebo	159		31.4	0.510		
		GLM (50mg/4weeks) + MTX	159		44.0	0.100		
		GLM (100mg/4weeks) + MTX	159		45.9	0.047		
TCZ	Burmester 2016 (FUNCTION) [25]	Placebo + MTX	287	12	19.5	referent		
		TCZ (4mg/kg/4weeks) + MTX	288		34.0	<0.0001		
		TCZ (8mg/kg/4weeks) + MTX	290		49.0	<0.0001		
		TCZ (8mg/kg/4weeks) + Placebo	292		39.4	<0.0001		

- *ABT, abatacept; ADA, adalimumab; CZP,certolizumab pegol; GLM, golimumab; TCZ, tocilizumab; MTX, methotrexate*

Table 33: Mixed DMARD-IR: Combination Biological DMARD +/- conventional synthetic DMARD vs. conventional synthetic DMARD - DAS28 remission and Low disease activity

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 remission (DAS28 <2.6) (%)	p	LDAS (DAS28 <3.2) (%)	p
CZP	Smolen 2015 (CERTAIN) [32]	Placebo + DMARD	98	6	5.5		16.5	
		CZP (200mg/2weeks) + DMARD	96		26.1		42.4	
ETN	Takeuchi 2013 [33]	MTX	176	12	19.3	referent		
		ETN (2×10mg/week)	192		31.9*	<0.01		
		ETN (2×25mg/week)	182		34.1	<0.01		
TCZ	Kivitz 2014 (BREVACTA) [35]	Placebo + DMARDs	219	6	4	referent		
		TCZ (162mg/2weeks sc) + DMARD	437		32	<0.0001		

- *CZP, certolizumab pegol; DMARD, disease modifying antirheumatic drug; ETN, etanercept; sc, subcutaneous; TCZ, tocilizumab*
- ** denominator = 191*

3.1.1.3 SDAI, CDAI and ACR-EULAR Boolean remission

Table 34: MTX-Naïve, MTX-IR and Mixed DMARD-IR: Combination Biological DMARD +/- MTX or other csDMARD vs. MTX or other csDMARD - SDAI, CDAI and ACR-EULAR Boolean remission

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
MTX naïve	ABT	Smolen 2015 (AGREE) [15]	Placebo + MTX	209*	12	12.4		16.3		5.7	
			ABT (10mg/kg) + MTX	210*		33.3		34.3		23.8	
	ABT	Emery 2015 (AVERT) [16]	Placebo + MTX	116	12	25.0		27.6		22.4	
			ABT (125mg/week sc)	116		29.3		31.0		26.7	
			ABT (125mg/week sc) + MTX	119		42.0		42.0		37.0	
	ADA	Takeuchi 2014 (HOPEFUL 1) [19]	Placebo + MTX	163	6	12.3	referent	11.0	referent	8.6	referent
			ADA (40mg/2weeks) + MTX	171		22.8	<0.001	20.5	<0.001	19.3	0.007
	CZP	Atsumi 2016 (C-	Placebo+ MTX	157	12	33.8	referent			28.0	referent

		OPERA) [21]	CZP (200mg/2weeks) + MTX	159		57.9	<0.001			45.3	0.002
	GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX	160	12	15.0	referent	16.3	referent		
			GLM (100mg/4weeks) + Placebo	159		13.8	0.77	13.2	0.44		
			GLM (50mg/4weeks) + MTX	159		23.3	0.06	25.2	0.05		
			GLM (100mg/4weeks) + MTX	159		23.3	0.06	22	0.19		
	TCZ	Burmester 2016 (FUNCTION) [25]	Placebo + MTX	287	12				referent		referent
			TCZ (4mg/kg/4weeks) + MTX	288					0.1338		0.1907
			TCZ (8mg/kg/4weeks) + MTX	290					0.0006		0.0095
			TCZ (8mg/kg/4weeks) + Placebo	292					0.2015		0.4070
MTX IR	GLM	Weinblatt 2013 (GO-FURTHER) [27]	Placebo + MTX	197	6	2		2.5			
			GLM (2mg/kg iv) + MTX	395		7.3		6.3			
Mixed DMARD IR	CZP	Smolen 2015 (CERTAIN) [32]	Placebo + DMARD	98	6	6.6		6.6			
			CZP (200mg/2weeks) + DMATD	96		18.5		19.6			
	TCZ	Kivitz 2014 (BREVACTA) [35]	Placebo + DMARDs	219	6	3.0					
			TCZ (162mg/2weeks sc) + DMARD	437		11.4					

- *ABT, abatacept; ADA, adalimumab; CZP,certolizumab pegol; DMARD, disease modifying antirheumatic drug; GLM, golimumab; MTX, methotrexate; sc, subcutaneous; TCZ, tocilizumab*
- ** Number of patients evaluated for efficacy*

3.1.1.4 EULAR responses

Table 35: MTX-Naïve and Mixed DMARD-IR: Combination Biological DMARD +/- MTX vs. MTX - EULAR responses

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	EULAR good or moderate response (%)	P	EULAR moderate response (%)	p	EULAR good response (%)	p
MTX naïve	ADA	Takeuchi 2014 (HOPEFUL 1) [19]	Placebo + MTX ADA (40mg/2weeks) + MTX	163 171	6			39.3 41.5	referent <0.001	22.7 47.4	referent <0.001
	GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX GLM (100mg/4weeks) + Placebo GLM (50mg/4weeks) + MTX GLM (100mg/4weeks) + MTX	160 159 159 159	12	61.3 64.8 72.3 76.7	referent 0.510 0.035 0.003				
Mixed DMARD IR	ETN	Takeuchi 2013 [33]	MTX ETN (2×10mg/week) ETN (2×25mg/week)	176 192 182	12			40.0 35.8 39.0	referent <0.001 <0.0001	29.7 44.2 50.0	referent <0.001 <0.0001

- *ADA, adalimumab; GLM, golimumab; MTX, methotrexate*

3.1.2 Radiographic responses

Table 36: MTX-Naïve, MTX-IR and mixed DMARD-IR: Combination Biological DMARD +/- MTX vs. MTX - Radiographic responses

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS* (mean (SD))	p	Δ mTSS* ≤0.5 (%)	p
MTX naïve	ADA	Takeuchi 2014 (HOPEFUL 1) [19]	Placebo + MTX ADA (40mg/2weeks) + MTX	163 171	6			42.2 73.3	referent <0.001
	ANA	Scott 2016 (CARDERA-2) [20]	Placebo + MTX ANA (100mg/day) + MTX	75 79	12	4.16** 2.50**	referent 0.29		

			Placebo + MTX	75	24	5.2**	referent		
			ANA (100mg/day) + MTX	79		5.1**	0.98		
	CZP	Weinblatt ACR 2015 (C-EARLY) [14],	Placebo + MTX	213	12	1.9 (4.8)	referent	49.7[#]	
		Emery EULAR 2016 (C-EARLY) [13]	CZP (200mg/2weeks) + MTX	655		0.2 (3.3)	<0.001	70.3[#]	
		Atsumi 2016 (C-OPERA) [21]	Placebo+ MTX	157	12	1.58 (4.86)	referent	70.7	referent
			CZP (200mg/2weeks) + MTX	159		0.36 (2.70)	<0.001	82.9	0.011
	GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX	160	12	1.37 (4.56)	referent	53.9[¥]	referent
			GLM (100mg/4weeks) + Placebo	159		1.25 (6.16)	0.4	59.9[¥]	0.46
			GLM (50mg/4weeks) + MTX	159		0.74 (5.23)	0.59	71.4[¥]	0.003
			GLM (100mg/4weeks) + MTX	159		0.07 (1.83)	0.13	61.2[¥]	0.24
	TCZ	Burmester 2016 (FUNCTION) [25]	Placebo + MTX	287	12	1.14	referent		
			TCZ (4mg/kg/4weeks) + MTX	288		0.42			
			TCZ (8mg/kg/4weeks) + MTX	290		0.08	0.0001		
			TCZ (8mg/kg/4weeks) + Placebo	292		0.26			
MTX IR	CZP	Yamamoto 2014 (J-RAPID) [26]	Placebo + MTX	76	6	2.8	referent		
			CZP (100mg/2weeks) + MTX	70		1.0	NS		
			CZP (200mg/2weeks) + MTX	81		0.2	<0.001		
			CZP (400mg/2weeks) + MTX	84		0.7	<0.01		
Mixed DMARD IR	CZP	Yamamoto 2014 (HIKARI) [31]	Placebo	114	6	2.45	referent		
			CZP (200mg/2weeks)	114		0.48	<0.0001		
	ETN	Takeuchi 2013 [33]	Placebo + MTX	171	12			25.7	referent
			ETN (2×10mg/week) + Placebo	190				45.3	<0.001
			ETN (2×25mg/week) + Placebo	181				49.2	<0.0001
		Kivitz 2014 (BREVACTA) [35]	Placebo + DMARD	219	6	1.23 (2.82)	referent		
			TCZ (162mg/2weeks sc) + DMARD	437		0.62 (2.69)	0.0149		

- *ADA, adalimumab; ANA, anakinda; CZP,certolizumab pegol; DMARD, disease modifying antirheumatic drug; ETN, etanercept; MTX, methotrexate; NS, nonsignificant; TCZ, tocilizumab*
- ** mTSS = van der Heijde modified sharp score; ** Larsen score; [#]radiographic nonprogression; [¥] Δ mTSS ≤ 0*

3.1.3 Patient reported outcomes

3.1.3.1 HAQ-DI

Table 37: DMARD-Naïve: Combination Biological DMARD + MTX vs. MTX - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ HAQ-DI (mean (SE))	p	HAQ-DI response (%)	p
CZP	Weinblatt ACR 2015 (C-EARLY) [14]	Placebo + MTX	213	12	-0.8 (0.04)	referent		
		CZP (200mg/2weeks) + MTX	655		-1.0 (0.03)	<0.001		

- *CZP, certolizumab pegol; MTX, methotrexate*

Table 38: MTX-Naïve: Combination Biological DMARD +/- MTX vs. MTX - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ HAQ-DI (mean (SD))	p	HAQ-DI response (%)	p
ABT	Furst EULAR 2015 (AVERT) [18]	Placebo + MTX	116	12			47.4*	referent
		ABT (125mg/week sc)	116				56.0*	
		ABT (125mg/week sc) + MTX	119				67.2*	<0.05
ADA	Takeuchi 2014 (HOPEFUL 1) [19]	Placebo + MTX	163	6	-0.4 (0.6)	referent	36.8**	referent
		ADA (40mg/2weeks) + MTX	171		-0.6 (0.6)	<0.001	60.2**	<0.001
TCZ	Burmester 2016 (FUNCTION) [25]	Placebo + MTX	287	12	-0.64	referent		
		TCZ (4mg/kg/4weeks) + MTX	288		-0.75	0.0515		
		TCZ (8mg/kg/4weeks) + MTX	290		-0.81	0.0024		
		TCZ (8mg/kg/4weeks) + Placebo	292		-0.67	0.5532		

- *ABT, abatacept; ADA, adalimumab; TCZ, tocilizumab; MTX, methotrexate*
- ** Δ HAQ DI ≥0.22; ** Patients achieving a HAQ DI <0.5; NS nonsignificant*

Table 39: MTX-IR: Combination Biological DMARD + MTX vs. MTX - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ HAQ-DI (mean (SD))	p	HAQ-DI response (%)	p
CZP	Yamamoto 2014 (J-RAPID) [26]	Placebo + MTX	77	6	-0.18 (0.06)	referent		
		CZP (100mg/2weeks) + MTX	72		-0.43 (0.06)	<0.005		
		CZP (200mg/2weeks) + MTX	82		-0.55 (0.05)	NS		
		CZP (400mg/2weeks) + MTX	85		-0.57 (0.05)	NS		
GLM	Weinblatt 2013 (GO-FURTHER) [27]/ Bingham 2014 (GO-FURTHER) [28]	Placebo + MTX	197	6	-0.21 (0.55)	referent	45.2*	referent
		GLM (2mg/kg iv) + MTX	395		-0.53 (0.64)	<0.001	67.3*	<0.001
	Li ACR 2013 [29]	Placebo + MTX	132	6			29.5*	referent
		GLM (50mg/4weeks) + MTX	132				49.2*	P= 0.001

- *CZP, certolizumab pegol; GLM, golimumab; TMX methotrexate*
- ** HAQ DI ≥0.25; NS nonsignificant*

Table 40: Mixed DMARD-IR: Combination Biological DMARD +/- conventional synthetic DMARD vs. conventional synthetic DMARD/ placebo - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	HAQ-DI (mean (SD))	p	Δ HAQ-DI (mean (SD))	p	HAQ-DI improvement(%)	p
CZP	Yamamoto 2014 (HIKARI) [31]	Placebo	114	6	0.12 (0.05)*	referent				
		CZP (200mg/2weeks)	116		-0.48 (0.05)*	<0.0001				
	Smolen 2015 (CERTAIN) [32]	Placebo + DMARD	98	6	1.00 (0.68)		-0.03 (0.49)	referent		
		CZP (200mg/2weeks) + DMARD	96		0.86 (0.63)		-0.25 (0.46)	≤0.01		
ETN	Takeuchi 2013 [33]	Placebo + MTX	176	12	0.7				29.2	referent
		ETN (2×10mg/week) + Placebo	192		0.6				53.7	<0.01
		ETN (2×25mg/week) + Placebo	182		0.5				58.1	<0.0001

- *CZP, certolizumab pegol; disease modifying antirheumatic drug; ETN, etanercept; MTX, methotrexate*
- ** mean (SE)*

3.1.3.2 SF36 PCS and MCS

Table 41: DMARD Naïve: Combination Biological DMARD + MTX vs. MTX - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean (SE))	p	Δ SF36 MCS (mean (SE))	p
CZP	EMERY EULAR 2015 (C-EARLY) [12]	Placebo + MTX	213	12	10.7 (0.6)	referent	6.8 (0.7)	
		CZP (200mg/2weeks) + MTX	655		12.4 (0.4)	<0.01	8.2 (0.5)	

