

Supplemental table 1 Characteristics of included studies

Registration/ Protocole	Sponsor	Period	Drug	Patients	Design	Sites	Randomized patients	Follow up	Primary outcome
NCT00647491/ VIV0000303	Abbvie	2004-2005	ADA	Active RA	4 arms: ADA 20mg/2w ADA 40mg/2w ADA 80mg/2w PLB	Japan	352	24 weeks	ACR 20 Week 24
NCT00420927/ VIV0000301 OPTIMA	Abbvie	2006-2010	ADA	Early RA	2 arms in period 1: ADA 40mg/2w +MTX, PLB +MTX	US, South America, Europe,	1032	78 weeks	DAS28, Sharp Week78
NCT00195663/ VIV0000296 PREMIER	Abbvie	2000-2012	ADA	Early RA, naïve from DMARD	3 arms: ADA 40mg/2w ADA 40mg/2w +MTX PLB +MTX	Australia, Canada, Europe, US	799	10 years	ACR50, Sharp Week52
NCT00195702/ VIV0000296	Abbvie	2000-2010	ADA	Active RA despite MTX	3 arms: ADA 20mg/2w +MTX ADA 40mg/2w +MTX PLB +MTX	US, Canada	619	10 years	ACR20 W24, Sharp W52, HAQ W52,
NCT00234845/ VIV00002980	Abbvie	2003- 2005	ADA	Early RA, naïve from DMARD	2 arms: ADA 40mg/2w +MTX PLB +MTX	US	148	60 weeks	Job loss measurement
NCT00235859/ VIV00002986	Abbvie	2003- 2005	ADA	Active RA despite MTX	2 arms: ADA40mg/2w +MTX PLB +MTX	South Korea	128	24 weeks	ACR20 Week 24
NCT00647920/ VIV00003035	Abbvie	2003- 2005	ADA	Active RA despite MTX	2 arms: ADA 40mg/2w +MTX PLB +MTX	Taiwan (single center)	47	12 weeks	ACR20 Week 12
NCT00538902/ VIV00003021	Abbvie	2007-2009	ADA	Active RA	3 arms: ADA 80mg/2w +MTX ADA 40mg/2w +MTX PLB +MTX	China	302	12 weeks	ACR20 Week 12
NCT00647270/ VIV00003032	Abbvie	2007-2009	ADA	Active RA	3 arms: ADA 80mg/4w ADA 40mg/2w PLB (12 weeks only)	US, Australia, Canada, Europe, Puerto Rico	420	24 weeks	ACR20 Week 12
PMID14719195 DE031 STAR	Abbvie	2003	ADA	Active RA	2 arms: ADA 40mg/2w PLB	US, Canada	636	24 weeks	Incidence of adverse events
NCT00870467/ VIV00003053	Abbvie	2009-2011	ADA	Early RA, naïve from MTX and TNF inhibitors	2 arms: ADA 40mg/2w +MTX PLB +MTX	Japan	334	52 weeks	Sharp Week 26
PMID 22739990 / HIT HARD	Detert	2012	ADA	Active early RA, naïve from DMARD	2 arms ADA 40mg/2w +MTX PLB/2w +MTX	Europe	172	48 weeks	DAS 28 Week 48

ACR = American College of Rheumatology, TNF inhibitors= anti-tumor necrosis factor, ADA= adalimumab, MTX= methotrexate, PLB= placebo, RA= rheumatoid arthritis.

