ORIGINAL ARTICLE

Network meta-analysis of biologic treatments for psoriasis using absolute Psoriasis Area and Severity Index values ≤1, 2, 3 or 5 derived from a statistical conversion method

U. Mrowietz,[1,*] R.B. Warren,[2] C.L. Leonardi,[3] D. Saure,[4] H. Petto,[5] S. Hartz,[6] M. Dossenbach,[5] K. Reich[7]

[1]Psoriasis-Center at the Department of Dermatology, University Medical Center Schleswig-Holstein, Kiel, Germany
[2]Dermatology Centre, Salford Royal NHS Foundation Trust Hospital, Manchester NIHR Biomedical Research Centre, Manchester, UK
[3]St. Louis University School of Medicine, St. Louis, MO, USA
[4]Lilly Deutschland GmbH, Bad Homburg, Germany
[5]Eli Lilly Austria GmbH, Vienna, Austria
[6]Eli Lilly and Company Ltd, Windlesham, UK
[7]Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf and Skinflammation® Center, Hamburg, Germany
*Correspondence: U. Mrowietz. E-mail: umrowietz@dermatology.uni-kiel.de

Abstract

Background In practice, the goal of treatment for patients with psoriasis is to achieve almost clear or clear skin and maintain disease control, regardless of baseline disease severity. However, identifying absolute Psoriasis Area and Severity Index (PASI) values for new treatment goals is challenging, as most clinical trials report relative PASI 50, 75, 90 or 100 improvements but rarely absolute PASI values achieved.

Objective Our objective was to illustrate a statistical conversion method that was developed to derive absolute PASI values from available clinical trial data on relative PASI improvements. The results of network meta-analyses (NMAs) based on these derived data were then compared with those of NMAs based on the corresponding relative PASI improvement data for selected biologics for moderate-to-severe psoriasis.

Methods The PASI statistical conversion method was applied to relative PASI improvement data for 11 biologic treatment regimens and placebo at 12 weeks using data from 50 published studies. The respective proportions of patients reaching absolute PASI values ≤1, 2, 3 or 5 were then calculated. Frequentist NMAs (Rücker method) were subsequently used to compare efficacy results across relative and absolute PASI data.

Results The ranking of included treatment regimens for patients achieving absolute PASI 0 to 8 was aligned with results for relative PASI scores (from 100 to 60) at end of induction therapy. Across the range of PASI scores considered, the most effective treatment regimens based on both absolute and relative PASI NMAs were brodalumab 210 mg every 2 weeks and ixekizumab 80 mg every 2 weeks, followed by guselkumab 100 mg every 8 weeks and risankizumab 150 mg every 12 weeks.

Conclusion Data generated using this mathematical model will be useful to inform ongoing scientific discussions on treatment goals in the absence of primary absolute PASI data for all available treatments for moderate-to-severe plaque psoriasis.

Received: 22 March 2018; Accepted: 14 January 2021

Conflict of interest

UM has been an advisor and/or received speaker's honoraria and/or received grants and/or participated in clinical trials of the following companies: AbbVie, Almirall, Amgen, Aristea, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Dr. Reddy's, Eli Lilly, Foamix, Formycon, Forward Pharma, Janssen, LEO Pharma, Medac, Novartis, Phi-Stone, Pierre Fabre, Sanofi-Aventis, UCB. RBW has received consulting fees from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Sanofi, Xenoport & UCB; and has received research grants from AbbVie, Almirall, Amgen, Celgene, Janssen, Lilly, LEO Pharma, Novartis, Pfizer & UCB. CLL has received funding from AbbVie, Actavis, Amgen, Celgene, Coherus, Dermira, Eli Lilly, Galderma, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Sandoz, Stiefel, UCB, and Wyeth. DS, HP, SH and MD are all full-time employees of Eli Lilly and Company. KR has served as an advisor and/or paid speaker for and/or participated in clinical trials sponsored by: AbbVie, Affibody, Almirall, Amgen,

Biogen-Idec, Boehringer Ingelheim Pharma, Bristol-Myers Squibb, Celgene, Covagen, Eli Lilly, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Medac, Merck Sharp & Dohme Corp., Miltenyi, Novartis, Ocean Pharma, Pfizer, Samsung Bioepis, Sandoz, Sun Pharma, Takeda, UCB Pharma, Valeant, XBiotech and Xenoport.

Funding sources

The study was funded by Eli Lilly and Company.

Introduction

Psoriasis is a chronic, often life-long inflammatory skin disease without a cure. The disease burden is high, particularly in moderate-to-severe psoriasis, and the associated quality of life impairment is considerable.

During treatment for psoriasis, the success of therapy should be regularly assessed. In practice, the goal of treatment for patients with psoriasis is not only to achieve almost clear or clear skin but also to ensure maintenance of disease control. Therefore, treatment goals should enable physicians to assess primary non-response after induction of a new treatment and secondary non-response during maintenance therapy thereafter. In 2011, a European consensus defined maintenance therapy as successful when a ≥75% reduction from baseline Psoriasis Area and Severity Index (PASI 75) is achieved and a failure when a ≥50% reduction from baseline PASI (PASI 50) is not achieved. In patients with a PASI 50 but not PASI 75, the Dermatology Life Quality Index (DLQI) should be used as a treatment decision-making tool.[1] More recently, improvement of 90% or better with respect to baseline PASI (PASI90) is considered as treatment success by the European Medicines Agency[2] and the latest guidelines are shifting away from percentage reduction and towards a target outcome.[3] Any relative (percentage) improvement measure will relate to a baseline value. For different baseline severities, the same relative improvement may therefore indicate very different outcomes. Defining appropriate targets for absolute PASI values emphasizes the goals of clear or almost clear skin and disease control, regardless of baseline disease severity. However, identifying absolute PASI values for new treatment goals is hampered by the fact that most clinical trial data report relative PASI 50, 75, 90 or 100 (100% reduction from baseline PASI) improvements but rarely absolute PASI values achieved.

Since publication of the European consensus,[1] there has been major progress in drug development, leading to the registration of new biologic agents.[4] Clear or almost clear skin (PASI 100 or absolute PASI 0) can now be achieved by many patients,[5–11] prompting ongoing discussion as to whether treatment goals should be adapted based on these new efficacy levels.

The objective of this analysis was to illustrate a statistical conversion method that was developed to derive absolute PASI values from available clinical trial data on relative PASI improvements. The results of network meta-analyses (NMAs) based on these derived absolute PASI data were then compared with the results of NMAs based on the corresponding relative PASI improvement data for selected biologic treatments for moderate-to-severe psoriasis. Should the results of these NMAs be aligned, our analysis will demonstrate the value of this mathematical model in filling an important data gap to inform evolving treatment goals.

Methods

Systematic literature review

A systematic literature review (SLR), conducted to evaluate systemic treatments for moderate-to-severe plaque psoriasis, provided data for the statistical conversion method. The literature review consisted of an original SLR and three updates that analysed data from January 1990 to October 2018, inclusive. Clinical efficacy data on systemic treatments for psoriasis were systematically identified through searches of databases (including Embase, Medline, Medline Daily Update, Medline In-Process and Cochrane databases), and grey literature [including selected conference proceedings, trial registries and Health Technology Assessment (HTA) websites]. Further detail on the methodology used in the original and updated SLRs is provided in Appendix S1.

Suitable studies for extraction of PASI data for the statistical model, i.e., Phase 2 or 3, comparator-controlled trials of biologic treatments for moderate-to-severe psoriasis with double-blind induction phases, were selected from the SLR. All systemic biologics licensed for the treatment of chronic plaque psoriasis available globally at the time of the SLR were included: pivotal studies of risankizumab were also included. A single-dose regimen was selected for each biologic based on the registered product label for each treatment. Studies, treatments and doses included in this analysis were selected to illustrate the statistical conversion method, not to undertake an NMA in line with HTA guidance aimed at determining the comparative efficacy of included therapies.