- *CZP, certolizumab pegol; MTX, methotrexate*

Table 42: MTX Naïve: Combination Biological DMARD +/- MTX vs. MTX - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean (SD))	p	Δ SF36 MCS (mean (SD))	p
ABT	Furst ACR 2014	MTX	116	12	10.9 (IQR 9.1, 12.8)	referent	7.2 (IQR 5.2, 9.3)	
	(AVERT) [17]	ABT (125mg/week sc)	116		10.2 (IQR 8.3, 12,1)		5.5 (IQR 3.4, 7.6)	
		ABT (125mg/week sc) + MTX	119		13.9 (IQR 12.1, 15.8)	<0.05	7.7 (IQR 5.6, 9.7)	
TCZ	Burmester EULAR	Placebo + MTX	287	12	10.7 (10.4)*	referent**	6.2 (12.1)*	referent**
	2014/ 2016	TCZ (4mg/kg/4weeks) + MTX	288		12.3 (10.5)*	0.2503**	8.3 (12.1)*	0.5446**
	(FUNCTION) [23] [25]	TCZ (8mg/kg/4weeks) + MTX	290		13.5 (9.8)*	0.0066**	8.3 (12.5)*	0.1919**
		TCZ (8mg/kg/4weeks) + Placebo	292		11.7 (10.7)*	0.8489**	8.4 (12.3)*	0.7434**

- *ABT, abatacept; MTX, methotrexate; IQR, interquartile range; TCZ, tocilizumab*
- ** from Burmester EULAR 2014; ** from Burmester 2016*

Table 43: MTX-IR: Combination Biological DMARD +/- MTX vs. MTX - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean (SD))	p	Δ SF36 MCS (mean (SD))	p
CZP	Yamamoto 2014 (J-RAPID) [26]	Placebo + MTX	77	6	4.3 (1.1)*	referent	1.2 (1.1)*	referent
		CZP (100mg/2weeks) + MTX	72		8.9 (1.2)*	<0.005	3.2 (1.1)*	NS
		CZP (200mg/2weeks) + MTX	82		10.2 (1.1)*	<0.0001	5.6 (1.0)*	<0.005
		CZP (400mg/2weeks) + MTX	85		11.4 (1.1)*	<0.0001	5.8 (1.0)*	<0.005
GLM	Bingham 2014 (GO-FURTHER) [28]	Placebo + MTX	197	6	3.82 (7.30)	referent	1.21 (10.07)	referent
		GLM (2mg/kg iv) + MTX	395		8.28 (8.32)	<0.001	6.94 (10.28)	<0.001
	Li ACR 2013 [29]	Placebo + MTX	132	6	-0.88 (6.92)	referent	-2.68 (12.07)	referent
		GLM (50mg/4weeks) + MTX	132		4.30 (7.05)	<0.001	2.23 (10.59)	<0.001
IFX	Kim 2013 [30]	Placebo + MTX	72	7	1.2	referent		
		IFX (3mg/kg) + MTX	71		6.1	<0.001		

- *CZP, certolizumab pegol; GLM, golimumab; IFX, infliximab; MTX, methotrexate; NS nonsignificant*
- ** mean (SE)*

Table 44: Mixed DMARD IR: Combination Biological DMARD +/- conventional synthetic DMARD vs. conventional synthetic DMARD/ placebo - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean (SD))	p	Δ SF36 MCS (mean (SD))	p
CZP	Yamamoto 2014 (HIKARI)	Placebo	108	6	-1.46 (0.90)*	referent	-0.94 (1.00)*	referent
	[31]	CZP (200mg/2weeks)	112		9.27 (0.89)*	<0.0001	5.24 (0.98)*	<0.0001
	Smolen 2015 (CERTAIN)	Placebo + DMARD	98	6	1.7 (7.6)	referent	0.5 (9.3)	referent
	[32]	CZP (200mg/2weeks) + DMARD	96		6.0 (7.5)	≤0.01	4.0 (9.8)	≤0.05

- *CZP, certolizumab pegol; disease modifying antirheumatic drug*
- ** mean (SE)*

3.1.3.3 FACIT-F

Table 45: MTX Naïve and MTX IR: Combination Biological DMARD +/- MTX vs. MTX - FACIT-F

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	FACIT-F (mean (SD))	p
MTX naïve	TCZ	Burmester EULAR 2014 (FUNCTION) [23]	Placebo + MTX	287	12	9.2 (12.1)	
			TCZ (4mg/kg/4weeks) + MTX	288		11.5 (11.6)	
			TCZ (8mg/kg/4weeks) + MTX	290		11.8 (11.7)	
			TCZ (8mg/kg/4weeks) + Placebo	292		10.8 (11.7)	
MTX IR	GLM	Bingham 2014 (GO-FURTHER) [28]	Placebo + MTX	197	6	2.54 (10.22)	referent
			GLM (2mg/kg iv) + MTX	395		7.96 (10.79)	<0.001
		Li ACR 2013 [29]	Placebo + MTX	132	6	-2.2 (11.2)	referent
			GLM (50mg/4weeks) + MTX	132		3.4 (9.4)	<0.001

- *GLM, golimumab; MTX, methotrexate; TCZ, tocilizumab*

3.1.3.4 FAS

Table 46: Mixed DMARD IR: Combination Biological DMARD +/- conventional synthetic DMARD vs. conventional synthetic DMARD/ placebo - FAS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ FAS (mean (SD))	p
CZP	Smolen 2015 (CERTAIN) [32]	Placebo + DMARD	98	6	0.1 (2.1)	referent
		CZP (200mg/2weeks) + DMARD	96		-1.2 (2.2)	≤0.01

- *CZP, certolizumab pegol; DMARD, disease modifying antirheumatic drug*

3.2 Outcome measures of combination biological DMARD + MTX compared to biological DMARD monotherapy

See also section 3.2 for the following RCTs which also have biological DMARD + MTX vs biological DMARD monotherapy arms: Emery (GO-BEFORE) [22] and Burmester (FUNCTION) [23] [24, 25].

3.2.1 Signs and symptoms

3.2.1.1 ACR responses

Table 47: MTX IR: Combination Biological DMARD + MTX vs Biological DMARD monotherapy studies - ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
TCZ	Dougados 2014 (ACT-RAY) [36]	TCZ (8mg/kg/4weeks) + placebo	276	12	69.2	referent	55.4	referent	31.2	referent
		TCZ (8mg/kg/4weeks) + MTX	277		70.8	0.62	50.2	0.22	31.4	0.99
	Kaneko 2016 (SURPRISE) [37]	TCZ (8mg/kg/4weeks) + Placebo	111	12	77.5	referent	63.1	referent	44.1	referent
		TCZ (8mg/kg/4weeks) + MTX	115		73.9	NS	62.6	NS	47.0	NS

- *MTX, methotrexate; NS, nonsignoficant; TCZ, tocilizumab*

3.2.1.2 DAS28 remission and low disease activity

Table 48: MTX IR: Combination Biological DMARD + MTX vs Biological DMARD monotherapy studies - DAS 28 remission and Low disease activity

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 CRP <2.6) (%)	p	DAS28 CRP <3.2 (%)	p
TCZ	Dougados 2014 (ACT-RAY) [36]	TCZ (8mg/kg/4weeks) + placebo	276	12	36.6	referent	57.2	referent
		TCZ (8mg/kg/4weeks) + MTX	277		45.5	0.03	62.5	0.12

- *MTX, methotrexate; TCZ, tocilizumab*

3.2.1.3 SDAI, CDAI and ACR-EULAR Boolean remission

Table 49: MTX IR: Combination Biological DMARD + MTX vs Biological DMARD monotherapy studies - SDAI, CDAI and ACR-EULAR Boolean remission

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
TCZ	Dougados 2014 (ACT-RAY) [36]	TCZ (8mg/kg/4weeks) + placebo	276	12	18.1	referent	15.9	referent	12.3	referent
		TCZ (8mg/kg/4weeks) + MTX	277		24.2	0.10	22.7	0.06	17.7	0.09
	Kaneko 2016 (SURPRISE) [37]	TCZ (8mg/kg/4weeks) + Placebo	111	12	46.8	referent	44.1	referent	35.1	referent
		TCZ (8mg/kg/4weeks) + MTX	115		52.2	0.43	47.8	0.60	37.1	0.78

- *MTX, methotrexate; TCZ, tocilizumab*

3.2.1.4 EULAR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	EULAR good or moderate response (%)	P	EULAR good response (%)	p
TCZ	Dougados 2014 (ACT-RAY) [36]	TCZ (8mg/kg/4weeks) + placebo	276	12	78.2	referent		
		TCZ (8mg/kg/4weeks) + MTX	277		84.5	0.12		

- *MTX, methotrexate; TCZ, tocilizumab*

3.2.2 Radiographic responses

Table 50: MTX IR: Combination Biological DMARD + MTX vs Biological DMARD monotherapy studies - Radiographic responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS (mean (SD))	p	Δ mTSS ≤ 1.5 (%)	p	Δ mTSS ≤ 0.5 (%)	p
TCZ	Dougados 2014 (ACT-RAY) [36]	TCZ (8mg/kg/4weeks) + placebo	276	12	0.63 (0.350)*#	referent	86.1*	referent		
		TCZ (8mg/kg/4weeks) + MTX	277		0.35 (0.370)*#	0.36	92.8*	0.016		
	Kaneko 2016 (SURPRISE) [37]	TCZ (8mg/kg/4weeks) + Placebo	111	12					64**	referent
		TCZ (8mg/kg/4weeks) + MTX	115						66**	0.92

- *MTX, methotrexate; TCZ, tocilizumab*
- ** Genant modified Sharp score; ** van der Heijde modified Sharp score; # mean (SE)*

3.2.3 Patient reported outcomes

3.2.3.1 HAQ-DI

Table 51: MTX IR: Combination Biological DMARD + MTX vs Biological DMARD monotherapy studies - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ HAQ-DI (mean (SD))	p	HAQ-DI response (%)	p
TCZ	Dougados 2014 (ACT-RAY) [36]	TCZ (8mg/kg/4weeks) + placebo	276	12	-0.67 (0.630)	referent		
		TCZ (8mg/kg/4weeks) + MTX	277		-0.59 (0.731)	0.14		
	Kaneko 2016 (SURPRISE) [37]	TCZ (8mg/kg/4weeks) + Placebo	111	12	-0.5 (0.6)	referent		
		TCZ (8mg/kg/4weeks) + MTX	115		-0.4 (0.6)	0.50		

- *MTX, methotrexate; TCZ, tocilizumab*

3.3 Outcome measures of head to head biological DMARD RCTs

3.3.1 Signs and symptoms

3.3.1.1 ACR responses

Table 52: MTX IR: Head to head Biological DMARD studies - ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
ABT vs ADA	Schiff 2014 (AMPLE) [38]	ABT (125mg/week) + MTX	318	24	59.7	referent	44.7	referent	31.1	referent
		ADA (40mg/2weeks) + MTX	328		60.1	NS	46.6	NS	29.3	NS

- *ABT, abatacept; ADA, adalimumab; MTX, methotrexate*

3.3.1.2 DAS28 remission and low disease activity

Table 53: MTX IR: Head to head Biological DMARD studies - DAS 28 remission and Low disease activity

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 CRP <2.6 (%)(95% CI)	p	DAS28 CRP <3.2 (%)(95% CI)	p
ABT vs ADA	Schiff 2014 (AMPLE) [38]	ABT (125mg/week) + MTX	318	24	50.6 (44.4, 56.8)	referent	65.3 (59.5, 71.2)	referent
		ADA (40mg/2weeks) + MTX	328		53.3 (47.0, 59.5)	NS	68.0 (62.2, 73.9)	NS

- *ABT, abatacept; ADA, adalimumab; MTX, methotrexate*

3.3.1.3 SDAI, CDAI and ACR-EULAR Boolean remission

Table 54: MTX IR: Head to head Biological DMARD studies - SDAI, CDAI and ACR-EULAR Boolean remission

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%) (95% CI)	p	CDAI remission (≤2.8) (%)(95% CI)	p
ABT vs ADA	Schiff 2014 (AMPLE) [38]	ABT (125mg/week) + MTX	318	24	31.2 (25.5, 36.9)	referent	32.0 (26.2, 37.8)	referent
		ADA (40mg/2weeks) + MTX	328		32.5 (26.6, 38.4)	NS	30.3 (24.6, 36.1)	NS

- *ABT, abatacept; ADA, adalimumab; MTX, methotrexate*

3.3.2 Radiographic responses

Table 55: MTX IR: Head to head Biological DMARD studies - Radiographic responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS * (Mean (SD))	p	Δ mTSS* ≤ SDC(%)	p
ABT vs ADA	Schiff 2014 (AMPLE) [38]	ABT (125mg/week) + MTX	318	24	0.89 (4.13)	referent	84.8	referent
		ADA (40mg/2weeks) + MTX	328		1.13 (8.66)	NS	83.8	NS

- *ABT, abatacept; ADA, adalimumab; MTX, methotrexate*
- ** mTSS = van der Heijde modified total sharp score*

3.3.3 Patient reported outcomes

3.3.3.1 HAQ-DI

Table 56: MTX IR: head to head Biological DMARD studies - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	HAQ-DI response (≥ 0.3) (%)	p
ABT vs ADA	Schiff 2014 (AMPLE) [38]	ABT (125mg/week) + MTX	318	24	54.1	referent
		ADA (40mg/2weeks) + MTX	328		48.8	NS

- *ABT, abatacept; ADA, adalimumab; MTX, methotrexate*

3.3.3.2 SF36 PCS and MCS

Table 57: MTX IR: head to head Biological DMARD studies DMARD - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean)	p	Δ SF36 MCS (mean)	p
ABT vs ADA	Fleischmann ACR 2013	ABT (125mg/week) + MTX	316	24	0.92	referent	0.77	referent
	(AMPLE) [39]	ADA (40mg/2weeks) + MTX	324		0.85	NS	0.67	NS