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Registration / Protocol	Sponsor	Period	Drug	Patients	Design	Sites	Randomized patients	Duration	Primary outcome
PMID 9920948/ 160014	Amgen	1998	ETN	Active RA despite MTX	2 arms: ETN 25mg x2/w +MTX PLB +MTX	US	89	24 weeks	ACR20 Week 24
NCT01313208/ 20070561	Amgen	2011-2013	ETN	Moderate RA despite MTX	2 arms: (12 weeks only) ETN 50mg/w +DMARDS PLB +DMARDS	US, Canada	210	24 weeks	DAS28 Week 12
NCT00445770/ B1801002	Pfizer	2006-2011	ETN	RA, naïve from TNF inhibitors	3 arms: ETN 10mg x2/w ENT 25mg x2/w MTX 8mg/w	Japan	550	52 weeks	Sharp Week 52
NCT00160602/ C87050	UCB	2005-2006	CZP	Patients with active RA despite MTX, naïve from TNF inhibitors	3 arms: CZP 400mg +MTX CZP 200mg +MTX PLB + MTX	US, Europe, South America, Israel, Russia	590	24 weeks	ACR 20 Week 24
NCT00152386/ C87027	UCB	2005-2006	CZP	Patients with active RA despite MTX, naïve from TNF inhibitors	3 arms: CZP 400mg/2w +MTX CZP 200mg/2w +MTX PLB +MTX	US, South America, Australia, Europe, Israel, Russia	950	52 weeks	ACR 20 Week 24
NCT00717236/ C87094 REALISTIC	UCB	2008-2011	CZP	Patients with active RA despite MTX, naïve from TNF inhibitors	2 arms: CZP 400mg/2w +DMARD PLB +DMARD	US, Canada, Europe	1648	12 weeks then extension	ACR 20 Week 12
NCT00548834/ C87011	UCB	2003-2004	CZP	Patients with active RA despite DMARD, naïve from TNF inhibitors	2 arms: (csDMARD prohibited) CZP 400mg/4w PLB/4w	US, Europe,	220	24 weeks	ACR 20 Week 24
NCT00674362/ C87076 CERTAIN	UCB	2008-2010	CZP	Patients with <u>moderate to low</u> disease activity RA	2 arms: CZP 200mg/2w + DMARDs PLB + DMARDs	Europe	194	52 weeks	CDAI Weeks 20, 24
NCT01519791/ RA0055Period1 C-EARLY	UCB	2012-2015	CZP	Patients with early active RA, naïve from DMARD	2 arms: CTZ 200mg/2w + MTX PLB + MTX	US, South America, Australia, Europe	880	52 weeks	DAS remission Week 52

ACR = American College of Rheumatology, TNF inhibitors= anti-tumor necrosis factor, ETN= etanercept, CZP = certolizumab, MTX= methotrexate, PLB= placebo, RA= rheumatoid arthritis.

Supplemental table 1 Characteristics of included studies

Registration / Protocol	Sponsor	Period	Drug	Patients	Design	Sites	Randomized patients	Duration	Primary outcome
C0524T05/ NCT00264537/ Go-Before	Centocor	2005-2008	GOL	Active RA naive from MTX and TNF inhibitors	4 arms: GOL 10 mg/4w GOL 50 mg/4w+ MTX GOL 100 mg/4w+ MTX PLB+ MTX	USA, Canada, South America, Australia, Europe, India, Thailand, Korea, Taiwan	637	52 weeks	ACR50 Week 24
C0524T06/ NCT00264550/ Go-Forward	Centocor	2005-2008	GOL	Active RA despite MTX	4 arms: GOL 10mg/4w GOL 50mg/4w+ MTX GOL 100mg/4w+ MTX PLB + MTX	USA, Canada, South America, Australia, Europe, Taiwan	444	52 weeks	ACR20 Week 14
C0524T11/ NCT00299546 / Go-After	Centocor	2005-2007	GOL	Active RA previously treated with TNF inhibitors	3 arms: GOL 50mg/4w GOL 100mg/4w (concomitant treatment by MTX, sulfasalazine or hydroxychloroquine is permitted but not required) PLB	USA, Canada, Europe, Australia, New Zealand	461	24 weeks	ACR20 Week 14
C0524T12/ NCT00361335/ Go-Live	Centocor	2006-2008	GOL	Active RA despite MTX	5 arms: GOL 2mg/kg/12w+ MTX GOL 2mg/kg/12w+ PLB GOL 4mg/kg/12w+ MTX GOL 4mg/kg/12w+ PLB PLB+ MTX	USA, Australia, Europe, South America, Malaysia	643	48 weeks	ACR50 Week 14
CNT0148ART3001/ NCT00973479/ Go-Further	Centocor	2009-2011	GOL	Active RA despite MTX	2 arms: GOL 2mg/kg+ MTX PLB + MTX	USA, South America, Australia, Europe, Korea, Malaysia, Russia, New Zealand	592	100 weeks	ACR20 Week 14
C0524T28 /NCT01248780	Centocor	2010-2013	GOL	Active RA despite MTX	2 arms: GOL 50mg/4w + MTX PLB + MTX	China	264	48 weeks	ACR20 Week 14
C0168T22/ NCT00269867/ ATTRACT	Centocor	1997-1998	INF	active RA despite MTX	5 arms: INF 3mg/kg/8w+ MTX INF 3mg/kg/4w+ MTX INF 10mg/kg/8w+ MTX INF 10mg/kg/4w+ MTX PLB+MTX	-	428	54 weeks	ACR20 Week 30
C0168T29/ NCT00236028/ ASPIRE	Centocor	2000-2003	INF	Patients with active RA from 3 month to 3 years, naive from MTX and TNF inhibitors	3 arms: INF 3mg/kg/8w+ MTX, INF 6mg/kg/8w + MTX (weeks 0,2, 6 and then every 8 weeks) PLB+ MTX	-	1049	58 weeks	ACR20,30, 50 Week 54 ACR50 Week 24