Extracted data for each study treatment group included sample size, the time at which the efficacy of induction therapy was assessed (assessment time), baseline PASI (both the minimum PASI allowed for entry into the study and the mean [standard

Table 1 Studies and data selected for analysis. Data presented in bold type are imputed

Study	Treatment regimen	Sample size	Assessment time (week)	Baseline PASI cut-off	Mean (SD) baseline PASI	PASI 50	PASI 75	PASI 90	PASI 100
AMAGINE-1 Papp et al. 2016[12]	Brodalumab 210 mg week 0, 1, 2, Q2W	222	12	12	19.4 (6.6)	**90.30**	83.3	70.3	41.9
	Placebo	220	12	12	19.7 (7.7)	**17.24**	2.7	0.9	0.5
AMAGINE-2 Lebwohl *et al.* 2015[22]	Brodalumab 210 mg week 0, 1, 2, Q2W	612	12	12	20.3 (8.3)	**93.66**	86.0	70.0	44.0
	Placebo	309	12	12	20.4 (8.2)	**23.43**	8.0	3.0	1.0
	Ustekinumab 45 mg ≤ 100 kg/ 90 mg > 100 kg† weeks 0 and 4	300	12	12	20.0 (8.4)	**84.99**	70.0	47.0	22.0
AMAGINE-3 Lebwohl *et al.* 2015[22]	Brodalumab 210 mg week 0, 1, 2, Q2W	624	12	12	20.4 (8.3)	**92.31**	85.0	69.0	37.0
	Placebo	315	12	12	20.1 (8.7)	**20.27**	6.0	2.0	0.3
	Ustekinumab 45 mg ≤ 100 kg/ 90 mg > 100 kg† weeks 0 and 4	313	12	12	20.1 (8.4)	**85.17**	69.0	48.0	19.0
Bachelez *et al.* 2015[23]	Etanercept 50 mg BIW	335	12	12	**19.4 (7.9)**	80.3	58.8	32.2	**15.73**
	Placebo	107	12	12	**19.5 (7.5)**	20.6	5.6	0.9	**0.44**
Bagel *et al.* 2012[24]	Etanercept 50 mg BIW	62	12	10	**19.5 (7.3)**	85.0	59.0	25.0	**10.50**
	Placebo	62	12	10	**20.1 (7.8)**	7.0	5.0	2.0	**0.06**
Cai *et al.* 2017[25]	Adalimumab 80 mg then 40 mg Q2W	338	12	10	28.2 (12.0)	**92.59**	77.8	55.6	13.3
	Placebo	87	12	10	25.6 (11.0)	**28.93**	11.5	3.4	1.1
CHAMPION Saurat *et al.* 2008[26]	Adalimumab 80 mg then 40 mg Q2W	108	12	10	20.2 (7.5)	90.7	76.9	48.1	11.1
	Placebo	53	12	10	19.2 (6.9)	26.4	15.1	7.5	0.0
CIMPACT Lebwohl *et al.* 2018[27]	Certolizumab pegol 400 mg week 0, 2, 4, Q2W	167	12	12	20.8 (7.7)	**87.78**	66.7	34.0	**12.77**
	Etanercept 50 mg BIW	170	12	12	21.0 (8.2)	**75.36**	53.3	27.1	**8.91**
	Placebo	57	12	12	19.1 (7.1)	**12.59**	5.0	0.2	**0.01**
Chaudhari *et al.* 2001[15]	Infliximab 5 mg/kg week 0, 2, 6, Q8W	11	10	**12**	22.1 (11.5)	**90.46**	82.0	**59.72**	**31.89**
	Placebo	11	10	**12**	20.3 (5.5)	**34.74**	18.0	**6.70**	**0.37**
CIMPASI-1 Gottlieb *et al.* 2018a[28]	Certolizumab pegol 400 mg week 0, 2, 4, Q2W	88	16	12	19.6 (7.9)	**90.40**	75.8	43.6	**18.51**
	Placebo	51	16	12	19.8 (7.5)	**17.78**	6.5	0.4	**0.24**
CIMPASI-2 Gottlieb *et al.* 2018b[28]	Certolizumab pegol 400 mg week 0, 2, 4,Q2W	87	16	12	19.5 (6.7)	**91.41**	82.6	55.4	**24.21**
	Placebo	49	16	12	17.3 (5.3)	**33.54**	11.6	4.5	**0.36**
CLARITY Bagel *et al.* 2018[29]	Secukinumab 300 mg week 0, 1, 2, 3, 4, QM	550	12	12	**20.7 (8.1)**	**96.92**	88.0	66.5	38.1
	Ustekinumab 45 mg ≤ 100 kg/ 90 mg > 100 kg† weeks 0 and 4	552	12	12	**20.8 (8.0)**	**90.16**	74.2	47.9	20.1
CLEAR Thaci *et al.* 2015[30]	Secukinumab 300 mg week 0, 1, 2, 3, 4, QM	337	12	12	21.7 (8.5)	**96.89**	91.0	72.8	38.9
	Ustekinumab 45 mg ≤ 100 kg/ 90 mg > 100 kg† weeks 0 and 4	339	12	**12**	21.5 (8.1)	**88.10**	79.1	53.4	25.7

Table 1 *Continued*

Study	Treatment regimen	Sample size	Assessment time (week)	Baseline PASI cut-off	Mean (SD) baseline PASI	PASI 50	PASI 75	PASI 90	PASI 100
de Vries *et al.* 2017[17]	Etanercept 50 mg BIW	23	12	10	15.9 (5.1)	60.9	21.7	0.0	0.0
	Infliximab 5 mg/kg week 0, 2, 6, Q8W	25	12	10	17.8 (9.7)	96.0	76.0	20.0	4.0
ERASURE	Placebo	248	12	12	21.4 (9.1)	**18.70**	4.5	1.2	0.8
Langley *et al.* 2014[31]	Secukinumab 300 mg week 0, 1, 2, 3, 4, QM	245	12	12	22.5 (9.2)	**91.39**	81.6	59.2	28.6
EXPRESS	Infliximab 5 mg/kg week 0, 2, 6, Q8W	301	10	**12**	22.9 (9.3)	91.0	80.0	57.0	**27.63**
Reich *et al.* 2005[32]	Placebo	77	10	**12**	22.8 (8.7)	8.0	3.0	1.0	**0.07**
EXPRESS II	Infliximab 5 mg/kg week 0, 2, 6, Q8W	314	10	12	20.4 (7.5)	**90.24**	75.5	45.2	**18.80**
Menter *et al.* 2007[33]	Placebo	208	10	12	19.8 (7.7)	**11.40**	1.9	0.5	**0.04**
FEATURE	Placebo	59	12	12	21.1 (8.5)	**9.47**	0.0	0.0	0.0
Blauvelt *et al.* 2015[34]	Secukinumab 300 mg week 0, 1, 2, 3, 4, QM	59	12	12	20.7 (8.0)	**90.12**	75.9	60.3	43.1
FIXTURE	Etanercept 50 mg BIW	326	12	12	23.2 (9.8)	**65.89**	44.0	20.7	4.3
Langley *et al.* 2014[31]	Placebo	326	12	12	24.1 (10.5)	**14.25**	4.9	1.5	0.0
	Secukinumab 300 mg week 0, 1, 2, 3, 4, QM	327	12	12	23.9 (9.9)	**89.06**	77.1	54.2	24.1
IXORA-S	Ixekizumab 160 mg then 80 mg Q2W	136	12	10	19.9 (8.2)	**96.10**	88.2	72.8	36.0
Paul *et al.* 2019[35]	Ustekinumab 45 mg ≤ 100 kg/ 90 mg > 100 kg† weeks 0 and 4	166	12	10	19.8 (9.0)	**86.20**	68.7	42.2	14.5
JUNCTURE	Placebo	61	12	12	19.4 (6.7)	**11.29**	3.3	0.0	0.0
Paul *et al.* 2015[36]	Secukinumab 300 mg week 0, 1, 2, 3, 4, QM	60	12	12	18.9 (6.4)	**96.06**	86.7	55.0	26.7
Leonardi *et al.* 2003[37]	Etanercept 50 mg BIW	164	12	10	18.4 (9.0)	74.0	49.0	22.0	**4.84**
	Placebo	166	12	10	18.3 (7.7)	14.0	4.0	1.0	**0.06**
M02-528	Adalimumab 80 mg then 40 mg Q2W	45	12	**12**	16.7 (7.1)	76.0	53.0	24.0	11.0
Gordon *et al.* 2006[38]	Placebo	52	12	**12**	16.0 (7.5)	**15.24**	4.0	**0.63**	0.0
M04-688	Adalimumab 80 mg then 40 mg Q2W	43	12	12	30.2 (10.9)	**75.48**	53.5	30.2	**11.85**
Asahina *et al.* 2010[39]	Placebo	46	12	12	29.1 (11.8)	**12.33**	2.2	0.0	**0.00**
M10-114	Etanercept 50 mg BIW	141	12	12	19.4 (8.0)	**80.62**	56.0	**32.64**	**15.29**
Gottlieb *et al.* 2011[40]	Placebo	68	12	12	18.5 (6.9)	**22.46**	7.4	**2.45**	**0.78**
M10-315	Etanercept 50 mg BIW	139	12	12	18.5 (6.0)	**66.27**	39.6	13.7	5.8
Strober *et al.* 2011[41]	Placebo	72	12	12	18.3 (6.4)	**19.53**	6.9	4.2	0.0
Nakagawa *et al.* 2015[42]	Brodalumab 210 mg week 0, 1, 2, Q2W	37	12	12	28.0 (14.3)	**95.72**	94.6	91.9	59.5
	Placebo	38	12	12	24.0 (8.9)	**19.05**	7.9	2.6	0.0
Ohtsuki *et al.* 2018[43]	Guselkumab 100 mg week 0, 4, Q8W	63	16	12	26.7 (12.2)	95.2	84.1	69.8	27.0
	Placebo	64	16	12	25.9 (12.3)	14.1	6.3	0.0	0.0
ORION	Guselkumab 100 mg week 0, 4, Q8W	62	12	12	**20.8 (7.8)**	90.3	77.4	54.8	30.6
Ferris *et al.* 2018[44]	Placebo	16	12	12	**23.6 (10.9)**	12.5	0.0	0.0	0.0
Papp *et al.* 2005[45]	Etanercept 50 mg BIW	194	12	10	19.5 (8.8)	77.0	49.0	21.0	5.05
	Placebo	193	12	10	18.6 (8.6)	9.0	3.0	1.0	0.07