- *ABT, abatacept; ADA, adalimumab; MTX, methotrexate*

3.4 Outcome measures of biological DMARD strategy RCTs

3.4.1 Signs and symptoms

3.4.1.1 ACR responses

Table 58: DMARD naïve: Biologic DMARD strategy studies - ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
ADA	Hørslev-Petersen 2014 (OPERA) [43]	Placebo + DMARD	91	12	78.0	referent	63.0	referent	45.0	referent
		ADA (40mg/2weeks) + DMARD	89		86.0	0.21	80.0	0.020	65.0	0.012
IFX	Nam 2014 (IDEA) [47]	IV MP (250mg) + MTX	57	18	71.1	referent	63.4	referent	50.1	referent
		IFX (3mg/kg) + MTX	55		70.7	0.973	64.3	0.953	46.2	0.669
TCZ	Bijlsma 2016 (U-ACT-EARLY) [48]	MTX + Placebo	108	24	61		48		35	
		TCZ (8mg/kg/4weeks) + Placebo	103		65		55		39	
		TCZ (8mg/kg/4weeks) + MTX	106		63		49		36	

- *ADA, adalimumab; DMARD, disease modifying antirheumatic drug; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; TCZ, tocilizumab*

Table 59: MTX naïve: Biologic DMARD strategy studies - ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX → GLM (100mg/4weeks)	125	24	86.4		64.8		43.2	
		GLM (100mg/4weeks) + Placebo	125		81.6		56.8		40.0	
		GLM (50mg/4weeks) + MTX	131		86.3		64.1		45.8	
		GLM (100mg/4weeks) + MTX	125		80.8		61.6		44.8	

- *GLM, golimumab; MTX, methotrexate*

Table 60: MTX IR: Biologic DMARD strategy studies - ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
GLM	Li ACR 2013 [29]	Placebo + MTX	132	12	56.8	referent				
		GLM (50mg/4weeks) + MTX	132		69.7	NS				
	Weinblatt 2014	Placebo + MTX → GLM (2mg/kg iv) + MTX	197	12	61.4		31.5		14.7	
	(GO-FURTHER) [50]	GLM (2mg/kg iv) + MTX	395		65.8		38.7		18.2	

- *CZP, certolizumab pegol; GLM, golimumab; MTX, methotrexate; NS nonsignificant*

Table : Mixed DMARD IR: Biologic DMARD strategy studies - ACR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
GLM	Takeuchi 2013	Placebo → GLM (50mg/4weeks)	105	6	17.1	referent	7.6	referent	1.9	referent
	(GO-MONO) [52]	GLM (50mg/4weeks)	101		46.5	<0.0001	27.7	0.0001	16.8	0.0002
		GLM (100mg/4weeks)	102		69.6	<0.0001	42.2	<0.0001	21.6	<0.0001

- *GLM, golimumab*

3.4.1.2 DAS remission and low disease activity

Table 61: DMARD naïve: Biologic DMARD strategy studies - DAS or DAS28 remission and low disease activity

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS/DAS28 remission (DAS<1.6* or DAS28** <2.6) (%)	p	LDAS (DAS<2.4# or DAS28 <3.2##) (%)	p
ADA	Heimans 2014 (IMPROVED) [42]	Early remission (MTX)	387	12	68*			
		Arm1 (Predonisone + SSZ + HCQ + MTX)	83		25*	referent		
		Arm2 (ADA 40mg/2weeks + MTX)	78		41*	<0.05		
		Outside protocol treatment	50		24*			
	Hørslev-Petersen 2014 (OPERA) [43]	Placebo + DMARD	91	12	49**	referent	76##	referent
		ADA (40mg/2weeks) + DMARD	89		74**	0.0008	80##	0.65
ETN	Nam 2014 (EMPIRE) [45]	Placebo + MTX	55	18	60.5*	referent	80.1#	referent
		ETN (50mg/week) + MTX	55		51.6*	0.329	82.5#	0.755
IFX	Nam 2014 (IDEA) [47]	IV MP (250mg) + MTX	57	18	50.0*	referent	80.4#	referent
		IFX (3mg/kg) + MTX	55		47.7*	0.792	72.7#	0.888
	Markusse 2016 (BeSt) [46]	Sequential Monotherapy	126	120	50.0*	referent	84.7#	referent
		Step-up Combination therapy	121		45.9*	NS	73.8#	NS
		Initial Combination Therapy With Prednisone	133		57.1*	NS	85.7#	NS
		Initial Combination Therapy With IFX	128		56.2*	NS	84.3#	NS
TCZ	Bijlsma 2016 (U-ACT-EARLY) [48]	MTX + Placebo	108	24	77***	referent		
		TCZ (8mg/kg/4weeks) + Placebo	103		88***	0.0356		
		TCZ (8mg/kg/4weeks) + MTX	106		86***	0.06		

- *ADA, adalimumab; DMARD, disease modifying antirheumatic drug; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; NS, nonsignificant; TCZ, tocilizumab*
- **** Sustained remission (DAS28 <2.6) during entire study*

Table 62: MTX naïve: Biologic DMARD strategy studies - DAS28 remission and Low disease activity

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 remission (DAS28 <2.6) (%)	p	LDAS (DAS28 <3.2) (%)	p
GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX → GLM (100mg/4weeks)	160	24	43.9			
		GLM (100mg/4weeks) + Placebo	159		41.5			
		GLM (50mg/4weeks) + MTX	159		53.5			
		GLM (100mg/4weeks) + MTX	159		47.5			

- *GLM, golimumab; MTX, methotrexate*

Table 63: MTX IR: Biologic DMARD strategy studies - DAS28 remission and Low disease activity

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 remission (DAS28 <2.6) (%)	p	LDAS (DAS28 <3.2) (%)	p
GLM	Takeuchi 2013 (GO-MONO) [52]	Placebo → GLM (50mg/4weeks)	92	6	8.7			
		GLM (50mg/4weeks)	93		17.2			
		GLM (100mg/4weeks)	100		19.0			

- *GLM, golimumab*

3.4.1.3 SDAI, CDAI and ACR-EULAR Boolean remission

Table 64: DMARD naïve: Biologic DMARD strategy studies - SDAI, CDAI and ACR-EULAR Boolean remission

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
ADA	Heimans 2014 (IMPROVED) [42]	Early remission (MTX)	387	12					32	
		Arm1 (Predonisone + SSZ + HCQ + MTX)	83						11	
		Arm2 (ADA 40mg/2weeks + MTX)	78						17	
		Outside protocol treatment	50						8	
	Hørslev-Petersen 2014 (OPERA) [43]	Placebo + DMARD	91	12	37	referent	41	referent	30	referent
		ADA (40mg/2weeks) + DMARD	89		57	0.007	61	0.008	48	0.014

ETN	Nam 2014 (EMPIRE) [45]	Placebo + MTX ETN (50mg/week) + MTX	55 55	18	38.5 39.5	referent 0.867			20.5 20.9	referent 0.947
IFX	Nam 2014 (IDEA) [47]	IV MP (250mg) + MTX IFX (3mg/kg) + MTX	57 55	18	49.4 37.6	referent 0.480			15.9 15.7	referent 0.950
TCZ	Bijlsma 2016 (U-ACT-EARLY) [48]	MTX + Placebo TCZ (8mg/kg/4weeks) + Placebo TCZ (8mg/kg/4weeks) + MTX	108 103 106	24			37* 47* 52*	referent 0.31 0.0369		

- *ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; SSZ, sulphasalazine; TCZ, tocilizumab*
- ** Sustained remission*

Table 65: MTX naïve: Biologic DMARD strategy studies - SDAI, CDAI and ACR-EULAR Boolean remission

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX → GLM (100mg/4weeks) GLM (100mg/4weeks) + Placebo GLM (50mg/4weeks) + MTX GLM (100mg/4weeks) + MTX	123*/125** 122*/124** 128*/130** 120*/122**	24	28.5 25.4 32.0 38.3		28.8 25.0 33.1 39.3			

- *GLM, golimumab; MTX, methotrexate*
- ** Number evaluated for SDAI remission; ** Number evaluated for CDAI remission*

Table 66: MTX IR: Biologic DMARD strategy studies - SDAI, CDAI and ACR-EULAR Boolean remission

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
GLM	Weinblatt 2014 (GO-FURTHER) [50]	Placebo + MTX → GLM (2mg/kg iv) + MTX GLM (2mg/kg iv) + MTX	197 395	12	8.1 9.1		7.6 8.4			

- *CZP, certolizumab pegol; GLM, golimumab; MTX, methotrexate; NS nonsignificant*

3.4.1.4 EULAR responses

Table 67: DMARD naïve: Biologic DMARD strategy studies - EULAR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	EULAR good or moderate (%)	p	EULAR moderate response (%)	p	EULAR good response (%)	p
ADA	Hørslev-Petersen 2014 (OPERA) [43]	Placebo + DMARD	91	12			20		74	
		ADA (40mg/2weeks) + DMARD	89				11		82	
TCZ	Bijlsma 2016 (U-ACT-EARLY) [48]	MTX + Placebo	108	24	76	referent	8		68	
		TCZ (8mg/kg/4weeks) + Placebo	103		84	0.13	8		76	
		TCZ (8mg/kg/4weeks) + MTX	106		74	0.87	8		66	

- *ADA, adalimumab; DMARD, disease modifying antirheumatic drug, MTX, methotrexate; TCZ, tocilizumab*

Table 68: MTX naïve: Biologic DMARD strategy studies - EULAR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	EULAR good or moderate (%)	p	EULAR moderate response (%)	p	EULAR good response (%)	p
GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX → GLM (100mg/4weeks)	123	24	96.7					
		GLM (100mg/4weeks) + Placebo	123		94.3					
		GLM (50mg/4weeks) + MTX	129		93.0					
		GLM (100mg/4weeks) + MTX	120		92.5					

- *GLM, golimumab; MTX, methotrexate*

Table 69: MTX IR: Biologic DMARD strategy studies - EULAR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	EULAR good or moderate (%)	p	EULAR moderate response (%)	p	EULAR good response (%)	p
GLM	Weinblatt 2014 (GO-FURTHER) [50]	Placebo + MTX → GLM (2mg/kg iv) + MTX	197	12	75.6					
		GLM (2mg/kg iv) + MTX	395		81.3					
TNFi	Scott 2015 (TACIT) [51]	DMARD combinations strategy	92	12					31.5	
		TNFi strategy	94						39.4	

- *DMARD, disease modifying antirheumatic drug; GLM, golimumab; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor*

Table 70: Mixed DMARD IR: Biologic DMARD strategy studies - EULAR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	EULAR good or moderate (%)	p	EULAR moderate response (%)	p	EULAR good response (%)	p
GLM	Takeuchi 2013	Placebo → GLM (50mg/4weeks)	105	6			61.5		23.1	
	(GO-MONO) [52]	GLM (50mg/4weeks)	101				69.9		22.6	
		GLM (100mg/4weeks)	102				78.0		31.0	

- *GLM, golimumab*

3.4.2 Radiographic responses

Table 71: DMARD naïve: Biologic DMARD strategy studies - Radiographic responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS * (Mean (SD))	p	Δ mTSS* ≤ 0.5 (%)	p
ADA	Heimans 2014	Early remission (MTX)	387	12	0**			
	(IMPROVED) [42]	Arm1 (Predonisone + SSZ + HCQ + MTX)	83		0**			
		Arm2 (ADA 40mg/2weeks + MTX)	78		0**			
		Outside protocol treatment	50		0**			
ETN	Nam 2014 (EMPIRE)	Placebo + MTX	55	18			35.9	referent
	[45]	ETN (50mg/week) + MTX	55				35.8	0.982
IFX	Nam 2014 (IDEA) [47]	IV MP (250mg) + MTX	57	18	3.19 (7.75)	referent	51.1	referent
		IFX (3mg/kg) + MTX	55		1.69 (3.28)	0.253	54.5	0.699
TCZ	Bijlsma 2016 (U-ACT-EARLY) [48]	MTX + Placebo	108	24	1.53 (2.421)	referent		
		TCZ (8mg/kg/4weeks) + Placebo	103		1.45 (4.272)	0.0381		
		TCZ (8mg/kg/4weeks) + MTX	106		1.18 (3.919)	0.0207		

- *ADA, adalimumab; DMARD, ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; SSZ, sulphasalazine; TCZ, tocilizumab*
- ** mTSS = van der Heijde modified sharp scores for all studies, ** median*

Table 72: MTX naïve: Biologic DMARD strategy studies - Radiographic responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS* (Mean (SD))	p	Δ mTSS* ≤ 0 (%)	p
GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX → GLM (100mg/4weeks)	131 † /125 ‡	24	0.94 (4.24)		56.8	
		GLM (100mg/4weeks) + Placebo	128 † /124 ‡		2.54 (13.77)		54.0	
		GLM (50mg/4weeks) + MTX	133 † /130 ‡		-0.03 (1.93)		66.2	
		GLM (100mg/4weeks) + MTX	127 † /125 ‡		-0.20 (4.10)		67.2	

- *GLM, golimumab ; MTX, methotrexate*
- ** mTSS = van der Heijde modified sharp score, † Number evaluated for Δ mTSS; ‡ Number evaluated for Δ mTSS ≤ 0*

Table 73: MTX IR: Biologic DMARD strategy studies Radiographic responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS* (Mean (SD))	p	Δ mTSS* ≤ 0 (%)	p
GLM	Weinblatt 2014 (GO-FURTHER) [50]	Placebo + MTX → GLM (2mg/kg iv) + MTX	193	12	1.22	referent		
		GLM (2mg/kg iv) + MTX	391		0.13	0.0001		
TNFi	Scott 2015 (TACIT) [51]	DMARD combinations strategy	104	12		referent		
		TNFi strategy	101			NS**		

- *DMARD, disease modifying antirheumatic drug; GLM, golimumab; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor*
- ** mTSS = van der Heijde modified sharp score*
- *** Larsen score*

Table 74: MTX IR: Biologic DMARD strategy studies Radiographic responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS* (Mean (SD))	p	Δ mTSS* ≤ 0 (%)	p
GLM	Takeuchi 2013 (GO-MONO) [52]	Placebo → GLM (50mg/4weeks)	105	6	2.6 (4.7)			
		GLM (50mg/4weeks)	101		1.9 (4.1)			
		GLM (100mg/4weeks)	102		2.1 (10.4)			

