

Biologic Therapies and Major Cardiovascular Events in Psoriasis: Updated Systematic Review and Meta-analysis

Supplementary Material

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Supplementary Table S1. Characteristics of included studies which evaluated the impacts of biologic therapies on MACE in patients with psoriasis. (IV = intravenous, SC = subcutaneous, NR = not reported)

Author (year, study acronym)	Study design	Intervention(s)	Control	Duration of randomised control stage (weeks)	Mean age	Gender		Duration of psoriasis (mean) Years (Intervention)	Duration of psoriasis (mean) Years (Control)	PASI score (mean) (Intervention)	PASI score (mean) (Control)	Sample size (intervention)	MACE (intervention)	Sample size (control)	MACE (control)
						M	F								
Gottlieb, 2003(27)	Single centre	Infliximab 5mg/kg infusion	Placebo IV infusion	10	51	NR	NR	NR	NR	NR	NR	22	0	11	0
Lebwohl, 2015 (AMAGINE-2)(34)	Multicentre study (142 sites)	Brodalumab 210mg or 140mg	Placebo SC	12	45	1258	573	19 (140mg)	18	20.5 (140mg)	20.4	1222	1	309	0
		Ustekinumab 45 mg or 90mg						19 (210mg)		20.3 (210mg)		300	1		
Lebwohl, 2015 (AMAGINE-3)(34)	Multicentre study (142 sites)	Brodalumab 210mg or 140mg	Placebo SC	12	45	1288	593	17 (140mg)	18	20.1 (140mg)	20.1	1253	2	315	0
		Ustekinumab 45 mg or 90mg						18 (210mg)		20.4 (210mg)		313	0		
								18		20.1					

Gordon, 2016 (UNCOVER-1)(24)	Multicentre study (100 sites)	Ixekizumab 160mg SC at week 0 then 80mg every 2 or 4 weeks	Placebo SC	12	46	883	41 3	19 (every 4 weeks) 20 (every 2 weeks)	20 20	20		865	0	431	0
Griffiths, 2015 (UNCOVER-2)(30)	Multicentre study (100 sites)	Etanercept SC 50mg	Placebo SC	12	45	821	39 1	19	19	19	21	358	1	168	1
		Ixekizumab 160mg SC at week 0 then 80mg every 2 or 4 weeks						19 (every 4 weeks) 18 (every 2 weeks)		20 (every 4 weeks) 19 (every 2 weeks)		686	1		
Griffiths, 2015 (UNCOVER-3)(30)	Multicentre study (100 sites)	Etanercept SC 50mg twice weekly	Placebo SC	12	46	918	42 8	18	18	21	21	382	1	193	1
		Ixekizumab 160mg SC at week 0 then 80mg every 2 or 4 weeks						18 (every 4 weeks) 18 (every two weeks)	21 (every 4 weeks) 21 (every 2 weeks)			771	1		
Blauvelt, 2015 (FEATURE)(22)	Multicentre study (32 sites)	Secukinumab 150 or 300 mg SC	Placebo SC	12	46	117	60	18 (300mg) 20.4 (150mg)	20.2	20.7 (300mg) 20.5 (150mg)	21.1	118	2	59	0

Langley, 2014 (FIXTURE)(33)	Multicentre study (231 sites)	Secukinumab 150 or 300 mg SC	Placebo SC	12	45	929	37 3	15.8 (300mg)	16.6	23.9 (300mg)	24.1	653	0	326	0
		Etanercept 50mg SC						17.3 (150mg) 16.4		23.7 (150mg) 23.2		323	0		
Langley, 2014 (ERASURE)(33)	Multicentre study (88 sites)	Secukinumab 150 or 300mg SC	Placebo SC	12	45	509	22 9	17.4 (300mg) 17.5 (150mg)	17.3	22.5 (300mg) 22.3 (150mg)	21.4	490	0	248	0
Bagel, 2017(18)	Multicentre (17 sites)	Secukinumab 300 mg SC weekly	Placebo SC	24	42	54	48	14.4	15.4	8.4	10.1	51	0	51	0
Papp, 2015(40)	Multicentre study (64 sites)	Tildrakizumab 5, 25, 100 or 200mg SC	Placebo SC	16	46	270	85	NR	NR	NR	NR	309	0	46	0
Reich, 2017 (reSURFACE 1)(47)	Multicentre study (118 sites)	Tildrakizumab 100 or 200mg SC	Placebo SC	16	47	533	23 9	NR	NR	20.7 (200mg) 20.0 (100mg)	19.3	617	1	155	0
Reich, 2017 (reSURFACE 2)(47)	Multicentre study (132 sites)	Etanercept 50mg SC	Placebo SC	16	44	779	31 1	NR	NR	20.2	20	313	0	156	0
		Tildrakizumab 100 or 200mg SC								19.8 (200mg) 20.5 (100mg)		621	0		