Table 1 *Continued*

Study	Treatment regimen	Sample size	Assessment time (week)	Baseline PASI cut-off	Mean (SD) baseline PASI	PASI 50	PASI 75	PASI 90	PASI 100
Papp *et al.* 2012[46]	Brodalumab 210 mg week 0, 1, 2, Q2W	40	12	12	20.6 (7.8)	90.0	82.0	75.0	62.0
	Placebo	38	12	12	18.9 (5.9)	16.0	0.0	0.0	0.0
Papp *et al.* 2015[47]	Placebo	46	12	12	**19.5 (7.8)**	**17.67**	4.0	**1.66**	**0.50**
	Tildrakizumab 100 mg week 0, 4, Q12W	89	12	12	**19.8 (7.6)**	**81.95**	61	**35.21**	**15.04**
Reich *et al.* 2012[48]	Certolizumab pegol 400 mg week 0, 2, 4, Q2W	58	12	12	22.0 (8.1)	93.0	82.8	46.6	**18.69**
	Placebo	59	12	12	22.6 (8.8)	12.0	6.8	1.7	**0.06**
reSURFACE 1 Reich *et al.* 2017b[49]	Placebo	155	12	12	19.3 (7.1)	**21.69**	5.8	2.6	1.3
	Tildrakizumab 100 mg week 0, 4, Q12W	309	12	12	20.0 (7.9)	**85.52**	63.8	34.6	13.9
reSURFACE2 Reich *et al.* 2017b[49]	Etanercept 50 mg BIW	313	12	12	20.2 (7.4)	**74.95**	48.2	21.4	4.8
	Placebo	156	12	12	20.0 (7.6)	**21.43**	5.8	1.3	0.0
	Tildrakizumab 100 mg week 0, 4, Q12W	307	12	12	20.5 (7.6)	**80.78**	61.2	38.8	12.4
REVEAL Menter *et al.* 2008[16]	Adalimumab 80 mg then 40 mg Q2W	814	12	12	19.0 (7.1)	**86.22**	68.0	37.0	14.0
	Placebo	398	12	12	18.8 (7.1)	**8.75**	5.0	2.0	**0.06**
SPIRIT Gottlieb *et al.* 2004[50]	Infliximab 5 mg/kg week 0, 2, 6, Q8W	99	10	12	**20.0 (7.8)**	97.0	87.9	57.6	**25.54**
	Placebo	51	10	12	**18.0 (7.4)**	21.6	5.9	2.0	**1.39**
Torii *et al.* 2010[18]	Infliximab 5 mg/kg week 0, 2, 6, Q8W	35	10	12	31.9 (12.8)	**85.17**	68.6	**39.77**	**14.28**
	Placebo	19	10	12	33.1 (15.6)	**17.56**	0.0	0.0	**0.00**
Tyring *et al.* 2006[51]	Etanercept 50 mg BIW	311	12	10	18.3 (7.6)	74.0	47.0	21.0	**4.88**
	Placebo	307	12	10	18.1 (7.4)	14.0	5.0	1.0	**0.05**
UltIMMA-1 Gordon *et al.* 2018[11]	Placebo	102	12	12	20.5 (6.7)	**22.90**	9.8	3.0	**0.59**
	Risankizumab 150 mg week 0, 4, Q12W	304	12	12	20.6 (7.7)	**95.70**	86.8	68.0	**32.02**
	Ustekinumab 45 mg ≤ 100 kg/ 90 mg > 100 kg† weeks 0 and 4	100	12	12	20.1 (6.8)	**84.34**	70.0	45.0	**21.12**
UltIMMA-2 Gordon *et al.* 2018[11]	Placebo	98	12	12	18.9 (7.3)	**23.36**	8.2	3.0	**0.80**
	Risankizumab 150 mg week 0, 4, Q12W	294	12	12	20.5 (7.8)	**96.42**	88.8	62.0	**30.90**
	Ustekinumab 45 mg ≤ 100 kg/ 90 mg > 100 kg† weeks 0 and 4	99	12	12	18.2 (5.9)	**85.25**	69.7	47.0	**18.81**
UNCOVER-1 Gordon *et al.* 2016[5]	Ixekizumab 160 mg then 80 mg Q2W	433	12	12	20.0 (8.0)	**96.06**	89.1	70.9	35.3
	Placebo	431	12	12	20.0 (9.0)	**12.40**	3.9	0.5	0.0
UNCOVER-2 Griffiths *et al.* 2015[6]	Etanercept 50 mg BIW	358	12	12	19.0 (7.0)	**64.94**	41.6	18.7	5.3
	Ixekizumab 160 mg then 80 mg Q2W	351	12	12	19.0 (7.0)	**96.68**	89.7	70.7	40.5
	Placebo	168	12	12	21.0 (8.0)	**17.81**	2.4	0.6	0.6
UNCOVER-3 Griffiths *et al.* 2015[6]	Etanercept 50 mg BIW	382	12	12	21.0 (8.0)	**77.16**	53.4	25.7	7.3
	Ixekizumab 160 mg then 80 mg Q2W	385	12	12	21.0 (8.0)	**96.80**	87.3	68.1	37.7
	Placebo	193	12	12	21.0 (8.0)	**18.40**	7.3	3.1	0.0

Table 1 *Continued*

Study	Treatment regimen	Sample size	Assessment time (week)	Baseline PASI cut-off	Mean (SD) baseline PASI	PASI 50	PASI 75	PASI 90	PASI 100
VIP Mehta *et al*. 2018[52]	Adalimumab 80 mg then 40 mg Q2W	33	12	12	19.0 (6.0)	**72.81**	47.0	**20.09**	**4.60**
	Placebo	31	12	12	18.0 (8.0)	**22.50**	7.0	**2.49**	**0.86**
VIP-U Gelfand *et al*. 2018[53]	Placebo	**175**	12	12	**20.3 (7.9)**	**23.65**	11.0	**3.35**	**0.69**
	Ustekinumab 45 mg ≤ 100 kg/ 90 mg > 100 kg† weeks 0 and 4	**271**	12	12	**20.9 (8.0)**	**90.07**	77.0	**50.10**	**17.82**
VOYAGE 1 Blauvelt *et al*. 2017[9]	Adalimumab 80 mg then 40 mg Q2W	334	16	12	22.4 (9.0)	**90.14**	73.1	49.7	17.1
	Guselkumab 100 mg week 0, 4, Q8W	329	16	12	22.1 (9.5)	**97.41**	91.2	73.3	37.4
	Placebo	174	16	12	20.4 (8.7)	**21.39**	5.7	2.9	0.6
VOYAGE 2 Reich *et al*. 2017a[10]	Adalimumab 80 mg then 40 mg Q2W	248	16	12	21.7 (9.0)	**85.20**	68.5	46.8	20.6
	Guselkumab 100 mg week 0, 4, Q8W	496	16	12	21.9 (8.8)	**94.99**	86.3	70.0	34.1
	Placebo	248	16	12	21.5 (8.0)	**22.62**	8.1	2.4	0.8
X-PLORE Gordon *et al*. 2015[54]	Adalimumab 80 mg then 40 mg Q2W	43	12	12	20.2 (7.6)	**85.24**	67.5	**39.84**	**13.69**
	Guselkumab 100 mg week 0, 4, Q8W	42	12	12	20.4 (7.7)	**90.34**	75.0	**47.37**	**19.47**
	Placebo	42	12	12	21.8 (10.0)	**17.53**	0.0	**0.00**	**0.00**
Yang *et al*. 2012[55]	Infliximab 5 mg/kg week 0, 2, 6, Q8W	84	12	**12**	23.9 (10.7)	**96.36**	87.3	**65.03**	**30.65**
	Placebo	45	12	**12**	25.3 (12.7)	50.76	20.9	**4.93**	**0.31**

Missing values imputed using the random forest algorithm (see Appendix S2) are highlighted in bold.
BIW, twice weekly; PASI 50/75/90/100, the percentage of patients achieving PASI improvement of ≥50%/75%/90%/100%; PASI, Psoriasis Area and Severity Index; Q12W, every 12 weeks; Q2W, every 2 weeks; Q8W, every 8 weeks; QM, every month.
†The dose of ustekinumab was based on patients' body weight: 45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg.

deviation (SD)] baseline PASI) and any relative PASI findings at the assessment time (PASI 50, PASI 75, PASI 90 and PASI 100, as reported).