- *GLM, golimumab*
- ** mTSS = van der Heijde modified sharp score*

3.4.3 Patient reported outcomes

3.4.3.1 HAQ-DI

Table 75: DMARD naïve: Biologic DMARD strategy studies - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	HAQ (mean (SD))	p	Δ HAQ-DI (mean (SD))	p	HAQ-DI response ≥0.22 (%)	p
ADA	Heimans 2013	Early remission (MTX)	387	12	0.38 (0.49)					
	(IMPROVED) [41]	Arm1 (Predonisone + SSZ + HCQ + MTX)	83		0.87 (0.66)	referent				
		Arm2 (ADA 40mg/2weeks + MTX)	78		0.81 (0.66)	0.60				
		Outside protocol treatment	50		0.77 (0.65)					
	Hørslev-Petersen	Placebo + DMARD	91	12	0.13 (0, 1.5)*	referent	-0.63 (-1.82, 0.38)	referent		
	2014 (OPERA) [43]	ADA (40mg/2weeks) + DMARD	89		0.25 (0, 1.44)*	0.14	-0.88 (-2.46, 0.13)	0.012		
ETN	Nam 2014	Placebo + MTX	55	18			-0.37	referent		
	(EMPIRE) [45]	ETN (50mg/week) + MTX	55				-0.34	0.688		
IFX	Nam 2014 (IDEA)	IV MP (250mg) + MTX	57	18			-0.79 (0.54)	referent		
	[47]	IFX (3mg/kg) + MTX	55				-0.85 (0.60)	0.826		
	Markusse 2016	Sequential Monotherapy	126	120	0.69	referent				
	(BeSt) [46]	Step-up Combination therapy	121		0.72	NS				
		Initial Combination Therapy With Prednisone	133		0.64	NS				
		Initial Combination Therapy With IFX	128		0.58	NS				
TCZ	Bijlsma 2016 (U-	MTX + Placebo	108	24	0.62 (0.50)				69	
	ACT-EARLY) [48]	TCZ (8mg/kg/4weeks) + Placebo	103		0.61 (0.61)				73	
		TCZ (8mg/kg/4weeks) + MTX	106		0.48 (0.55)				76	

- *ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; NS, nonsignificant; SSZ, sulphasalazine; TCZ, tocilizumab*
- ** median*

Table 76: MTX naïve: Biologic DMARD strategy studies - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	HAQ (mean (SD))	p	Δ HAQ-DI (mean (SD))	p	HAQ-DI response ≥0.5(%)	p
GLM	Emery 2013 (GO-BEFORE) [22]	Placebo + MTX → GLM (100mg/4weeks)	125	24					84.8	
		GLM (100mg/4weeks) + Placebo	124						78.2	
		GLM (50mg/4weeks) + MTX	130						80.0	
		GLM (100mg/4weeks) + MTX	124						80.6	

- *GLM, golimumab; MTX, methotrexate*

Table: MTX IR: Biologic DMARD strategy studies - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	HAQ (mean (SD))	p	Δ HAQ-DI (mean (IQR))	p	HAQ-DI response ≥0.25(%)	p
GLM	Li ACR 2013 [29]	Placebo + MTX→ GLM (50mg/4weeks)	132	12					49.2	referent
		GLM (50mg/4weeks) + MTX	132						65.9	NS
	Weinblatt 2014 (GO-FURTHER) [50]	Placebo + MTX → GLM (2mg/kg iv) + MTX	197	12					62.4	
		GLM (2mg/kg iv) + MTX	395						64.1	
TNFi	Scott 2015 (TACIT) [51]	DMARD combinations strategy	104	12			-0.45 (-0.55, -0.34)	referent		
		TNFi strategy	101				-0.30 (-0.42, -0.19)	NS		

- *DMARD, disease modifying antirheumatic drug; GLM, golimumab; MTX, methotrexate; NS, nonsignificant; TNFi, tumour necrosis factor inhibitor*

Table 77: Mixed DMARD IR: Biologic DMARD strategy studies - HAQ-DI

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	HAQ (mean (95% CI))	p	Δ HAQ-DI (mean (SD))	p	HAQ-DI response (%)	p
GLM	Takeuchi 2013 (GO-MONO) [52]	Placebo → GLM (50mg/4weeks)	105	6	-0.03 (-0.13, 0.07)	referent				
		GLM (50mg/4weeks)	101		0.23 (0.13, 0.33)	0.0003				
		GLM (100mg/4weeks)	102		0.33 (0.23. 0.43)	<0.0001				

- *GLM, golimumab*

3.4.3.2 SF36 PCS and MCS

Table 78: DMARD naïve: Biologic DMARD strategy studies - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SF36 PCS (mean)	p	Δ SF36 PCS (mean)	p	SF36 MCS (mean)	P	Δ SF36 MCS (mean)	p
ADA	Heimans 2013 (IMPROVED) [41]	Early remission (MTX) Arm1 (Predonisone + SSZ + HCQ + MTX) Arm2 (ADA 40mg/2weeks + MTX) Outside protocol treatment	387 83 78 50	12	48.6 (9.8) 39.9 (10.3) 43.0 (11.4) 42.6 (10.9)	 referent 0.10			53.1 (8.6) 50.5 (10.3) 50.5 (10.1) 50.4 (11.9)	 referent 0.97		
	Hørslev-Petersen 2014 (OPERA) [43]	Placebo + DMARD ADA (40mg/2weeks) + DMARD	91 89	12	43.3 (26.1, 55.8)* 49.2 (29.9, 56.6)*	referent 0.016	10.6 (-11.2, 22.7)* 13.2 (-2.3, 33)*	referent 0.015	54.8 (40.4, 63.7)* 55.7 (35.8, 62.6)*	referent 0.68	4.3 (-9.3, 27.4)* 5.5 (-8.5, 20.1)*	referent 0.83
ETN	Nam 2014 (EMPIRE) [45]	Placebo + MTX ETN (50mg/week) + MTX	55 55	18			7.06 6.50	referent 0.607			2.94 2.48	referent 0.533

- *ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; HCQ, hydroxychloroquine; MTX, methotrexate; NS, nonsignificant; SSZ, sulphasalazine; TCZ, tocilizumab*
- ** median (IQR)*

Table 79: MTX IR: Biologic DMARD strategy studies - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SF36 PCS (mean)	p	Δ SF36 PCS (mean)	p	SF36 MCS (mean)	P	Δ SF36 MCS (mean)	p
GLM	Li ACR 2013 [29]	Placebo + MTX→ GLM (50mg/4weeks) GLM (50mg/4weeks) + MTX	132 132	12			3.6 (7.1) 6.8 (8.9)	referent NS			0.2 (9.8) 3.9 (11.0)	referent NS
TNFi	Scott 2015 (TACIT) [51]	DMARD combinations strategy TNFi strategy	104 101	12				referent NS				referent NS

- *DMARD, disease modifying antirheumatic drug; GLM, golimumab; MTX, methotrexate; NS, nonsignificant; TNFi, tumour necrosis factor inhibitor*

3.5 Outcome measures of biological DMARD switching studies in TNF-IR RA

3.5.1.1 DAS28, DAS28 remission and low disease activity

Table 80: TNFi IR: Biological DMARD switching study – DAS28, DAS28 remission and low disease activity

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Mean DAS28 (SD)	OR (95% CI), p	DAS28 <2.6 (%)	OR (95% CI), p	DAS28 <3.2 (%)	OR (95% CI), p
TNFi	Manders 2015 (DREAM) [53]	ABT	43	12	3.8 (1.2)	NS				
		RTX	46		3.4 (1.2)	NS				
		TNFi	50		3.5 (1.2)	NS				
	Gottenberg ACR 2015 (ROC) [55]	Non-TNFi (ABT, RTX, TCZ)	146	12			26.9	referent	40.8	referent
		2nd TNFi (ADA, CZP, ETN, IFX)	146				13.6	0.34 (1.24, 4.39), 0.009	23.5	2.24 (1.32, 3.82), 0.003

- *ABT, abatacept; ADA, adalimumab; CZP,certolizumab pegol; ETN, etanercept; IFX, infliximab; NS, nonsignificant; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor*

3.5.1.2 EULAR responses

Table 81: TNFi IR: Biological DMARD switching study – EULAR responses

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	EULAR good or moderate (%)	OR (95% CI), p	EULAR moderate response (%)	OR (95% CI), p	EULAR good response (%)	OR (95% CI), p
TNFi	Gottenberg ACR 2015 (ROC) [55]	Non-TNFi (ABT, RTX, TCZ)	146	12	60.0	referent	22.3		37.7	
		2nd TNFi (ADA, CZP, ETN, IFX)	146		43.2	1.97 (1.21, 3.24), 0.007	22.0		21.2	

- *ABT, abatacept; ADA, adalimumab; CZP,certolizumab pegol; ETN, etanercept; IFX, infliximab; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor*

3.6 Outcome measures of RCTs addressing biological DMARD stopping

3.6.1 Signs and symptoms

3.6.1.1 ACR responses

Table 82: Studies addressing Biological DMARD stopping - ACR responses

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
MTX naïve	ABT	Emery 2015 (AVERT) [16]	MTX → no treatment	116	18 (12+6†)	15.5		9.5		6.0	
			ABT (125mg/week sc) → no treatment	116		16.4		14.7		9.2	
			ABT (125mg/week sc) + MTX → no treatment	119		21.8		16.0		10.3	
	ADA	Smolen 2014 (OPTIMA) [57]	MTX monotherapy	112	18 (6+12†)	91.1		76.8		61.6	
			ADA continuation (40mg/2weeks) + MTX	105		95.2	referent	88.6	referent	77.1	referent
			ADA withdrawal + MTX	102		94.1	0.72	80.4	0.10	64.7	0.0486
MTX IR	CZP	Furst 2015 (DOSEFLEX) [60]	CZP (200mg/2weeks) + MTX → Placebo + MTX	69	8 (4+4†)	44.9	referent	30.4	referent	15.9	referent
			CZP (200mg/2weeks) + MTX → CZP (200mg/2weeks) + MTX	70		67.1	0.009	50.0	<0.05	30.0	NS
			CZP (200mg/2weeks) + MTX → CZP (400mg/week) + MTX	70		65.2	0.017	52.2	<0.05	37.7	<0.01

- *ABT, abatacept; ADA, adalimumab; CZP, certolizumab pegol; MTX, methotrexate; NS, nonsignificant*
- † *Treatment-withdrawal phase*

3.6.1.2 DAS remission and low disease activity

Table 83: Studies addressing Biological DMARD stopping - DAS remission and low disease activity

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 <2.6 (%)	p	DAS28 <3.2 (%)	p
DMARD naïve	ADA	Hørslev-Petersen 2016 (OPERA) [44]	Placebo + DMARD	91	24 (12+12 †)	69	referent	84	referent
			ADA (40mg/2weeks) + DMARD	89		66	0.79	83	1.00
MTX naïve	ABT	Emery 2015 (AVERT) [16]	MTX → no treatment	116	18 (12+6 †)	9.5			
			ABT (125mg/week sc) → no treatment	116		12.1			
			ABT (125mg/week sc) + MTX → no treatment	119		18.5			
	ADA	Smolen 2014 (OPTIMA) [57]	ADA continuation (40mg/2weeks) + MTX	105	18 (6+12 †)	85.7	referent	91.4	referent
			ADA withdrawal + MTX	102		66.3	0.0014	81.2	0.0361
MTX IR	CZP	Furst 2015 (DOSEFLEX) [60]	CZP (200mg/2weeks) + MTX → Placebo + MTX	69	8 (4+4 †)	5.8		21.7	
			CZP (200mg/2weeks) + MTX → CZP (200mg/2weeks) + MTX	70		24.3		47.2	
			CZP (200mg/2weeks) + MTX → CZP (400mg/week) + MTX	70		36.2		56.5	
		Yamanaka 2016 (ENCOURAGE) [61]	ETN (2×25mg/week) + MTX → MTX	23	24 (12+12 †)	53.6	referent		
			ETN (2×25mg/week) + MTX → ETN (2×25mg/week) + MTX	29		87.5	<0.01		
	TCZ	Huizinga 2015 (ACT-RAY) [62]	TCZ (8mg/kg/4weeks) + Placebo	276	24 (12+12 †)	35.1	referent		
			TCZ (8mg/kg/4weeks) + MTX	277		38.3	0.452		

- *ABT, abatacept; ADA, adalimumab; CZP, certolizumab pegol; DMARD, disease modifying antirheumatic drug; ETN, etanercept; MTX, methotrexate; TCZ, tocilizumab*
- *† Treatment-withdrawal phase*

3.6.1.3 SDAI, CDAI and ACR-EULAR Boolean remission

Table 84: Studies addressing Biological DMARD stopping - SDAI, CDAI and ACR-EULAR Boolean remission

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
DMARD naïve	ADA	Hørslev-Petersen 2016 (OPERA) [44]	Placebo + DMARD	91	24 (12+12 †)	54	referent	55	referent	44	referent
			ADA (40mg/2weeks) + DMARD	89		49	0.66	57	0.87	45	1.00
MTX naïve	ABT	Emery 2015 (AVERT) [16]	MTX → no treatment	116	18 (12+6 †)	6.9		6.0		3.4	
			ABT (125mg/week sc) → no treatment	116		8.6		10.3		6.9	
			ABT (125mg/week sc) + MTX → no treatment	119		10.9		10.9		9.2	
	ADA	Smolen 2014 (OPTIMA) [57]	ADA continuation (40mg/2weeks) + MTX	105	18 (6+12 †)	62	0.0988				
			ADA withdrawal + MTX	102		50	referent				
MTX IR	CZP	Furst 2015 (DOSEFLEX) [60]	CZP (200mg/2weeks) + MTX → Placebo + MTX	69	8 (4+4 †)	13		17.4			
			CZP (200mg/2weeks) + MTX → CZP (200mg/2weeks) + MTX	70		22.9		27.1			
			CZP (200mg/2weeks) + MTX → CZP (400mg/week) + MTX	70		36.2		31.9			
	TCZ	Huizinga 2015 (ACT-RAY) [62]	TCZ (8mg/kg/4weeks) + Placebo	276	24 (12+12 †)	18.1	referent	18.1	referent	9.4	referent
			TCZ (8mg/kg/4weeks) + MTX	277		22.7	0.627	22.7	0.203	14.8	0.048

- *ABT, abatacept; ADA, adalimumab; CZP, certolizumab pegol; DMARD, disease modifying antirheumatic drug; MTX, methotrexate; TCZ, tocilizumab*
- *† Treatment-withdrawal phase*

