Efficacy and safety of biological and targeted synthetic DMARDs: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis

Online supplementary material

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1. LITERATURE SEARCH STRATEGY

1.1 Search terms

Medline

1. exp Spondylitis/
2. (ankylos$ or spondyl$).tw.
3. SpA.tw.
4. (bekhterev$ or bechterew$).tw.
5. or/1-4
6. exp biological therapy/
7. exp antibodies, monoclonal/
8. exp monokines/
9. exp receptors, interleukin-1/
10. exp receptors, interleukin-6/
11. exp immunoglobulin g/
12. exp immunoconjugates/
13. exp polyethylene glycols/
14. exp immunoglobulin fab fragments/
15. exp t-lymphocytes/
16. biologic$.tw.
17. infliximab.tw.
18. remicade.tw.
19. adalimumab.tw.
20. humira.tw.
21. trudexa.tw.
22. abatacept.tw.
23. orencia.tw.
24. anakinra.tw.
25. kineret.tw.

26. Certolizumab.tw.

27. cimzia.tw.

28. Etanercept.tw.

29. enbrel.tw.

30. Golimumab.tw.

31. simponi.tw.

32. rituximab.tw.

33. rituxan.tw.

34. mabthera.tw.

35. Tocilizumab.tw.

36. actemra.tw.

37. RoActemra.tw.

38. secukinumab.tw.

39. Cosentyx.tw.

40. ustekinumab.tw.

41. Stelara.tw.

42. brodalumab.tw.

43. ixekizumab.tw.

44. or/6-43

45. 5 and 44

46. (animals not (humans and animals)).sh.

47. 45 not 46

48. limit 47 to yr="2009 -Current"

EMBASE

1. 'spondylitis'/exp
2. ankylos*:ab,ti OR spondyl*:ab,ti
3. spa:ab,ti
4. bekhterev*:ab,ti OR bechterew*:ab,ti

5. #1 OR #2 OR #3 OR #4
6. 'biological therapy'/exp
7. biologic*:ab,ti
9. 'monoclonal antibody'/exp
10. 'infliximab':ab,ti
11. remicade:ab,ti
12. adalimumab:ab,ti
13. humira:ab,ti
14. trudexa:ab,ti
15. abatacept:ab,ti
16. orencia:ab,ti
17. anakinra:ab,ti
18. kineret:ab,ti
19. certolizumab:ab,ti
20. cimzia:ab,ti
22. 'etanercept'/de
23. etanercept:ab,ti
24. enbrel:ab,ti
25. golimumab:ab,ti
27. simponi:ab,ti
28. rituximab:ab,ti
29. rituxan:ab,ti
30. mabthera:ab,ti
31. tocilizumab:ab,ti
32. actemra:ab,ti
33. roactemra:ab,ti
34. secukinumab:ab,ti
35. cosentyx:ab,ti
36. ustekinumab:ab,ti

37. stelara:ab,ti

38. brodalumab:ab,ti

39. ixekizumab:ab,ti

40. #6 OR #7 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #22 OR #23 OR #24 OR #25 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39

41. #5 AND #40

42. #5 AND #40 AND [humans]/lim AND [embase]/lim

43. #43 AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py)

44. 44 AND AND ('article'/it OR 'article in press'/it OR 'review'/it)

Cochrane Central

#1. MeSH descriptor: [Spondylitis] explode all trees

#2. (ankylos* or spondyl*):ti,ab

#3. spa:ti,ab

#4. (bekhterev* or bechterew*):ti,ab

#5. #1 or #2 or #3 or #4

#6. MeSH descriptor: [Biological Therapy] explode all trees

#7. MeSH descriptor: [Antibodies, Monoclonal] explode all trees

#8. MeSH descriptor: [Monokines] explode all trees

#9. MeSH descriptor: [Receptors, Interleukin-1] explode all trees

#10. MeSH descriptor: [Receptors, Interleukin-6] explode all trees

#11. MeSH descriptor: [Immunoglobulin G] explode all trees

#12. MeSH descriptor: [Immunoconjugates] explode all trees

#13. MeSH descriptor: [Polyethylene Glycols] explode all trees

#14. MeSH descriptor: [Immunoglobulin Fab Fragments] explode all trees

#15. MeSH descriptor: [T-Lymphocytes] explode all trees

#16. biologic*:ti,ab

#17. infliximab:ti,ab

#18. remicade:ti,ab

#19. adalimumab:ti,ab

#20. humira:ti,ab

#21. trudexa:ti,ab

#22. abatacept:ti,ab

#23. orencia:ti,ab

#24. anakinra:ti,ab

#25. kineret:ti,ab

#26. Certolizumab:ti,ab

#27. cimzia:ti,ab

#28. Etanercept:ti,ab

#29. enbrel:ti,ab

#30. Golimumab:ti,ab

#31. simponi:ti,ab

#32. rituximab:ti,ab

#33. rituxan:ti,ab

#34. mabthera:ti,ab

#35. Tocilizumab:ti,ab

#36. actemra:ti,ab

#37. RoActemra:ti,ab

#38. secukinumab:ti,ab

#39. Cosentyx:ti,ab

#40. ustekinumab:ti,ab

#41. Stelara:ti,ab

#42. brodalumab:ti,ab

#43. ixekizumab:ti,ab

#44. #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43

#45. #5 and #44 Publication Year from 2009 to 2015

1.2 Review flow chart

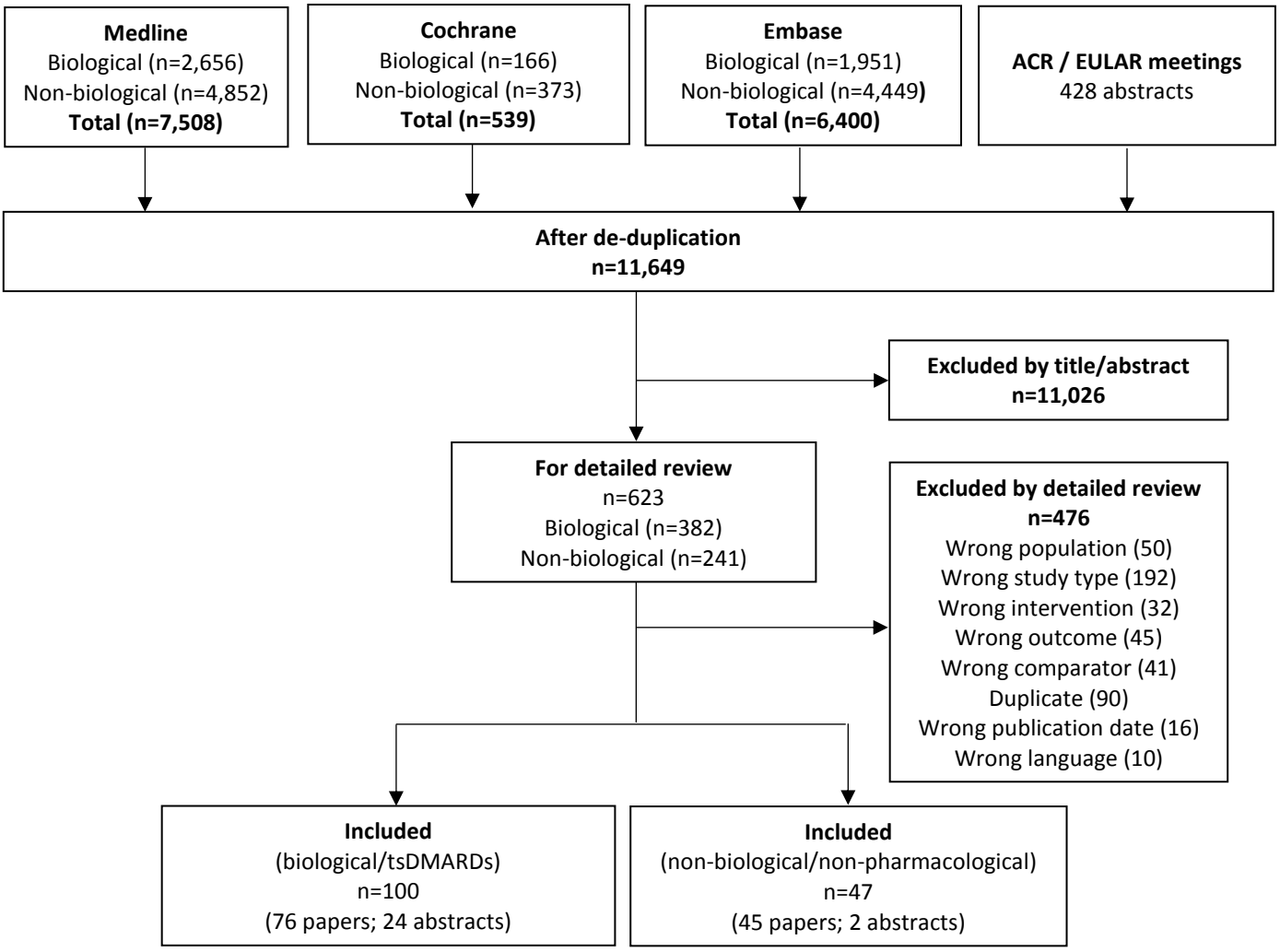

Figure S1. Flowchart for the systematic literature.

2. SUMMARY OF PUBLICATIONS

Table S1. Number of publications from clinical trials according to the study population.

Drug	r-axSpA (mNY)	axSpA¥ (ASAS)	nr-axSpA* (ASAS)	nr-axSpA* (other)	SpA (Amor)	SpA (ESSG)	Total publications	Total trials
Etanercept	14	7	5	0	1	0	**27**	**14**
Infliximab	6	4	0	1	0	0	**11**	**7**
Adalimumab	8	0	6	0	0	1	**15**	**6**
Golimumab	7	1	3	0	0	0	**11**	**5**
Certolizumab pegol	0	13	0	0	0	0	**13**	**1**
Secukinumab	5	0	0	0	0	0	**5**	**1**
Ustekinumab	1	0	0	0	0	0	**1**	**1**
Rituximab	2	0	0	0	0	0	**2**	**1**
Abatacept	1	0	0	0	0	0	**1**	**1**
Tocilizumab	1	0	0	0	0	0	**1**	**1**
Sarilumab	1	0	0	0	0	0	**1**	**1**
Apremilast	1	0	0	0	0	0	**1**	**1**
Tofacitinib	1	0	0	0	0	0	**1**	**1**
CT-P13	2	0	0	0	0	0	**2**	**1**
Total publications	50	25	14	1	1	1	**92†**	**42**

¥ Both nr-axSpA and r-axSpA (mNY) patients included in the same study; *excluding patients fulfilling the mNY; † plus one Cochrane review; CT-P13, infliximab biosimilar.

Table S1.1. Number of clinical trials according to the study population.

Drug (range publication year)	N trials	r-axSpA (mNY)	axSpA¥ (ASAS)	nr-axSpA* (ASAS)	nr-axSpA* (other)	SpA (Amor)	SpA (ESSG)
Etanercept (2009-2015)	14	10	2	1	0	1	0
Infliximab (2009-2014)	7	5	1	0	1	0	0
Adalimumab (2009-2016)	6	3	0	2	0	0	1
Golimumab (2012-2015)	5	3	1	1	0	0	0
Certolizumab pegol (2014; 2015)	1	0	1	0	0	0	0
Secukinumab (2013-2015)	1	1	0	0	0	0	0
Ustekinumab (2014)	1	1	0	0	0	0	0
Rituximab (2010; 2013)	1	1	0	0	0	0	0
Abatacept (2011)	1	1	0	0	0	0	0
Tocilizumab (2014)	1	1	0	0	0	0	0
Sarilumab (2015)	1	1	0	0	0	0	0
Apremilast (2013)	1	1	0	0	0	0	0
Tofacitinib (2015)	1	1	0	0	0	0	0
CT-P13 (2013; 2016)	1	1	0	0	0	0	0
Total	**42**	**30**	**5**	**4**	**1**	**1**	**1**

¥ Both nr-axSpA and r-axSpA (mNY) patients included in the same study; *excluding patients fulfilling the mNY; CT-P13, infliximab biosimilar.

Table S2. Observational cohort studies.

Adverse event	Prospective cohort (comparator)	Prospective cohort (SIR* reported)	Total studies
Malignancies	0	3	3
Infections / serious infections	2	0	2
Tuberculosis	2	0	2
Total	4	3	7

*SIR, Standardized Incidence Ratio (the ratio between observed and expected cases in the general population).

3. RANDOMIZED CONTROLLED TRIALS AND LTE OF TNF INHIBITORS

Different publications stemming from the same study are included provided additional data for at least one of the pre-defined outcomes is reported. However, not all outcomes included in the PICO for this SLR are shown here (eg. patient global assessment, quality of life according to SF-36, work-participation), thus some studies do not have data for the selected (main) outcomes. If more than one publication from the same study is available different colours are used to identify each publication and the respective data. Given the time-span (2009-2016) of the SLR the main phase 3 RCTs for etanercept, infliximab, adalimumab and golimumab in r-axSpA were not included, but only their LTE or other (subsequent) trials in different populations.

3.1 Etanercept

Table S3: Study and patients' main characteristics (etanercept)

Study	Type of patients	Interventions	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration (years)	Previous TNFi (%)
Dijkmans 2009 Rheuma	r-axSpA†	ETA 25 TW PBO	39 42	NR NR	NR NR	NR NR	NR NR	NR
Martín-Mola 2010 C&ER	r-axSpA†	ETA 25 TW	59	44.2	76.3	NR	14.1	NR
Barkham 2010 ARD	r-axSpA†	ETA 25 TW PBO	20 20	40.8 (9.7) 39.4 (10.1)	75 85	NR	132 month£ 240 months£	TNFi-naive
Dougados 2010 ARD (HEEL)	SpA‡	ETA 50 QW PBO	12 12	34.5 (12.4) 40 (10.4)	58.3 75.0	75 66.7	2.5 (1.9) 3.3 (3.3)	TNFi-naive
Dougados 2011 ARD (SPINE) Dougados 2012 Rheuma (SPINE)	r-axSpA†	ETA 50 QW PBO	39 43	46 (11) 48 (10)	95 91	79 86	19 (10) 23 (11)	TNFi-naive
Baraliakos 2013 AR&T	axSpA‡	ETA 25 TW	16	36 (7.5)	87.5	100	13 (7.7)	NR
Dougados 2014 A&R (EMBARK) Dougados 2015 JR (EMBARK) Maksymowych 2015 ARD (EMBARK) Dougados 2015 ACR (EMBARK) Brown 2015 ACR (EMBARK)	nr-axSpA¥	ETA 50 QW PBO	106 109	31.9 (7.8) 32.0 (7.8)	64.1 56.9	67 76.2	2.4 (1.9) 2.5 (1.8)	TNFi-naive

Dougados 2014 AR&T (SPARSE)	axSpA[¥]	ETA 50 + NSAIDs PBO + NSAIDs	42 48	38.8 (12.3) 38.9 (11.4)	57.1 66.7	66.7 64.6	6 (9.0) 5.5 (7.4)	TNFi-naive

† according to modified New York criteria; ‡ according to Amor criteria; ¥ according to ASAS criteria; £ Median.

Table S4: Cochrane risk of bias assessment (etanercept)

Study	Intervention	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall RoB
Dijkmans 2009 Rheuma	L	L	L	L	L	L	L	L
Martín-Mola 2010 C&ER	L	M	H	H	M	L	H	H
Barkham 2010 ARD	L	L	L	L	L	L	L	L
Dougados 2010 ARD (HEEL)	L	L	L	L	L	L	L	L
Dougados 2011 ARD (SPINE) Dougados 2012 Rheuma (SPINE)	L	L	L	L	L	L	L	L
Baraliakos 2013 AR&T	L	M	H	H	M	L	H	H
Dougados 2014 A&R (EMBARK) Dougados 2015 JR (EMBARK) Maksymowych 2015 ARD (EMBARK) Dougados 2015 ACR (EMBARK) Brown 2015 ACR (EMBARK)	L	L	L	L	L	L	L	L
Dougados 2014 AR&T (SPARSE)	L	L	L	L	L	L	L	L

H= high risk; L = low risk; U = unclear risk.