ACR American College of Rheumatology, TNF inhibitors= anti-tumor necrosis factor, GOL= golimumab, INF = infliximab, MTX= methotrexate, PLB= placebo, RA= rheumatoid arthritis

Supplemental table 2: Mean difference of final DAS28(CRP) between TNF inhibitors and placebo by clinical and biological baseline characteristics.

	Number of studies	Number of patients		Mean Difference (95% CI)	Heterogeneity		p for subgroup difference
		TNF inhibitors	Placebo		I ² (%)	p	
Smoking							
Yes	14	1409	685	-0.42 [-0.63 ; -0.22]	50	0.02	0.77
No		2329	1070	-0.47 [-0.64 ; -0.29]	65	< 0.01	
Physical activity							
Yes	5	297	138	-0.25 [-0.54 ; 0.03]	0	0.86	0.58
No		1488	610	-0.36 [-0.58 ; -0.13]	52	0.08	
Sex							
Women	27	5585	2513	-0.56 [-0.70 ; -0.43]	75	< 0.01	0.64
Men		1526	689	-0.51 [-0.68 ; -0.34]	30	0.08	
Age							
>50	27	4760	1876	-0.51 [-0.63 ; -0.38]	60	< 0.01	0.15
<=50		3315	1407	-0.65 [-0.81 ; -0.50]	64	< 0.01	
BMI							
>= 30	28	2125	828	-0.48 [-0.59 ; -0.37]	0	0.63	0.12
< 30		5977	2492	-0.62 [-0.77 ; -0.48]	78	< 0.01	
RF status							
Positive	28	6480	2668	-0.61 [-0.75 ; -0.47]	78	< 0.01	0.28
Negative		1425	559	-0.50 [-0.64 ; -0.35]	14	0.27	
ACPA status							
Positive	13	3058	1462	-0.44 [-0.66 ; -0.22]	83	< 0.01	0.99
Negative		920	368	-0.44 [-0.67 ; -0.21]	38	0.09	
Disease duration							
< 2 years	22	2781	1416	-0.52 [-0.70 ; -0.34]	60	< 0.01	0.07
2-10 years		1104	535	-0.39 [-0.57 ; -0.21]	26	0.15	
=>10 years		688	333	-0.78 [-1.05 ; -0.50]	40	0.07	
Baseline DAS28							
> 5.1	27	6097	2344	-0.61 [-0.75 ; -0.47]	75	< 0.01	0.44
<= 5.1		1948	899	-0.53 [-0.67 ; -0.39]	56	< 0.01	

ACPA = Anti-citrullinated protein antibodies, Baseline DAS28 = DAS28(CRP) score at baseline, BMI = Body mass index, RF= Rheumatoid factor.

Supplemental table 3: Odds-Ratios of good EULAR response of TNF inhibitors versus placebo, by clinical and biological baseline characteristics.