3.6.1.4 EULAR responses

Table 85: Studies addressing Biological DMARD stopping - EULAR responses

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	EULAR good or moderate response (%)	P	EULAR moderate response (%)	p	EULAR good response (%)	p
MTX IR	TCZ	Huizinga 2015 (ACT-RAY) [62]	TCZ (8mg/kg/4weeks) + Placebo	276	24 (12+12 †)	66.7	referent				
			TCZ (8mg/kg/4weeks) + MTX	277		75.8	0.056				

- *MTX, methotrexate; TCZ, tocilizumab, † Treatment-withdrawal phase*

3.6.2 Radiographic responses

Table 86: Studies addressing Biological DMARD stopping - Radiographic responses

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS * (Mean (SD))	p	Δ mTSS ≤0.5 (%)	p	Δ mTSS ≤SDC (%)	p
DMARD naïve	ADA	Hørslev-Petersen 2016 (OPERA) [44]	Placebo + DMARD ADA (40mg/2weeks) + DMARD	91 89	24 (12+12 †)	0.99*¥ 0.78*¥	referent 0.45	61*¥# 60*¥#	referent 1.00		
MTX naïve	ADA	Smolen 2014 (OPTIMA) [57]	MTX monotherapy ADA continuation (40mg/2weeks) + MTX ADA withdrawal + MTX	112 105 102	18 (6+12 †)			78.0* 89.3* 80.6*	 referent 0.06		
MTX IR	ETN	Yamanaka 2016 (ENCOURAGE) [61]	ETN (2×25mg/week) + MTX → MTX ETN (2×25mg/week) + MTX → ETN (2×25mg/week) + MTX	23 29	24 (12+12 †)			82.6* 89.7*	referent NS		
	TCZ	Huizinga 2015 (ACT-RAY) [62]	TCZ (8mg/kg/4weeks) + Placebo TCZ (8mg/kg/4weeks) + MTX	276 277	24 (12+12 †)	0.95** (0.32) 0.35** (0.35)	referent 0.034			91.10** 94.40**	referent 0.098

- *ABT, abatacept; ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; MTX, methotrexate; NS, nonsignificant; SDC, smallest detectable change; TCZ, tocilizumab*
- ** mTSS = van der Heijde modified total Sharp score; ** mTSS = Genant modified total Sharp score; ¥ change between year 1 and year 2; # Δ mTSS ≤0*
- *† Treatment-withdrawal phase*

3.6.3 Patient reported outcomes

3.6.3.1 HAQ-DI

Table 87: Studies addressing Biological DMARD stopping - HAQ-DI

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	HAQ-DI (mean (SD))	p	Δ HAQ-DI (mean (SD))	p	HAQ-DI response (%) (95% CI)	p
DMARD naïve	ADA	Hørslev-Petersen 2016 (OPERA) [44]	Placebo + DMARD ADA (40mg/2weeks) + DMARD	91 89	24 (12+12 †)	0.13 (0, 1.63)* 0.13 (0, 1.5)*	referent 0.37				

	CZP	Bingham EULAR 2016 (C-EARLY)[8] [56]	CZP (200mg/2weeks) + MTX → Placebo + MTX CZP (200mg/2weeks) + MTX → CZP (200mg/4weeks) + MTX CZP (200mg/2weeks) + MTX → CZP (200mg/2weeks) + MTX	79 126 84	24 (12+12 †)	0.57 (0.65) 0.41 (0.57) 0.37 (0.48)					
MTX naïve	ABT	Emery 2015 (AVERT) [16]	MTX → no treatment ABT (125mg/week sc) → no treatment ABT (125mg/week sc) + MTX → no treatment	116 116 119	18 (12+6 †)					10.3 (4.8, 15.9) 16.4 (9.6, 23.1) 21.8 (14.4, 29.3)	
	ADA	Smolen 2014 (OPTIMA) [57]	MTX monotherapy ADA continuation (40mg/2weeks) + MTX ADA withdrawal + MTX	112 105 102	18 (6+12 †)	0.39 0.35 0.38 (0.58)					
MTX IR	CZP	Furst 2015 (DOSEFLEX) [60]	CZP (200mg/2weeks) + MTX → Placebo + MTX CZP (200mg/2weeks) + MTX → CZP (200mg/2weeks) + MTX CZP (200mg/2weeks) + MTX → CZP (400mg/week) + MTX	69 70 69	8 (4+4 †)	1.05 (0.68) 0.81 (0.60) 0.79 (0.64)					
	ETN	Yamanaka 2016 (ENCOURAGE) [61]	ETN (2×25mg/week) + MTX → MTX ETN (2×25mg/week) + MTX → ETN (2×25mg/week) + MTX	23 29	24 (12+12 †)					64.3 87.1	referent NS
	TCZ	Huizinga 2015 (ACT-RAY) [62]	TCZ (8mg/kg/4weeks) + Placebo TCZ (8mg/kg/4weeks) + MTX	276 277	24 (12+12 †)			-0.69 (0.59) -0.67 (0.71)	referent 0.833		

- *ABT, abatacept; ADA, adalimumab; CZP, certolizumab pegol; DMARD, disease modifying antirheumatic drug; ETN, etanercept; MTX, methotrexate; NS, nonsignificant; TCZ, tocilizumab*
- ** median (IQR)*
- *† Treatment-withdrawal phase*

3.6.3.2 SF36 PCS and MCS

Table 88: Studies addressing Biological DMARD stopping - SF36 PCS and MCS

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean (IQR))	p	Δ SF36 PCS ≥ 2.5 (%)	p	Δ SF36 MCS (mean (IQR))	p
DMARD naïve	ABT	Furst ACR 2014/ EULAR 2015 (AVERT) [17] [18]	MTX → no treatment	116	18 (12+6 †)	-4.7 (-7.8, -1.5)*		62.2*		-5.0 (-8.5, -1.5)*	
			ABT (125mg/week sc) → no treatment	116		-5.7 (-8.8, -2.5)*		55.0*		-1.1 (-4.7, 2.4)*	
			ABT (125mg/week sc) + MTX → no treatment	119		-7.8 (-10.5, -5)*		62.5*		-4.9 (-8.1, -1.8)*	

- *ABT, abatacept; MTX, methotrexate*
- ** Change between month 12 and 18*
- *† Treatment-withdrawal phase*

3.7 Outcome measures of RCTs addressing biological DMARD dose reduction or interval spacing

3.7.1 Signs and symptoms

3.7.1.1 ACR responses

Table 89: Studies addressing Biological DMARD dose reduction or interval spacing - ACR responses

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
MTX naïve	ETN	Emery 2014 (PRIZE) [58]	ETN (50mg/week) + MTX → Placebo → no treatment	65	21*	46.2	referent	44.6	referent	36.9	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65		76.2	<0.001	71.4	<0.01	61.9	<0.01
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63		88.9	≤0.0001	77.8	≤0.0001	71.4	≤0.0001
			ETN (50mg/week) + MTX → Placebo → no treatment	32	27*	35.4	referent	35.4	referent	23.1	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	46		41.3	NS	38.1	NS	28.6	NS
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	53		47.6	NS	46.0	NS	41.3	NS

- *ETN, etanercept; MTX, methotrexate; NS, nonsignificant; * time from study start*

3.7.1.2 DAS28 remission and low disease activity

Table 90: Studies addressing Biological DMARD dose reduction or interval spacing - DAS remission and low disease activity

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 <2.6 (%)	p	DAS28 <3.2 (%)	p
MTX naïve	ETN	Emery 2014 (PRIZE) [58]	ETN (50mg/week) + MTX → Placebo → no treatment	65	21*			46.2	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65				69.2	<0.001
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63				88.9	<0.0001
			ETN (50mg/week) + MTX → Placebo → no treatment	32	27*			36.9	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	46				43.1	NS
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	53				55.6	NS
Mixed DMARD IR	TNFi	van Herwaarden 2015 (DRESS) [66]	Dose reduction (ADA or ETN)[÷]	121	18	71	referent	85	referent
			Usual care	59		80	0.218	90	0.464

- *ADA, adalimumab; ETN, etanercept; MTX, methotrexate; NS, nonsignificant; TNFi, tumour necrosis factor inhibitor; * time from study start*

3.7.1.3 SDAI, CDAI and ACR-EULAR Boolean remission

Table 91: Studies addressing Biological DMARD dose reduction or interval spacing - SDAI, CDAI and ACR-EULAR Boolean remission

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
MTX naïve	ETN	Emery 2014 (PRIZE) [58]	ETN (50mg/week) + MTX → Placebo → no treatment	65	21*					22.6	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65						46.0	<0.001
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63						67.7	<0.0001
			ETN (50mg/week) + MTX → Placebo → no treatment	32	27*					16.1	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	46						25.4	NS
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	53						46.8	<0.0001
Mixed DMARD IR	TNFi	van Herwaarden 2015 (DRESS) [66]	Dose reduction (ADA or ETN)[±]	121	18					24	referent
			Usual care	59						41	0.021

- *ADA, adalimumab; ETN, etanercept; MTX, methotrexate; NS, nonsignificant; TNFi, tumour necrosis factor inhibitor; * time from study start*

3.7.2 Radiographic responses

Table 92: Studies addressing Biological DMARD dose reduction or interval spacing - Radiographic responses

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS * (Mean (SD))	p	Δ mTSS ≤SDC* (%)	p	Δ mTSS >0.5* (%)	p
MTX naïve	ETN	Emery 2014 (PRIZE) [58]	ETN (50mg/week) + MTX → Placebo → no treatment	65	21[¥]	0.4 (0.2)**	referent				
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65		0.0 (0.2)**	0.34				
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63		0.1 (0.1)**	0.48				
Mixed	TNFi	Fautrel 2016	S-arm (ADA or ETN Injection spacing[¥])	64	18	0.0 (0.0-1.5)[#]	0.7	66	0.8		

DMARD IR		(STRASS) [65]	M-arm (Maintenance)	73		0.0 (0.0-1.5) #	referent	69	referent		
		van Herwaarden 2015 (DRESS) [66]	Dose reduction (ADA or ETN)ǂ	121	18	0.75 (1.5)				32	
			Usual care	59		0.15 (1.1)				15	

- *ADA, adalimumab; ETN, etanercept; MTX, methotrexat; NS, nonsignificant; SDC, smallest detectable change; TNFi, tumour necrosis factor inhibitor*
- ** mTSS = modified van der Heijde total Sharp score; ǂ time from study start, ** change from 12 months; # median (IQR)*

3.7.3 Patient reported outcomes

3.7.3.1 HAQ-DI

Table 93: Studies addressing Biological DMARD dose reduction or interval spacing - HAQ-DI

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	HAQ-DI	p	Δ HAQ-DI (mean (SD))	p
MTX naïve	ETN	Emery 2014 (PRIZE) [58]	ETN (50mg/week) + MTX → Placebo → no treatment	65	21*			0.5 (0.1)**	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65				0.2 (0.1)**	0.001
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63				0.1 (0.1)**	<0.001
			ETN (50mg/week) + MTX → Placebo → no treatment	32	27*			0.5 (0.1)**	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	46				0.3 (0.1)**	0.04
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	53				0.2 (0.1)**	0.01
Mixed DMARD IR	TNFi	Galloway EULAR 2015 (OPTTIRA) [67]	Control	50	6	0.73 (0.51, 0.96)#	referent		
			33% Taper (Tapering ADA or ETN doses)	48		0.78 (0.56, 0.99) #	NS		
			66% Taper (Tapering ADA or ETN doses)	38		0.72 (0.44, 1.00) #	NS		
		van Herwaarden 2015 (DRESS) [66]	Dose reduction (ADA or ETN)ǂ	121	18	-0.45 (-0.55, -0.34) #	referent		
			Usual care	59		-0.30 (-0.42, -0.19) #	NS		

- *ADA, adalimumab; ETN, etanercept; MTX, methotrexate; NS, nonsignificant; TNFi, tumour necrosis factor inhibitor*
- ** Time from study start; ** change from 12 months, # mean (IQR)*

3.7.3.2 SF36 PCS and MCS

Table 94: Studies addressing Biological DMARD dose reduction or interval spacing - SF36 PCS and MCS

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean (SE))	p	Δ SF36 PCS ≥ 5 (%)	p	Δ SF36 MCS (mean (SE))	p	Δ SF36 MCS ≥ 5 (%)	p
MTX naïve	ETN	Wiland 2016 (PRIZE) [59]	ETN (50mg/week) + MTX → Placebo → no treatment	65	21*	-7.7 (1.0)**		42.2	referent	-8.7** (1.2)		34.4	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65		-3.3 (1.0) **		76.6	<0.001	-5.9 (1.2) **		62.5	0.003
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63		-1.0 (1.0) **		79.4	<0.001	-4.5 (1.2) **		58.7	0.008
			ETN (50mg/week) + MTX → Placebo → no treatment	65	27*	-5.0 (1.0) **		35.9	referent	-5.8 (1.1) **		39.1	referent
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65		-1.7 (1.0) **		46.9	0.282	-3.4 (1.1) **		39.1	1.000
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63		0.1 (1.0) **		58.7	0.013	-1.5 (1.1) **		60.3	0.021

- *ETN, etanercept; MTX, methotrexate; * time from study stat; ** change from 12 months*

3.7.3.3 FACIT-F

Table 95: Studies addressing Biological DMARD dose reduction or interval spacing - FACIT-F

Patient group	Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	FACIT-F (mean (SD))	p	Δ FACIT-F (mean (SE))	p
MTX naïve	ETN	Wiland 2016 (PRIZE) [59]	ETN (50mg/week) + MTX → Placebo → no treatment	65	21*	36.2 (12.1)	referent	-7.3 (1.1)**	
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65		41.4 (9.1)	≤0.05	-2.9 (1.1)**	
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63		43.2 (8.2)	≤0.05	-1.1 (1.1)**	
			ETN (50mg/week) + MTX → Placebo → no treatment	65	27*	35.0	referent	-8.6 (1.2)**	
			ETN (50mg/week) + MTX → Placebo + MTX → no treatment	65		39.2	≤0.05	-5.1 (1.2)**	
			ETN (50mg/week) + MTX → ETN (25mg/week) + MTX → no treatment	63		40.8	≤0.05	-3.6 (1.2)**	