Table S5: ASAS response outcomes (etanercept)

Study	Interventions	Time-point (months)	ASAS 20 (%)	p-value	ASAS 40 (%)	p-value	ASAS 5/6 (%)	p-value	ASAS PR (%)	p-value
Dijkmans 2009 Rheuma	ETA 25 TW PBO	3	60 23	NR	NR	NR	NR	NR	NR	NR
Martín-Mola 2010 C&ER*	ETA 25 TW	66	75	NR	68	NR	32	NR	31	NR
Barkham 2010 ARD	ETA 25 TW PBO	3	NR	NR	NR	NR	NR	NR	NR	NR
Dougados 2010 ARD (HEEL)	ETA 50 QW PBO	3	NR	NR	NR	NR	NR	NR	NR	NR
Dougados 2011 ARD (SPINE)	ETA 50 QW PBO	3	68.4 35.9	0.003 REF	44.7 25.6	0.053 REF	21 5	0.044 REF	18 5	0.073 REF
Dougados 2012 Rheuma (SPINE)†	ETA 50 QW PBO/ETA 50	6	84.2 66.7	NR NR	68.4 53.9	NR NR	15.8 18	NR NR	29 23.1	NR NR
Baraliakos 2013 AR&T*	ETA 25 TW	84	NR	NR	68.8	NR	NR	NR	31.3	NR
Dougados 2014 A&R (EMBARK) Dougados 2015 JR (EMBARK) Maksymowych 2015 ARD (EMBARK) Dougados 2015 ACR (EMBARK)† Brown 2015 ACR (EMBARK)	ETA 50 QW PBO ETA / ETA PBO /ETA	3 26 	52.4 36.1 61 65.7	<0.05 REF NR NR	33.3 14.8 49 51.4	<0.05 REF NR NR	34.3 11.9 NR NR	NR NR NR NR	24.8 11.9 NR NR	NR NR NR NR
Dougados 2014 AR&T (SPARSE)	ETA 50 + NSAIDs PBO + NSAIDs	2	44.4 23.8	0.05 ref	44.4 21.4	0.028 ref	NR NR	NR NR	4.9 4.4	0.911 ref

*Completers analysis (observed data); † ITT analysis (NRI)

Table S6: ASDAS outcomes (etanercept)

Study	Interventions	Time-point (months)	Mean ASDAS change (SD)	p-value	ASDAS CII (%)	p-value	ASDAS MI (%)	p-value	ASDAS I (%)	p-value
Dijkmans 2009 Rheuma	ETA 25 TW PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR
Martín-Mola 2010 C&ER	ETA 25 TW	66	NR	NR	NR	NR	NR	NR	NR	NR

Barkham 2010 ARD	ETA 25 TW PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dougados 2010 ARD (HEEL)	ETA 50 QW PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dougados 2011 ARD (SPINE)	ETA 50 QW PBO	3	-1.51 (0.87) -0.49 (0.87)	<0.001 REF	64.1 17.1	<0.001 REF	38.5 2.4	<0.001 REF	43.6 85.4	<0.001 REF
Dougados 2012 Rheuma (SPINE)†	ETA 50 PBO/ETA 50	6	-1.9 (1.2) -1.7 (1.1)	NR NR	76.3 63.2	NR NR	50 34.2	NR NR	26.3 38.5	NR NR
Baraliakos 2013 AR&T*	ETA 25 TW	84	NR	NR	NR	NR	62.5	NR	43.8	NR
Dougados 2014 A&R (EMBARK) Dougados 2015 JR (EMBARK) Maksymowych 2015 ARD (EMBARK) Dougados 2015 ACR (EMBARK)† Brown 2015 ACR (EMBARK)	ETA 50 QW PBO ETA / ETA PBO /ETA	3 26 	-1.1 (0.1) -0.5 (0.1) -1.6 (0.2) -1.7 (0.1)	<0.001 REF NR NR	NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR NR	40 17.4 48 59.1	<0.001 REF NR NR
Dougados 2014 AR&T (SPARSE)	ETA 50 + NSAIDs PBO + NSAIDs	2	1.2 (0.1) 0.5 (0.1)	0.001 REF	NR	NR	NR	NR	19.5 13.3	1.2 (0.1) 0.5 (0.1)

*Completers analysis (observed data); † ITT analysis (NRI)

Table S7: Other disease-activity outcomes (etanercept)

Study	Interventions	Time-point (months)	Mean BASDAI change (SD)	p-value	BASDAI 50 (%)	p-value	Mean CRP change (SD)	p-value	Mean TJC (SD)	p-value
Dijkmans 2009 Rheuma	ETA 25 TW PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR
Martín-Mola 2010 C&ER	ETA 25 TW	66	NR	NR	NR	NR	NR	NR	NR	NR
Barkham 2010 ARD	ETA 25 TW PBO	3	-1,97 -0,10	0.012 REF	NR	NR	NR	NR	NR	NR
Dougados 2010 ARD (HEEL)	ETA 50 QW PBO	3	-19.93 (20.8) -4.64 (20.8)	0.09 REF	NR	NR	NR	NR	NR	NR
Dougados 2011 ARD (SPINE)	ETA 50 QW PBO	3	-26 (20) -14 (20)	0.008 REF	46 23	0.031 REF	-16 (14) -1 (14)	<0.001 REF	NR NR	NR NR
Dougados 2012 Rheuma (SPINE)†	ETA 50 PBO/ETA 50	6	-37.6 (22.4) -28.6 (24.3)	NR NR	65.8 48.7	NR NR	NR NR	NR NR	-16.1 (33.0) -9.6 (13)	NR NR
Baraliakos 2013 AR&T	ETA 25 TW	84	NR	NR	NR	NR	NR	NR	NR	NR

Dougados 2014 A&R (EMBARK) Dougados 2015 JR (EMBARK) Maksymowych 2015 ARD (EMBARK) Dougados 2015 ACR (EMBARK)† Brown 2015 ACR (EMBARK)	ETA 50 QW PBO ETA / ETA PBO /ETA	3 26	-2,0 (0,3) -1,3 (0,13) -3.4 (0.2) -3.9 (0.2)	0.019 REF NR	43.8 23.9 57 62.9	<0.05 REF NR	-3,0 (1,1) 0,1 (1,0) NR	0.004 REF NR	-1,6 (0.4) -1,6 (0.4) NR	0.989 REF NR
Dougados 2014 AR&T (SPARSE)	ETA 50 + NSAIDs PBO + NSAIDs	2	2.0 (0,3) 1.1 (0,3)	0.051 REF	39 17.8	0.032 REF	NR	NR	NR	NR

† ITT analysis (NRI)

Table S8: Mobility, function and quality of life outcomes (etanercept)

Study	Interventions	Time-point (months)	Mean BASFI change (SD)	p-value	Mean BASMI change (SD)	p-value	Mean ASQoL change	p-value
Dijkmans 2009 Rheuma	ETA 25 TW PBO	NR	NR	NR	NR	NR	NR	NR
Martín-Mola 2010 C&ER	ETA 25 TW	66	NR	NR	NR	NR	NR	NR
Barkham 2010 ARD	ETA 25 TW PBO	NR	-1.35 0.21	0.012 REF	NR	NR	-3.26 -0.11	0.012 REF
Dougados 2010 ARD (HEEL)	ETA 50 QW PBO	NR	NR	NR	NR	NR	NR	NR
Dougados 2011 ARD (SPINE) Dougados 2012 Rheuma (SPINE)†	ETA 50 QW PBO ETA 50 PBO/ETA 50	3 6	-2.2 (1.8) -1.0 (1.8) -28.9 (20.8) -21.8 (20.9)	0.004 REF NR	-0.57 (0.65) -0.2 (0.65) -0.8 (0.8) -0.5 (0.7)	0.011 REF NR	NR -1.9 (1.2) -1.7 (1.1)	NR NR
Baraliakos 2013 AR&T	ETA 25 TW	84	NR	NR	NR	NR	NR	NR
Dougados 2014 A&R (EMBARK) Dougados 2015 JR (EMBARK) Maksymowych 2015 ARD (EMBARK) Dougados 2015 ACR (EMBARK)† Brown 2015 ACR (EMBARK)	ETA 50 QW PBO ETA / ETA PBO /ETA	3 26	-1.4 (0.2) -0.8 (0.2) -2.4 (0.2) -2.4 (0.2)	0.016 REF NR	-0.3 (0.2) -0.3 (0.1) NR	0.687 REF NR	-1.9 (0.5) -1.4 (0.5) NR	0.329 REF NR
Dougados 2014 AR&T (SPARSE)	ETA 50 + NSAIDs PBO + NSAIDs	2	1.7 (0.3) 0.8 (0.3)	0.03 ref	0.4 (0.2) 0.1 (0.2)	0.3 REF	NR	NR

† ITT analysis (NRI)

3.2 Infliximab

Table S9: Study and patients' main characteristics (infliximab)

Study	Type of patients	Interventions	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration (years)	Previous TNFi (%)
Barkham 2009 A&R	nr-axSpA*	INF 5 mg/Kg PBO	20 20	29.5 28.2	75 75	100 100	17.2 months 13.4 months	TNFi-naïve
Inman 2010 JR	r-axSpA†	INF 3 mg/Kg PBO	39 37	42.9 (10.4) 39.3 (9.0)	82 78	72 72	11.1 (10.3) 11.7 (10.6)	TNFi-naïve
Maksymowych 2010 JR	r-axSpA†	INF 3 mg/Kg PBO	16 16	43.6 (11.8) 41.7 (9.3)	77.8 77.8	77.8 72.2	20.0 (11.8) 20.2 (11.5)	TNFi-naïve
Baraliakos 2011 Rheuma	r-axSpA†	IFN 3 mg/Kg	33	37.8 (8)	75.8	96.9	NR	TNFi-naive

* nr-axSpA defined by: IBP (Calin definition) within 3 months to 3 years AND MRI-SI positive AND HLA-B27 +; † according to modified New York criteria; ‡ according to ASAS criteria.

Table S10: Cochrane risk of bias assessment (infliximab)

Study	Intervention	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall RoB
Barkham 2009 A&R	L	L	L	L	L	L	L	L
Inman 2010 JR	L	L	L	L	L	L	L	L
Maksymowych 2010 JR	L	L	L	L	L	L	L	L
Baraliakos 2011 Rheuma	L	M	H	H	M	L	H	H

H= high risk; L = low risk; U = unclear risk.

Table S11: ASAS response outcomes (infliximab)

Study	Interventions	Time-point (months)	ASAS 20 (%)	p-value	ASAS 40 (%)	p-value	ASAS 5/6 (%)	p-value	ASAS PR (%)	p-value
Barkham 2009 A&R	INF 5 mg/Kg PBO	4	NR	NR	61.1 17.6	0.009 REF	44.4 13.3	0.053 REF	55.6 12.5	0.009 REF
Inman 2010 JR	INF 3 mg/Kg PBO	3	54 31	0.042 REF	46 8	<0.001 REF	51 3	<0.001 REF	NR	NR
Maksymowych 2010 JR	INF 3 mg/Kg PBO	12	68.8 37.5	0.08 REF	56.3 12.5	0.009 REF	NR	NR	NR	NR
Baraliakos 2011 Rheuma*	IFN 3 mg/Kg	96	84.8	NA	63.6	NA	63.6	NA	24.2	NA

*Completers analysis (observed data)

Table S12: ASDAS outcomes (infliximab)

Study	Interventions	Time-point (months)	Mean ASDAS change (SD)	p-value	ASDAS CIII (%)	p-value	ASDAS MI (%)	p-value	ASDAS I (%)	p-value
Barkham 2009 A&R	INF 5 mg/Kg PBO	4	NR	NR	NR	NR	NR	NR	NR	NR
Inman 2010 JR	INF 3 mg/Kg PBO	3	NR	NR	NR	NR	NR	NR	NR	NR
Maksymowych 2010 JR	INF 3 mg/Kg PBO	12	NR	NR	NR	NR	NR	NR	NR	NR
Baraliakos 2011 Rheuma	IFN 3 mg/Kg	96	NR	NR	NR	NR	NR	NR	NR	NR

Table S13: Other disease-activity outcomes (infliximab)

Study	Interventions	Time-point (months)	Mean BASDAI change (SD)	p-value	BASDAI 50 (%)	p-value	Mean CRP change (SD)	p-value	Mean TJC (SD)	p-value
Barkham 2009 A&R	INF 5 mg/Kg PBO	4	NR	NR	NR	NR	NR	NR	NR	NR
Inman 2010 JR	INF 3 mg/Kg PBO	3	-2.1 -0.7	0.003 REF	28 12	0.064 REF	NR	NR	NR	NR

Maksymowych 2010 JR	INF 3 mg/Kg PBO	12	-2.3 (1.9) -0.8 (2.2)	0.05 REF	31.3 6.3	NS REF	NR	NR	NR	NR
Baraliakos 2011 Rheuma*	IFN 3 mg/Kg	96	NR	NR	63.6	NR	NR	NR	NR	NR

*Completers analysis (observed data)

Table S14: Mobility, function and quality of life outcomes (infliximab)

Study	Interventions	Time-point (months)	Mean BASFI change (SD)	p-value	Mean BASMI change (SD)	p-value	Mean ASQoL change	p-value
Barkham 2009 A&R	INF 5 mg/Kg PBO	4	-2.70 (2.36) -0.47 (2.25)	0.004 REF	NR	NR	-6.18 -1	0.007 REF
Inman 2010 JR	INF 3 mg/Kg PBO	3	-1.8 -0.4	0.004 REF	-0.45 (1.03) 0.24 (0.60)	0.001 REF	NR	NR
Maksymowych 2010 JR	INF 3 mg/Kg PBO	12	NR	NR	NR	NR	NR	NR
Baraliakos 2011 Rheuma	IFN 3 mg/Kg	96	NR	NR	NR	NR	NR	NR

3.3 Adalimumab

Study	Type of patients	Interventions	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration (years)	Previous TNFi (%)
van der Heijde 2009 ARD (ATLAS) van der Heijde 2009 AR&T (ATLAS) Maksymowych 2010 JR (ATLAS) Sieper 2012 ARD (ATLAS) van der Heijde 2015 Rheuma (ATLAS)	r-axSpA†	ADA 40 Q2W PBO	311 208	43.2 (11.6)	74.9	NR	10.9 (9.5)	TNFi-naïve
Hu 2012 IJRD	r-axSpA†	ADA 40 Q2W PBO	26 20	28.6 (6.9) 27.4 (7.2)	92.3 100	96.2 95	7.4 (5.7) 7.6 (4.6)	NR
Sieper 2013 ARD (ABILITY-1) van der Heijde 2014 EULAR (ABILITY-1)	nr-axSpA‡	ADA 40 Q2W PBO ADA40 Q4W	91 94 122	37.6 38.4 NR	48 43 NR	82 74 NR	10.1 (9.0) 10.1 (8.8) NR	TNFi-naïve
Huang 2014 ARD	r-axSpA†	ADA 40 Q2W PBO	229 115	30.1 (8.7) 29.67 (7.5)	80.8 82.6	95.6 94.8	8.1 (6.0) 7.7 (4.7)	TNFi-naïve
Pedersen 2016 A&R	SpA¥	ADA 40 Q2W PBO	25 27	39.6 (12.4) 37.5 (9.4)	77.8 76	96 79.2	10.9 (10.8) 8.2 (8.1)	TNFi-naïve

Table S15: Study and patients' main characteristics (adalimumab)

† according to modified New York criteria; ‡ according to ASAS criteria; ¥ according to the ESSG criteria.

Table S16: Cochrane risk of bias assessment (adalimumab)

Study	Intervention	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall RoB
van der Heijde 2009 ARD (ATLAS) van der Heijde 2009 AR&T (ATLAS) Maksymowych2010 JR (ATLAS) Sieper 2012 ARD (ATLAS) van der Heijde 2015 Rheuma (ATLAS)	L	L	L	L	L	L	L	L
Hu 2012 IJRD	L	L	L	L	L	U	U	L
Sieper 2013 ARD (ABILITY-1)	L	L	L	L	L	U	L	L

van der Heijde 2014 EULAR (ABILITY-1)								
Huang 2014 ARD	L	L	L	L	L	U	U	L
Pedersen 2016 A&R	L	L	L	L	L	L	L	L

H= high risk; L = low risk; U = unclear risk.