Warren, 2020 (IMMerge)(50)	Multicentre study	Risankizumab 150mg SC	Secukinumab 300mg SC	64	47	213	114	Risankizumab 18.6	Secukinumab 17.4	Risankizumab 19.8	Secukinumab 20.1	164	2	163	0
Reich, 2019 (ECLIPSE)(45)	Multicentre study	Guselkumab 100mg SC	Secukinumab 300mg SC	56	46	707	341	Guselkumab 18.5	Secukinumab 18.3	Guselkumab 20.0	Secukinumab 21.1	534	1	514	2
Reich, 2019 (IMMvent)(46)	Multicentre study	Risankizumab 150mg SC	Adalimumab 80mg SC	16	46	422	183	NR	NR	Risankizumab 20.0	Adalimumab 19.7	304	1	301	1
Papp, 2017(41)	Multicentre study (32 sites)	Risankizumab 18, 90 or 180mg SC	Ustekinumab 45 or 90mg SC	16	46	109	58	NR	NR	Risankizumab 19 (18mg) 19 (90mg) 20 (180mg)	Ustekinumab 20	127	2	40	0
Blauvelt, 2020 (IXORA-R)(19)	Multicentre study (124 sites)	Ixekizumab 80mg SC	Guselkumab 100mg SC	24	49	650	375	Ixekizumab 17.5	Guselkumab 16.3	Ixekizumab 19.5	Guselkumab 19.3	519	4	506	2
Papp, 2016 (AMAGINE-1)(43)	Multicentre study (73 sites)	Brodalumab 210 or 140mg SC	Placebo SC	12	46	484	155	19 (140mg) 20 (210mg)	21	20.0 (140mg) 19.4 (210mg)	19.7	419	0	220	0

Leonardi, 2012(35)	Multicentre study	Ixekizumab 10, 25, 75 or 150mg SC at week 0,2,4,8,12 and 16	Placebo SC	20	46	81	61	21 (10mg) 18 (25mg) 13 (75mg) 15 (150mg)	15	19.2 (10mg) 18.6 (25mg) 17.2 (75mg) 17.7 (150mg)	16.5	115	0	27	0
Krueger et al, 2007(32)	Multicentre study (46 global sites)	Ustekinumab 45 mg, 90 mg, 4 weekly and 45 mg or 4 weekly 90 mg	Placebo	20	45	222	98	19.1 (45mg) 17.9 (90mg) 19.8 (4x45mg) 17.3 (4x90mg)	16.9	19.0 (45mg) 18.8 (90mg) 18.9 (4x45mg) 19.0 (4x90mg)	19.9	256	3	64	0

Gordon et al, 2015 (X-PLORE)(25)	Multicentre study (31 sites in North America and 12 sites in Europe)	Guselkumab 5 mg at weeks 0 and 4 and every 12 weeks thereafter, 15 mg every 8 weeks, 50 mg at weeks 0 and 4 and every 12 weeks thereafter, 100 mg every 8 weeks, or 200 mg at weeks 0 and 4 and every 12 weeks thereafter	Placebo	16	45	207	86	18.5	18.0	20.9	21.8	208	1	42	0
		Adalimumab 80 mg at week 0 and 40 mg at week 1 and every other week thereafter						19.3		20.2		43	0		
Gottlieb et al, 2003(29)	Multicentre study	Etanercept	Placebo	24	47	70	42	23	20	17.8	19.5	57	0	55	1
Nakagawa et al, 2015(37)	Multicentre study (Japan)	Brodalumab 70 mg, 140 mg, or 210 mg of brodalumab, SC at baseline and weeks 1, 2, 4, 6, 8, and 10	Placebo	10	46	120	31	13.32 (70mg) 14.52 (140mg) 14.67 (210mg)	16.86	27.58 (70mg) 28.53 (140mg) 27.98 (210mg)	23.97	113	1	38	0

Gordon et al, 2006(26)	Multicentre study (18 sites in Canada and U.S.A)	Adalimumab 40 mg every other week or 40 mg/weekly	Placebo	12	44	99	48	21 (40mg every other week) 18 (40mg weekly)	19	16.7 (40mg every other week) 14.5 (40mg weekly)	16	95	2	52	0
Cai et al, 2016(23)	Multicentre study	Adalimumab 40 mg every-other-week (following a single 80 mg dose)	Placebo	12	43	312	113	14.8	15.8	28.2	25.6	338	2	87	0
Gottlieb et al, 2011(28)	Multicentre study (33 sites in U.S.A)	Briakinumab 200 mg at weeks 0 and 4 followed by 100 mg briakinumab at week 8	Placebo	12	43	234	113	16.1	19.1	18.4	18.5	138	0	63	0
		Etanercept 50 mg of twice weekly 3–4 days apart at weeks 0–11						17.0		19.4		141	0		