- *ETN, etanercept; MTX, methotrexate; * time from study stat; ** change from 12 months*

3.8 Outcome measures of targeted synthetic and biological DMARDs

3.8.1 Signs and symptoms

3.8.1.1 ACR responses

Table 96: Targeted synthetic vs. Biological DMARDs - ACR responses

Targeted synthetic and Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
Baricitinib and ADA	Taylor ACR 2015 (RA-BEAM) [69]	Placebo + MTX	488	3	40		17		5	
		Baricitinib (4mg/day) + MTX	487		70	referent	45	referent	19	referent
		ADA (40mg/2weeks) + MTX	330		61	≤0.05	35	≤0.01	13	≤0.05
		Placebo + MTX	488	6	37		19		8	
		Baricitinib (4mg/day) + MTX	487		74	referent	50	referent	30	referent
		ADA (40mg/2weeks) + MTX	330		66	≤0.05	46	NS	22	≤0.05

- *ADA, adalimumab; MTX, methotrexate; NS, nonsignificant*

3.8.1.2 DAS28 remission and low disease activity

Table 97: Targeted synthetic vs. Biological DMARDs - DAS remission and low disease activity

Targeted synthetic and Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 <2.6 (%)	p	DAS28 <3.2 (%)	p
Baricitinib and ADA	Taylor ACR 2015 (RA-BEAM) [69]	Placebo + MTX	488	3	2		7	
		Baricitinib (4mg/day) + MTX	487		11	referent	24	referent
		ADA (40mg/2weeks) + MTX	330		12	NS	21	NS
		Placebo + MTX	488	6	5		10	
		Baricitinib (4mg/day) + MTX	487		18	referent	32	referent
		ADA (40mg/2weeks) + MTX	330		18	NS	34	NS

- *ADA, adalimumab; MTX, methotrexate; NS, nonsignificant*

3.8.1.3 SDAI, CDAI and ACR-EULAR Boolean remission

Table 98: Targeted synthetic vs. Biological DMARDs - SDAI, CDAI and ACR-EULAR Boolean remission

Targeted synthetic and Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
Baricitinib and ADA	Taylor ACR 2015 (RA-BEAM) [69]	Placebo + MTX	488	3	2		2			
		Baricitinib (4mg/day) + MTX	487		8	referent	8	referent		
		ADA (40mg/2weeks) + MTX	330		8	NS	7	NS		
		Placebo + MTX	488	6	3		4			
		Baricitinib (4mg/day) + MTX	487		16	referent	16	referent		
		ADA (40mg/2weeks) + MTX	330		14	NS	12	NS		

- *ADA, adalimumab; MTX, methotrexate; NS, nonsignificant*

3.8.2 Patient reported outcomes

3.8.2.1 HAQ-DI

Table 99: Targeted synthetic vs. Biological DMARDs - HAQ-DI

Targeted synthetic and Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ HAQ-DI (mean (SD))	p	HAQ-DI response ≥0.22(%)	p
Baricitinib and ADA	Taylor ACR 2015 (RA-BEAM) [69]	Placebo + MTX	488	3			58	
		Baricitinib (4mg/day) + MTX	487				75	referent
		ADA (40mg/2weeks) + MTX	330				71	NS
		Placebo + MTX	488	6			45	
		Baricitinib (4mg/day) + MTX	487				73	referent
		ADA (40mg/2weeks) + MTX	330				64	≤0.05

- *ADA, adalimumab; MTX, methotrexate; NS, nonsignificant*

3.9 Outcome measures comparing new biological DMARDs +/- conventional synthetic DMARDS vs. conventional synthetic DMARDS

3.9.1 Signs and symptoms

3.9.1.1 3.6.1.1 ACR responses

Table 100: MTX IR: Combination new Biological DMARD +/- MTX vs MTX - ACR responses

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
Sarilumab	Genovese 2015 (MOBILITY) [71]	Placebo + MTX	398	12	31.7	referent	18	referent	9	referent
		Sarilumab (150mg/2weeks) + MTX	400		53.5	<0.0001	40	<0.0001	25	<0.0001
		Sarilumab (200mg/2weeks) + MTX	399		58.6	<0.0001	43	<0.0001	27	<0.0001
Clakizumab	Weinblatt 2015 [73]	MTX+ Placebo	61	6	37.7				6.6	
		ADA (40mg/2weeks) + MTX	59		66.1				18.6	
		Clakizumab (100mg/4weeks) + Placebo	60		58.3				16.7	
		Clakizumab (200mg/4weeks) + Placebo	59		57.6				25.4	
		Clakizumab (25mg/4weeks) + MTX	59		81.4				27.1	
		Clakizumab (100mg/4weeks) + MTX	60		65.0				40.0	
		Clakizumab (200mg/4weeks) + MTX	60		66.7				30.0	
Ustekinumab and Guselkumab	Smolen EULAR 2015 [76]	Placebo + MTX	55	6	40.0	referent				
		Ustekinumab (90mg/8weeks) + MTX	55		52.7	0.184				
		Ustekinumab (90mg/12weeks) + MTX	55		54.5	0.130				
		Ustekinumab + MTX	110		53.6	0.101				
		Guselkumab (50mg/8weeks) + MTX	55		38.2	0.832				
		Guselkumab (200mg/8weeks) + MTX	54		44.4	0.642				
		Guselkumab + MTX	109		41.3	0.877				
Tabalumab	Smolen 2015 [77]	Placebo + MTX	349	6	25.1	referent	10.1	referent	3.0	referent
		Tabalumab (90mg/2weeks) + MTX	347		32.8	NS	11.1	NS	3.0	NS
		Tabalumab (120mg/4weeks) + MTX	345		29.7	NS	10.6	NS	3.9	NS

- *ADA, adalimumab; MTX, methotrexate; NS, nonsignificant*

Table 101: Mixed DMARD IR: Combination new Biological DMARD +/- csDMARD vs csDMARD - ACR responses

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
Mavrilimumab	Burmester ACR 2014/ EULAR 2015 [74] [75]	Placebo + MTX	81	6	24.7	referent	12.3	referent	3.7	referent
		Mavrilimumab (30mg/2weeks) + MTX	81		50.6	<0.001	28.4	<0.05	12.3	NS
		Mavrilimumab (100mg/2weeks) + MTX	85		61.2	<0.001	25.9	<0.05	10.6	NS
		Mavrilimumab (150mg/2weeks) + MTX	79		73.4	<0.001	40.5	<0.001	13.9	<0.05
Tabalumab	Genovese 2015 (FLEX-O) [81]	Placebo + DMARD	251	6	31.5	referent	12.7	referent	4.7	referent
		Tabalumab (90mg/2weeks) + DMARD	374		33.5	0.536	11.7	NS	6.3	NS
		Tabalumab (120mg/4weeks) + DMARD	379		34.4	0.430	11.6	NS	4.7	NS

- *DMARD, disease modifying antirheumatic drug; MTX, methotrexate; NS, nonsignificant*

Table 102: TNF IR: Combination new Biological DMARD +/- csDMARD vs csDMARD - ACR responses

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
Sarilumab	Fleischmann ACR 2015 (TARGET) [82]	Placebo + DMARD	181	6	34	referent	18	referent	7	referent
		Sarilumab (150mg/2weeks) + DMARD	181		56	<0.0001	37	<0.0001	20	<0.025
		Sarilumab (200mg/2weeks) + DMARD	184		61	<0.0001	41	<0.0001	16	<0.025
Tabalumab	Schiff 2015 (FLEX V) [84]	Placebo + DMARD	155	6	20.0	referent				
		Tabalumab (90mg/2weeks) + DMARD	148		24.3	NS				
		Tabalumab (120mg/4weeks) + DMARD	153		17.6	NS				

- *DMARD, disease modifying antirheumatic drug; NS, nonsignificant*

3.9.1.2 DAS28 remission and low disease activity

Table 103: MTX IR: Combination new Biological DMARD +/- MTX vs MTX – DAS28 remission and low disease activity

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 <2.6 (%)	p	DAS28 <3.2 (%)	p
Sarilumab	Genovese 2015 (MOBILITY) [71]	Placebo + MTX	398	6	10.1	referent	16.8	referent
		Sarilumab (150mg/2weeks) + MTX	400		27.8	<0.0001	39.8	<0.0001
		Sarilumab (200mg/2weeks) + MTX	399		34.1	<0.0001	49.1	<0.0001
	Genovese ACR 2015 (MOBILITY) [72]	Placebo + MTX	398	12	8.5	referent		
		Sarilumab (150mg/2weeks) + MTX	400		31	<0.0001		
		Sarilumab (200mg/2weeks) + MTX	399		34.1	<0.0001		
Clakizumab	Weinblatt 2015 [73]	MTX+ Placebo	61	6	11.5			
		ADA (40mg/2weeks) + MTX	59		23.7			
		Clakizumab (100mg/4weeks) + Placebo	60		25.0			
		Clakizumab (200mg/4weeks) + Placebo	59		35.6			
		Clakizumab (25mg/4weeks) + MTX	59		49.2			
		Clakizumab (100mg/4weeks) + MTX	60		40.0			
		Clakizumab (200mg/4weeks) + MTX	60		41.7			

- *ADA, adalimumab; MTX, methotrexate*

Table 104: Mixed DMARD IR: Combination new Biological DMARD vs Placebo – DAS28 remission and low disease activity

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 <2.6 (%)	p	DAS28 <3.2 (%)	p
Sirukumab	Thorne EULAR 2016 [79]	Placebo, Bio-naïve	360	6	9.0			
		Placebo, Bio-experienced	196		8.7	referent		
		Sirukumab (50mg/4weeks), Bio-naïve	382		30.6	<0.001		
		Sirukumab (50mg/4weeks), Bio-experienced	175		28.6	<0.001		
		Sirukumab (100mg/2weeks), Bio-naïve	345		31.2	<0.001		
		Sirukumab (100mg/2weeks), Bio-experienced	212		30.5	<0.001		

3.9.1.3 SDAI, CDAI and ACR-EULAR Boolean remission

Table 105: MTX IR: Combination new Biological DMARD +/- MTX vs MTX - SDAI, CDAI and ACR-EULAR Boolean remission

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
Sarilumab	Genovese 2015/	Placebo + MTX	398	6	4.8	referent	5.0	referent	3.8	referent
	ACR 2015	Sarilumab (150mg/2weeks) + MTX	400		10.3	0.0032	10.3	<0.0001	6.5	0.0810
	(MOBILITY) [71] [72]	Sarilumab (200mg/2weeks) + MTX	399		13.0	<0.0001	13.8	<0.0001	10.5	0.0002
	Genovese ACR 2015	Placebo + MTX	398	12	4.0	referent	4.8	referent	3.0	referent
	(MOBILITY) [72]	Sarilumab (150mg/2weeks) + MTX	400		15.0	<0.0001	14.8	<0.0001	10.5	<0.0001
		Sarilumab (200mg/2weeks) + MTX	399		18.5	<0.0001	18	<0.0001	14.0	<0.0001
Clakizumab	Weinblatt 2015 [73]	MTX+ Placebo	61	6	4.9		1.6		1.6	
		ADA (40mg/2weeks) + MTX	59		8.5		8.5		10.2	
		Clakizumab (100mg/4weeks) + Placebo	60		6.7		6.7		5.0	
		Clakizumab (200mg/4weeks) + Placebo	59		6.8		6.8		5.1	
		Clakizumab (25mg/4weeks) + MTX	59		18.6		15.3		10.2	
		Clakizumab (100mg/4weeks) + MTX	60		20.0		21.7		13.3	
		Clakizumab (200mg/4weeks) + MTX	60		23.3		20.0		18.3	

- *ADA, adalimumab; MTX, methotrexate*

3.9.2 Radiographic responses

Table 106: MTX IR: Combination new Biological DMARD +/- MTX vs MTX - Radiographic responses

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS* (Mean (SD))	p	Δ mTSS ≤0 (%)	p
Sarilumab	Genovese 2015 (MOBILITY) [71]	Placebo + MTX	398	12	2.78 (7.73)	referent	38.7	referent
		Sarilumab (150mg/2weeks) + MTX	400		0.90 (4.66)	<0.0001	47.8	<0.0001
		Sarilumab (200mg/2weeks) + MTX	399		0.25 (4.61)	<0.0001	55.6	<0.0001
Tabalumab	Smolen 2015 [77]	Placebo + MTX	349	6	1.57 (0.27)**	referent		
		Tabalumab (90mg/2weeks) + MTX	347		0.84 (0.27)**	0.052		
		Tabalumab (120mg/4weeks) + MTX	345		1.43 (0.27)**	0.704		

- ** mTSS = van der Heijde modified total Sharp score; ** mean (SE)*

Table 107: Mixed DMARD IR: Combination new Biological DMARD vs Placebo – Radiographic responses

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS* (Mean (SD))	p	Δ mTSS ≤0 (%)	p
Sirukumab	Thorne EULAR 2016 [79]	Placebo, Bio-naïve	360	6	3.38 (9.02)			
		Placebo, Bio-experienced	196		4.27 (9.65)	referent		
		Sirukumab (50mg/4weeks), Bio-naïve	382		0.42 (3.00)	<0.001		
		Sirukumab (50mg/4weeks), Bio-experienced	175		0.67 (2.88)	<0.001		
		Sirukumab (100mg/2weeks), Bio-naïve	345		0.67 (3.41)	<0.001		
		Sirukumab (100mg/2weeks), Bio-experienced	212		0.11 (2.98)	<0.001		