Table S17: ASAS response outcomes (adalimumab)

Study	Interventions	Time-point (months)	ASAS 20 (%)	p-value	ASAS 40 (%)	p-value	ASAS 5/6 (%)	p-value	ASAS PR (%)	p-value
van der Heijde 2009 ARD (ATLAS) van der Heijde 2009 AR&T (ATLAS) Maksymowych2010 JR (ATLAS) Sieper 2012 ARD (ATLAS)* van der Heijde 2015 Rheuma (ATLAS)	ADA40 Q4W	60	89	NR	70.4	NR	NR	NR	50.8	NR
Hu 2012 IJRD	ADA 40 Q2W PBO	3	NR	NR	NR	NR	NR	NR	NR	NR
Sieper 2013 ARD (ABILITY-1) van der Heijde 2014 EULAR (ABILITY-1)*	ADA 40 Q2W PBO ADA40 Q4W	3 36	51.6 30.9 83	0.004 REF NR	36 15 66	<0.001 REF NR	31 6 NR	<0.001 REF NR	16 5 43	0.01 REF NR
Huang 2014 ARD	ADA 40 Q2W PBO	3	67.2 30.4	<0.001 REF	44.5 9.6	<0.001 REF	55.9 12.2	<0.001 REF	21.8 3.5	<0.001 REF
Pedersen 2016 A&R	ADA 40 Q2W PBO	3	NR	NR	NR	NR	NR	NR	NR	NR

*Completers analysis (observed data)

Table S18: ASDAS outcomes (adalimumab)

Study	Interventions	Time-point (months)	Mean ASDAS change (SD)	p-value	ASDAS CII (%)	p-value	ASDAS MI (%)	p-value	ASDAS I (%)	p-value

van der Heijde 2009 ARD (ATLAS) van der Heijde 2009 AR&T (ATLAS) Maksymowych2010 JR (ATLAS) Sieper 2012 ARD (ATLAS)* van der Heijde 2015 Rheuma (ATLAS)	ADA40 Q4W	60	NR	NR	NR	NR	65.3	NR	60.5	NR
Hu 2012 IJRD	ADA 40 Q2W PBO	3	NR	NR	NR	NR	NR	NR	NR	NR
Sieper 2013 ARD (ABILITY-1) van der Heijde 2014 EULAR (ABILITY-1)*	ADA 40 Q2W PBO ADA40 Q4W	3 36	-1.00 -0.30 NR	<0.00 1 REF NR	NR NR 69	NR NR NR	19 3 40	<0.001 REF NR	24 4 46	<0.001 REF NR
Huang 2014 ARD	ADA 40 Q2W PBO	3	-2.0 (1.1) -0.6 (0.8)	<0.00 1 REF	80.8 24.3	<0.001 REF	51.1 7.8	<0. 001 REF	40.2 5.2	<0.001 REF
Pedersen 2016 A&R	ADA 40 Q2W PBO	3	-1.90 (1.73) -0.56 (1.24)	0.003 REF	NR	NR	48.1 7.4	0.002 REF	NR	NR

*Completers analysis (observed data)

Table S19: Other disease-activity outcomes (adalimumab)

Study	Interventions	Time-point (months)	Mean BASDAI change (SD)	p-value	BASDAI 50 (%)	p-value	Mean CRP change (SD)	p-value	Mean TJC (SD)	p-value
van der Heijde 2009 ARD (ATLAS) van der Heijde 2009 AR&T (ATLAS) Maksymowych2010 JR (ATLAS) Sieper 2012 ARD (ATLAS)* van der Heijde 2015 Rheuma (ATLAS)	ADA 40 Q2W PBO ADA40 Q4W	6 60	-2.8 -1.0 NR	<0.001 REF NR	-2.8 -1.0 77.4	<0.001 REF NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR
Hu 2012 IJRD	ADA 40 Q2W PBO	3	NR	NR	NR	NR	NR	NR	NR	NR
Sieper 2013 ARD (ABILITY-1) van der Heijde 2014 EULAR (ABILITY-1)*	ADA 40 Q2W PBO ADA40 Q4W	3 36	-1.9 -1 NR	0.004 REF NR	NR NR 70	NR NR NR	-4.3 -0.3 NR	<0.001 REF NR	NR NR NR	NR NR NR
Huang 2014 ARD	ADA 40 Q2W PBO	3	-2.8 (1.9) -1.4 (1.9)	<0.001 REF	49.8 16.5	<0.001 REF	-17.8 (23.8) -4.2 (21.2)	<0.001 REF	-1.2 (3.0) -0.7 (1.8)	0.004 REF

Pedersen 2016 A&R	ADA 40 Q2W PBO	3	-24 (24) -11 (19)	0.04 REF	52 22.2	0.03 REF	NR	NR	NR	NR

*Completers analysis (observed data)

Table S20: Mobility, function and quality of life outcomes (adalimumab)

Study	Interventions	Time-point (months)	Mean BASFI change (SD)	p-value	Mean BASMI change (SD)	p-value	Mean ASQoL change	p-value
van der Heijde 2009 ARD (ATLAS) van der Heijde 2009 AR&T (ATLAS) Maksymowych2010 JR (ATLAS) Sieper 2012 ARD (ATLAS) van der Heijde 2015 Rheuma (ATLAS)*	ADA 40 Q2W PBO ADA40 Q4W	6 60	-2.0 -0.5 NR	<0.001 REF NR	NR NR -0.6	NR NR NR	-3.5 -1.1 NR	<0.001 REF NR
Hu 2012 IJRD	ADA 40 Q2W PBO	3	NR	NR	NR	NR	NR	NR
Sieper 2013 ARD (ABILITY-1) van der Heijde 2014 EULAR (ABILITY-1)*	ADA 40 Q2W PBO ADA40 Q4W	3 36	-1.1 -0.6 NR	0.053 REF NR	-0.1 -0.1 NR	NS REF NR	NR NR NR	NR NR NR
Huang 2014 ARD	ADA 40 Q2W PBO	3	-17.5 (20.2) -4.7 (16.4)	<0.001 REF	-0.5 (0.6) -0.2 (0.7)	<0.001 REF	NR	NR
Pedersen 2016 A&R	ADA 40 Q2W PBO	3	NR	NR	NR	NR	NR	NR

*Completers analysis (observed data)

3.4 Golimumab

Table S21: Study and patients' main characteristics (golimumab)

Study	Type of patients	Interventions	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration (years)	Previous TNFi (%)
Bao 2014 Rheuma	r-axSpA†	GOL 50 Q4W PBO	108 105	30.6 (8.6) 30.5 (10.23)	83.9 83.3	100 100	7.5 (6.06) 6.8 (6.43)	TNFi-naive
Tam 2014 Rheuma	r-axSpA†	GOL 50 Q4W PBO	20 21	35.6 (9.9) 34.2 (10)	90 90	100 100	8 (3-17)¥ 11 (6-17.5)¥	NR NR
Sieper 2015 A&R (GO-AHEAD) van der Heijde 2015 ACR (GO-AHEAD)	nr-axSpA‡	GOL 50 Q4W PBO	98 100	30.7 (7.1) 31.7 (7.2)	62.2 52	82.7 82.0	68.4% 1Y 65% 1Y	TNFi-naive
Braun 2012 ARD (GO-RAISE) van der Heijde 2014 JR (GO-RAISE) van der Heijde 2014 Rheuma (GO-RAISE) Braun 2014 ARD(GO-RAISE) Deodhar 2015 ARD (GO-RAISE)	r-axSpA†	GOL 50 Q4W GOL 100 Q4W PBO	138 140 78	39.2 (12.5) 38.6 (11.3) 40.6 (12.7)	73.9 70.0 70.5	NR	7.9 (8.1) 8.1 (8.3) 10.8 (10.0)	TNFi-naive

† According to modified New York criteria; ‡ according to ASAS criteria; ¥ median (interquartile range).

Table S22: Cochrane risk of bias assessment (golimumab)

Study	Intervention	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall RoB
Bao 2014 Rheuma	GOL 50 Q4W PBO	L	L	L	L	U	L	L
Tam 2014 Rheuma	GOL 50 Q4W PBO	L	L	L	L	U	H	U
Sieper 2015 A&R (GO-AHEAD) van der Heijde 2015 ACR (GO-AHEAD)	GOL 50 Q4W PBO	L	L	L	L	L	L	L

Braun 2012 ARD (GO-RAISE) van der Heijde 2014 JR (GO-RAISE) van der Heijde 2014 Rheuma (GO-RAISE) Braun 2014 ARD(GO-RAISE) Deodhar 2015 ARD (GO-RAISE))	GOL 50 Q4W GOL 100 Q4W PBO	L	L	L	L	L	L	L

H= high risk; L = low risk; U = unclear risk.

Table S23: ASAS outcomes (golimumab)

Study	Interventions	Time-point (months)	ASAS 20 (%)	p-value	ASAS 40 (%)	p-value	ASAS 5/6 (%)	p-value	ASAS PR (%)	p-value
Bao 2014 Rheuma	GOL 50 Q4W PBO	6	50 22.9	<0.001 REF	NR	NR	NR	NR	NR	NR
Tam 2014 Rheuma	GOL 50 Q4W PBO	6	55 14	0.006 REF	NR	NR	NR	NR	NR	NR
Sieper 2015 A&R (GO-AHEAD) van der Heijde 2015 ACR (GO-AHEAD)†	GOL 50 Q4W PBO GOL 50/GOL 50 PBO/GOL 50	4 13	71.1 40 NR	<0.001 REF NR	56.7 23 NR	<0.001 REF NR	NR NR NR	NR NR NR	NR NR NR	NR NR NR
Braun 2012 ARD (GO-RAISE)* van der Heijde 2014 JR (GO-RAISE) van der Heijde 2014 Rheuma (GO-RAISE) Braun 2014 ARD (GO-RAISE) Deodhar 2015 ARD (GO-RAISE)†	GOL 50 GOL 100 PBO/GOL 50 GOL50+GOL100	26 64	85.6 82.8 77.4 66	NR NR NR NR	82.2 68.8 90.3 57	NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR NR	NR NR NR NR

*Completers analysis (observed data); † ITT analysis (NRI)

Table S24: ASDAS outcomes (golimumab)

Study	Interventions	Time-point (months)	Mean ASDAS change (SD)	p-value	ASDAS CII (%)	p-value	ASDAS MI (%)	p-value	ASDAS I (%)	p-value
Bao 2014 Rheuma	GOL 50 Q4W PBO	6	NR	NR	NR	NR	NR	NR	NR	NR
Tam 2014 Rheuma	GOL 50 Q4W PBO	6	-1.69 (1.30) -0.38 (0.81)	<0.001 REF	NR	NR	NR	NR	NR	NR

Sieper 2015 A&R (GO-AHEAD)	GOL 50 Q4W	4	NR	NR	NR	NR	NR	NR	NR	NR
	PBO		NR	NR	NR	NR	NR	NR	NR	NR
van der Heijde 2015 ACR (GO-AHEAD)†	GOL 50/GOL 50	13	-2.20	NR	NR	NR	NR	NR	NR	NR
	PBO/GOL 50		-1.70	NR	NR	NR	NR	NR	NR	NR
Braun 2012 ARD (GO-RAISE)	GOL 50 Q4W	6	--1.6 (1.2)	<0.001	NR	NR	39.4	<0.001	27.3	<0.001
van der Heijde 2014 JR (GO-RAISE)	GOL 100 Q4W		-1.7 (1.3)	<0.001	NR	NR	39	<0.001	27.2	<0.001
van der Heijde 2014 Rheuma (GO-RAISE)*	PBO		-0.3 (1)	REF	NR	NR	4.2	REF	2.8	REF
Braun 2014 ARD(GO-RAISE)	GOL 50	26	-2.1 (1.1)	NS	NR	NR	NR	NR	NR	NR
Deodhar 2015 ARD (GO-RAISE)	GOL 100		-2.0 (1.2)	NS	NR	NR	NR	NR	NR	NR
	PBO/GOL 50		-2.3 (1.0)	REF	NR	NR	NR	NR	NR	NR

*Completers analysis (observed data); † ITT analysis (NRI)

Table S25: Other disease-activity outcomes (golimumab)

Study	Interventions	Time-point (months)	Mean BASDAI change (SD)	p-value	BASDAI 50 (%)	p-value	Mean CRP change (SD)	p-value	Mean TJC (SD)	p-value
Bao 2014 Rheuma	GOL 50 Q4W	6	NR	NR	NR	NR	NR	NR	NR	NR
	PBO									
Tam 2014 Rheuma	GOL 50 Q4W	6	-1.82 (1.64)	0.015	NR	NR	-18.5 (21.2)	0.034	NR	NR
	PBO		-0.06 (1.24)	REF			-4.83 (18.6)	REF		
Sieper 2015 A&R (GO-AHEAD)	GOL 50 Q4W	4	NR	NR	57.7	<0.001	NR	NR	NR	NR
van der Heijde 2015 ACR (GO-AHEAD)	PBO				30	REF				
Braun 2012 ARD (GO-RAISE)										
van der Heijde 2014 JR (GO-RAISE)	GOL 50		2.1 (1.1)	NS						
van der Heijde 2014 Rheuma (GO-RAISE)*	GOL 100	26	2.0 (1.2)	NS	NR	NR	NR	NR	NR	NR
Braun 2014 ARD(GO-RAISE)	PBO/GOL 50		2.3 (1.0)	REF						
Deodhar 2015 ARD (GO-RAISE)										

*Completers analysis (observed data)

Table S26: Mobility, function and quality of life outcomes (golimumab)

Study	Interventions	Time-point (months)	Mean BASFI change (SD)	p-vale	Mean BASMI change (SD)	p-value	Mean ASQoL change	p-value
Bao 2014 Rheuma	GOL 50 Q4W PBO	6	-1.26 (2.57) 0.11 (2.1)	<0.001 REF	-0.42 (0.91) -0.19 (0.72)	0.021 REF	NR	NR
Tam 2014 Rheuma	GOL 50 Q4W PBO	6	-1.27 (2.49) 1.73 (7.20)	0.085 REF	-1 0	0.018 REF	NR	NR
Sieper 2015 A&R (GO-AHEAD) van der Heijde 2015 ACR (GO-AHEAD)	GOL 50 Q4W PBO	4	NR	NR	NR	NR	NR	NR
Braun 2012 ARD (GO-RAISE)* van der Heijde 2014 JR (GO-RAISE) van der Heijde 2014 Rheuma (GO-RAISE) Braun 2014 ARD(GO-RAISE) Deodhar 2015 ARD (GO-RAISE)	GOL 50 GOL 100 PBO/GOL 50	26	-2.7 (2.07) 2.9 (2.21) -2.6 (2.23)	NR	-0.8 (0.79) -0.8 (0.96) -0.8 (0.95)	NR	NR	NR

*Completers analysis (observed data)

3.5 Certolizumab Pegol

Table S27: Study and patients' main characteristics (certolizumab pegol)

Study	Type of patients‡	PBO-controlled period (months)	Interventions	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration¥ (years)	Previous TNFi (%)

van der Heijde 2012 EULAR (RAPID-axSpA)	axSpA	24	CZP 200	111	39.1 (11.9)	60.4	78.4	6.9 (0.3; 34.2)	13.5
Landewé 2013 ACR (RAPID-axSpA)	axSpA	24	CZP 400	107	39.8 (11.3)	63.6	75.7	7.9 (0.3; 44.8)	10.3
van der Heijde 2013 EULAR (RAPID-axSpA)	axSpA	24	CZP 200+400	218	39.5 (11.6)	NR	NR	7.8 (0.3; 44.8)	NR
van der Heijde 2014 ACR (RAPID-axSpA)	axSpA	24	PBO	107	39.9 (12.4)	60.7	81.3	7.7 (0.3; 50.9)	24.3
Landewé 2014 ARD (RAPID-axSpA)	r-axSpA	24	CZP 200	65	41.0 (10.8)	72.3	81.5	8.8 (0.3; 32.7)	16.9
Mease 2014 EULAR (RAPID-axSpA)	r-axSpA	24	CZP 400	56	41.9 (11.5)	73.2	78.6	8.8 (0.3; 44.8)	16.1
Rosenbaum 2014 ACR (RAPID-axSpA)	r-axSpA	24	CZP 200+400	121	41.4 (11.1)	NR	NR	8,8 (0.3; 44.8)	NR
Rudwaleit 2914 EULAR (RAPID-axSpA)	r-axSpA	24	PBO	57	41.6 (12.8)	71.9	84.2	10.2 (0.3; 50.9)	28.1
Sieper 2015 AC&R (RAPID-axSpA)	nr-axSpA	24	CZP 200	46	36.6 (13.0)	43.5	73.9	4.8 (0.3; 34.2)	8.7
Sieper 2015 A&R (RAPID-axSpA)	nr-axSpA	24	CZP 400	51	37.5 (10.8)	52.9	72.5	7.3 (0.3; 25.3)	3.9
Braun 2015 ARD (RAPID-axSpA)	nr-axSpA	24	CZP 200+400	97	37.1 (11.8)	NR	NR	5.9 (0.3; 34.2)	NR
	nr-axSpA	24	PBO	50	38.0 (11.8)	48	78	4.5 (0.5; 41.5)	20.0

‡ according to ASAS criteria; ¥ median (min; max).

Study	Intervention	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall RoB
van der Heijde 2012 EULAR (RAPID-axSpA)								
Landewé 2013 ACR (RAPID-axSpA)								
van der Heijde 2013 EULAR (RAPID-axSpA)								
van der Heijde 2014 ACR (RAPID-axSpA)								
Landewé 2014 ARD (RAPID-axSpA)								
Mease 2014 EULAR (RAPID-axSpA)	L	L	L	L	L	L	L	L
Rosenbaum 2014 ACR (RAPID-axSpA)								
Rudwaleit 2914 EULAR (RAPID-axSpA)								
Sieper 2015 AC&R (RAPID-axSpA)								
Sieper 2015 A&R (RAPID-axSpA)								
Braun 2015 ARD (RAPID-axSpA)								

Table S28: Cochrane risk of bias assessment (certolizumab pegol)

H= high risk; L = low risk; U = unclear risk.