When available, 12-week data were selected because this was the most common primary assessment time-point. For treatments with different induction periods (adalimumab, certolizumab pegol and guselkumab, 16 weeks; infliximab, 10 weeks), data for these assessment times were used and were analysed as per the available 12-week data.

The current version of the PASI conversion method[12] needed complete sets of baseline PASI values and response rates for all four PASI thresholds (PASI 50, 75, 90 and 100) at the assessment time for all study treatments. Therefore, where required data could not be extracted from the literature, missing values [baseline PASI cut-offs (inclusion criteria), mean (SD) baseline PASI values, and PASI 50, PASI 75, PASI 90 and PASI 100 response rates at the assessment time-point] were imputed using a random forest algorithm[13] trained on all non-missing values from the complete SLR (see Appendix S2 for details). Study treatments and data included in this analysis are summarized in Table 1.

Statistical conversion method

The PASI statistical conversion method used in this analysis has been described in detail elsewhere.[12] In brief, the method uses available relative PASI data to estimate the proportion of patients with absolute PASI less than or equal to a given bound. In this manuscript, the focus is on absolute PASI ≤1, 2, 3 or 5 at a given assessment time (i.e. 12 weeks). It is based on a statistical model describing the relationship between absolute mean (SD) baseline and assessment time-point PASI values (ranging from 0 to 72), baseline PASI study inclusion criteria and relative PASI improvements (PASI 50, PASI 75, PASI 90 and PASI 100) achieved at the assessment time-point. The proportion of patients reaching PASI ≤1, 2, 3 or 5 (or any other PASI cut-off point), as well as other statistics such as mean (SD) assessment time-point PASI values, can be derived based on this model. In this analysis, the PASI conversion method was applied to the full set of relative PASI results

(summarized in Table 1; missing values imputed). For all treatment regimens and studies in the network, the resulting parameter estimates were used to derive the proportion of patients achieving absolute PASI values in the range from 0 to 8 (at steps of 0.2) to show the efficacy across cut-offs. The parameter estimates from the PASI conversion method were also used to derive respective relative PASI values in the range from PASI 100 to PASI 60 (at steps of 1%) to compare the cumulative distributions for the absolute as well as the relative PASI values at the assumed assessment time-point of 12 weeks.

Network meta-analyses

Frequentist fixed-effect NMA (Rücker method[14]) was applied to each of the calculated absolute PASI values in the range from 0 to 8 (at steps of 0.2) and to each of the relative PASI values in the range from PASI 100 to PASI 60 (at steps of 1%), using placebo as reference. Placebo profiles were obtained by pooling the placebo results obtained from using the PASI conversion method on all placebo-controlled studies (weighted means). Risk difference (RD) was selected as the effect measure for this analysis, as it is generally well understood and consistent with other effect measures. The RDs of each treatment from placebo (parameter estimates from the NMAs) were added to these basic pooled placebo profiles, allowing a respective PASI profile to be obtained for each treatment. These profiles were then plotted as network diagrams and forest plots of RD from placebo for the NMA results at absolute PASI ≤1, 2, 3 and 5.

The 95% confidence intervals (CIs) for RD presented are only indicative, as variability resulting from the estimation process of the PASI conversion method was not incorporated. No formal testing of the precision of the values or the significance of the relative rankings was undertaken.

To contrast the findings of the absolute PASI NMA with the results of the relative PASI NMA, graphs are also presented for PASI 75, PASI 90 and PASI 100.

All calculations were performed in R version 3.0.1, and R package netmeta was used for performing the Rücker NMAs.

Results

Description of selected study data

Overall, data were extracted from 50 studies involving 12 treatment regimens (including placebo) identified in the SLR for inclusion in these analyses (Table 1). The dosage regimens evaluated are summarized in Table 1. Inclusion criteria for most studies specified a baseline PASI cut-off value (lowest PASI allowed at study entry) of 12, although eight studies specified a cut-off value of 10. For five studies that did not specify the baseline PASI cut-off, a value of 12 was assigned.

The treatment groups included from each study ranged in size from 11 to 814 patients (Table 1). The smallest study sample size was that of a placebo-controlled evaluation of infliximab[15] and the largest was in a placebo-controlled evaluation of adalimumab.[16] The observed mean baseline PASI values ranged from 15.9 (etanercept)[17] to 33.1 (placebo),[18] although most mean baseline PASI values were between 18 and 23. The greatest variability was in a study evaluating infliximab (SD of 15.6 for placebo),[18] and the lowest was in a study comparing etanercept and infliximab (SD of 5.1 for etanercept).[17] Mean baseline PASI values were not reported and were imputed in 10 instances counting individual treatment arms within studies; 14 SD values were

Table 2 PASI conversion method-estimated proportion of patients with absolute PASI ≤ 1, 2, 3 and 5 and derived relative PASI 75, 90 and 100 after approximately 12 weeks of treatment

Treatment regimen	Proportion of patients achieving absolute PASI (%)				Proportion of patients achieving relative PASI (%)		
	PASI ≤ 1	PASI ≤ 2	PASI ≤ 3	PASI ≤ 5	PASI 100	PASI 90	PASI 75
Adalimumab 80 mg then 40 mg Q2W	23.94	40.41	54.03	72.23	14.16	40.97	70.41
Brodalumab 210 mg week 0, 1, 2, Q2W	56.07	71.83	81.34	89.88	41.28	71.77	88.06
Certolizumab pegol 400 mg week 0, 2, 4, Q2W	27.44	44.78	58.00	74.43	16.69	44.15	72.74
Etanercept 50 mg BIW	10.53	21.18	32.62	51.79	6.48	21.29	49.64
Guselkumab 100 mg week 0, 4, Q8W	49.77	67.39	78.01	88.66	33.02	68.09	87.59
Infliximab 5 mg/kg week 0, 2, 6, Q8W	34.47	51.89	64.85	80.97	21.66	52.84	80.32
Ixekizumab 160 mg then 80 mg Q2W	55.10	71.85	81.93	92.39	37.94	70.37	90.62
Placebo	0.37	0.64	1.30	3.81	0.34	0.73	4.32
Risankizumab 150 mg week 0, 4, Q12W	48.37	66.12	76.47	86.02	31.05	64.99	85.12
Secukinumab 300 mg week 0, 1, 2, 3, 4, QM	41.68	57.56	69.14	83.08	29.84	58.54	82.11
Tildrakizumab 100 mg week 0, 4, Q12W	20.00	33.97	46.50	64.13	13.06	33.70	62.08
Ustekinumab 45 mg ≤ 100 kg/90 mg > 100 kg† weeks 0 and 4	26.76	42.54	55.59	72.59	17.82	42.59	70.56

BIW, twice weekly; PASI 75/90/100, the percentage of patients achieving PASI improvement of ≥75%/90%/100%; PASI, Psoriasis Area and Severity Index; Q12W, every 12 weeks; Q2W, every 2 weeks; Q8W, every 8 weeks; QM, every month.
†The dose of ustekinumab was based on patients' body weight: 45mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg.