- ** mTSS = van der Heijde modified total Sharp score*

3.9.3 Patient reported outcomes

3.9.3.1 HAQ-DI

Table 108: MTX IR: Combination new Biological DMARD +/- MTX vs MTX - HAQ-DI

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ HAQ-DI (mean (SD))	p	HAQ-DI response ≥ 0.22 (%)	p
Sarilumab	Genovese 2015 (MOBILITY) [71]	Placebo + MTX	398	6	-0.3 (0.03)	referent	33.4**	referent
		Sarilumab (150mg/2weeks) + MTX	400		-0.6 (0.03)	<0.0001	51.0**	<0.0001
		Sarilumab (200mg/2weeks) + MTX	399		-0.6 (0.03)	<0.0001	51.4**	<0.0001
		Placebo + MTX	398	12			26.1**	referent
		Sarilumab (150mg/2weeks) + MTX	400				47.0**	<0.0001
		Sarilumab (200mg/2weeks) + MTX	399				47.6**	<0.0001
Clakizumab	Weinblatt 2015 [73]	MTX+ Placebo	61	6	-0.62		44.3	
		ADA (40mg/2weeks) + MTX	59		-0.66		71.2	
		Clakizumab (100mg/4weeks) + Placebo	60		-0.64		51.7	
		Clakizumab (200mg/4weeks) + Placebo	59		-0.60		59.3	
		Clakizumab (25mg/4weeks) + MTX	59		-0.68		72.9	
		Clakizumab (100mg/4weeks) + MTX	60		-0.79		65.0	
		Clakizumab (200mg/4weeks) + MTX	60		-0.71		66.7	
Ustekinumab and Guselkumab	Smolen EULAR 2015 [76]	Placebo + MTX	55	6	-0.30 (0.07)*	referent		
		Ustekinumab (90mg/8weeks) + MTX	55		-0.48 (0.07)*	0.060		
		Ustekinumab (90mg/12weeks) + MTX	55		-0.44 (0.07)*	0.134		
		Ustekinumab + MTX	110		-0.46 (0.05)*	0.088		
		Guselkumab (50mg/8weeks) + MTX	55		-0.40 (0.08)*	0.345		
		Guselkumab (200mg/8weeks) + MTX	54		-0.41 (0.08)*	0.280		
		Guselkumab + MTX	109		-0.40 (0.05)*	0.230		
Tabalumab	Smolen 2015 [77]	Placebo + MTX	349	6	-0.20 (0.03)*	referent		
		Tabalumab (90mg/2weeks) + MTX	347		-0.30 (0.03)*	0.007		
		Tabalumab (120mg/4weeks) + MTX	345		-0.26 (0.03)*	0.132		

- *MTX, methotrexate; * mean (SE) ; ** HAQ-DI response ≥0.3(%)*

Table 109: Mixed DMARD IR: Combination new Biological DMARD + csDMARD vs csDMARD/ Placebo - HAQ-DI

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ HAQ-DI (mean (SD))	p	HAQ-DI ≤ 0.5 (%)	p
Sirukumab	Thorne EULAR 2016 [79]	Placebo	556	12	-0.23 (0.57)	referent	12.4	referent
		Sirukumab (50mg/4weeks)	557		-0.45 (0.61)	<0.001	27.5	<0.001
		Sirukumab (100mg/2weeks)	557		-0.47 (0.60)	<0.001	29.3	<0.001
Tabalumab	Genovese 2015 (FLEX-O) [81]	Placebo + DMARD	213	6	-0.23 (0.6)			
		Tabalumab (90mg/2weeks) + DMARD	316		-0.24 (0.5)			
		Tabalumab (120mg/4weeks) + DMARD	320		-0.28 (0.5)			

- *DMARD, disease modifying antirheumatic drug*

Table 110: TNFi IR: Combination new Biological DMARD + csDMARD vs csDMARD - HAQ-DI

New biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ HAQ-DI (mean (SD))	p	HAQ-DI response ≥ 0.22 (%)	p
Sarilumab	Fleischmann ACR 2015 (TARGET) [82]	Placebo + DMARD	181	6	-0.29 (0.54)	referent	35	referent
		Sarilumab (150mg/2weeks) + DMARD	181		-0.50 (0.64)	0.0007	48	<0.025
		Sarilumab (200mg/2weeks) + DMARD	184		-0.49 (0.56)	0.0004	56	<0.025

- *DMARD, disease modifying antirheumatic drug*

3.9.3.2 SF36 PCS and MCS

Table 111: MTX IR: Combination new Biological DMARD +/- MTX vs MTX - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean)	p	Δ SF36 MCS (mean)	p
Sarilumab	Strand ACR 2014 (MOBILITY) [70]	Placebo + MTX	398	12	5.27	referent	3.98	referent
		Sarilumab (150mg/2weeks) + MTX	400		8.16	<0.0001	5.1	0.0200
		Sarilumab (200mg/2weeks) + MTX	399		8.83	<0.0001	7.79	<0.0001

- *MTX, methotrexate*

Table 112: Mixed DMARD IR: Combination new Biological DMARD vs Placebo - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean)	p	SF36 PCS ≥ 5 (%)	p	Δ SF36 MCS (mean)	p	SF36 MCS ≥ 5 (%)	p
Sirukumab	Karpouzas	Placebo	556	12	2.42 (6.81)	referent	31.1	referent	2.69 (9.57)	referent	34.4	referent
	EULAR 2016	Sirukumab (50mg/4weeks)	557		5.66 (7.74)	<0.001	48.8	<0.001	5.35 (9.64)	<0.001	46.7	<0.001
	[80]	Sirukumab (100mg/2weeks)	557		6.16 (7.23)	<0.001	49.7	<0.001	4.77 (9.80)	<0.001	44.2	<0.001

Table 113: TNFi IR: Combination new Biological DMARD + csDMARD vs csDMARD - SF36 PCS and MCS

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ SF36 PCS (mean)	p	Δ SF36 MCS (mean)	p
Sarilumab	Strand ACR 2015 (TARGET)	Placebo + DMARD	181	6	6.51	referent	6.04	0.2026
	[83]	Sarilumab (150mg/2weeks) + DMARD	181		8.54	0.0004	7.52	0.0854
		Sarilumab (200mg/2weeks) + DMARD	184		9.87	<0.0001	7.55	<0.0001

- *DMARD, disease modifying antirheumatic drug*

3.9.3.3 FACIT-F

Table 114: MTX IR: Combination new Biological DMARD +/- MTX vs MTX - FACIT-F

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ FACIT-F (mean)	p	Δ FACIT-F ≥ 4 (%)	p
Sarilumab	Strand ACR 2014	Placebo + MTX	398	12	6.49	referent		
	(MOBILITY) [70]	Sarilumab (150mg/2weeks) + MTX	400		9.1	<0.0001		
		Sarilumab (200mg/2weeks) + MTX	399		10.16	<0.0001		

- *MTX, methotrexate*

Table 115: Mixed DMARD IR: Combination new Biological DMARD vs Placebo - FACIT-F

Biological DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ FACIT-F (mean (SD))	p	Δ FACIT-F ≥ 4 (%)	p
Sirukumab	Karpouzas EULAR 2016 [80]	Placebo	556	12	2.7 (9.6)	referent	41.0	referent
		Sirukumab (50mg/4weeks)	557		6.7 (9.5)	<0.001	59.1	<0.001
		Sirukumab (100mg/2weeks)	557		6.8 (9.5)	<0.001	60.5	<0.001

3.10 Outcome measures of biosimilar vs. biological DMARDs

3.10.1 Signs and symptoms

3.10.1.1 ACR responses

Table 116: MTX IR: Biosimilar vs. Biological DMARDs - ACR responses

Biological originator DMARD	Biosimilar DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
ADA	ABP 501	Matsumoto ACR 2015 [85]	ABP 501 (40mg/2weeks) + MTX ADA (40mg/2weeks) + MTX	264 262	6	74.6 72.4		49.2 52.0		26.0 22.9	
	SB5	Weinblatt ACR 2015 [87]	SB5 (40mg/2weeks) + MTX ADA (40mg/2weeks) + MTX	271 273	6	72.5 72.0		38.3 39.8		19.2 20.3	
		Weinblatt EULAR 2016 [89]	SB5 (40mg/2weeks) + MTX → SB5 (40mg/2weeks) + MTX ADA (40mg/2weeks) + MTX → SB5 (40mg/2weeks) + MTX ADA (40mg/2weeks) + MTX → ADA (40mg/2weeks) + MTX	254 125 127	12	76.9 81.1 71.2					
ETN	HD203	Bae 2016 (HERA) [90]	HD203 (50mg/week) + MTX ETN (50mg/week) + MTX	115 118	12	87.27 86.49	referent NS	68.18 54.46	referent NS	38.18 33.93	referent NS
	SB4	Emery 2015 [91]	SB4 (50mg/week) + MTX ETN (50mg/week) + MTX	298 297	6	73.8 71.7	referent NS	43.0 39.1	referent NS	23.2 19.9	referent NS
		Vencovsky ACR 2015 [92]	SB4 (50mg/week) + MTX ETN (50mg/week) + MTX	299 297	12	70.2 65.7	referent NS	47.8 42.1	referent NS	30.4 24.6	referent NS
IFX	CT-P13	Takeuchi 2015 [95]	CT-P13 (3mg/kg) + MTX IFX (3mg/kg) + MTX	50 51	12	64.0 49.0	referent 0.161	50.0 31.4	referent 0.070	42.0 13.7	referent 0.002
	SB2	Choe 2015 [93]	SB2 (3mg/kg) + MTX IFX (3mg/kg) + MTX	290 293	6	55.5 59.0	referent NS	30.7 33.8	referent NS	15.5 17.1	referent NS
		Choe ACR 2015 [94]	SB2 (3mg/kg) + MTX IFX (3mg/kg) + MTX	291 293	12	50.7 52.6	referent NS	32.1 29.7	referent NS	18.3 17.7	referent NS

- *ADA, adalimumab; ETN, etanercept ; IFX, infliximab; MTX, methotrexate; NS, nonsignificant*

Table 117: Mixed DMARD IR: Biosimilar vs. Biological DMARDs - ACR responses

Biological originator DMARD	Biosimilar DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
IFX	CT-P13	Yoo ACR 2013 [96]	CT-P13 (3mg/kg) + MTX → CT-P13 (3mg/kg) + MTX	151	24	72.2	referent	48.3	referent	24.5	referent
			IFX (3mg/kg) + MTX → CT-P13 (3mg/kg) + MTX	142		71.8	NS	51.4	NS	26.1	NS

- *IFX, infliximab; MTX, methotrexate*

Table 118: TNFi IR: Biosimilar vs. Biological DMARDs - ACR responses

Biological originator DMARD	Biosimilar DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	ACR20(%)	p	ACR50(%)	p	ACR70(%)	p
RTX	BCD-020	Eremeeva EULAR 2016 [97]	BCD-020 (2×1000mg) + MTX	NR	6	84.14	referent	52.44		29.27	
			RTX (2×1000mg) + MTX	NR		87.01	0.773	55.84		35.07	

- *MTX, methotrexate; NR, not recorded; RTX, rituximab*

3.10.1.2 DAS28 remission and low disease activity

Table 119: MTX IR: Biosimilar vs. Biological DMARDs - DAS remission and low disease activity

Biological originator DMARD	Biosimilar DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	DAS28 <2.6 (%)	p	DAS28 <3.2 (%)	p
ADA	SB5	Kay EULAR 2016 [88]	SB5 (40mg/2weeks) + MTX	271	6	20.4	referent	32.3	referent
			ADA (40mg/2weeks) + MTX	273		18.7	NS	33.0	NS
ETN	HD203	Bae 2016 (HERA) [90]	HD203 (50mg/week) + MTX	115	6	27.83	referent		
			ETN (50mg/week) + MTX	118		25.42	NS		
	SB4	Emery 2015 [91]	SB4 (50mg/week) + MTX	299	6	16.7	referent	31.4	referent
			ETN (50mg/week) + MTX	297		16.2	NS	27.6	NS
IFX	SB2	Choe 2015 [93]	SB2 (3mg/kg) + MTX	290	6	14.6	referent	11.1	referent
			IFX (3mg/kg) + MTX	293		15.9	NS	9.8	NS

- *ADA, adalimumab; ETN, etanercept; IFX, infliximab; MTX, methotrexate; NS, nonsignificant*

3.10.1.3 SDAI, CDAI and ACR-EULAR Boolean remission

Table 120: MTX IR: Biosimilar vs. Biological DMARDs - SDAI, CDAI and ACR-EULAR Boolean remission

Biological originator DMARD	Biosimilar DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
ETN	HD203	Bae 2016 (HERA) [90]	HD203 (50mg/week)+ MTX ETN (50mg/week) + MTX	115 118	6					13.91 14.41	referent NS
IFX	SB2	Choe 2015 [93]	SB2 (3mg/kg) + MTX IFX (3mg/kg) + MTX	290 293	6	9.5 10.9	referent NS				

- *ETN, etanercept; IFX, infliximab; MTX, methotrexate; NS, nonsignificant*

Table 121: TNFi IR: Biosimilar vs. Biological DMARDs - SDAI, CDAI and ACR-EULAR Boolean remission

Biological originator DMARD	Biosimilar DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	SDAI remission (≤3.3) (%)	p	CDAI remission (≤2.8) (%)	p	ACR-EULAR Boolean remission (%)	p
RTX	BCD-020	Eremeeva EULAR 2016 [97]	BCD-020 (2×1000mg) + MTX RTX (2×1000mg) + MTX	NR NR	6					14.63 14.29	

- *MTX, methotrexate; NR, not recorded; RTX, rituximab*

3.10.1.4 EULAR responses

Table 122: MTX IR: Biosimilar vs. Biological DMARDs - EULAR responses

Biological originator DMARD	Biosimilar DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	EULAR good or moderate response (%)	p	EULAR moderate response (%)	p	EULAR good response (%)	p
ETN	HD203	Bae 2016 (HERA) [90]	HD203 (50mg/week) + MTX ETN (50mg/week) + MTX	115 118	12			45.45 47.75		50.91 42.34	
	SB4	Emery 2015 [91]	SB4 (50mg/week) + MTX ETN (50mg/week) + MTX	299 297	6			55.1 58.3	referent NS	32.1 29.8	referent NS
IFX	CT-P13	Takeuchi 2015 [95]	CT-P13 (3mg/kg) + MTX IFX (3mg/kg) + MTX	50 51	12	72.0 66.7	referent 0.667				
	SB2	Choe 2015 [93]	SB2 (3mg/kg) + MTX IFX (3mg/kg) + MTX	253 265	6			58.1 54.7	referent NS	25.7 25.7	referent NS