Table S29: ASAS outcomes (certolizumab pegol)

Study	Interventions	Time-point	ASAS 20	p-value	ASAS 40 (%)	p-value	ASAS 5/6	p-value	ASAS PR	p-value

		(months)	(%)				(%)		(%)	
van der Heijde 2012 EULAR (RAPID-axSpA)	axSpA CZP 200	24	66.7	0.004	51.4	NR	36.9	NR	30.6	NR
Landewé 2013 ACR (RAPID-axSpA)	axSpA CZP 400	24	70.1	<0.001	52.3	NR	47.7	NR	29.9	NR
van der Heijde 2013 EULAR (RAPID-axSpA)	axSpA CZP 200+400	24	62.8	NR	50.5	NR	42.2	NR	28.4	NR
van der Heijde 2014 ACR (RAPID-axSpA)	axSpA PBO	24	29	REF	15	NR	4.7	NR	8.4	NR
Landewé 2014 ARD (RAPID-axSpA)	r-axSpA CZP 200	24	67.7	<0.001	47.7	<0.001	33.8	NR	30.8	NR
Mease 2014 EULAR (RAPID-axSpA)	r-axSpA CZP 400	24	69.6	<0.001	58.9	<0.001	46.4	NR	25	NR
Rosenbaum 2014 ACR (RAPID-axSpA)	r-axSpA CZP 200+400	24	64.5	NR	50.4	NR	43.0	NR	24.8	NR
Rudwaleit 2914 EULAR (RAPID-axSpA)	r-axSpA PBO	24	33.3	REF	15.8	REF	5.3	NR	7	NR
Sieper 2015 AC&R (RAPID-axSpA)	nr-axSpA CZP 200	24	65.2	<0.001	56.5	<0.001	41.3	NR	30.4	NR
Sieper 2015 A&R (RAPID-axSpA)	nr-axSpA CZP 400	24	70.6	<0.001	45.1	<0.001	49	NR	35.3	NR
Braun 2015 ARD (RAPID-axSpA)	nr-axSpA CZP 200+400	24	60.8	NR	50.5	NR	41.2	NR	33.0	NR
	nr-axSpA PBO	24	24	REF	14	REF	4	NR	10	NR

Table S30: ASDAS outcomes (certolizumab pegol)

Study	Interventions	Time-point (months)	Mean ASDAS change (SD)	p-value	ASDAS CII (%)	p-value	ASDAS MI (%)	p-value	ASDAS I (%)	p-value
van der Heijde 2012 EULAR (RAPID-axSpA)	axSpA CZP 200	24	-1.90	<0.001	73.9	NR	45.9	<0.001	29.7	<0.001
Landewé 2013 ACR (RAPID-axSpA)	axSpA CZP 400	24	-1.70	<0.001	68.2	NR	39.3	<0.001	30.8	<0.001
van der Heijde 2013 EULAR (RAPID-axSpA)	axSpA CZP 200+400	24	-1.90	NR	NR	NR	49.5	NR	33.9	NR
van der Heijde 2014 ACR (RAPID-axSpA)	axSpA PBO	24	-0.50	REF	NR	NR	0.9	REF	3.7	REF
Landewé 2014 ARD (RAPID-axSpA)	r-axSpA CZP 200	24	-1.90	<0.001	76.9	NR	46.2	NR	26.2	NR
Mease 2014 EULAR (RAPID-axSpA)	r-axSpA CZP 400	24	-1.7	<0.001	71.4	NR	39.2	NR	28.6	NR
Rosenbaum 2014 ACR (RAPID-axSpA)	r-axSpA CZP 200+400	24	-1.90	NR	NR	NR	51.2	NR	30.6	NR
Rudwaleit 2914 EULAR (RAPID-axSpA)	r-axSpA PBO	24	-0.60	REF	NR	NR	1.8	NR	3.5	NR
Sieper 2015 AC&R (RAPID-axSpA)	nr-axSpA CZP 200	24	-1.8	<0.001	69.6	NR	45.7	NR	34.8	NR
Sieper 2015 A&R (RAPID-axSpA)	nr-axSpA CZP 400	24	-1.7	<0.001	64.7	NR	39.2	NR	33.3	NR
Braun 2015 ARD (RAPID-axSpA)	nr-axSpA CZP 200+400	24	-1.80	NR	NR	NR	47.7	NR	38.1	NR
	nr-axSpA PBO	24	-0.40	REF	NR	NR	0	NR	4	NR

Table S31: Other disease-activity outcomes (certolizumab pegol)

Study	Interventions	Time-point	Mean BASDAI	p-value	BASDAI 50 (%)	p-value	Mean CRP change (SD)	p-value	Mean TJC (SD)	p-value

		(months)	change (SD)						
van der Heijde 2012 EULAR (RAPID-axSpA) Landewé 2013 ACR (RAPID-axSpA) van der Heijde 2013 EULAR (RAPID-axSpA) van der Heijde 2014 ACR (RAPID-axSpA) Landewé 2014 ARD (RAPID-axSpA) Mease 2014 EULAR (RAPID-axSpA) Rosenbaum 2014 ACR (RAPID-axSpA) Rudwaleit 2914 EULAR (RAPID-axSpA) Sieper 2015 AC&R (RAPID-axSpA) Sieper 2015 A&R (RAPID-axSpA) Braun 2015 ARD (RAPID-axSpA)	axSpA CZP 200	24	-3.2	<0.001	50.5	<0.001	NR	NR	NR	NR
	axSpA CZP 400	24	-3.1	<0.001	54.2	<0.001	NR	NR	NR	NR
	axSpA CZP 200+400	24	-3.4	NR	47.7	NR	NR	NR	-2.7	NR
	axSpA PBO	24	-1.1	REF	17.9	REF	NR	NR	-0.4	NR
	r-axSpA CZP 200	24	-3.1	<0.001	43.1	NR	NR	NR	NR	NR
	r-axSpA CZP 400	24	-2.9	<0.001	55.4	NR	NR	NR	NR	NR
	r-axSpA CZP 200+400	24	-3.3	NR	46.3	NR	NR	NR	-2.9	NR
	r-axSpA PBO	24	-1.2	REF	15.8	NR	NR	NR	-0.7	NR
	nr-axSpA CZP 200	24	-3.3	<0.001	60.9	NR	NR	NR	NR	NR
	nr-axSpA CZP 400	24	-3.2	<0.001	52.9	NR	NR	NR	NR	NR
	nr-axSpA CZP 200+400	24	-3.6	NR	49.5	NR	NR	NR	-2.5	NR
	nr-axSpA PBO	24	-1	REF	20.4	NR	NR	NR	-0.2	NR

Study	Interventions	Time-point (months)	Mean BASFI change (SD)	p-vale	Mean BASMI change (SD)	p-value	Mean ASQoL change	p-value
van der Heijde 2012 EULAR (RAPID-axSpA) Landewé 2013 ACR (RAPID-axSpA) van der Heijde 2013 EULAR (RAPID-axSpA) van der Heijde 2014 ACR (RAPID-axSpA) Landewé 2014 ARD (RAPID-axSpA) Mease 2014 EULAR (RAPID-axSpA) Rosenbaum 2014 ACR (RAPID-axSpA) Rudwaleit 2914 EULAR (RAPID-axSpA) Sieper 2015 AC&R (RAPID-axSpA) Sieper 2015 A&R (RAPID-axSpA) Braun 2015 ARD (RAPID-axSpA)	axSpA CZP 200	24	-2.4	<0.001	-0.6	<0.001	-5.13	NR
	axSpA CZP 400	24	-2.3	<0.001	-0.6	<0.001	-5.1	NR
	axSpA CZP 200+400	24	-2.6	NR	-0.7	NR	NR	NR
	axSpA PBO	24	-0.5	REF	-0.2	REF	-1.7	NR
	r-axSpA CZP 200	24	-2.3	<0.001	-0.7	0.05	-4.73	NR
	r-axSpA CZP 400	24	-2.3	<0.001	-0.6	NS	-4.89	NR
	r-axSpA CZP 200+400	24	-2.6	NR	-0.7	NR	NR	NR
	r-axSpA PBO	24	-0.9	REF	-0.4	REF	-1.8	NR
	nr-axSpA CZP 200	24	-2.5	<0.001	-0.6	<0.001	-2.22	NR
	nr-axSpA CZP 400	24	-2.3	<0.001	-0.5	0.05	-1.57	NR
	nr-axSpA CZP 200+400	24	-2.6	NR	-0.7	NR	NR	NR
	nr-axSpA PBO	24	-0.1	REF	0.1	REF	-1.2	NR

Table S32: Mobility, function and quality of life outcomes (certolizumab pegol)

Table S33: Proportion of completers from studies reporting the longest follow-up

Study	Intervention	N baseline	Completers 2 years (%)	Completers 5 years (%)	Completers 7 years (%)	Completers 8 years (%)

Baraliakos 2013 AR&T	ETA 25 BiW	26	21 (80.8)	NR	16 (61.5)	NA
Baraliakos 2011 Rheuma	INF 5mg/Kg Q6W	69	49 (71.0)	38 (55.1)	38 (55.1)	33 (47.8)
van der Heijde 2015 Rheuma	ADA 40 Q2W	208	NR	125 (60.1)	NA	NA
Deodhar 2015 ARD	GOL 50 Q4W	137	109 (79.6)	95 (69.3)	NA	NA
Sieper 2015 A&R	CZP 200 Q2W	111	88 (79.3)	NA	NA	NA

3.6. Axial inflammation on MRI

Table S34: Effect of TNFi on axial inflammation

	r-axSpA (mNY)				nr-axSpA (ASAS)			
	Improvement treatment*	**Improvement placebo***	**SMD (95% CI)**	**p-value treatment vs PBO**	**Improvement treatment***	**Improvement placebo***	**SMD (95% CI)**	**p-value treatment vs PBO**
MRI spine SPARCC (Δ baseline to 12W)								
Etanercept (50 QW); EMBARK (n=215)	NA	NA	NA	NA	2.1 (0.5)	1.2 (0.5)	1.80 (1.48; 2.12)	0.041
Adalimumab (40QW); ABILITY-1 (n=185)	NA	NA	NA	NA	1.8	0.2	n/e	0.001
MRI ASspiMRI-a (Δ baseline to W14)								
Golimumab 50 Q4W; GO-RAISE (n=216)	5.9 (7.1)	2.5 (8.9)	0.44 (0.15; 0.72)	0.011	NA	NA	NA	NA
Certolizumab; RAPID-axSpA (n=218)	NR	NR	NR	<0.001	NR	NR	NR	<0.001
MRI SII SPARCC (Δ baseline to W12)								
Etanercept (50 QW); EMBARK (n=215)	NA	NA	NA	NA	3.8 (0.7)	0.8 (0.6)	4.61 (4.09; 5.12)	<0.001
Adalimumab; ABILITY-1 (n=185)	NA	NA	NA	NA	3.2	0.6	n/e	0.003
Golimumab 50 Q4W; GO-AHEAD (n=161)	NA	NA	NA	NA	5.3	1.0	n/e	<0.001
Certolizumab; RAPID-axSpA (n=218)	NR	NR	NR	<0.001	NR	NR	NR	NS

*Mean (SD) improvement compared to baseline value: SPARCC MRI spinal score (range: 0-108); SPARCC MRI-SI score (range: 0-72); ASspiMRI-a score (range: 0-138).

3.7. Safety outcomes

Details on the included studies are provided above. Only placebo-controlled data is shown. If only absolute values are reported, proportions were calculated.

Table S35: Main safety outcomes (etanercept)

Study	Interventions	Time-point (months)	N	Withdrawals AE (%)	p-value	Serious AE (%)	p-value	Any infection (%)	p-value	Serious infections (%)	p-value	Tuberculosis (%)	p-value	Malignancies (%)	p-value
Dougados 2010 ARD	ETA 50 PBO	3	12 12	8.3 0	NR	8.3 0	NR	41.7 8.3	NR	8.3 0	NR	0 0	NR	NR	NR
Dougados 2011 ARD	ETA 50 PBO	3	39 43	2.6 2.3	NR	5.1 2.3	NR	NR	NR	0 0	NR	0 0	NR	2.6 0	NR
Dougados 2015 JR	ETA 50 PBO	3	111 113	2.7 0.9	NR	1.8 1.8	NR	9.9 8.8	NR	0 0.9	NR	NR	NR	2.6 0	NR

Table S36: Other safety outcomes (etanercept)

Study	Interventions	Time-point (months)	N	Any CVD event (%)	p-value	Any hematological abnormality (%)	p-value	Any GI event (%)	p-value	Injection reactions %)	p-value	Headache (%)	p-value	Elevated Liver enzymes (%)	p-value
Dougados 2010 ARD	ETA 50 PBO	3	12 12	NR	NR	NR	NR	NR	NR	25 0	NR	NR	NR	NR	NR
Dougados 2011 ARD	ETA 50 PBO	3	39 43	NR	NR	NR	NR	NR	NR	7.7 0	NR	NR	NR	NR	NR
Dougados 2015 JR	ETA 50 PBO	3	111 113	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table S37: Main safety outcomes (infliximab)

Study	Interventions	Time-point (months)	N	Withdrawals AE (%)	p-value	Serious AE (%)	p-value	Any infection (%)	p-value	Serious infections (%)	p-value	Tuberculosis (%)	p-value	Malignancies (%)	p-value
Barkham 2009 A&R	IFN 5 mg/Kg PBO	3	20 20	5 0	NR	0 0	NR	NR	NR	0 0	NR	0 0	NR	0 0	NR
Inman 2010 JR	IFN 3 mg/Kg PBO / INF	12	32 34	NR	NR	15.4 21.6	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table S38: Other safety outcomes (infliximab)

Study	Interventions	Time-point (months)	N	Any CVD event (%)	p-value	Any hematological abnormality (%)	p-value	Any GI event (%)	p-value	Injection reactions %)	p-value	Headache (%)	p-value	Elevated Liver enzymes (%)	p-value
Barkham 2009 A&R	IFN 5 mg/Kg PBO	3	20 20	NR	NR	NR	NR	NR	NR	5 0	NR	NR	NR	NR	NR
Inman 2010 JR	IFN 3 mg/Kg PBO / INF	12	32 34	NR	NR	NR	NR	NR	NR	0 5.4	NR	2.6 5.4	NR	NR	NR

Table S39: Main safety outcomes (adalimumab)

Study	Interventions	Time-point (months)	N	Withdrawals AE (%)	p-value	Serious AE (%)	p-value	Any infection (%)	p-value	Serious infections (%)	p-value	Tuberculosis (%)	p-value	Malignancies (%)	p-value
Sieper 2013 ARD	ADA 40 PBO	3	91 94	2.1 1.0	NR	3.2 1.0	NR	29.5 28.9	NR	0 0	NR	0 0	NR	0 0	NR
Huang 2014 ARD	ADA 40 PBO	3	229 115	1.7 0.0	NR	0.4 0.9	NR	10.4 17.5	NR	0.0 0.9	NR	0 0	NR	NR	NR

Table S40: Other safety outcomes (adalimumab)

Study	Interventions	Time-point (months)	N	Any CVD event (%)	p-value	Any hematological abnormality (%)	p-value	Any GI event (%)	p-value	Injection reactions %)	p-value	Headache (%)	p-value	Elevated Liver enzymes (%)	p-value
Sieper 2013 ARD	ADA 40 PBO	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Huang 2014 ARD	ADA 40 PBO	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table S41: Main safety outcomes (golimumab)

Study	Interventions	Time-point (months)	N	Withdrawals AE (%)	p-value	Serious AE (%)	p-value	Any infection (%)	p-value	Serious infections (%)	p-value	Tuberculosis (%)	p-value	Malignancies (%)	p-value
Bao 2014 Rheuma	GOL 50 PBO	6	105 108	0.9 1.0	NR	5.6 0	NR	16.7 17.1	NR	0.9 0	NR	0.9 0	NR	0.9 0	NR

Sieper 2015 A&R	GOL 50 PBO	4	97 100	2.1 1	NR	1 2	NR	NR	NR	0 0	NR	0 0	NR	0 0	NR

Table S42: Other safety outcomes (golimumab)

Study	Interventions	Time-point (months)	N	Any CVD event (%)	p-value	Any hematological abnormality (%)	p-value	Any GI event (%)	p-value	Injection reactions %	p-value	Headache (%)	p-value	Elevated Liver enzymes (%)	p-value
Bao 2014 Rheuma	GOL 50 PBO	6	105 108	NR	NR	NR	NR	NR	NR	0.2 0.0	NR	NR	NR	NR	NR
Sieper 2015 A&R	GOL 50 PBO	4	97 100	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table S43: Main safety outcomes (certolizumab pegol)

Study	Interventions	Time-point (months)	N	Withdrawals AE (%)	p-value	Serious AE (%)	p-value	Any infection (%)	p-value	Serious infections (%)	p-value	Tuberculosis (%)	p-value	Malignancies (%)	p-value
Landewé 2014 ARD	axSpA CZP 200	6	111	1.8	NR	3.6	NR	NR	NR	0	NR	0	NR	0	NR
	axSpA CZP 400		107	3.7		2.8				0		0		0	
	axSpA PBO		107	1.9		6.5				0		0		0	

Table S44: Other safety outcomes (certolizumab pegol)

Study	Interventions	Time-point (months)	N	Any CVD event (%)	p-value	Any hematological abnormality (%)	p-value	Any GI event (%)	p-value	Injection reactions %)	p-value	Headache (%)	p-value	Elevated Liver enzymes (%)	p-value
Landewé 2014 ARD	axSpA CZP 200	6	111	0.0	NR	0.9	NR	0.0	NR	9.0	NR	6.3	NR	NR	NR
	axSpA CZP 400		107	0.9		0.0		0.9		4.7		8.4			
	axSpA PBO		107	0.0		0.0		0.9		0.9		6.5			

4. OBSERVATIONAL STUDIES OF TNF INHIBITORS

4.1. Malignancies

Table S45: Outcome and exposure definition

Study	Register / cohort	Total patient-years	Outcome definition	Validation outcome	Biologic causal attribution	Notes on analysis	Censoring at event
Carmona 2011 SA&R	BIOBADASER	2,288	Any new cancer (except skin)	Treating physician	On-drug (+ after follow-up case by case)	SIR as compared to general population	yes
Dreyer 2013 ARD	DANBIO	NR	First cancer diagnosis	NR	On-drug (assumed)	SIR as compared to general population	yes
Westhovens 2014 C&ER	BIOSPAR	1,194	Any malignancy	NR	On-drug	SIR as compared to general population	yes

Table S46: Study and patients' main characteristics

Study	Type of patients	Interventions and controls	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration (years)	Previous TNFi (%)
Carmona 2011 SA&R	r-axSpA (not further defined)	3 TNFi (IFN. ETA. ADA) General population	761 NA	NR	NR	NR	NR	TNFi-naive
Dreyer 2013 ARD	r-axSpA (not further defined)	3 TNFi (IFN. ETA. ADA) General population	861 NA	NR	NR	NR	NR	TNFi-naive
Westhovens 2014 C&ER	r-axSpA (not further defined)	Treated (male) (4 TNF*i) General population (male) Treated (female) (4 TNFi*) General population (female)	74 NA 157 NA	48.05 (12.61) (overall)	68 (overall)	NR	NR	TNFi-naïve (and 2nd and 3rd)

* Etanercept, infliximab, adalimumab and golimumab.