	Number of studies	Number of patients		Odds-Ratios (Peto, fixed, 95% CI)	Heterogeneity		p for subgroup difference
		TNF inhibitors	Placebo		I ² (%)	p	
Smoking							
Yes	14	1409	685	1.93 [1.42 ; 2.61]	38	0.08	0.95
No		2329	1070	1.95 [1.43 ; 2.67]	63	< 0.01	
Physical activity							
Yes	5	297	138	1.52 [0.89 ; 2.59]	11	0.34	0.87
No		1191	472	1.60 [1.12 ; 2.29]	41	0.15	
Sex							
Women	27	5585	2513	2.14 [1.80 ; 2.55]	47	< 0.01	0.50
Men		1526	689	1.95 [1.58 ; 2.40]	0	0.84	
Age							
>50 years	27	4760	1876	2.03 [1.71 ; 2.41]	30	0.07	0.59
<=50 years		3315	1407	2.17 [1.81 ; 2.60]	20	0.18	
BMI							
>= 30 kg/cm ²	28	2125	828	1.87 [1.49 ; 2.36]	7	0.37	0.22
< 30 kg/cm ²		5977	2492	2.24 [1.88 ; 2.68]	49	< 0.01	
RF status							
Positive	27	6480	2668	2.19 [1.83 ; 2.62]	51	< 0.01	0.61
Negative		1425	559	2.01 [1.54 ; 2.63]	3	0.42	
ACPA status							
Positive	13	3058	1462	2.00 [1.58 ; 2.54]	52	0.01	0.79
Negative		920	368	2.12 [1.51 ; 2.97]	2	0.43	
Disease duration							
< 2 years	22	2781	1416	1.95 [1.69 ; 2.24]	0	0.69	0.69
2-10 years		1104	535	2.14 [1.62 ; 2.81]	0	0.46	
=>10 years		688	333	1.65 [0.94 ; 2.91]	40	0.05	
Baseline DAS28							
> 5.1	27	6097	2344	2.19 [1.77 ; 2.72]	53	< 0.01	0.73
<= 5.1		1948	899	2.32 [1.86 ; 2.89]	23	0.14	

ACPA = Anti-citrullinated protein antibodies, Baseline DAS28 = DAS28(CRP) score at baseline, BMI = Body mass index, RF= Rheumatoid factor.

Supplemental table 4: Odds-Ratios of EULAR non-response of TNF inhibitors versus placebo, by clinical and biological baseline characteristics.

	Number of studies	Number of patients		Odds-Ratios (Peto, fixed, 95% CI)	Heterogeneity		p for subgroup difference
		TNF inhibitors	Placebo		I ² (%)	p	
Smoking							
Yes	14	1409	685	0.44 [0.33 ; 0.59]	25	0.19	0.97
No		2329	1070	0.44 [0.34 ; 0.59]	51	0.01	
Physical activity							
Yes	5	297	138	0.57 [0.36 ; 0.89]	0	0.59	0.95
No		1191	472	0.58 [0.45 ; 0.74]	15	0.32	
Sex							
Women	27	5585	2513	0.40 [0.33 ; 0.49]	60	< 0.01	0.94
Men		1526	689	0.41 [0.31 ; 0.53]	10	0.32	
Age							
>50 years	27	4760	1876	0.43 [0.35 ; 0.53]	45	< 0.01	0.34
<=50 years		3315	1407	0.38 [0.31 ; 0.46]	23	0.15	
BMI							
>= 30 kg/cm ²	28	2125	828	0.52 [0.43 ; 0.63]	0	0.97	0.01
< 30 kg/cm ²		5977	2492	0.36 [0.30 ; 0.45]	62	< 0.01	
RF status							
Positive	27	6480	2668	0.38 [0.31 ; 0.46]	58	< 0.01	0.13
Negative		1425	559	0.48 [0.38 ; 0.61]	0	0.83	
ACPA status							
Positive	13	3058	1462	0.42 [0.31 ; 0.57]	69	< 0.01	0.29
Negative		920	368	0.52 [0.39 ; 0.70]	0	0.51	
Disease duration							
< 2 years	22	2781	1416	0.44 [0.33 ; 0.58]	44	0.02	0.33
2-10 years		1104	535	0.52 [0.38 ; 0.71]	29	0.13	
=>10 years		688	333	0.35 [0.23 ; 0.54]	31	0.12	
Baseline DAS28							
> 5.1	27	6097	2344	0.42 [0.35 ; 0.51]	53	0.01	0.31
<= 5.1		1948	899	0.36 [0.27 ; 0.47]	39	0.02	

ACPA = Anti-citrullinated protein antibodies, Baseline DAS28 = DAS28(CRP) score at baseline, BMI = Body mass index, RF= Rheumatoid factor.

Supplemental table 5: Intervals adaptation for the categories "age" and "disease duration" for Certolizumab studies.