Blauvelt et al, 2020(20)	Multicentre study (60 sites in 9 countries [Australia, Belgium, Canada, Czech Republic, France, Germany, Japan, South Korea and U.S.A])	Risankizumab 150 mg SC at week 0 and 4	Placebo	4	49	356	151	NR	NR	17.2	18.9	407	0	100	1
Blauvelt et al, 2017 (VOYAGE 1)(21)	Multicentre study (101 global sites)	Guselkumab 100 mg week 0 and 4 then every 8 weeks	Placebo	16	44	608	229	17.9	17.6	22.1	20.4	329	1	174	0
		Adalimumab 80 mg week 0 then 40 mg week 1 then 40 mg every 2 weeks through week 47													
Ohtsuki et al, 2019(38)	Multicentre study (Japan)	Risankizumab 75 mg or 150mg SC at week 0,4 and 16	Placebo	16	52	143	28	NR	NR	26.9 (75mg) 26.3 (150mg)	24.0	113	1	58	0

Papp et al, 2013 (42)	Multicentre study (19 sites in 6 countries [Canada, Estonia, Iceland, Japan, Latvia and U.S.A)	Secukinumab 1 x 25 mg, 3 x 25 mg, 3x 75mg or 3x 150mg at week 0,4 and 8	Placebo	12	46	91	34	19.8 (1 x 25mg) 17.7 (3 x 25mg) 17.1 (3x 75mg) 16.2 (3 x150mg)	21.4	21.6 (1 x 25mg) 20.5 (3 x 25mg) 19.7 (3x 75mg) 21.3 (3 x150mg)	21.7	103	0	22	2
Tsai et al, 2011 (PEARL)(49)	Multicentre study (13 sites in Korea and Taiwan)	Ustekinumab 45 mg SC at week 0 and 4	Placebo	12	41	103	18	11.9	13.9	25.2	22.9	61	0	60	0
Zhu et al, 2013 (LOTUS)(51)	Multicentre study (14 sites in China)	Ustekinumab 45 mg SC at week 0 and 4	Placebo	12	40	248	74	14.6	14.2	23.2	22.7	160	0	162	0
Igarashi et al, 2012(31)	Multicentre study (35 sites in Japan)	Ustekinumab 45mg or 90mg at week 0, 4 and every 12 weeks	Placebo	12	47	126	31	15.8 (45mg) 17.3 (90mg)	16.0	30.1 (45mg) 28.7 (90mg)	30.3	126	0	32	0
Leonardi et al, 2008 (PHOENIX 1)(36)	Multicentre study (48 sites in U.S.A, Canada and Belgium)	Ustekinumab 45 mg or 90 mg SC at week 0 and 4 then every 12 weeks	Placebo	12	45	531	235	19.7 (45mg) 19.6 (90mg)	20.4	20.5 (45mg) 19.7 (90mg)	20.4	511	1	255	0

Strober et al, 2011(48)	Multicentre study (41 sites in U.S.A)	Briakinumab 200 mg at week 0-4 and followed by 100mg SC at week 8	Placebo	12	45	224	126	16.3	15.5	19.4	18.3	139	0	72	0
		Etanercept 50 mg SC twice weekly						15.2		18.5		139	0		
Paul et al, 2014 (JUNCTURE)(44)	Multicentre study (38 sites worldwide)	Secukinumab 300 mg or 150 mg SC once weekly to week 4 then every 4 weeks	Placebo	12	45	125	57	21.0 (300mg) 20.6 (150mg)	19.86	18.9 (300mg) 22.0 (150mg)	19.4	121	0	61	0
Ohtsuki et al, 2018(39)	Multicentre study (35sites in Japan)	Guselkumab 50 mg or 100 mg SC at week 0, 4 and every 8 weeks	Placebo SC	16	49	145	47	15.25 (50mg) 14.39 (100mg)	13.66	25.60 (50mg) 26.73 (100mg)	25.92	128	0	64	0
Papp et al. (2018) (BE ABLE 1) (53)	Multicentre study (6 countries)	Bimekizumab 64 mg, 160 mg, 160 mg with 320 mg baseline loading dose at, 320 mg or 480 mg SC every 4 weeks	Placebo SC	12	44	163	87	15 (64 mg) 15.9 (160 mg) 14.5 (160 mg with 320 mg loading dose) 15.9 (320 mg) 13.9 (480 mg)	15.0	18.6 (64 mg) 20.6 (160 mg) 18.9 (160 mg with 320 mg loading dose) 19.4 (320 mg) 18.4 (480 mg)	18.9	208	0	42	0