Table S47: Effect size intervention and control and comparison

Study	Interventions and controls	Incidence rate (95% CI)	Adjusted IR (95% CI)	Type of ratio (I vs C)	uRatio	aRatio	Adjusted for
Carmona 2011 SA&R	3 TNFi (IFN. ETA. ADA) General population	NR	NR	SIR	NR	0.92 (0.44; 1.70)*	Age and gender
Dreyer 2013 ARD	3 TNFi (IFN. ETA. ADA) General population	NR NR	NR	SIR	0.82 (0.41; 1.64)	NR	NA
Westhovens 2014 C&ER	Treated (female) (4 TNF*i) General population (female) Treated (male) (4 TNFi*) General population (male)	770.1 /100,000 py 499.1 /100,000 py 370.2 /100,000 py 283.4 /100,000 py	NR	SIR	1.54 ref 1.31 ref	NR	NA

* Colon and rectum: 2.38 (0.49; 6.96); Lung: 1.66 (0.34; 4.85); Prostate: 1.10 (0.03; 6.13); Bladder: 0.96 (0.02; 5.37); non-Hodgkin lymphoma: 2.72 (0.07; 15.1); leukemia: 3.97 (0.10; 22.13).

Table S48: Risk of bias assessment (Hayden tool)

Study	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall RoB
Carmona 2011 SA&R	M	L	L	M	H	L	M
Dreyer 2013 ARD	M	L	L	M	H	M	M
Westhovens 2014 C&ER	M	L	L	L	H	M	M

H= high risk; L = low risk; M = moderate risk.

4.2. Infections / serious infections

Table S49: Outcome and exposure definition

Study	Register / cohort	Total patient-years	Outcome definition	Validation outcome	Biologic causal attribution	Notes on analysis	Censoring at event
Wallis 2015 Rheuma	Toronto Western Hospital AS clinic	1,712	Serious infection: infection requiring i.v. antibiotics or hospitalization	NR	On drug (+ 1 year before inclusion and after study end)	Multivariable GEE	yes
Moura 2015 EULAR	NA	NR	Serious infection: first occurrence of an infection requiring hospitalization	Hospital records	On-drug	Multivariable Cox regression	yes

Table S50: Study and patients' main characteristics

Study	Type of patients	Interventions and controls	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration (years)	Previous TNFi (%)
Wallis 2015 Rheuma	axSpA (ASAS)	Any TNF*i (any infection) no-TNFi (any infection) Any TNFi* (serious infection) no-TNFi (serious infection	264 186 264 186	38.3 (12.8) (overall)	73.2 (overall)	NR	14.7 (10.7) (overall)	TNFi-naive
Moura 2015 EULAR	r-axSpA (ICD-9 and 10 code)	TNFi* (+/ csDMARDs) Only csDMARDs None	714 (all)	50.3 (14.1) (overall)	65.7 (overall)	NR	NR	TNFi-naive

Table S51: Effect size intervention and control and comparison

Study	Interventions and controls	Incidence rate (95% CI)	Adjusted IR (95% CI)	Type of ratio (I vs C)	uRatio	aRatio	Adjusted for
Wallis 2015 Rheuma	Any TNF*i (any infection) no-TNFi (any infection) Any TNFi* (serious infection) no-TNFi (serious infection	19/100 py (16; 22) 14/100 py (11; 17) 1.5/100 py (0.7; 3) 1.8/100 py (1.0; 3.0)	NR	OR	1.14 (0.86; 1.51)] (for any infection)	1.25 (0.90; 1.73) (for any infection)	age, disease duration, smoking, csDMARDs, oral steroids, BASDAI, BASFI, co-morbidity score, hospitalization
Moura 2015 EULAR	TNFi* (+/ csDMARDs) Only csDMARDs None	2.44/100 py 4.12/100 py 2.25/100 py	NR	HR	NR	1.05 (0.45; 2.45) 1.77 (0.78; 4.02) REF	Baseline patient socio-demographics, comorbidity, prior health service use, and time dependent use of NSAIDs, and corticosteroids.

Table S52: Risk of bias assessment (Hayden tool)

Study	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall RoB
Wallis 2015 Rheuma	L	L	M	L	L	M	L
Moura 2015 EULAR	a	a	a	a	a	a	a

H= high risk; L = low risk; M = moderate risk.

4.3. Tuberculosis

Table S53: Outcome and exposure definition

Study	Register / cohort	Total patient -years	Outcome definition	Validation outcome	Biologic causal attribution	Notes on analysis	Censoring at event
Kim 2011 JR	NA	1,784	TB defined as 1 of the following criteria: (1) typical symptoms and isolation of Mycobacterium tuberculosis; or (2) typical symptoms and radiological or histological findings of TB; or (3) clinical symptoms and/or radiological signs and/or histological findings are compatible with TB and improvement with anti-TB medications.	NR	On-drug (assumed)	Cox-regression	yes
Kim 2014 ClinRheum	NA	1,166	TB infection was diagnosed according to the presence of symptoms in conjunction with evidence of infection by Mycobacterium tuberculosis (positive culture, a positive TB PCR result, the presence of caseating granulomas on biopsy, and/or a clinical improvement upon anti-TB treatment).	NR	On-drug (assumed)	Cox-regression	yes

Table S54: Study and patients' main characteristics

Study	Type of patients	Interventions and controls	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration (years)	Previous TNFi (%)
Kim 2011 JR	r-axSpA (mNY)	Infliximab Adalimumab Etanercept Controls	78 66 210 909	36.7 (11.6) 33.3 (10.3) 35.9 (10.2) 35.5 (10.5)	88.5 86.4 81.9 84.3	89.7 84.4 82.4 92	11.5 (7.3) 11.6 (9.0) 13.3 (6.9) 10.2 (8.7	NR
Kim 2014 ClinRheum	r-axSpA (mNY)	TNFi (ETA, INF, ADA, GOL, CZP) Controls	336 986	36.6 (12.3) NR	79 NR	NR NR	69.1 months NR	NR

Table S55: Effect size intervention and control and comparison

Study	Interventions and controls	Incidence rate (95% CI)	Adjusted IR (95% CI)	Type of ratio (I vs C)	uRatio	aRatio	Adjusted for
Kim 2011 JR	Infliximab Adalimumab Etanercept Controls	540//100,000 py 308//100,000 py 0/100,000 py 308/100,000 py	NR	HR	0.53 (0.14: 1.91) 1.57 (0.34; 7.18) 1.33 (0.17; 10.44) NA REF	NR	NA
Kim 2014 ClinRheum	TNFi (ETA, INF, ADA, GOL, CZP Controls	600.2/100,000 py 123.1/100,000 py	NR	HR	4.9 (1.5; 15.4) REF	NR	NA

Study	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall RoB
Kim 2011 JR	L	L	L	L	H	M	M
Kim 2014 ClinRheum	L	L	L	L	H	H	M

Table S56: Risk of bias assessment (Hayden tool)

H= high risk; L = low risk; M = moderate risk.

5. TRIALS ON NEW TREATMENT TARGETS

5.1. Description of included studies, baseline characteristics and risk of bias assessment

Table S57: Study and patients' main characteristics (new treatment targets)

Study	Study design	Type of patients	Interventions	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration (years)	Previous TNFi (%)
Song 2010 A&R Song 2013 ARD	POC non-controlled open-label	r-axSpA†	RTX TNFi-naive RTX TNFi-failure	10 10	37.2 (10.5) 42.2 (10.6)	80 70	100 80	13 (8.9) 20.5 (8.9)	0 100
Sieper 2015 ARD (ALIGN)	RCT phase 2 double-blind	r-axSpA‡	SAR 100 Q2W SAR 150 Q2W SAR 100 QW SAR 200 Q2W SAR 150 QW PBO	49 50 52 50 50 50	42.4 (10.8) 43 (11.3) 40.4 (11.5) 37.2 (10.4) 41.1 (11.1) 40.3 (11.7)	61.2 68 71.2 80 78 76	78.7 76 78.8 78 81.6 74	NR	TNFi-naive
Sieper 2014 ARD (BUILDER-1)	RCT phase 2 double-blind	r-axSpA†	TOC 8 mg/Kg PBO	51 51	41.6 (11.2) 42.7 (12.6)	71 78	84 88	5.4 (6.1) 7.5 (8.1)	TNFi-naive
Baeten 2013 Lancet Baraliakos 2013 ARD	RCT phase 2 double-blind	r-axSpA†	SEC 10 mg/Kg PBO	24 6	41.1 45	58 83	70 83	10.1 10.2	43 50
Baeten 2015 NEJM (MEASURE-1¥) Baraliakos 2015 ARD (MEASURE-1¥)	RCT phase 3 double-blind	r-axSpA†	SEC 150 SEC 75 PBO	125 124 122	40.1 (11.6) 42.3 (13.2) 43.1 (12.4)	67 71 70	69 80 74	6.5 (6.9) 7.9 (9.7) 8.3 (8.9)	74 73 73
Baeten 2015 NEJM (MEASURE-2¥) Sieper 2016 ARD (MEASURE-2¥)	RCT phase 3 double-blind	r-axSpA†	SEC 150 SEC 75 PBO SEC 150 TNFi-naive SEC 75 TNFi-naive PBO TNFi-naïve SEC 150 TNFi- failure SEC 75 TNFi- failure PBO TNFi- failure	72 73 74 44 45 45 28 28 29	72 73 74 43.7 (12.9) 43.9 (14.1) 43.5 (13.3) 39.3 (11.6) 45.2 (11.3) 43.8 (13.2)	41.9 (12.5) 44.4 (13.1) 43.6 (13.2) 26 (59.1) 31 (68.9) 35 (77.8) 20 (71.4) 20 (71.4) 21 (72.4)	64 70 76 75 71.1 75 85.7 75 85.7	79 73 78 6.1 (8.6) 3.7 (5.7) 3.9 (6.2) 8.5 (7.6) 7.7 (9.0) 10.2 (11.0)	7 (8.2) 5.3 (7.4) 6.4 (8.9) 0 0 0 100 100 100
Poddubnyy 2014 ARD (TOPAS)	POC non-controlled open-label	r-axSpA†	UST 90	20	37.5 (10.8)	75	90	13.3 (10.5)	5
Song 2011 ARD	POC non-controlled open-label	r-axSpA†	ABA TNFi-naive ABA TNFi-failure	15 15	38.0 (7.2) 45.3 (9.8)	60 73	100 93	14.5 (10.3) 20.5 (10.8)	0 100
Pathan 2013 ARD	RCT phase 2 double-blind	r-axSpA†	APR 30 PBO	17 19	44.88 (11.1) 39.21	NR	NR	20.88 (12.32) 18.39 (10.17)	5.9 10.5
van der Heijde 2015 ACR	RCT phase 2 double-blind	r-axSpA†	TOFA 2 bid TOFA 5 bid TOFA 10 bid PBO	52 52 52 51	NR	NR	NR	NR	TNFi-naive

† According to modified New York criteria; ‡ not defined; ¥ Loading dose in MEASURE-1: 10 mg/Kg IV 0. 2. 4 weeks and MEASURE-2: 150/75 mg SC 0. 1. 2. 3 weeks.

Table S58: Cochrane risk of bias assessment (new treatment targets)

Study	Study design	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall RoB
Song 2010 A&R	POC non-controlled open-label	H	L	H	L	L	L	H
Sieper 2015 ARD (ALIGN)	RCT phase 2 double-blind	L	L	L	L	L	L	L
Sieper 2014 ARD (BUILDER-1)	RCT phase 2 double-blind	L	L	L	L	L	L	L
Baeten 2013 Lancet	RCT phase 2 double-blind	L	L	L	L	U	L	L
Baeten 2015 NEJM (MEASURE-1)	RCT phase 3 double-blind	L	L	L	L	L	L	L
Baeten 2015 NEJM (MEASURE-2) Sieper 2016 ARD (MEASURE-2)	RCT phase 3 double-blind	L	L	L	L	L	L	L
Poddubnyy 2014 ARD (TOPAS)	POC non-controlled open-label	H	L	H	L	H	L	H
Song 2011 ARD	POC non-controlled open-label	H	L	H	L	H	L	H
Pathan 2013 ARD	RCT phase 2 double-blind	L	L	L	L	L	L	L
van der Heijde 2015 ACR	RCT phase 2 double-blind	a	a	a	a	a	a	a

H= high risk; L = low risk; U = unclear risk.

5.2. Efficacy outcomes

5.2.1. ASAS response outcomes

Table S59: ASAS outcomes (new treatment targets)

Study	Interventions	Time-point (months)	ASAS 20 (%)	p-value	ASAS 40 (%)	p-value	ASAS 5/6 (%)	p-value	ASAS PR (%)	p-value
Song 2010 A&R	RTX TNFi-naive RTX TNFi-failure	6	50 30	NR	40 10	NR	NR	NR	30 0	NR
Sieper 2015 ARD (ALIGN)	SAR 100 Q2W	3	24.5	NS	14.3	NS	12.2	NS	8.2	NS
	SAR 150 Q2W		30.0	NS	16	NS	10	NS	2	NS
	SAR 100 QW		19.2	NS	5.8	NS	13.5	NS	1.9	NS
	SAR 200 Q2W		30.0	NS	18	NS	14	NS	2	NS
	SAR 150 QW		38.0	NS	20	NS	32	<0.01	8	NS
	PBO		24.0	REF	8	REF	6	REF	2	REF

Sieper 2014 ARD (BUILDER-1)	TOC 8 mg/Kg PBO	3	37.3 27.5	0.282 REF	11.8 19.6	0.2694 REF	NR	NR	NR	NR
Baeten 2013 Lancet	SEC 10 mg/Kg PBO	7	30 17	NR	9 0	NR	4 0	NR	NR	NR
Baeten 2015 NEJM (MEASURE-1)	SEC 150 SEC 75 PBO	4	61 60 29	<0.001 <0.001 REF	42 33 13	<0.001 <0.001 REF	49 45 13	<0.001 <0.001 REF	15 16 3	<0.001 <0.001 REF
Baeten 2015 NEJM (MEASURE-2) Sieper 2016 ARD (MEASURE-2)	SEC 150 SEC 75 PBO SEC 150 TNFi-naive SEC 75 TNFi-naive PBO TNFi-naïve SEC 150 TNFi- failure SEC 75 TNFi- failure PBO TNFi- failure	4	61 41 28 68.2 51.1 31.1 50.0 25.0 24.1	<0.001 NS REF <0.001 NS REF <0.05 NS REF	36 26 11 43.2 31.1 17.8 25.0 17.9 0.0	<0.001 NS REF <0.05 NS REF <0.01 <0.05 REF	43 34 8 50.0 40.0 13.3 32.1 25.0 0.0	<0.001 NS REF <0.001 <0.01 REF <0.01 <0.01 REF	14 15 4 18.2 20.0 6.7 7.1 7.1 0.0	NS NS REF NS NS REF NS NS REF
Poddubnyy 2014 ARD (TOPAS)	UST 90	6	75	NR	65	NR	50	NR	30	NR
Song 2011 ARD	ABA TNFi-naive ABA TNFi-failure	6	26.7 20	NR	13.3 0	NR	NR	NR	6.7 0	NR
Pathan 2013 ARD	APR 30 PBO	3	35.3 15.8	0.25 REF	23.5 5.3	0.17 REF	17.6 5.3	NR	NR	NR
van der Heijde 2015 ACR	TOFA 2 bid TOFA 5 bid TOFA 10 bid PBO	3	51.9 80.8 55.8 41.2	NS <0.001 NS REF	42.3 46.2 38.5 19.6	<0.05 <0.01 <0.05 REF	NR	NR	NR	NR