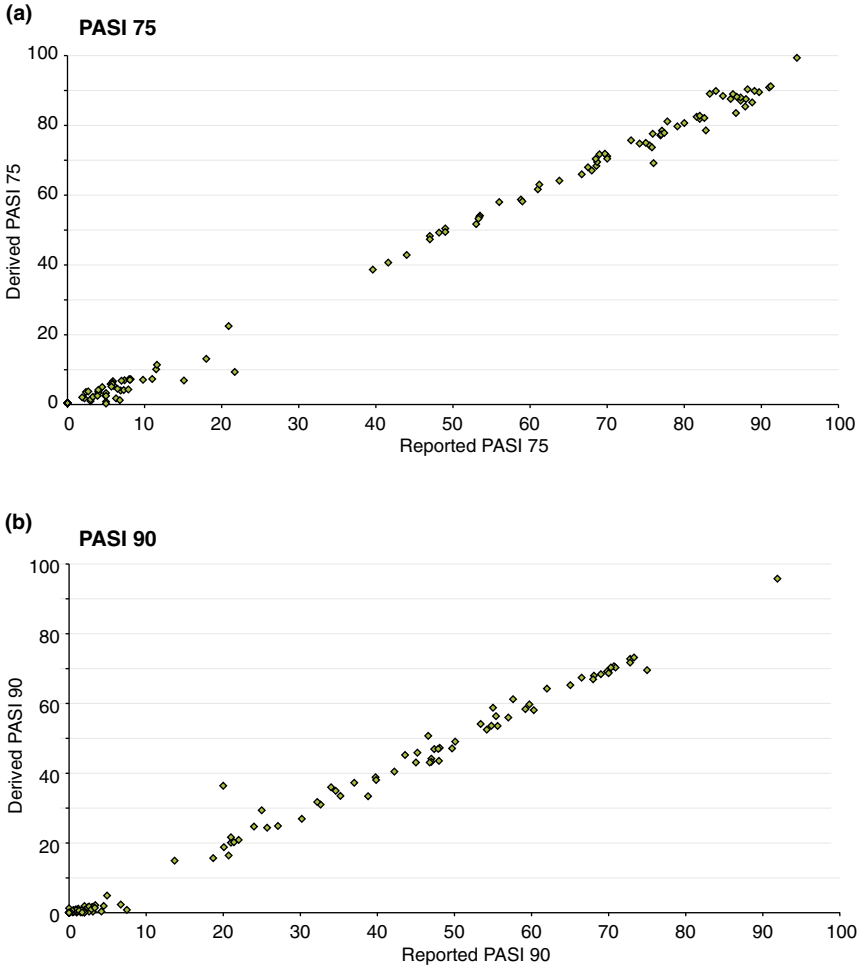


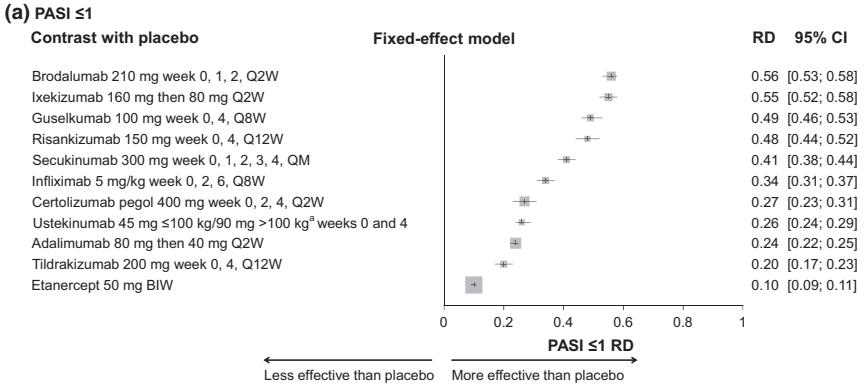
Figure 1 Scatter plots for derived and reported Psoriasis Area and Severity Index (PASI) 75 and PASI 90 values; derived values were estimated using the PASI conversion method.

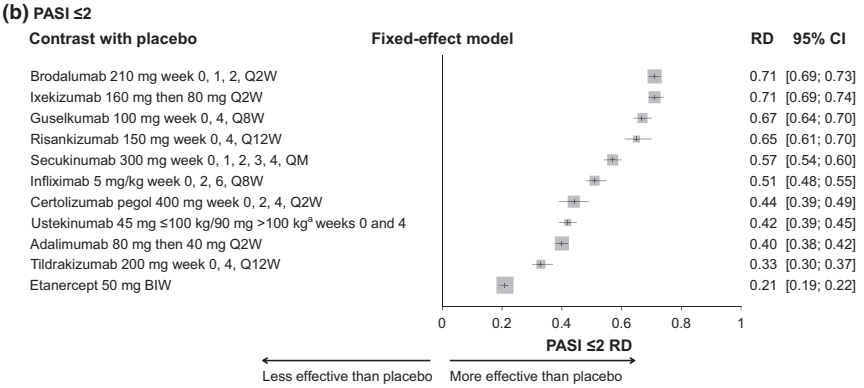
imputed. Missing values imputed using the random forest algorithm are highlighted in bold in Table 1. PASI score was reported after 12 weeks in 40 studies. The closest available values to the 12 weeks were reported after 10 weeks in five studies and after 16 weeks in five studies.

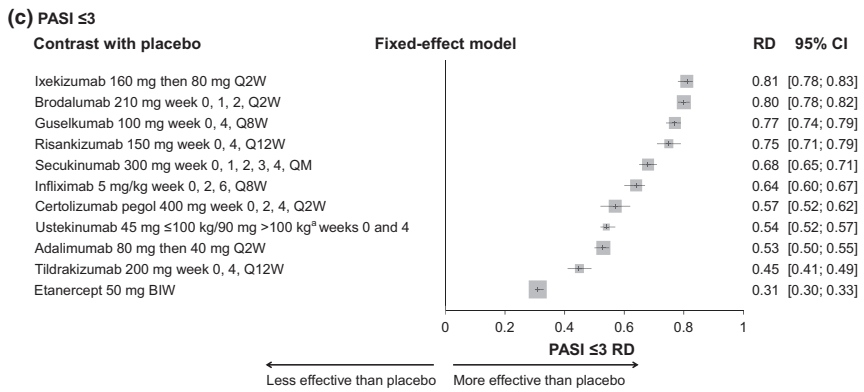
Application of the PASI conversion method to the study data

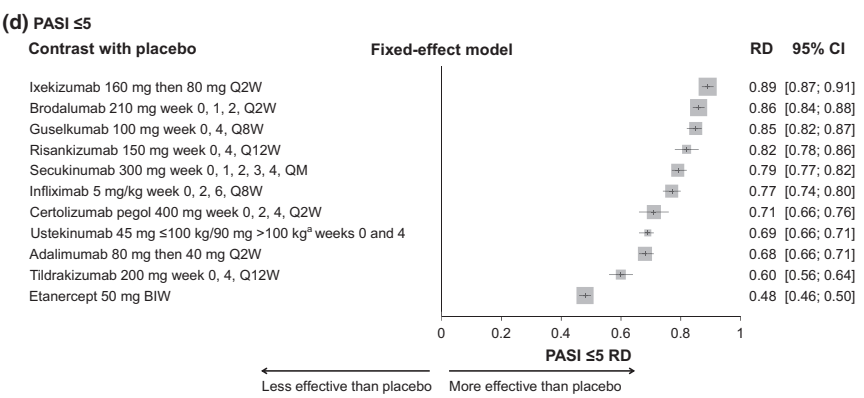
Table 2 shows the PASI conversion method-estimated proportions of patients with absolute PASI ≤1, 2, 3 and 5 after 12 weeks of treatment. The biologics brodalumab (210 mg at weeks 0, 1, 2 and then every 2 weeks) and ixekizumab (at a loading dose of 160 mg followed by 80 mg every 2 weeks) had the highest proportions of patients achieving absolute PASI scores of ≤1, ≤2, ≤3 or ≤5; guselkumab (100 mg at weeks 0, 4 and then every 8 weeks), risankizumab (150 mg at weeks 0, 4 and then every 12 weeks) and secukinumab (300 mg at weeks 0, 1, 2, 3, 4 and then every month) had the next highest proportions of patients achieving these absolute PASI scores.

Figure 2 Fixed-effect model forest plots (RD and 95% CI) for absolute PASI NMAs. RD 95% CIs are only indicative and should be interpreted cautiously, as the variability coming from the estimation process of the PASI method was not incorporated. [a]The dose of ustekinumab was based on patients' body weight: 45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg. BIW, twice weekly; CI, confidence interval; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QM, every month; RD, risk difference.