Registration	Age	
	<=50 years	>50 years
NCT00160602	(<49)	(49-62) (>62)
NCT00152386	(18-47)	(48-55) (56-63) (>63)
NCT00717236	(18-47)	(48-55) (56-62) (>62)
NCT00548834	(<45)	(45-<56) (56-<65) (>65)
NCT00674362	(<49)	(49-59) (>59)
NCT01519791	(<42) (42-48)	(49-55) (56-62) (63-69) (>69)

Registration	Disease duration		
	<2 years	Between 2 et 10 years	>10 years
NCT00160602	(<=3)	(>3)	
NCT00152386	(<=3)	(>3)	
NCT00717236	(<2)	(>=2)	
NCT00674362	(<2)	(>=2)	

*In bold the intervals where patients may have been misclassified.

Supplemental table 6: Final EULAR response and disease activity in TNF inhibitors groups

Studies	Arm	Patients analyzed	Week of assessment	Good response (%)	Intermediate response (%)	Non response (%)	Mean final TJC28	Mean final SJC28	Mean final PGA	Mean final CRP (mg/l)	Mean final DAS28CRP
NCT00647491	Adalimumab	235	24	17	45.5	37.4	8.31	7.82	44.97	34.17	4.8
NCT00420927	Adalimumab	433	26	52.7	37.6	9.7	5.12	3.43	24.73	7.18	3.23
NCT00195663	Adalimumab	427	24	39.3	49.2	11.5	5.6	4.68	24.72	13.79	3.6
NCT00195702	Adalimumab	345	24	41.2	47	11.9	4.64	5.14	22.44	9.12	3.57
NCT00234845	Adalimumab	53	24	66	26.4	7.5	2.64	1.92	16.72	5.36	2.66
NCT00235859	Adalimumab	59	24	59.3	28.8	11.9	4.31	2.14	33.54	6.85	3.14
NCT00647920	Adalimumab	32	12	18.8	50	31.3	9.12	5.97	52.69	13.51	4.27
NCT00538902	Adalimumab	223	12	26.5	52	21.5	7.48	3.33	41.07	9.75	3.89
NCT00647270	Adalimumab	296	24	26.7	44.9	28.4	8.86	6.36	36.28	7.69	4.12
DE31	Adalimumab	288	24	31.9	46.2	21.9	6.36	7.3	28.98	8.85	3.84
NCT00870467	Adalimumab	144	26	51.4	43.8	4.9	3.15	2.48	17.87	5.85	2.64
PMID 22739990	Adalimumab	73	24	61.6	32.9	5.5					
PMID9920948	Etanercept	43	24	27.9	62.8	9.3	4.28	5.28	27.67	12.6	3.57
NCT01313208	Etanercept	98	24	30.6	39.8	29.6				4.21	
NCT00445770	Etanercept	325	24	46.2	45.8	8	2.81	2.64	24.66	4.58	2.81
NCT00160602	Certolizumab	351	24	27.4	67.8	4.8	4.93	3.33	30.28	10.25	3.49
NCT00152386	Certolizumab	545	24	32.1	63.1	4.8	4.53	3.15	26.54	10.03	3.39
NCT00717236	Certolizumab	754	12	21.9	53.3	24.8	6.96	5.15	36.41	9.71	3.92
NCT00548834	Certolizumab	75	24	18.7	54.7	26.7	5.56	5.88	24.13	13.73	3.71
NCT00674362	Certolizumab	76	24	36.8	40.8	22.4	2.96	1.68	26.13	8.02	3.01
NCT01519791	Certolizumab	649	24	44.8	46.4	8.8	4.07	2.6	22.92	7.56	2.94
NCT00264537	Golimumab	422	24	38.6	39.3	22	6.82	4.48	34.66	10.86	3.76
NCT00264550	Golimumab	282	24	34.8	40.1	25.2	6.56	4.12	34.8	11.08	3.78
NCT00299546	Golimumab	223	24	21.5	43.9	34.5	8.82	5.91	41.32	12.38	4.25
NCT00361335	Golimumab	449	24	16.9	40.8	42.3	8.85	6.19	43.67	16.04	4.49
NCT00973479	Golimumab	362	24	39.5	47.8	12.7	4.72	2.73	36.27	10.46	3.54
NCT01248780	Golimumab	112	24	31.3	40.2	28.6	4.9	2.41	46.27	11.07	3.6
NCT00269867	Infliximab	225	30	31.1	47.6	21.3	7.15	7.08	33.88	11.93	4.03
NCT00236028	Infliximab	617	30	43.8	43.8	12.5	5.51	4.6	27.29	7.81	3.53

TJC28 =Tender joint count, SJC28: Swollen joint count; PGA: Patient Global assessment.