5.2.2. ASDAS outcomes

Table S60: ASDAS outcomes (new treatment targets)

Study	Interventions	Time-point (months)	Mean ASDAS change (SD)	p-vale	ASDAS CII (%)	p-value	ASDAS MI (%)	p-value	ASDAS I (%)	p-value
Song 2010 A&R	RTX TNFi-naive RTX TNFi-failure	6	NR	NR	NR	NR	NR	NR	NR	NR
Sieper 2015 ARD (ALIGN)	SAR 100 Q2W SAR 150 Q2W SAR 100 QW SAR 200 Q2W SAR 150 QW PBO	3	-0.5 (0.9) -0.8 (1.2) -1.1 (0.8) -1.2 (0.9) -1.6 (0.9) -0.4 (0.7)	NS NS NS NS NS REF	NR	NR	NR	NR	NR	NR
Sieper 2014 ARD (BUILDER-1)	TOC 8 mg/Kg PBO	3	NR	NR	NR	NR	NR	NR	NR	NR
Baeten 2013 Lancet	SEC 10 mg/Kg PBO	7	NR	NR	NR	NR	NR	NR	NR	NR
Baeten 2015 NEJM (MEASURE-1)	SEC 150 SEC 75 PBO	4	NR	NR	NR	NR	NR	NR	NR	NR
Baeten 2015 NEJM (MEASURE-2) Sieper 2016 ARD (MEASURE-2)	SEC 150 SEC 75 PBO SEC 150 TNFi-naive SEC 75 TNFi-naive	4	NR	NR	NR	NR	NR	NR	NR	NR

	PBO TNFi-naïve SEC 150 TNFi- failure SEC 75 TNFi- failure PBO TNFi- failure								
Poddubnyy 2014 ARD (TOPAS)	UST 90	6	20	NR		50	NR	20	NR
Song 2011 ARD	ABA TNFi-naive ABA TNFi-failure	6	NR	NR		NR	NR	NR	NR
Pathan 2013 ARD	APR 30 PBO	3	-0.46 (0.66) -0.15 (0.71)	0.35 REF		NR	NR	NR	NR
van der Heijde 2015 ACR	TOFA 2 bid TOFA 5 bid TOFA 10 bid PBO	3	-1.2 (0.1)* -1.4 (0.1)* -1.4 (0.1)* -0.7 (0.1)*	<0.01 <0.001 <0.001 REF		NR	NR	NR	NR

* Least squares (standard error).

5.2.3. Other disease-activity outcomes

Table S61: Other disease-activity outcomes (new treatment targets)

Study	Interventions	Time-point (months)	Mean BASDAI change (SD)	p-vale	BASDAI 50 (%)	p-value	Mean CRP change (SD)	p-value	Mean TJC (SD)	p-value
Song 2010 A&R	RTX TNFi-naive RTX TNFi-failure	6	-2.0 (2.2) -0.9 (1.3)	NR	50 0	NR	-5.5 (7.2) -1.4 (18.5)	NR	NR	NR
Sieper 2015 ARD (ALIGN)	SAR 100 Q2W SAR 150 Q2W SAR 100 QW SAR 200 Q2W SAR 150 QW PBO	3	-0.8 (1.9) -1.1 (2) -0.4 (1.4) -0.9 (1.8) -1.2 (1.8) -0.9 (1.7)	NS NS NS NS NS REF	NR	NR	-1.2 (17.9) -5.8 (27.6) -13.5 (20.3) -11.5 (17.5) -14.3 (15.3) -3.7 (19.1)	NS NS <0.001 <0.001 <0.001 REF	NR	NR
Sieper 2014 ARD (BUILDER-1)	TOC 8 mg/Kg PBO	3	NR	NR	NR	NR	-1.34 -0.17	-1.34 -0.17	NR	NR
Baeten 2013 Lancet	SEC 10 mg/Kg PBO	7	6.26 (2.41) 5.53 (1.72)	NR	NR	NR	NR	NR	NR	NR
Baeten 2015 NEJM (MEASURE-1)	SEC 150 SEC 75 PBO	4	NR	NR	NR	NR	NR	NR	NR	NR
Baeten 2015 NEJM (MEASURE-2) Sieper 2016 ARD (MEASURE-2)	SEC 150 SEC 75 PBO SEC 150 TNFi-naive SEC 75 TNFi-naive PBO TNFi-naïve SEC 150 TNFi- failure SEC 75 TNFi- failure PBO TNFi- failure	4	NR NR NR -2.6 (0.3)* -2.3 (0.3)* -1.2 (0.3)* -1.6 (0.4)* -1.4 (0.4)* -0.6 (0.4)*	NR NR NR <0.01 <0.05 REF NS NS NS	NR	NR	NR	NR	NR	NR
Poddubnyy 2014 ARD (TOPAS)	UST 90	6	NR	NR	50	NR	NR	NR	NR	NR
Song 2011 ARD	ABA TNFi-naive ABA TNFi-failure	6	NR	NR	6.7 0	NR	NR	NR	NR	NR

Pathan 2013 ARD	APR 30 PBO	3	-1.59 (1.48) -0.77 (1.47)	0.139 REF	NR	NR	NR	NR	NR	NR
van der Heijde 2015 ACR	TOFA bid TOFA 5 bid TOFA 10 bid PBO	3	NR	NR	46.2 42.3 42.3 23.5	<0.01 <0.01 <0.01 REF	NR	NR	NR	NR

* Least squares (standard error).

5.2.4. Mobility, function and quality of life outcomes

Table S62: Mobility, function and quality of life outcomes (new treatment targets)

Study	Interventions	Time-point (months)	Mean BASFI change (SD)	p-vale	Mean BASMI change (SD)	p-value	Mean ASQoL change	p-value
Song 2010 A&R	RTX TNFi-naive RTX TNFi-failure	6	-1.3 (2.2) -0.5 (1.6)	NR	-0.4 (0.6) -0.3 (0.7)	-1.3 (2.2) -0.5 (1.6)	-3.3 (3.4) -3.1 (5.2)	NR
Sieper 2015 ARD (ALIGN)	SAR 100 Q2W SAR 150 Q2W SAR 100 QW SAR 200 Q2W SAR 150 QW PBO	3	NR	NR	-0.2 (0.9) -0.2 (0.8) -0.4 (0.9) -0.1 (0.8) -0.2 (0.7) -0.2 (0.8)	NS NS NS NS NS REF	NR	NR
Sieper 2014 ARD (BUILDER-1)	TOC 8 mg/Kg PBO	3	NR	NR	NR	NR	NR	NR
Baeten 2013 Lancet	SEC 10 mg/Kg PBO	7	NR	NR	NR	NR	10.6 (4.80) 9.30 (5.91)	
Baeten 2015 NEJM (MEASURE-1)	SEC 150 SEC 75 PBO	4	NR	NR	NR	NR	-3.58 (0.42) -3.61 (0.42) -1.04 (0.44)	NR
Baeten 2015 NEJM (MEASURE-2) Sieper 2016 ARD (MEASURE-2)	SEC 150 SEC 75 PBO SEC 150 TNFi-naive SEC 75 TNFi-naive PBO TNFi-naïve SEC 150 TNFi- failure SEC 75 TNFi- failure PBO TNFi- failure	4	NR	NR	NR	NR	-4.00 (0.53) -3.33 (0.54) -1.37 (0.53) -5.0 (0.7)* -4.0 (0.7)* -1.9 (0.7)* -2.4 (0.8)* -2.5 (0.9)* -0.5 (0.8)*	NR NR NR <0.01 <0.05 REF NS NS NS
Poddubnyy 2014 ARD (TOPAS)	UST 90	6	NR	NR	NR	NR	NR	NR
Song 2011 ARD	ABA TNFi-naive ABA TNFi-failure	6	NR	NR	NR	NR	NR	NR
Pathan 2013 ARD	APR 30 PBO	3	-1.74 (1.91) -0.28 (1.61)	0.108 REF	-0.51 (1.02) -0.21 (0.67)	0.617 REF	NR	NR
van der Heijde 2015 ACR	TOFA 2 bid TOFA 5 bid TOFA 10 bid PBO	3	-1.9 (0.3)* -2.4 (0.3)* -2.2 (0.3)* -1.4 (0.3)*	NS <0.01 <0.01 REF	-0.3 (0.1)* -0.4 (0.1)* -0.6 (0.1)* -0.2 (0.1)*	NS NS <0.01 REF	NR	NR

* Least squares (standard error).

5.3. Safety outcomes

Only studies reporting safety outcomes are shown. In case only absolute values were reported, these were used to calculate proportions.

Table S63: Main safety outcomes (secukinumab; 52 weeks)

Treatment arm	SAEs n (cases/100 py)	Withdrawals n (cases/100 py)	Any infection n (cases/100 py)	Opportunistic infections n (cases/100 py)	Tuberculosis n (cases/100 py)	Malignancies n (cases/100 py)	Crohn's disease n (cases/100 py)
MEASURE-1							
SEC (150 + 75)	35 (8.3)	15 (-)	187 (66.1)	3* (0.7)	0 (0)	4 (-)	3 (0.7)
MEASURE-2							
SEC (150 + 75)	17 (7.1)	9 (-)	111 (73.7)	3* (1.7)	0 (0)	1(-)	2 (0.8)
MEASURE-1 and MEASURE-2							
SEC (150 + 75)	52 (7.9)	24 (-)	298 (68.8)	6* (0.9)	0 (0)	5 (-)	**5 (0.7)**

*All Candida spp infections.

Table S64: Main safety outcomes (other new targets)

Study	Interventions	Time-point (months)	N	Withdrawals AE (%)	p-value	Serious AE (%)	p-value	Any infection (%)	p-value	Serious infections (%)	p-value	Tuberculosis (%)	p-value	Malignancies (%)	p-value
Song 2010 A&R	RTX	6	20	0	NR	20	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sieper 2015 ARD	SAR 100 Q2W SAR 150 Q2W SAR 100 QW SAR 200 Q2W SAR 150 QW PBO	3	49 50 52 50 50 50	4.1 9.8 9.6 4.1 12.2 0	NR	2 7.8 1.9 0 2 0	NR	26.5 21.6 25 18.4 28.6 18	NR	NR	NR	NR	NR	NR	NR
Sieper 2014 ARD	TOC 8 mg/Kg PBO	3	51 51	0 0	NR	4.2 0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Poddubnyy 2014 ARD	UST 90	6	20	0	NR	5	NR	NR	NR	NR	NR	NR	NR	0	NR
Song 2011 ARD	ABA TNFi-naive ABA TNFi-failure	6	15 15	NR	6.7 6.7	20 13.3	NR	0 0	NR	NR	NR	NR	NR	0 0	NR
Pathan 2013 ARD	APR 30 PBO	3	17 19	NR	NR	0 0	NR	NR	NR	NR	NR	NR	NR	NR	NR
van der Heijde 2015 ACR	TOFA 2 bid TOFA 5 bid TOFA 10 bid PBO	3	52 52 52 51	0 1.9 1.9 5.9	NR	0 0 0 2	NR	*	NR	0 0 0 0	NR	0 0 0 0	NR	0 0 0 0	NR

*Two treatment-related herpes zoster cases (1 each with TOFA 2 and 10 mg).

Table S65: Other safety outcomes (other new targets)

Study	Interventions	Time-point (months)	N	Any CVD event (%)	p-value	Any hematological abnormality (%)	p-value	Any GI event (%)	p-value	Injection reactions %)	p-value	Headache (%)	p-value	Elevated Liver enzymes (%)	p-value
Song 2010 A&R4	RTX TNFi-naive RTXTNFi-failure	6	20	NR	NR	NR	NR	NR	NR	25	NR	NR	NR	NR	NR
Sieper 2015 ARD	SAR 100 Q2W SAR 150 Q2W SAR 100 QW SAR 200 Q2W SAR 150 QW PBO	3	49 50 52 50 50 50	NR	NR	NR	NR	NR	NR	18.4 15.7 17.3 14.3 8.2 6	NR	8.2 3.9 0 4.1 2 0	NR	NR	NR
Sieper 2014 ARD	TOC 8 mg/Kg PBO	3	51 51	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Poddubnyy 2014 ARD	UST 90	6	20	NR	NR	NR	NR	NR	NR	0	NR	8	NR	NR	NR
Song 2011 ARD	ABA TNFi-naive ABA TNFi-failure	6	15 15	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pathan 2013 ARD	APR 30 PBO	3	17 19	NR	NR	NR	NR	NR	NR	NR	NR	42.1 26.4	NR	NR	NR
van der Heijde 2015 ACR	TOFA 2 bid TOFA 5 bid TOFA 10 bid PBO	3	52 52 52 51	NR	NR	¥	NR	0 0 0 0	NR	NR	NR	NR	NR	0[£] 3.8[£] 2.0[£] 2.0[£]	NR

¥mean (SD) CBL in ANC (TOFA 2: -0.3 (1.66), TOFA 5: -0.3 (1.4), TOFA 10: -0.9 (1.6), PBO: -0.3 (1.2)); mean (SD) CBL in ALC (TOFA 2: 0.1 (0.4), TOFA 5: -0.1 (0.4), TOFA 10: 0.0 (0.4), PBO: 0.0 (0.4)); mean (SD) CBL in Hgb (TOFA 2: 0.1 (0.6), TOFA 5

6. ACTIVE COMPARATOR TRIALS

6.1. Description of included studies, baseline characteristics and risk of bias assessment

Table S66: Study and patients' main characteristics (active comparator trials)

Study	Study design	Type of patients	Interventions	N	Age (years)	Males (%)	HLA-B27+ (%)	Disease duration (years)	Previous TNFi (%)
Giardina 2010 RheumaInt	RCT open-label	r-axSpA†	ETA 50 QW INF 5m/Kg Q6W	25 25	32.6 (6.8) 31.9 (9.2)	80 76	96 92	NR	TNFi-naive
Park 2013 ARD (PLANETAS) Park 2016 AR&T (PLANETAS)	Non-inferiority trial	r-axSpA†	CT-P13 5 mg/Kg INF 5 mg/Kg	125 125	38 (18; 69)¥ 38 (18-66)¥	79.2 82.4	NR	NR	TNFi-naive
Braun 2011 A&R (ASCEND) Moots 2012 Rheuma (ASCEND) Braun 2012 JR (ASCEND)	RCT double-blind	r-axSpA†	ETA 50 QW SSZ 3g/day	379 187	40.7 (11.7) 40.9 (12.2)	73.6 74.9	NR	NR	TNFi-naive
Song 2011 ARD (ESTHER) Song 2013 ARD (ESTHER) Song 2014 JR (ESTHER) Poddubnyy 2015 EULAR (ESTHER) Song 2016 SAR (ESTHER)	RCT open-label	axSpA‡	ETA 25 TW SSZ 2-3 g/day	40 36	34.5 (8.6) 32.8 (8.4)	57.5 58.3	85 77.8	2.6 (1.7) 3 (1.8)	TNFi-naive
Sieper 2014 ARD (INFAST-1) Sieper 2012 ACR (INFAST-1) Poddubnyy 2014 ACR (INFAST-1)	RCT double-blind	axSpA‡	INF 5 + NPX 1000 PBO + NPX 1000	105 51	31.7 (8.51) 30.7 (7.34)	68.6 78.4	82.1 90.4	1.76 (0.896) 1.91 (1.439)	TNFi-naive
Mok 2015 SJR	RCT open-label	axSpA‡	GOL 50 Q4W PAM 60 Q4W	20 10	32.0 (10.7) 36.3 (11.4)	80 90	NR NR	4.2 (3.3) 5.0 (3.7)	NR
Viapiana 2014 Rheuma	CCT open-label	r-axSpA†	INF 5 Q6W Neridronate 100	30 30	43.13 (12.18) 49.43 (15.02)	66.67 70	NR	129 (107) months 142 (145) months	NR
Mulleman 2011 AR&T	RCT open-label	r-axSpA†	INF 5 Q6W INF 5 + MTX 10	12 14	42.5 (27-59)¥ 45.5 (29-55)¥	75 79	75 71	4 (0-28)¥ 4.5 (1-19)¥	17 14
Huang 2011 C&ER	CCT open-label	r-axSpA†	ETA 12.5 betamethasone	5 7	NR	NR	NR	NR	NR

† According to modified New York criteria; ‡ according to ASAS criteria; ¥ median (interquartile range).