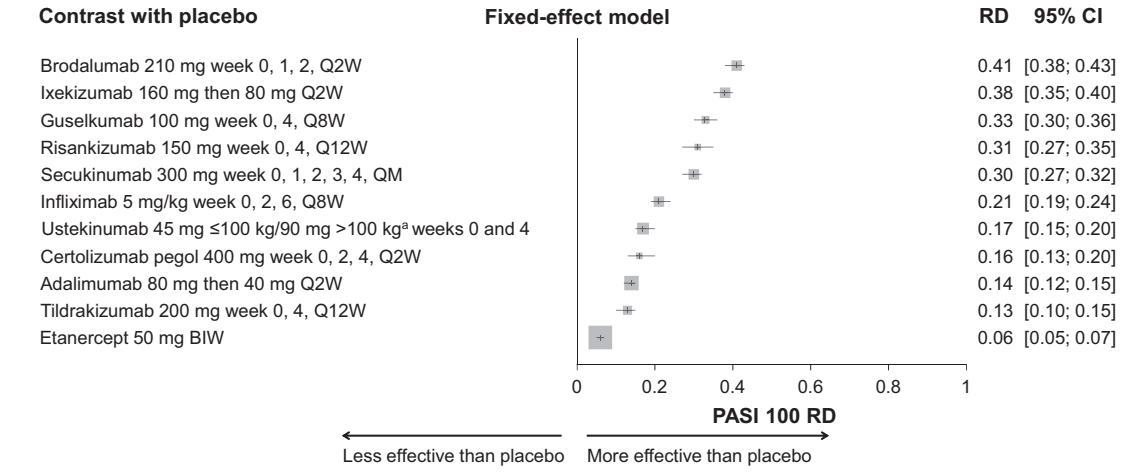




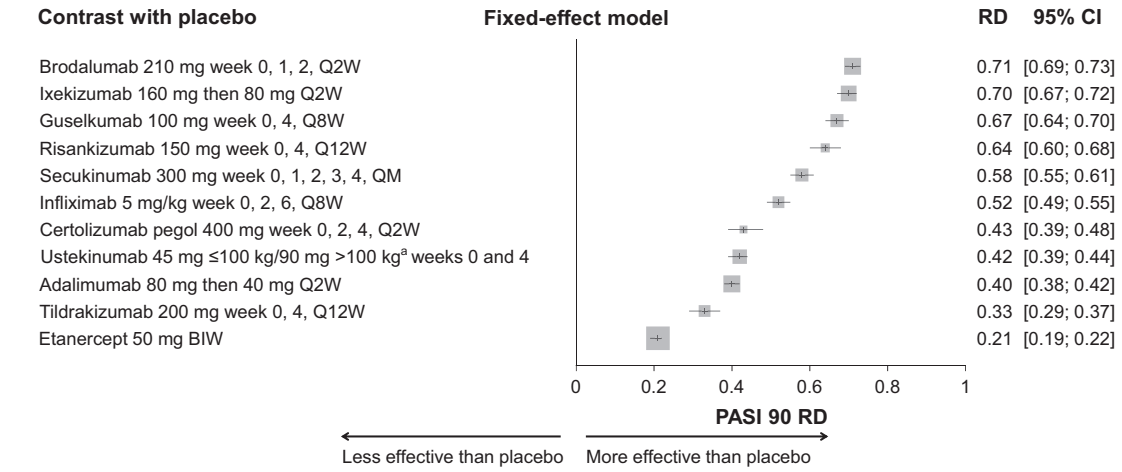




(a) PASI 100



(b) PASI 90



(c) PASI 75

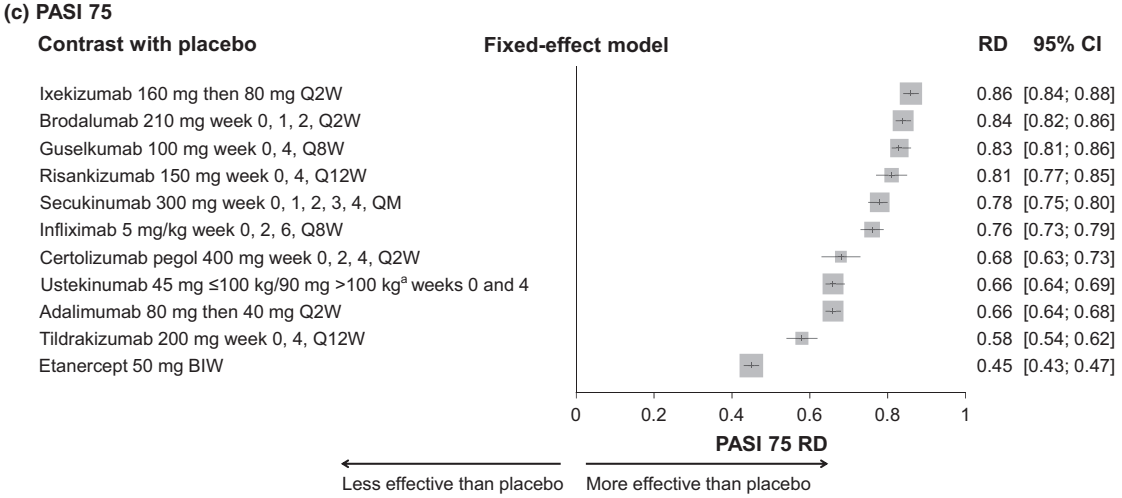


Figure 3 Fixed-effect model forest plots (RD and 95% CI) for relative PASI NMAs. [a]The dose of ustekinumab was based on patients' body weight: 45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg. BIW, twice weekly; CI, confidence interval; PASI, Psoriasis Area and Severity Index; PASI 50/75/90/100, the percentage of patients achieving PASI improvement of ≥50%/75%/90%/100%; Q2W, every 2 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QM, every month; RD, risk difference.

Table 2 also summarizes the derived PASI 75, 90 and 100 values. The same pattern of results with respect to treatments with the highest proportions of patients achieving relative PASI 75, 90 and 100 improvements was observed. Close to perfect correlations ($r = 0.998$, $r = 0.996$) between derived and reported PASI 75 and PASI 90 values, respectively, were observed (Fig. 1). PASI 100 rates for derived and reported values are completely identical because the observed values were directly incorporated into the PASI conversion method estimation.

Network meta-analyses of absolute and relative PASI

Fixed-effect model forest plots for absolute PASI ≤1, 2, 3 and 5, illustrating RDs with 95% CIs for each treatment comparative to placebo, and corresponding full network diagrams are shown in Fig. 2 and Fig. S2 (Supporting Information), respectively. When fixed-effect model forest plots (versus placebo) and corresponding full network diagrams for relative PASI 75, 90 and 100 were considered (Fig. 3 and Fig. S3, Supporting Information, respectively), findings were similar to the respective values for absolute PASI ≤5, ≤2 and ≤1.

Compared with placebo, treatment with brodalumab showed the greatest difference in the proportion of patients achieving PASI ≤1 (RD 56%), followed by ixekizumab (RD 55%), guselkumab (RD 49%), risankizumab (RD 48%) and secukinumab 300 mg (RD 41%; Fig. 2a). The treatments with the smallest difference from placebo were etanercept 50 mg twice weekly (RD 10%), tildrakizumab 100 mg at weeks 0, 4 and then every 12 weeks (RD 20%) and adalimumab at a loading dose of 80 mg followed by 40 mg every 2 weeks (RD 24%). Confidence intervals are indicative of the precision of the RD estimates. The same general ranking of treatments was observed in the results of the relative PASI NMA: treatment with brodalumab showed the greatest difference in the proportion of patients achieving PASI 100 (RD 41%) versus placebo, followed by ixekizumab (RD 38%), guselkumab (RD 33%), risankizumab (RD 31%) and secukinumab (RD 30%; Fig. 3a). Similarly, treatments with the smallest difference from placebo were the same as in the absolute PASI ≤1 analysis.

Results for PASI ≤2 showed the same general ranking of treatments (Fig. 2b), with brodalumab and ixekizumab (both RD 71%), followed by guselkumab (RD 67%), risankizumab (RD 65%), and secukinumab (RD 57%) showing the greatest differences compared with placebo. Again, the smallest differences versus placebo were observed for etanercept (RD 21%), tildrakizumab (RD 33%) and adalimumab (RD 40%). Very similar results were observed for PASI 90 analyses, with brodalumab (RD 71%) followed by ixekizumab (RD 70%), guselkumab (RD 67%), risankizumab (RD 64%) and secukinumab (RD 58%) showing the greatest differences compared with placebo (Fig. 3b). Etanercept, tildrakizumab and adalimumab were the treatments with the smallest difference from placebo.

When PASI ≤3 and PASI ≤5 were considered (Fig. 2c,d), ixekizumab (RDs 81% and 89%, respectively), followed by brodalumab (RDs 80% and 86%, respectively), guselkumab (RDs 77% and 85%, respectively), risankizumab (RDs 75% and 82%, respectively) and secukinumab (RDs 68% and 79%, respectively) showed the greatest differences compared with placebo. The smallest differences versus placebo were seen with etanercept (PASI ≤3 RD 31% and PASI ≤5 RD 48%), tildrakizumab (RDs 45% and 60%, respectively) and adalimumab (RDs 53% and 68%, respectively). The same general ranking of treatments was observed for PASI 75 analysis: treatment with ixekizumab showed the greatest difference in the proportion of patients achieving PASI 75 (RD 86%) versus placebo, followed by brodalumab (RD 84%), guselkumab (RD 83%), risankizumab (RD 81%) and secukinumab (RD 78%; Fig. 3c). Once again, the treatments with the smallest difference from placebo were also the same as in the absolute PASI ≤5 analysis.

Details of the cumulative proportions of patients achieving absolute PASI 0 to 8 at week 12 (derived from the PASI conversion method) with each of the included treatment regimens are presented in Fig. 4a. More than 80% of patients achieved PASI ≤8 with all biologic treatment regimens except those of etanercept and tildrakizumab. However, the consistently most effective treatment regimens at each absolute PASI cut-off (PASI ≤1, 2, 3 and 5) were ixekizumab and brodalumab, followed by guselkumab and risankizumab, and then infliximab 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks and secukinumab. The consistently least effective biologic regimens were those containing etanercept and tildrakizumab. This was again in line with results for relative PASI scores at week 12 (from 100 to 60; Fig. 4b).