- *ETN, etanercept; IFX, infliximab; MTX, methotrexate*

3.10.2 Radiographic responses

Table 123: MTX IR: Biosimilar vs. Biological DMARDs - Radiographic responses

Biological originator DMARD	Biosimilar DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	Δ mTSS* (Mean)	p	Δ mTSS* ≤ 0.5 (%)	p
ADA	SB5	Weinblatt EULAR 2016 [89]	SB5 (40mg/2weeks) + MTX → SB5 (40mg/2weeks) + MTX ADA (40mg/2weeks) + MTX → SB5 (40mg/2weeks) + MTX ADA (40mg/2weeks) + MTX → ADA (40mg/2weeks) + MTX	254 125 127	12	0.17 0.25 0.50			
ETN	SB4	Vencovsky ACR 2015 [92]	SB4 (50mg/week) + MTX ETN (50mg/week) + MTX	299 297	12	0.45 0.74			
IFX	SB2	Choe ACR 2015 [94]	SB2 (3mg/kg) + MTX IFX (3mg/kg) + MTX	291 293	12	0.38 0.37			

- *ADA, adalimumab; ETN, etanercept; IFX, infliximab; MTX, methotrexate*
- ** mTSS = modified van der Heijde total Sharp score*

3.10.3 Patient reported outcomes

3.10.3.1 HAQ-DI

Table 124: MTX IR: Biosimilar vs. Biological DMARDs - HAQ-DI

Biological originator DMARD	Biosimilar DMARD	Study	Intervention	No. of patients	Time-point evaluated (months)	HAQ-DI (mean (SD))	p	Δ HAQ-DI (mean (SD))	p	HAQ-DI response (%)	p
ADA	ABP 501	Cohen EULAR 2016 [86]	ABP 501 (40mg/2weeks) + MTX ADA (40mg/2weeks) + MTX	264 262	6	0.97 (0.69) 0.95 (0.68)					
IFX	CT-P13	Takeuchi 2015 [95]	CT-P13 (3mg/kg) + MTX IFX (3mg/kg) + MTX	50 51	12			-0.54 (0.59) -0.25 (0.47)	referent 0.007		
	SB2	Choe 2015 [93]	SB2 (3mg/kg) + MTX IFX (3mg/kg) + MTX	253 265	6			-0.5 (0.6) -0.5 (0.6)			

- *ADA, adalimumab ; IFX, infliximab; MTX, methotrexate*

3.11 RCT safety outcome measures of new biological DMARDs

Table 125: MTX IR: Description of included RCTs and Safety Outcomes: RCTs of new Biological DMARDs

New biological DMARD	Study	Interventions	No. of patients	No. of deaths total	No. of deaths (%)	No. of malignancies total	No. of malignancies (%)	No. of infections total	No. of infections (%)	No. of other AE total	No. of other AE (%)
Tabalumab	Smolen 2015 [77]	Placebo + MTX	349	1	0.3	NR	NR	91/5	26.1/0.3[§]	8	2.3**
		Tabalumab (90mg/2weeks) + MTX	347	0	0	NR	NR	78/2[§]	22.6/0.6[§]	15	4.3**
		Tabalumab (120mg/4weeks) + MTX	345	2	0.6	NR	NR	83/6[§]	24.1/1.7[§]	8	2.3**
Sarilumab	Genovese 2015 (MOBILITY) [71]	Placebo + MTX	398	2	0.5	1	NR	133	31.1	NR	2.8[#]
		Sarilumab (150mg/2weeks) + MTX	400	2	0.5	4	NR	173	40.1	NR	16.7[#]
		Sarilumab (200mg/2weeks) + MTX	399	1	0.2	3	NR	168	39.6	NR	13.0[#]
Ustekinumab and Guselkumab	Smolen EULAR 2015 [76]	Placebo + MTX	55	0	0	0	0	NR	29.1	NR	NR
		Ustekinumab (90mg/8weeks) + MTX	55	1	1.8	0	0	NR	29.6	NR	NR
		Ustekinumab (90mg/12weeks) + MTX	55	0	0	1	1.8	NR		NR	NR
		Guselkumab (50mg/8weeks) + MTX	55	0	0	0	0	NR	22.9	NR	NR
		Guselkumab (200mg/8weeks) + MTX	54	0	0	1	1.9	NR		NR	NR
Clakizumab	Weinblatt 2015 [73]	MTX+ Placebo	61	0	0	0	0	4[†]/7[ʃʃ]	6.6[†]/11.5[ʃʃ]	2[##]	3.3[##]
		ADA (40mg/2weeks) + MTX	59	0	0	0	0	2[†]/0[ʃʃ]	3.4[†]/0[ʃʃ]	3[##]	5.1[##]
		Clakizumab (100mg/4weeks) + Placebo	60	0	0	0	0	3[†]/1[ʃʃ]	5[†]/1.7[ʃʃ]	5[##]	8.3[##]
		Clakizumab (200mg/4weeks) + Placebo	59	0	0	0	0	3[†]/7[ʃʃ]	5.1[†]/11.9[ʃʃ]	8[##]	13.6[##]
		Clakizumab (25mg/4weeks) + MTX	59	0	0	0	0	2[†]/5[ʃʃ]	3.4[†]/8.5[ʃʃ]	5[##]	8.5[##]
		Clakizumab (100mg/4weeks) + MTX	60	0	0	0	0	4[†]/3[ʃʃ]	6.7[†]/5.0[ʃʃ]	5[##]	8.3[##]
		Clakizumab (200mg/4weeks) + MTX	60	0	0	0	0	7[†]/1[ʃʃ]	11.7[†]/1.7[ʃʃ]	5[##]	8.3[##]

- *ADA, adalimumab; AE, adverse events; DMARD, disease modifying antirheumatic drug; MTX, methotrexater; NR, not recorded*
- *[†] Nasopharyngitis, [‡] Bronchitis, * Headache, [§] Serious infectious events, ** Injection-site or infusion related reactions, [ʃʃ] Upper respiratory tract infection*
- *[#] Positive results on the antidrug antibody, [##] Serious adverse events*

Table 126: Mixed DMARD IR: Description of included RCTs and Safety Outcomes: RCTs of new Biological DMARDs

New biological DMARD	Study	Interventions	No. of patients	No. of deaths total	No. of deaths (%)	No. of malignancies total	No. of malignancies (%)	No. of infections total	No. of infections (%)	No. of other AE total	No. of other AE (%)
Mavrilimumab	Burmester EULAR 2015 [75]	Placebo + MTX	81	0	0	NR	NR	NR	7.4†/7.4‡	NR	2.5*
		Mavrilimumab (30mg/2weeks) + MTX	81	0	0	NR	NR	NR	4.9†/3.7‡	NR	6.2*
		Mavrilimumab (100mg/2weeks) + MTX	85	0	0	NR	NR	NR	3.5†/1.2‡	NR	4.7*
		Mavrilimumab (150mg/2weeks) + MTX	79	0	0	NR	NR	NR	7.6†/5.1‡	NR	7.6*
Tabalumab	Genovese 2015 (FLEX-O) [81]	Placebo + DMARD	251	0	0	NR	NR	9†/10ℒℒ	3.6†/4.0ℒℒ	6*	2.4*
		Tabalumab (90mg/2weeks) + DMARD	374	1	0.3	NR	NR	14†/28ℒℒ	3.8†/7.5ℒℒ	13*	3.5*
		Tabalumab (120mg/4weeks) + DMARD	379	2	0.5	NR	NR	17†/12ℒℒ	4.5†/3.2ℒℒ	16*	4.2*

- *AE, adverse events; DMARD, disease modifying antirheumatic drug; MTX, methotrexater; NR, not recorded*
- *† Nasopharyngitis, ‡ Bronchitis, * Headache, ℒℒ Upper respiratory tract infection*

Table 127: TNF IR: Description of included RCTs and Safety Outcomes: RCTs of new Biological DMARDs

New biological DMARD	Study	Interventions	No. of patients	No. of deaths total	No. of deaths (%)	No. of malignancies total	No. of malignancies (%)	No. of infections total	No. of infections (%)	No. of other AE total	No. of other AE (%)
Tabalumab	Schiff 2015 (FLEX V) [84]	Placebo + DMARD	154	0	0	NR	NR	9ℒℒ	5.8ℒℒ	NR	NR
		Tabalumab (90mg/2weeks) + DMARD	147	0	0	NR	NR	7ℒℒ	4.8ℒℒ	NR	NR
		Tabalumab (120mg/4weeks) + DMARD	153	0	0	NR	NR	9ℒℒ	5.9ℒℒ	NR	NR
Sarilumab	Fleischmann ACR 2015 (TARGET) [82]	Placebo + DMARD	181	1	0.6	NR	NR	NR	NR	NR	3.3##
		Sarilumab (150mg/2weeks) + DMARD	181	0	0	NR	NR	NR	NR	NR	5.4##
		Sarilumab (200mg/2weeks) + DMARD	184	0	0	NR	NR	NR	NR	NR	3.3##

- *AE, adverse events; DMARD, disease modifying antirheumatic drug; MTX, methotrexater; NR, not recorded*
- *ℒℒ Upper respiratory tract infection, ## Serious adverse events*

3.12 RCT safety outcome measures of biosimilar DMARDs

Table : MTX IR: Description of included RCTs and Safety Outcomes: RCTs of Biosimilar DMARDs

Biological original DMARD	Biosimilar DMARD	Study	Interventions	No. of patients	No. of deaths total	No. of deaths (%)	No. of malignancies total	No. of malignancies (%)	No. of infections total	No. of infections (%)	No. of other AE total	No. of other AE (%)
ADA	SB5	Weinblatt EULAR 2016 [89]	SB5 (40mg/2weeks) + MTX → SB5 (40mg/2weeks) + MTX	254	0	0	1	0.4	0[§]	0[§]	6[##]	2.4[##]
			ADA (40mg/2weeks) + MTX → SB5 (40mg/2weeks) + MTX	125	0	0	1	0.8	2[§]	1.6[§]	4[##]	3.2[##]
			ADA (40mg/2weeks) + MTX → ADA (40mg/2weeks) + MTX	127	0	0	1	0.8	0[§]	0[§]	4[##]	3.1[##]
		Weinblatt ACR 2015 [87]	SB5 (40mg/2weeks) + MTX	268	0	0	0	0	1[§]	0.3[§]	3[##]	1.1[##]
			ADA (40mg/2weeks) + MTX	273	2	0.7	2	0.7	2[§]	0.7[§]	7[##]	2.6[##]
ETN	HD203	Bae 2016 (HERA) [90]	HD203 (50mg/week) + MTX	147	0	0	NR	NR	22[†]/8[ʃʃ]	15[†]/5.4[ʃʃ]	19[##]	12.9[##]
			ETN (50mg/week) + MTX	146	2	1.4	NR	NR	34[†]/10[ʃʃ]	23.3[†]/6.9[ʃʃ]	18[##]	12.3[##]
	SB4	Emery 2015 [91]	SB4 (50mg/week) + MTX	299	1	NR	NR	NR	21[ʃʃ]/14[†]	7.0[ʃʃ]/4.7[†]	13[##]	NR
			ETN (50mg/week) + MTX	297	0	NR	NR	NR	15[ʃʃ]/15[†]	5.1[ʃʃ]/5.1[†]	13[##]	NR
		Vencovsky ACR 2015 [92]	SB4 (50mg/week) + MTX	299	2	0.7	4	1.3	1[§]	0.3[§]	18[##]	6.0[##]
			ETN (50mg/week) + MTX	297	0	0	1	0.3	5[§]	1.7[§]	15[##]	5.1[##]
IFX	SB2	Choe 2015 [93]	SB2 (3mg/kg) + MTX	290	0	0	2	0.7	9[※]	3.1[※]	15**	5.2**
			IFX (3mg/kg) + MTX	293	1	0.3	0	0	6[※]	2.0[※]	13**	4.4**
	CT-P13	Takeuchi 2015 [95]	CT-P13 (3mg/kg) + MTX	51	NR	NR	NR	NR	10[†]/7[ʃʃ]	19.6[†]/13.7[ʃʃ]	8[##]/7**	15.7[##]/13.7**
			IFX (3mg/kg) + MTX	53	NR	NR	NR	NR	13[†]/2[ʃʃ]	24.5[†]/3.8[ʃʃ]	8[##]/7**	15.1[##]/13.2**

- *ADA, adalimumab; AE, adverse events; DMARD, disease modifying antirheumatic drug; ETN, etanercept; IFX, infliximab; MTX, methotrexater; NR, not recorded*
- *[†] Nasopharyngitis, [§] Serious infectious events, ** Injection-site or infusion related reactions, [ʃʃ] Upper respiratory tract infection, [##] Serious adverse events, [※] Serious infections or tuberculosis*

Table 128: Mixed DMARD IR: Description of included RCTs and Safety Outcomes: RCTs of Biosimilar DMARDs

Biological original DMARD	Biosimilar DMARD	Study	Interventions	No. of patients	No. of deaths total	No. of deaths (%)	No. of malignancies total	No. of malignancies (%)	No. of infections total	No. of infections (%)	No. of other AE total	No. of other AE (%)
IFX	CT-P13	Yoo ACR 2013 [96]	CT-P13 (3mg/kg) + MTX → CT-P13 (3mg/kg) + MTX	159	1	0.6	1	0.6	50	31.4	7[##]	4.4[##]
			IFX (3mg/kg) + MTX → CT-P13 (3mg/kg) + MTX	143	0	0	4	0	47	32.9	8[##]	5.6[##]

- *AE, adverse events; DMARD, disease modifying antirheumatic drug; IFX, infliximab; MTX, methotrexater; NR, not recorded*
- [##] *Serious adverse events*

Table 129: TNF IR: Description of included RCTs and Safety Outcomes: RCTs of Biosimilar DMARDs

Biological original DMARD	Biosimilar DMARD	Study	Interventions	No. of patients	No. of deaths total	No. of deaths (%)	No. of malignancies total	No. of malignancies (%)	No. of infections total	No. of infections (%)	No. of other AE total	No. of other AE (%)
RTX	BCD-020	Eremeeva EULAR 2016 [97]	BCD-020 (2×1000mg) + MTX	NR	NR	NR	NR	NR	NR	NR	NR	0[##]
			RTX (2×1000mg) + MTX	NR	NR	NR	NR	NR	NR	NR	NR	2.35[##]

- *AE, adverse events; DMARD, disease modifying antirheumatic drug; MTX, methotrexater; NR, not recorded; RTX, rituximab*
- [##] *Serious adverse events*

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