Table S67: Cochrane risk of bias assessment (active comparator trials)

Study	Study design	Intervention	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall RoB
Giardina 2010 RheumaInt	RCT open-label	ETA 50 QW INF 5m/Kg Q6W	L	L	H	L	L	L	H
Park 2013 ARD (PLANETAS) Park 2016 AR&T (PLANETAS)	Non-inferiority trial	CT-P13 5 mg/Kg INF 5 mg/Kg	L	L	L	L	L	L	L
Braun 2011 A&R (ASCEND) Moots 2012 Rheuma (ASCEND) Braun 2012 JR (ASCEND)	RCT double-blind	ETA 50 QW SSZ 3g/day	L	L	L	L	L	L	L
Song 2011 ARD (ESTHER) Song 2013 ARD (ESTHER) Song 2014 JR (ESTHER) Poddubnyy 2015 EULAR (ESTHER) Song 2016 SAR (ESTHER)	RCT open-label	ETA 25 BiW SSZ 2-3 g/day	L	L	H	L	L	L	U
Sieper 2014 ARD (INFAST-1) Sieper 2012 ACR (INFAST-1) Poddubnyy 2014 ACR (INFAST-1)	RCT double-blind	IFN 5 + NPX 1000 PBO + NPX 1000	L	L	L	L	L	L	L
Mok 2015 SJR	RCT open-label	GOL 50 Q4W PAM 60 Q4W	L	L	H	H	L	L	U
Viapiana 2014 Rheuma	CCT open-label	IFN 5 Q6W Neridronate 100	H	L	H	L	L	L	H
Mulleman 2011 AR&T	RCT open-label	IFN 5 Q6W INF 5 + MTX 10	L	L	H	L	H	H	H
Huang 2011 C&ER	CCT open-label	ETA 12.5 betamethasone	L	H	L	L	L	H	H

H= high risk; L = low risk; U = unclear risk.

6.2. Efficacy outcomes

6.2.1. ASAS response outcomes

Table S68: ASAS outcomes (active comparator trials)

Study	Interventions	Time-point (months)	ASAS 20 (%)	p-value	ASAS 40 (%)	p-value	ASAS 5/6 (%)	p-value	ASAS PR (%)	p-value
Giardina 2010 RheumaInt	ETA 50 QW INF 5m/Kg Q6W	3	60 75	NR	44 55	NR	NR	NR	NR	NR
Park 2013 ARD (PLANETAS)	CT-P13 5 mg/Kg	7.5	70.5	NR	51.8	NR	NR	NR	NR	NR
	INF 5 mg/Kg	7.5	72.4	NR	47.4	NR	NR	NR	NR	NR
Park 2016 AR&T (PLANETAS)	CT-P13 5 mg/Kg	13.5	67.0	NR	54.7	NR	NR	NR	19.8	NR
	INF 5 mg/Kg	13.5	69.4	NR	49.1	NR	NR	NR	17.6	NR
Braun 2011 A&R (ASCEND) Moots 2012 Rheuma (ASCEND) Braun 2012 JR (ASCEND)	ETA 50 QW	3	75.9	<0.0001	59.8	<0.001	NR	NR	33.3	<0.001
	SSZ 3g/day	3	52.9	REF	32.6	REF	NR	NR	15.5	REF
	ETA 50 (peripheral)	4	68.6	0.02	NR	NR	40.3	0.002	34.7	0.007
	SSZ 3 (peripheral)	4	50	REF	NR	NR	17.9	REF	15	REF
	ETA 50 (non-peripheral)	4	79.1	<0.001	NR	NR	48.1	<0.001	32.8	<0.001
	SSZ 3 (non-peripheral)	4	54.8	REF	NR	NR	23.1	REF	15.3	REF
Song 2011 ARD (ESTHER) Song 2013 ARD (ESTHER) Song 2014 JR (ESTHER)	ETA nr-axSpA	36	NR	NR	NR	NR	NR	NR	33	NR
	ETA r-axSpA		NR	NR	NR	NR	NR	NR	26	NR
Poddubnyy 2015 EULAR (ESTHER) Song 2016 SAR (ESTHER)	ETA nr-axSpA	72	NR	NR	82.4	NR	NR	NR	64.7	NR
	ETA r-axSpA		NR	NR	80	NR	NR	NR	53.3	NR
Sieper 2014 ARD (INFAST-1) Sieper 2012 ACR (INFAST-1) Poddubnyy 2014 ACR (INFAST-1)	IFN 5 + NPX 1000 PBO + NPX 1000	7	81 72.5	0.3 REF	75.2 56.9	0.03 REF	NR	NR	61.9 35.3	0.002 REF
Mok 2015 SJR	GOL 50 Q4W PAM 60 Q4W	12	65 56	NS REF	35 11	NS REF	NR	NR	NR	NR
Viapiana 2014 Rheuma	IFN 5 Q6W Neridronate 100	6	69 68	NS REF	45 39	NS REF	NR	NR	NR	NR
Mulleman 2011 AR&T	IFN 5 Q6W INF 5 + MTX 10	4.5	58.3 71.4	NS REF	NR	NR	NR	NR	NR	NR
Huang 2011 C&ER	ETA 12.5 betamethasone	3	NR	NR	NR	NR	NR	NR	NR	NR

5.2.2. ASDAS outcomes

Table S69: ASDAS outcomes (active comparator trials)

Study	Interventions	Time-point (months)	Mean ASDAS change (SD)	p-vale	ASDAS CII (%)	p-value	ASDAS MI (%)	p-value	ASDAS I (%)	p-value
Giardina 2010 RheumaInt	ETA 50 QW INF 5m/Kg Q6W	3	NR	NR	NR	NR	NR	NR	NR	NR
Park 2013 ARD (PLANETAS)	CT-P13 5 mg/Kg INF 5 mg/Kg	7.5	-1.8 (1.2) -1.7 (1.2)	NR	NR	NR	NR	NR	NR	NR
Park 2016 AR&T (PLANETAS)	CT-P13 5 mg/Kg INF 5 mg/Kg	13.5	-1.7 (1.3) -1.7 (1.3)	NR	NR	NR	NR	NR	NR	NR
Braun 2011 A&R (ASCEND) Moots 2012 Rheuma (ASCEND) Braun 2012 JR (ASCEND	ETA 50 QW SSZ 3g/day	3	NR	NR	NR	NR	NR	NR	NR	NR
Song 2011 ARD (ESTHER) Song 2013 ARD (ESTHER) Song 2014 JR (ESTHER) Poddubnyy 2015 EULAR (ESTHER) Song 2016 SAR (ESTHER)	ETA nr-axSpA ETA r-axSpA	36	NR	NR	NR	NR	37 26	NR	50 32	37 26
Sieper 2014 ARD (INFAST-1) Sieper 2012 ACR (INFAST-1) Poddubnyy 2014 ACR (INFAST-1)	INF 5 + NPX 1000 PBO + NPX 1000	7	NR	NR	87.9 70.5	0.01 REF	73.6 34.1	<0.001 REF	51.4 19.6	<0.001 REF
Mok 2015 SJR	GOL 50 Q4W PAM 60 Q4W	12	NR	NR	NR	NR	NR	NR	NR	NR
Viapiana 2014 Rheuma	INF 5 Q6W Neridronate 100	6	NR	NR	NR	NR	NR	NR	NR	NR
Mulleman 2011 AR&T	INF 5 Q6W INF 5 + MTX 10	4.5	NR	NR	NR	NR	NR	NR	NR	NR
Huang 2011 C&ER	ETA 12.5 betamethasone	3	NR	NR	NR	NR	NR	NR	NR	NR

6.2.3. Other disease-activity outcomes

Table S70: Other disease-activity outcomes (active comparator trials)

Study	Interventions	Time-point (months)	Mean BASDAI change (SD)	p-vale	BASDAI 50 (%)	p-value	Mean CRP change (SD)	p-value	Mean TJC (SD)	p-value
Giardina 2010 RheumaInt	ETA 50 QW INF 5m/Kg Q6W	3	NR	NR	NR	NR	NR	NR	NR	NR
Park 2013 ARD (PLANETAS)	CT-P13 5 mg/Kg INF 5 mg/Kg	7.5	-3.1 -2.5	NR	NR	NR	NR	NR	NR	NR
Park 2016 AR&T (PLANETAS)	CT-P13 5 mg/Kg INF 5 mg/Kg	13.5	-3.1 (2.3) -2.8 (2.2)	NR	NR	NR	NR	NR	NR	NR
Braun 2011 A&R (ASCEND) Moots 2012 Rheuma (ASCEND) Braun 2012 JR (ASCEND	ETA 50 QW SSZ 3g/day	3	NR	<0.001 REF	NR	NR	NR	<0.001 REF	NR	<0.0187 REF
Song 2011 ARD (ESTHER) Song 2013 ARD (ESTHER) Song 2014 JR (ESTHER) Poddubnyy 2015 EULAR (ESTHER) Song 2016 SAR (ESTHER)	ETA 25 BiW SSZ 2-3 g/day ETA nr-axSpA ETA r-axSpA	6 72	NR NR NR NR	0.002 REF NR NR	NR NR 82.4 86.7	NR NR NR NR	NR NR NR NR	0.07 REF NR NR	NR NR NR NR	NR NR NR NR
Sieper 2014 ARD (INFAST-1) Sieper 2012 ACR (INFAST-1) Poddubnyy 2014 ACR (INFAST-1)	INF 5 + NPX 1000 PBO + NPX 1000	7	NR	NR	77.3 51.1	0.003 REF	-1.24 (6.209) -0.55 (1.315)	0.59 REF	-3.29 (6.385) -2.93 (5.101)	0.73 REF
Mok 2015 SJR	GOL 50 Q4W PAM 60 Q4W	12	NR	NR	NR	NR	NR	NR	NR	NR
Viapiana 2014 Rheuma	INF 5 Q6W Neridronate 100	6	-1.72 (1.75) -1.62 (2.10)	NS REF	42.9 33.3	NS REF	-7.9 (10.8) -1.6 (13.4)	<0.05 REF	NR	NR
Mulleman 2011 AR&T	INF 5 Q6W INF 5 + MTX 10	4.5	NR	NR	58.3 57.1	NS REF	NR	NR	NR	NR
Huang 2011 C&ER	ETA 12.5 betamethasone	3	NR	NR	NR	NR	NR	NR	NR	NR

5.2.4. Mobility, function and quality of life outcomes

Table S71: Mobility, function and quality of life outcomes (active comparator trials)

Study	Interventions	Time-point (months)	Mean BASFI change (SD)	p-vale	Mean BASMI change (SD)	p-value	Mean ASQoL change	p-value
Giardina 2010 RheumaInt	ETA 50 QW INF 5m/Kg Q6W	3	NR	NR	NR	NR	NR	NR
Park 2013 ARD (PLANETAS)	CT-P13 5 mg/Kg INF 5 mg/Kg	7.5	-2.6 -2.2	NR	-1 -1	NR	NR	NR
Park 2016 AR&T (PLANETAS)	CT-P13 5 mg/Kg INF 5 mg/Kg	13.5	-2.9 (2.3) -2.7 (2.1)	NR	-1.1 (1.5) -0.9 (1.6)	NR	NR	NR
Braun 2011 A&R (ASCEND) Moots 2012 Rheuma (ASCEND) Braun 2012 JR (ASCEND	ETA 50 QW SSZ 3g/day	3	NR	<0.001 REF	NR	<0.001 REF	NR	NR
Song 2011 ARD (ESTHER) Song 2013 ARD (ESTHER) Song 2014 JR (ESTHER) Poddubnyy 2015 EULAR (ESTHER) Song 2016 SAR (ESTHER)	ETA 25 BiW SSZ 2-3 g/day	6	NR	0.005 REF	NR	0.28 REF	NR	<0.001 REF
Sieper 2014 ARD (INFAST-1) Sieper 2012 ACR (INFAST-1) Poddubnyy 2014 ACR (INFAST-1)	IFN 5 + NPX 1000 PBO + NPX 1000	7	NR	NR	-1.1 (1.13) -0.6 (0.72)	<0.001 REF	NR	NR
Mok 2015 SJR	GOL 50 Q4W PAM 60 Q4W	12	NR	NR	NR	NR	NR	NR
Viapiana 2014 Rheuma	IFN 5 Q6W Neridronate 100	6	-0.61 (1.78) -0.49 (1.25)	NS REF	-0.28 (1.01) -0.74 (0.92)	NS REF	NR	NR
Mulleman 2011 AR&T	IFN 5 Q6W INF 5 + MTX 10	4.5	NR	NR	NR	NR	NR	NR
Huang 2011 C&ER	ETA 12.5 betamethasone	3	NR	NR	NR	NR	NR	NR

6.3. Safety outcomes

Table S72: Main safety outcomes (active comparator trials)

Study	Interventions	Time-point (months)	N	Withdrawals AE (%)	p-value	Serious AE (%)	p-value	Any infection (%)	p-value	Serious infections (%)	p-value	Tuberculosis (%)	p-value	Malignancies (%)	p-value
Giardina 2010 RheumaInt	ETA 50 QW INF 5m/Kg Q6W	3	25 24	NR	NR	4 8	NR	NR	NR	NR	NR	NR	NR	NR	NR
Park 2013 ARD (PLANETAS)	CT-P13 INF 5	7.5	125 125	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	0.8 0.8	NR NR	NR NR	NR NR
Park 2016 AR&T (PLANETAS)	CT-P13 5 INF 5	13.5	128 122	8.6 7.4	NR NR	7.8 6.6	NR NR	NR NR	NR NR	NR NR	NR NR	1.6 0.8	NR NR	0 0	NR NR
Braun 2011 A&R (ASCEND) Moots 2012 Rheuma (ASCEND) Braun 2012 JR (ASCEN)	ETA 50 QW SSZ 3g/day	4	379 187	4 6.4	NR	1.8 2.1	NR	NR	NR	0 0	NR	0 0	NR	0 0	NR
Song 2011 ARD (ESTHER) Song 2013 ARD (ESTHER) Song 2014 JR (ESTHER) Poddubnyy 2015 EULAR (ESTHER) Song 2016 SAR (ESTHER)	ETA 25 BiW SSZ 2-3 g/day	6	40 36	NR	NR	7.5 19.4	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sieper 2014 ARD (INFAST-1) Sieper 2012 ACR (INFAST-1) Poddubnyy 2014 ACR (INFAST-1)	INF 5 + NPX 1000 PBO + NPX 1000	7	105 52	3.8 1.9	NR	4.8 5.8	NR	NR	NR	NR	NR	1 0	NR	NR	NR
Mok 2015 SJR	GOL 50 Q4W PAM 60 Q4W	12	20 10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Viapiana 2014 Rheuma	INF 5 Q6W Neridronate 100	6	30 30	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mulleman 2011 AR&T	INF 5 Q6W INF 5 + MTX 10	4.5	12 14	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Huang 2011 C&ER	ETA 12.5 betamethasone	3	5 7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Study	Interventions	Time-point (months)	N	Any CVD event (%)	p-value	Any hematological abnormality (%)	p-value	Any GI event (%)	p-value	Injection reactions %)	p-value	Headache (%)	p-value	Elevated Liver enzymes (%)	p-value
Giardina 2010 RheumaInt	ETA 50 QW INF 5m/Kg Q6W	3	25 24	NR	NR	NR	NR	NR	NR	25 4	NR	28 32	NR	NR	NR
Park 2013 ARD (PLANETAS)	CT-P13 5 INF 5	7.5	128 122	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	3.9 4.9	NR NR	2.3 0.3	NR NR	23.4 23	NR NR
Park 2016 AR&T (PLANETAS)	CT-P13 5 INF 5	13.5	128 122	NR NR	NR NR	NR NR	NR NR	NR NR	NR NR	8.6 12.3	NR NR	2.3 0.8	NR NR	12.5 12.3	NR NR
Braun 2011 A&R (ASCEND) Moots 2012 Rheuma (ASCEND) Braun 2012 JR (ASCEND)	ETA 50 QW SSZ 3g/day	3	379 187	NR	NR	NR	NR	NR	NR	10.8 1.6	NR	NR	NR	NR	NR
Song 2011 ARD (ESTHER) Song 2013 ARD (ESTHER) Song 2014 JR (ESTHER) Poddubnyy 2015 EULAR (ESTHER) Song 2016 SAR (ESTHER)	ETA 25 BiW SSZ 2-3 g/day	6	40 36	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sieper 2014 ARD (INFAST-1) Sieper 2012 ACR (INFAST-1) Poddubnyy 2014 ACR (INFAST-1)	IFN 5 + NPX 1000 PBO + NPX 1000	7	105 51	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mok 2015 SJR	GOL 50 Q4W PAM 60 Q4W	12	20 10	NR	NR	NR	NR	NR	NR	0 30	0.03	NR	NR	10 0	0.54
Viapiana 2014 Rheuma	IFN 5 Q6W Neridronate 100	6	30 30	NR	NR	NR	NR	NR	NR	3.3 13.3	NR	NR	NR	NR	NR
Mulleman 2011 AR&T	IFN 5 Q6W INF 5 + MTX 10	4.5	12 14	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Huang 2011 C&ER	ETA 12.5 betamethasone	3	5 7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table S73: Other safety outcomes (active-comparator trials)

7. STRATEGY AND COST-EFFECTIVENESS TRIALS

7.1. Treatment stop

Table S74: Treatment stop (etanercept)

Study	Treatment group in phase 1	Phase 2 (strategy trial)* N baseline	Remission baseline	Flare after treatment stop† (%)	Time to flare (weeks)	Remission end follow-up after re-treatment‡ (%)	RoB
ESTHER Song 2012 ARD Population: Early(≤5Y) axSpA (ASAS) Study design (phase 2): open-label extension (no comparator) Follow-up: 48 weeks	ETA 25 TW SC	40	13/40 (33%)	9/13 (69%)	24.4	3/9 (33.3%) (ASAS PR: 5/9; 56%)	Unclear
	SSZ 2-3g/day oral	36	4 /36 (11%)	3/4 (75%)	39.6	1/3 (33.3%) (ASAS PR: 2/3; 66.7%)	

* Study design (phase 2): Patients in remission at the end of phase 1 (1 year) were followed up without active treatment. In case of a flare, they were started on ETA (same dose) for another year. Patients who did not flare were taken off the study at the end of 1 year (total follow-up: 2 years); † BASDAI increase of 2 points compared to baseline of phase 2; ‡ ASAS PR + MRI remission (no inflammation on spine and SI (whole-body MRI).