Discussion

Descriptions of drug efficacy and, subsequently, definitions of treatment goals for chronic plaque psoriasis have been based on the proportions of patients achieving 50%, 75%, 90% or 100% relative improvements from baseline in PASI. However, relative PASI data have major shortcomings, as any relative improvement relates to a baseline value, resulting in the same relative improvement indicating very different outcomes for different patients. In clinical practice, the aim of any moderate-to-severe psoriasis treatment is to obtain clear or almost clear skin. This goal is relevant from both the patient's and the physician's

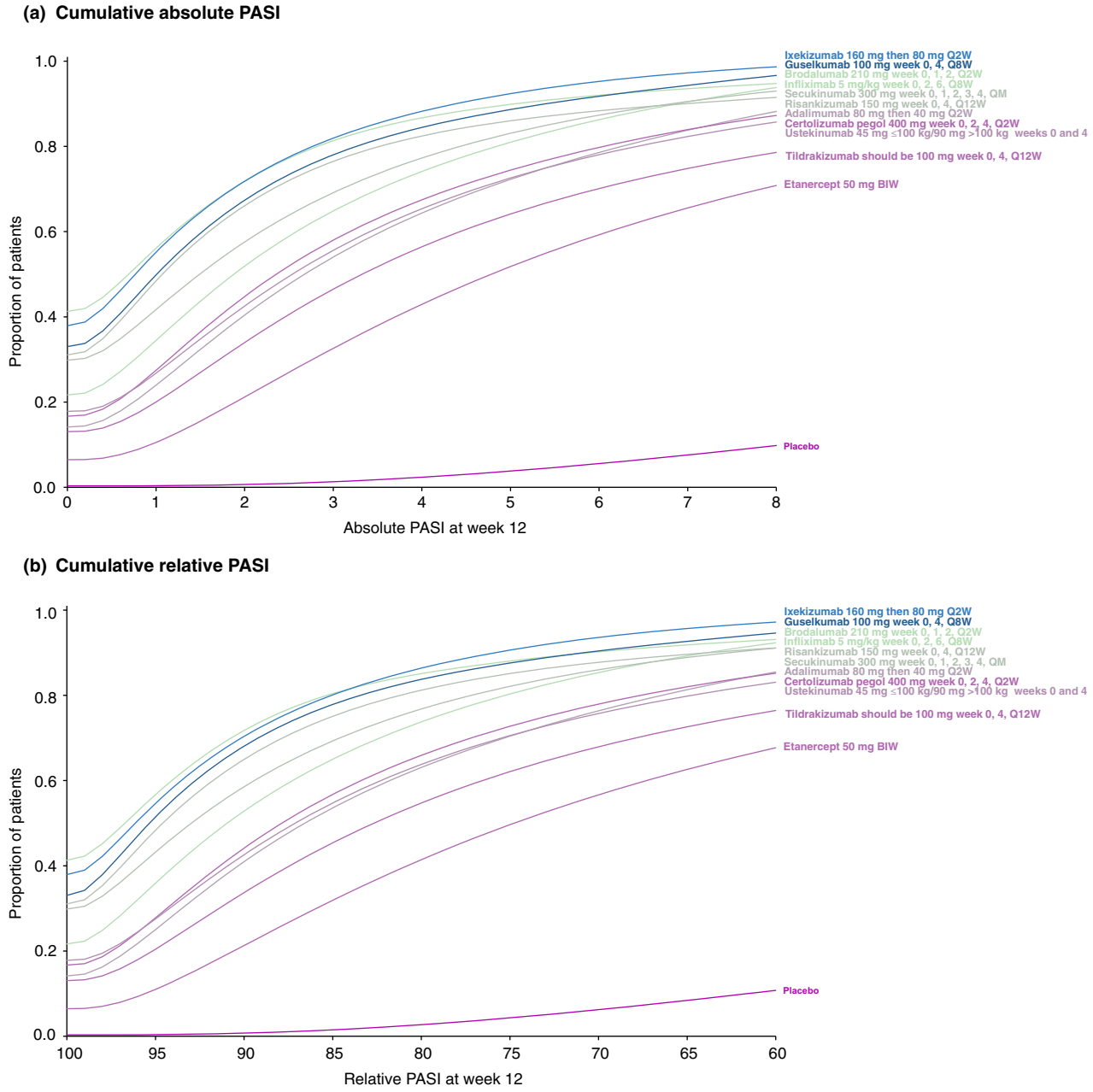


Figure 4 Cumulative PASI plots. [a]The dose of ustekinumab was based on patients' body weight: 45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg. BIW, twice weekly; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QM, every month.

perspective to ensure ongoing control of the disease and related inflammation. However, in cases where examination of the entire body to confirm PASI 100 might be challenging in clinical practice, establishing absolute PASI values may serve as a useful and relevant alternative. Unfortunately, the definition of treatment goals using absolute PASI thresholds has been hindered by a lack of data, since absolute PASI values have only been assessed and published in few studies until very recently.[6,19]

Using this statistical conversion method, it was possible to calculate absolute PASI data from clinical trials of recommended

and new biologic therapies in which baseline PASI values and relative improvement rates were reported. The data generated with this method provide a sound basis for the re-assessment of treatment goals using absolute PASI. In the clinical trial programme for ixekizumab, both relative and absolute PASI values were assessed. Using these trial results for the analyses demonstrated that a comparable number of patients (about 80% for ixekizumab 160 mg then 80 mg every 2 weeks) reached PASI 90 and PASI <2 and a similar proportion (approximately 90%) reached PASI 75 and PASI <5.[20] Similarly, another recent study used data from a UK real-world population-based cohort to evaluate treatment targets in psoriasis.[21] Based on data from 13 422 patients, this study found that both an absolute PASI ≤2 and Physician Global Assessment (PGA) clear/almost clear were concordant with PASI 90 in 90% of cases. These findings were robust to subgroups based on timing of assessment, baseline disease severity and treatment modality, suggesting an absolute PASI ≤2 and PGA clear/almost clear represent relevant disease endpoints to inform future treatment goals in psoriasis.

This study has some inherent limitations. For the majority of the included therapies, absolute PASI levels are not published, so the statistical conversion method could only be assessed using the large dataset of patient-level data for ixekizumab and etanercept from the UNCOVER studies.[5,6] In the absence of head-to-head trials, NMAs offer the best possible approach to comparing treatments. However, the selection of studies for an NMA is always subject to debate, and the ongoing publication of new studies with new therapies will require updates to this analysis in the future if used to determine the comparative efficacy of included therapies (e.g. for HTA or clinical decision-making), rather than as an illustration of the value of the statistical method, as per this analysis. Additionally, the NMA statistical method used could be questioned. Random effects NMA or Bayesian NMA (with non-informative priors because we had no prior information) could have been used as an alternative to the fixed-effect frequentist approach; however, the Rücker method chosen is an established scientific method. RD was chosen as the effect measure for this analysis, but other effect measures could of course be analysed based on the available data. The RD CIs presented have only indicative character, as variability resulting from the PASI conversion method estimation process was not incorporated. The imputation of missing PASI information also added further uncertainty to the findings (see Appendix S2 for details). Finally, NMAs, in general, are based on various assumptions that are very hard to verify (i.e. homogeneity of the included studies with respect to e.g., assessment time-points, dose selection, definitions of endpoints), although statistical methods were applied in this analysis to address heterogeneity wherever possible. Thus, results and, in particular, the presented rank order of drug effects (resulting from the tool) should be interpreted with care. Furthermore, psoriasis requires long-term treatment and some systemic treatments are faster acting than others. The current analysis considered only treatment efficacy at 10–16 weeks; therefore, it would also be preferable to be able to make a comparative assessment of therapies over several years rather than only over the first few months of treatment. However, long-term, randomized, active comparator studies to inform this type of analysis are unfortunately sparse at best.

In conclusion, the short-term data generated using this mathematical model will be useful to inform the scientific discussion on evolving treatment goals for plaque psoriasis in the absence of absolute PASI data on all available treatments and support treatment decision-making in clinical practice. Although illustrative, results support the use of brodalumab, ixekizumab, guselkumab, risankizumab and secukinumab in patients with moderate-to-severe psoriasis to achieve absolute PASI as well as traditional relative PASI improvement treatment goals.

Acknowledgements

The authors thank Sue Williamson and Caroline Spencer (Rx Communications, Mold, UK) for medical writing assistance during the preparation of this manuscript, which was funded by Eli Lilly and Company. RBW is supported by the Manchester NIHR Biomedical Research Centre.

Author contributions

All authors have contributed to the conception, design, analysis and interpretation of the data, and have approved the presented findings. All authors have revised the manuscript critically for intellectual content and have given final approval for publication. All authors agree to be accountable for all aspects of the work.