Supplemental table 7: Final EULAR response and disease activity in Placebo groups

Studies	Arm	Patients analyzed	Week of assessment	Good response (%)	Intermediate response (%)	Non response (%)	Final TJC28	Final SJC28	Final PGA	Final CRP (mg/l)	Final DAS28CRP
NCT00647491	Placebo	77	24	7.8	31.2	61	10.56	10.1	52.31	42.62	5.4
NCT00420927	Placebo	424	26	30.4	47.9	21.7	7.1	5.26	33.41	11.1	3.94
NCT00195663	Placebo	203	24	28.1	57.6	14.3	6.19	6.14	23.74	14.43	3.86
NCT00195702	Placebo	147	24	12.2	57.1	30.6	7.93	8.65	36.73	14.7	4.54
NCT00234845	Placebo	41	24	48.8	39	12.2	3.9	2.54	17.44	7.32	3.02
NCT00235859	Placebo	59	24	15.3	50.8	33.9	7.02	5.17	45.14	13.88	4.27
NCT00647920	Placebo	11	12	9.1	27.3	63.6	11.91	10.36	64.91	21.55	5.31
NCT00538902	Placebo	55	12	23.6	30.9	45.5	10.51	4.98	45.24	16.25	4.5
NCT00647270	Placebo	40	24	17.5	42.5	40	9.9	8.82	39.17	15.45	4.61
DE31	Placebo	286	24	17.1	34.6	48.3	9.14	9.74	41.13	12.45	4.62
NCT00870467	Placebo	120	26	36.7	29.2	34.2	1.96	1.35	14.93	9.84	2.49
PMID 22739990	Placebo	61	24	47.5	41	11.5					
PMID9920948	Placebo	21	24	4.8	61.9	33.3	7.86	8.95	42.86	20.48	4.72
NCT01313208	Placebo	97	24	19.6	29.9	50.5				8.88	
NCT00445770	Placebo	137	24	29.2	51.1	19.7	3.82	3.73	29.99	9.51	3.37
NCT00160602	Placebo	17	24	11.8	76.5	11.8	9.82	9.76	35.59	27.18	4.66
NCT00152386	Placebo	42	24	14.3	71.4	14.3	6.66	6.28	32.57	16.45	4.08
NCT00717236	Placebo	182	12	4.9	44.5	50.5	9.91	7.53	49.74	18.57	4.82
NCT00548834	Placebo	28	24	7.1	53.6	39.3	7.32	5.68	26.07	10.42	3.98
NCT00674362	Placebo	67	24	16.4	20.9	62.7	5.35	3.66	34.27	11.82	3.83
NCT01519791	Placebo	211	24	33.6	52.6	13.7	5.03	3.85	26.24	9.82	3.37
NCT00264537	Placebo	144	24	30.6	34.7	34.7	7.8	4.72	37.42	13.7	4.05
NCT00264550	Placebo	114	24	21.1	43	36	7.28	4.8	39.65	11.76	4.13
NCT00299546	Placebo	112	24	13.4	36.6	50	10.03	7.26	44.79	15.57	4.7
NCT00361335	Placebo	118	24	14.4	39.8	45.8	9.58	7.19	42.6	11.63	4.52
NCT00973479	Placebo	184	24	18.5	44.6	37	6.53	3.96	45.01	13.53	4.18
NCT01248780	Placebo	122	24	19.7	28.7	51.6	6.35	3.7	54.09	15.7	4.19
NCT00269867	Placebo	51	30	7.8	41.2	51	9.92	11.27	45.53	28.24	5.05
NCT00236028	Placebo	230	30	32.6	48.7	18.7	7	6.17	31.41	9.41	3.95

Results are expressed as mean. TJC28 =Tender joint count, SJC28: Swollen joint count; PGA: Patient Global assessment.

Supplemental figure 1: Forest plot - EULAR Non-response between TNF inhibitors versus Placebo by BMI.