Gordon et al. (2021) (BE READY) (52)	Multicentre study (77 sites in 9 countries)	Bimekizumab 320mg SC every 4 weeks	Placebo	16	44	313	122	19.6	19.1	20.4	20.1	349	0	86	0
Warren et al. (2021) (BE SURE) (56)	Multicentre study (77 sites in 9 countries)	Bimekizumab 320mg SC every 4 weeks, or 320mg every 4 weeks for 16 weeks then every 8 weeks	Adalimumab 80mg SC, then 40mg 1 week later, then 40mg every 2 weeks	56	45	328	150	20.4 (320 mg every 4 weeks) 17.3 (320 mg every 4 weeks then every 8 weeks)	16.2	20.5 (320 mg every 4 weeks) 19.9 (320 mg every 4 weeks then every 8 weeks)	19.0	319	0	159	0
Reich et al (2021) (BE VIVID) (54)	Multicentre study (105 sites in 11 countries)	Bimekizumab 320 mg SC every 4 weeks	Placebo SC	16	46	406	161	16.0 (Bimekizumab) 17.8 (Ustekinumab)	19.7	22.0 (Bimekizumab) 21.3 (Ustekinumab)	20.1	321 (Bimekizumab) 163 (Ustekinumab)	1 (Bimekizumab)	83	0
		Ustekinumab 45 or 90 mg (weight based) at weeks 0 and 4, then every 12 weeks													
Reich et al. (2021) (BE RADIANT) (55)	Multicentre study (77 sites in 11 countries)	Bimekizumab 320 mg SC every 4 weeks	Secukinumab 300 mg weekly for 4 doses, then every 4 weeks	48	45	486	257	18.4	17.2	20.2	19.7	373	0	370	2

Supplementary Table S2. Summary of findings and with certainty of evidence assessment (GRADE)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biologics	Placebo	Relative (95% CI)	Absolute (95% CI)		
Composite endpoints of MACE (follow-up: range 4 weeks to 64 weeks)												
38	randomised trials	not serious	not serious ^a	not serious	serious ^b	none	21/11471 (0.2%)	6/4387 (0.1%)	OR 1.26 (0.53 to 3.01)	1 more per 1,000 (from 1 fewer to 3 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; OR: odds ratio

- a. Low Heterogeneity < 40%
- b. There was a short period of placebo-controlled phase with the biologics reducing the chance of detecting a potential difference in the rare outcome of MACE which could have been significant

Supplementary Table S3. Search strategy

1 exp Psoriasis/
2 psoriasis\$.ti,ab.
3 psoriatic\$.ti,ab.
4 1 or 2 or 3
5 exp Biological Products/
6 biologic\$ product\$.ti,ab.
7 exp Biological Therapy/
8 biologic\$ therap\$.ti,ab.
9 biologic\$ treatment\$.ti,ab.
10 biologic\$ medicine\$.ti,ab.
11 biologic\$ medication\$.ti,ab.
12 biologic\$ agent\$.ti,ab.
13 tumo?r necrosis factor inhibitor\$.ti,ab.
14 tumo?r necrosis factor alpha inhibitor\$.ti,ab.
15 TNF inhibitor\$.ti,ab.
16 TNF blocker\$.ti,ab.
17 TNFi\$.ti,ab.
18 TNF-alpha inhibitor\$.ti,ab.
19 anti-TNF treatment\$.ti,ab.
20 anti-TNF therap\$.ti,ab.
21 anti-TNF alpha therap\$.ti,ab.
22 anti-TNF alpha treatment\$.ti,ab.
23 Anti-TNF agent\$.ti,ab.
24 Anti-TNF-alpha agent\$.ti,ab.
25 adalimumab.ti,ab.
26 Humira.ti,ab.
27 etanercept.ti,ab.
28 Enbrel.ti,ab.
29 infliximab.ti,ab.
30 Remicade.ti,ab.
31 exp Antibodies, Monoclonal/
32 monoclonal antibod\$.ti,ab.
33 ustekinumab.ti,ab.
34 Stelara.ti,ab.
35 secukinumab.ti,ab.
36 Cosentyx.ti,ab.
37 ixekizumab.ti,ab.
38 Taltz.ti,ab.
39 risankizumab.ti,ab.

40 Skyrizi.ti,ab.
41 guselkumab.ti,ab.
42 Tremfya.ti,ab.
43 tildrakizumab.ti,ab.
44 Ilumya.ti,ab.
45 Ilumetri.ti,ab.
46 5 or 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 or 44 or 45
47 "randomized controlled trial".pt.
48 (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
49. (retraction of publication or retracted publication).pt.
50. or/47-49
51 (animals not humans).sh.
52. ((comment or editorial or meta-analysis or practice-guideline or review or letter or
journal correspondence) not "randomized controlled trial").pt.
53. (random sampl\$ or random digit\$ or random effect\$ or random survey or random
regression).ti,ab. not "randomized controlled trial".pt.
54. 50 not (51 or 52 or 53)
55. 4 and 46 and 54