References

1 Mrowietz U, Kragballe K, Reich K *et al*. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**: 1–10.
2 Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. *J Eur Acad Dermatol Venereol* 2015; **29**: 645–648.
3 Nast A, Smith C, Spuls PI*et al*. EuroGuiDerm Guideline for the systematic treatment of psoriasis vulgaris; 2020. URL https://www.edf.one/dam/jcr:c80dd166-c66f-4548-a7ed-754f5e2687d0/Living_Euroguiderm_guideline_psoriasis_vulgaris.pdf (last accessed: 04 November 2020).
4 Cline A, Hill D, Lewallen R, Feldman SR. Current status and future prospects for biologic treatments of psoriasis. *Expert Rev Clin Immunol.* 2016; **12**: 1273–1287.
5 Gordon KB, Blauvelt A, Papp KA *et al*. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med*. 2016; **375**: 345–356.
6 Griffiths CE, Reich K, Lebwohl M *et al*. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet* 2015; **386**: 541–551.
7 Umezawa Y, Nakagawa H, Niiro H, Ootaki K. Long-term clinical safety and efficacy of brodalumab in the treatment of Japanese patients with moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol* 2016; **30**: 1957–1960.
8 Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C *et al*. A prospective phase III, randomized, double-blind, placebo-controlled

study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol* 2016; **175**: 273–286.
9 Blauvelt A, Papp KA, Griffiths CE *et al*. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol* 2017; **76**: 405–417.
10 Reich K, Armstrong AW, Foley P *et al*. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol* 2017; **76**: 418–431.
11 Gordon KB, Strober B, Lebwohl M *et al*. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet* 2018; **392**: 650–661.
12 Petto H, Wilhelm S, Mallbris L, Dutronc Y, Leonardi C, Warren R. A statistical tool to convert published PASI 75, PASI 90 and PASI 100 response rates into absolute PASI values. *J Am Acad Dermatol* 2016; **74**(Suppl1): AB234.
13 Stekhoven DJ, Buhlmann P. MissForest - non-parametric missing value imputation for mixed-type data. *Bioinformatics* 2012; **28**: 112–118.
14 Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* 2012; **3**: 312–324.
15 Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet* 2001; **357**: 1842–1847.
16 Menter A, Tyring SK, Gordon K *et al*. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008; **58**: 106–115.
17 de Vries AC, Thio HB, de Kort WJ *et al*. A prospective randomized controlled trial comparing infliximab and etanercept in patients with moderate-to-severe chronic plaque-type psoriasis: the Psoriasis Infliximab vs. Etanercept Comparison Evaluation (PIECE) study. *Br J Dermatol* 2017; **176**: 624–633.
18 Torii H, Nakagawa H. Japanese Infliximab Study Investigators. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. *J Dermatol Sci* 2010; **59**: 40–49.
19 Papp KA, Langley RG, Lebwohl M *et al*. PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371**: 1675–1684.
20 Burkhardt N, Mrowietz U, Carrascosa JM*et al*. Absolute and relative PASI over 1 year of treatment with ixekizumab (IXE): Descriptive analysis in patients with moderate-to-severe plaque psoriasis. Dermcoll 2017, 50th Annual Scientific Meeting 6–9 May 2017; Sydney, NSW: abstract no. 128.
21 Mahil SK, Wilson N, Dand N *et al*. Psoriasis treat to target: defining outcomes in psoriasis using data from a real-world, population-based study (the British Association of Dermatologists and Immunomodulators Register, BADBIR). *Br J Dermatol* 2020; **182**: 1158–1166.
22 Lebwohl M, Strober B, Menter A *et al*. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med* 2015; **373**: 1318–1328.
23 Bachelez H, van de Kerkhof PC, Strohal R *et al*. OPT Compare Investigators. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet* 2015; **386**: 552–561.
24 Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. *J Am Acad Dermatol* 2012; **67**: 86–92.
25 Cai L, Gu J, Zheng J, Zheng M, Wang G, Xi LY *et al*. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. *J Eur Acad Dermatol Venereol* 2017; **31**: 89–95.
26 Saurat JH, Stingl G, Dubertret L *et al*. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008; **158**: 558–566.
27 Lebwohl M, Blauvelt A, Paul C *et al*. Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks of a phase 3, multicenter, randomized, double-blind, etanercept- and placebo-controlled study (CIMPACT). *J Am Acad Dermatol* 2018; **79**: 266–276.e5.
28 Gottlieb AB, Blauvelt A, Thaci D *et al*. Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks from 2 phase 3, multicenter, randomized, double-blinded, placebo-controlled studies (CIMPASI-1 and CIMPASI-2). *J Am Acad Dermatol.* 2018; **79**: 302–314.e6.
29 Bagel J, Nia J, Hashim P *et al*. Secukinumab is superior to ustekinumab in clearing skin of patients with moderate-to-severe plaque psoriasis: CLARITY, a randomized, controlled, Phase IIIb trial. *J Clin Aesthet Dermatol* 2018; **11**: S27–S28.
30 Thaçi D, Blauvelt A, Reich K *et al*. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol* 2015; **73**: 400–409.
31 Langley RG, Elewski BE, Lebwohl M *et al*. Secukinumab in plaque psoriasis – results of two phase 3 trials. *N Engl J Med* 2014; **371**: 326–338.
32 Reich K, Nestle FO, Papp K *et al*. EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366**: 1367–1374.
33 Menter A, Feldman SR, Weinstein GD *et al*. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2007; **56**: 31.e1–15.
34 Blauvelt A, Prinz JC, Gottlieb AB *et al*. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). *Br J Dermatol* 2015; **172**: 484–493.
35 Paul C, Griffiths CEM, van de Kerkhof PCM *et al*. Ixekizumab provides superior efficacy compared with ustekinumab over 52 weeks of treatment: results from IXORA-S, a phase 3 study. *J Am Acad Dermatol.* 2019; **80**: 70–79.e3.
36 Paul C, Lacour JP, Tedremets L *et al*. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). *J Eur Acad Dermatol Venereol* 2015; **29**: 1082–1090.
37 Leonardi CL, Powers JL, Matheson RT *et al*. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349**: 2014–2022.
38 Gordon KB, Langley RG, Leonardi C *et al*. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006; **55**: 598–606.
39 Asahina A, Nakagawa H, Etoh T, Ohtsuki M. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. *J Dermatol* 2010; **37**: 299–310.
40 Gottlieb AB, Leonardi C, Kerdel F, Mehlis S, Olds M, Williams DA. Efficacy and safety of briakinumab vs. etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *Br J Dermatol* 2011; **165**: 652–660.
41 Strober BE, Crowley JJ, Yamauchi PS, Olds M, Williams DA. Efficacy and safety results from a phase III, randomized controlled trial comparing the safety and efficacy of briakinumab with etanercept and placebo in patients with moderate to severe chronic plaque psoriasis. *Br J Dermatol* 2011; **165**: 661–668.

42 Nakagawa H, Niiro H, Ootaki K. Japanese brodalumab study g. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: efficacy and safety results from a phase II randomized controlled study. *J Dermatol Sci* 2016; **81**: 44–52
43 Ohtsuki M, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. *J Dermatol* 2018; **45**: 1053–1062.
44 Ferris L, Ott E, Jiang G, Chih-Ho Hong H, Baran W. Efficacy and safety of guselkumab administered with a novel self-injection device for the treatment of moderate-to-severe psoriasis: results from the Phase III ORION self-dose study through week 16. *Acta Derm Venereol* 2018; **98** (Suppl 219): 29.
45 Papp KA, Tyring S, Lahfa M *et al*. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; **152**: 1304–1312.
46 Papp KA, Leonardi C, Menter A *et al*. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *New Engl J Med* 2012; **366**: 1181–1189.
47 Papp K, Thaci D, Reich K *et al*. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol* 2015; **173**: 930–939.
48 Reich K, Ortonne JP, Gottlieb AB *et al*. Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: results of a phase II randomized, placebo-controlled trial with a re-treatment extension. *Br J Dermatol* 2012; **167**: 180–190.
49 Reich K, Papp KA, Blauvelt A *et al*. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet* 2017; **390**: 276–288.
50 Gottlieb AB, Evans R, Li S *et al*. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51**: 534–542.
51 Tyring S, Gottlieb A, Papp K *et al*. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006; **367**: 29–35.
52 Mehta NN, Shin DB, Joshi AA *et al*. Effect of 2 psoriasis treatments on vascular inflammation and novel inflammatory cardiovascular biomarkers: a randomized placebo-controlled trial. *Circ Cardiovasc Imaging* 2018; **11**: e007394.
53 Gelfand JM, Takeshita J, Dey A *et al*. A Phase IV, randomised, double-blind, placebo-controlled crossover study of the effects of ustekinumab on vascular inflammation in psoriasis (the VIP-U trial). *J Investig Med* 2018; **66**: 697.
54 Gordon KB, Duffin KC, Bissonnette R *et al*. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *N Engl J Med* 2015; **373**: 136–144.
55 Yang HZ, Wang K, Jin HZ *et al*. Infliximab monotherapy for Chinese patients with moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled multicenter trial. *Chin Med J (Engl)* 2012; **125**: 1845–1851.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Systematic literature review methodology.
Appendix S2. Imputation of missing study information.
Figure S1. Combined Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for original systematic literature review and all updates.
Figure S2. Full network diagrams for absolute PASI network meta-analyses.
Figure S3. Full network diagrams for relative PASI network meta-analyses.
Table S1. Systematic literature review search termsa.
Table S2. List of systematic literature review criteria for the studies.