Table S75: Treatment stop (infliximab)

Study	Phase 2 (strategy trial)* Treatment group	N baseline	Remission baseline	Flare after treatment stop† (%)	Time to flare (weeks)	Remission end follow-up‡ (%)	RoB
INFAST-2 Sieper 2014 ARD Population: Early (≤3Y) axSpA (ASAS – 'imaging arm') Study design (INFAST-2): open-label RCT Randomization: 1:1 (no stratification) Follow-up: 52 weeks	NPX oral	41	41/41	1/40 (2.5%)	23	19/40 (47.5%)	Low
	No-treatment	41	41/41	3/40 (7.5%)	12.6	16/40 (40.0%)	

* Study design: In INFAST-1 patients were randomized 2:1 to receive 28 weeks of treatment with either INF 5 mg/kg IV + NPX 1000 mg/d or IV PBO+NPX 1000 mg/d. In Infast-2 those achieving ASAS PR at W28 (in phase 1) stopped IFN and were re-randomized to either NPX (open-label) or no treatment (1:1 ratio) until week 52; † BASDAI ≥3 during two consecutive visits within 1–3 weeks of each other between weeks 28 and 52; ‡ ASAS PR.

Table S76: Treatment stop (adalimumab)

Study	Treatment group in phase 1	Phase 2 (strategy trial)*					
		N baseline	Response baseline	Flare after treatment stop† (%)	Time to loss of response (weeks)	Response end follow-up after re-treatment‡ (%)	RoB
Haibel 2013 A&R Population: Early (≤5Y) nr-axSpA Study design (phase 2): open-label extension (no comparator) Follow-up: 52 weeks	ADA 40 Q2W SC	24	24/24	19/24 (79%)	14.7 (5.5)	15/19 (73.7%)	Unclear

* Patients in whom an ASAS40 response was achieved at the end of phase 1 (1 year) treatment with ADA 40Q2W was stopped and were followed up for 2 years. In patients who experienced a flare, therapy was reintroduced and treatment was administered for an additional 2 years. †Loss of an established ASAS40 response as compared to baseline at any time point; ‡ ASAS 40.

7.2. Dose tapering

Table S77: Dose tapering (etanercept)

Study	Treatment group in phase 1	Phase 2 (strategy trial)*					
		N baseline	Response baseline‡	Flare during follow-up† (%)	Time flare (months)	Response end follow-up‡ (%)	RoB
Yates 2015 Rheuma Population: Late (> 5Y) AS (mNY) Study design (phase 2): RCT open-label Randomization: 1:1 (stratified on study-site) Follow-up: 24 weeks	ETA 50 QW SC	24	24/24	NR	NR	22 (91.7%)	Unclear
	ETA 25 QW SC	23	23/23	NR	NR	12 (52.2%)	

* Study design (phase 2): After 6 months of ETN 50 mg QW patients were randomly assigned (1:1. stratified on site) to taper to 25 mg QW or continue on 50 mg QW for an additional 6 months; † increase in BASDAI ≥ 2 (or a 5-point increase as compared to the baseline score) observed on at least 2 recall visits AND an increase in the spinal VAS of ≥ 2 4. AND the participant and physician considered reinstatement of the 50 mg dosage appropriate; ‡ BASDAI 50 (50% reduction or fall ≥ 2 units and a ≥ 2-unit reduction in BASDAI spinal pain).

Table S78: Dose tapering (etanercept)

Study	Treatment group in phase 1	Phase 2 (strategy trial)*					
		N baseline	Remission baseline	Flare during follow-up† (%)	Time to flare (months)	Remission end follow-up‡ (%)	RoB
Cantini 2013 Biologics Population: Late (> 5Y) AS (mNY) Study design (phase 2): RCT open-label Randomization: 1:1 Follow-up: mean (SD) 25 (11) months	ETA 50 QW SC	21	21/21	2/21 (9.5%)	10 (11.1)	19/21 (90.4%)	Unclear
	ETA 50 Q2W SC	22	22/22	3/22 (13.6%)	8 (3.2)	19/22 (86.3)	

* Study design (phase 2): Patients in remission after phase 1 were randomized (1:1) to ETA 50 mg QW or ETA 50 mg Q2W, * After flare for those on ETA 50 Q2W, dose escalation to 50 mg QW resulted in remission for all after a mean (SD) 5.1 (2.4) months, Patients on ETA 50QW were switched to other TNFi; † BASDAI > 4 or any peripheral articular and extra-articular manifestations independently of elevation of acute-phase reactants; ‡BASDAI <4, no extra-axial manifestations, peripheral arthritis, dactylitis, tenosynovitis, or anterior uveitis, and a normal ESR and CRP.

7.3. High dose

Table S79: High dose vs standard dose (etanercept)

Study	Treatment group	N patients	Time-point (weeks)	ASAS 20 (%)	p-value	ASAS 40 (%)	p-value	ASAS PR (%)	p-value	RoB
LOADET Navarro-Sarabia 2011 Rheuma Study design: RCT double-blind Population: Late (> 5Y) r-axSpA (mNY) patients TNFi-naïve Randomization: 1:1. no stratification	ETA 50 QW SC	54	12	37	NS	25	NS	NR	NR	Low
	ETA 50 TW SC	54	12	34		25		NR		

7.4. Cost-effectiveness

Table S80: Cost-effectiveness of infliximab continuous vs on-demand

Study	Treatment group	N patients	Time-point (months)	ASAS 20 (%)	p-value	ASAS 40 (%)	p-value	Total costs (Euros)	p-value	RoB
Fautrel 2010 ARD Study design: RCT Population: Late (> 5Y) r-axSpA (mNY) patients Randomization: 1:1. no stratification	Continuous INF 5 mg/Kg Q6W	116	12	75.9	<0.001	27.6	<0.001	22.388	<0.001	Low
	On-demand INF 5 mg/Kg Q6W	114		45.6		7.0		17.596		

Mean incremental cost-effectiveness ratio (ICER) for:

1 additional ASAS 20 response: 15,841 euros;

1 additional ASAS PR: 23,296 euros;

1 QALY gained: 50,760 euros (Acceptability threshold: 50,000 euros per QALY).

8. LIST OF PUBLICATIONS

Publications are listed in order of appearance in the supplemental material.

8.1. Randomized controlled trials and LTE of TNF inhibitors

Dijkmans B, Emery P, Hakala M, et al. Etanercept in the longterm treatment of patients with ankylosing spondylitis. J Rheumatol 2009;36:1256-64.

Martín-Mola E, Sieper J, Leirisalo-Repo M, et al. Sustained efficacy and safety, including patient-reported outcomes, with etanercept treatment over 5 years in patients with ankylosing spondylitis. Clin Exp Rheumatol. 2010;28:238-45.

Barkham N, Coates LC, Keen H, et al. Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis. Ann Rheum Dis 2010;69:1926-8.

Dougados M, Combe B, Braun J, et al. A randomised, multicentre, double-blind, placebo-controlled trial of etanercept in adults with REFractory heel enthesitis in spondyloarthritis: the **HEEL** trial. Ann Rheum Dis 2010;69:1430-5.

Dougados M, Braun J, Szanto S, et al. Efficacy of etanercept on rheumatic signs and pulmonary function tests in advanced ankylosing spondylitis: results of a randomised double-blind placebo-controlled study (**SPINE**). Ann Rheum Dis 2011;70:799-804.

Dougados M, Braun J, Szanto S, et al. Continuous efficacy of etanercept in severe and advanced ankylosing spondylitis: results from a 12-week open-label extension of the **SPINE** study. Rheumatology (Oxford) 2012;51:1687-96.

Baraliakos X, Haibel H, Fritz C, et al. Long-term outcome of patients with active ankylosing spondylitis with etanercept-sustained efficacy and safety after seven years. Arthritis Res Ther 2013;15:R67.

Dougados M, van der Heijde D, Sieper J, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol 2014;66:2091-102. **[EMBARK]**

Dougados M, Tsai WC, Saaibi DL, et al. Evaluation of Health Outcomes with Etanercept Treatment in Patients with Early Nonradiographic Axial Spondyloarthritis. J Rheumatol 2015;42:1835-41. **[EMBARK]**

Maksymowych WP, Dougados M, van der Heijde D, et al. Clinical and MRI responses to etanercept in early non-radiographic axial spondyloarthritis: 48-week results from the EMBARK study. Ann Rheum Dis 2015; 12. pii: annrheumdis-2015-207596. **[EMBARK]**

Dougados M, van der Heijde D, Sieper J, et al. Clinical and Imaging Efficacy of Etanercept in Early Non-Radiographic Axial Spondyloarthritis: 104-Week Treatment Results [abstract]. Arthritis Rheumatol 2015; 67 (suppl 10). **[EMBARK]**

Brown MA, Bird PA, Robinson PC, et al. Baseline MRI and CRP As Predictors of Response to Etanercept in the Management of Patients with Non-Radiographic Axial Spondyloarthritis (nr-axSpA) [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10). **[EMBARK]**

Dougados M, Wood E, Combe B, et al. Evaluation of the nonsteroidal anti-inflammatory drug-sparing effect of etanercept in axial spondyloarthritis: results of the multicenter, randomized, double-blind, placebo-controlled SPARSE study. Arthritis Res Ther 2014;16:481. **[SPARSE]**

Barkham N, Keen HI, Coates LC, et al. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis Rheum 2009;60:946-54.

Inman RD, Maksymowych WP; CANDLE Study Group. A double-blind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis. J Rheumatol 2010;37:1203-10.

Maksymowych WP, Salonen D, Inman RD, et al. Low-dose infliximab (3 mg/kg) significantly reduces spinal inflammation on magnetic resonance imaging in patients with ankylosing spondylitis: a randomized placebo-controlled study. J Rheumatol 2010;37(8):1728-34.

Baraliakos X, Listing J, Fritz C, et al. Persistent clinical efficacy and safety of infliximab in ankylosing spondylitis after 8 years--early clinical response predicts long-term outcome. Rheumatology (Oxford) 2011;50:1690-9.

van der Heijde D, Schiff MH, Sieper J, e al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis 2009;68:922-9. **[ATLAS]**

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Maksymowych WP, Gooch KL, Wong RL, et al. Impact of age, sex, physical function, health-related quality of life, and treatment with adalimumab on work status and work productivity of patients with ankylosing spondylitis. J Rheumatol 2010;37:385-92. **[ATLAS]**

Sieper J, van der Heijde D, Dougados M, et al. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. Ann Rheum Dis 2012;71:700-6. **[ATLAS]**

van der Heijde D, Breban M, Halter D, et al. Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab. Rheumatology (Oxford). 2015;54:1210-9. **[ATLAS]**

Hu Z, Xu M, Li Q, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. Int J Rheum Dis 2012;15:358-65.

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Huang F, Gu J, Zhu P, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. Ann Rheum Dis. 2014;73:587-94.

Pedersen SJ, Poddubnyy D, Sørensen IJ, et al. Course of Magnetic Resonance Imaging-Detected Inflammation and Structural Lesions in the Sacroiliac Joints of Patients in the Randomized, Double-Blind, Placebo-Controlled Danish Multicenter Study of Adalimumab in Spondyloarthritis, as Assessed by the Berlin and Spondyloarthritis Research Consortium of Canada Methods. Arthritis Rheumatol 2016;68:418-29.

Bao C, Huang F, Khan MA, et al. Safety and efficacy of golimumab in Chinese patients with active ankylosing spondylitis: 1-year results of a multicentre, randomized, double-blind, placebo-controlled phase III trial. Rheumatology (Oxford) 2014;53:1654-63.

Tam LS, Shang Q, Kun EW, et al. The effects of golimumab on subclinical atherosclerosis and arterial stiffness in ankylosing spondylitis—a randomized, placebo-controlled pilot trial. Rheumatology (Oxford) 2014;53:1065-74.

Sieper J, van der Heijde D, Dougados M, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2015;67:2702-12. **[GO-AHEAD]**

van der Heijde D, Dougados M, Maksymowych W, et al. Long-Term Tolerability and Efficacy of Golimumab in Active Nonradiographic Axial Spondyloarthritis: Results from the Open-Label Extension of a Randomized, Double-Blind Study [abstract]. Arthritis Rheumatol 2015; 67 (suppl 10). **[GO-AHEAD]**

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Deodhar A, Braun J, Inman RD, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the **GO-RAISE** study. Ann Rheum Dis 2015;74:757-61.

Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73:39-47. **[RAPID-axSpA]**

Sieper J, Kivitz A2, van Tubergen A, et al. Impact of Certolizumab Pegol on Patient-Reported Outcomes in Patients With Axial Spondyloarthritis. Arthritis Care Res (Hoboken) 2015;67:1475-80. **[RAPID-axSpA]**

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8.6. Cochrane review

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9. LIST OF ABBREVIATIONS

ABA	abatacept
A&R	Arthritis & Rheumatology
ACR	American College of Rheumatology (annual conference)
ADA	adalimumab
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APR	apremilast
AR&T	Arthritis Research & Therapy
aRatio	adjusted ratio
ARD	Annals of Rheumatic Diseases
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	Ankylosing Spondylitis Disease Activity Score

ASDAS CII	ASDAS clinically important improvement (Δ≥1.1)
ASDAS I	ASDAS inactive (<1.3)
ASDAS MI	ASDAS major improvement (Δ≥2.0)
ASQoL	Ankylosing Spondylitis Quality of Life index
ASspiMRI-a	Ankylosing Spondylitis spine MRI score for activity
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	BATH Ankylosing Spondylitis Metrology Index
bid	twice a day
BL	baseline
C	control
C&ER	Clinical and Experimental Rheumatology
CBL	change from baseline
CCT	controlled clinical trial
CI	confidence interval
ClinRheuma	Clinical Rheumatology
CRP	C reactive protein
csDMARD	conventional synthetic disease modifying antirheumatic drugs
CVD	cardiovascular disease
CZP	certolizumab pegol
ES	effect size
ESSG	European Spondyloarthropathy Study Group
ETA	etanercept
EULAR	European League Against Rheumatism (annual conference)
GEE	generalized estimating equation
GI	gastrointestinal
GOL	golimumab
Hgb	hemoglobin
HLA-B27	Human Leucocyte Antigen B27
HR	hazard ratio
I	intervention
ITT	intention to treat
IBD	inflammatory bowel disease
IBP	inflammatory back pain
ICD	international classification of diseases
IJRD	International Journal of Rheumatic Diseases
INF	infliximab
IV	intravenous
JR	Journal of Rheumatology
LTE	long-term extensions

mNY	modified New York criteria
MRI	magnetic resonance imaging
MTX	methotrexate
n/e	not possible to estimate
NA	not applicable
NEJM	New England Journal of Medicine
NNT	number needed to treat
NPX	naproxen
NR	not reported
nr-axSpA	non-radiographic axial spondyloarthritis
NRI	non-responder imputation
NS	not significant
NSAID	Nonsteroidal anti-inflammatory drugs
PAM	pamidronate
PBO	placebo
POC	proof of concept trial
PR	partial remission
PY	patient-years
Q2W	Every 2 weeks
Q4W	Every four weeks
Q6W	Every 6 weeks
QALY	Quality-adjusted life year
QW	Every week
r-axSpA	radiographic axial spondyloarthritis
RCT	randomized clinical trial
REF	reference group
Rheuma	Rheumatology
Rheumaint	Rheumatology international
RR	risk ratio
RTX	rituximab
SA&R	Seminars in Arthritis and Rheumatism
SAE	serious adverse event
SAR	sarilumab
SC	subcutaneous
SD	standard deviation
SEC	secukinumab
SII	sacroiliitis
SIR	standardized incidence ratio
SJR	Scandinavian Journal of Rheumatology
SMD	standardized mean difference
SpA	spondyloarthritis

SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	sulfasalazine
TB	tuberculosis
TJC	tender joint count
TNFi	Tumour necrosis factor inhibitor
TOC	tocilizumab
TOFA	tofacitinib
TW	Twice a week
uRatio	unadjusted ratio
UST	ustekinumab