Comparison of cumulative clinical benefits of biologics for the treatment of psoriasis over 16 weeks: Results from a network meta-analysis

Richard B. Warren, MD, PhD,[a] Melinda Gooderham, MD,[b] Russel Burge, PhD,[c,d] Baojin Zhu, PhD,[c] David Amato, DO,[c] Karen Huayu Liu, PhD,[c] David Shrom, PhD,[c] Jiaying Guo, MS,[c] Alan Brnabic, MSc,[c] and Andrew Blauvelt, MD, MBA[e]

Manchester, United Kingdom; Peterborough, Ontario, Canada; Indianapolis, Indiana; and Portland, Oregon

Background: Cumulative clinical improvement and speed of improvement are important to psoriasis patients.

Objective: Compare cumulative benefits of biologics over 12 to 16 weeks in the treatment of moderate to severe psoriasis.

Methods: A systematic literature review identified phase III trial data on Psoriasis Area and Severity Index (PASI) responses for biologics during 12 and 16 weeks of treatment. Cumulative clinical benefit, measured by the area under the curve for PASI ≥75% improvement (PASI 75), ≥90% improvement (PASI 90), and 100% improvement (PASI 100), was compared using the network meta-analysis and Bayesian methodology on the relative probability of achieving percentage of maximum area under the curve.

Results: Among biologics approved for psoriasis treatment, anti−interleukin-17 biologics demonstrated consistently greater cumulative clinical benefits on PASI 75, PASI 90, and PASI 100 over the 12- or 16-week period than anti−interleukin-23 and other biologics. For biologics with 12-week data, ixekizumab and brodalumab showed greater cumulative benefits for PASI 75, PASI 90, and PASI 100 than secukinumab, followed by guselkumab, infliximab, adalimumab, ustekinumab, and etanercept. Ixekizumab showed greater cumulative benefits than all other biologics reporting 16-week data.

From the Salford Royal NHS Foundation Trust, The University of Manchester, National Institute for Health Research Manchester Biomedical Research Centre[a]; SKiN Centre for Dermatology, Peterborough[b]; Lilly Corporate Center, Indianapolis[c]; the University of Cincinnati[d]; and the Oregon Medical Research Center.[e]

Funding sources: Eli Lilly and Company.

Conflicts of interest: Warren has served as an advisor, clinical investigator, or both, for AbbVie, Almirall, Boehringer Ingelheim, Celgene, Eli Lilly and Company, GlaxoSmithKline, Janssen, LEO Pharma, Merck Sharp & Dohme, Novartis, Sanofi Genzyme, and UCB Pharma and as a paid speaker for AbbVie, Almirall, Amgen, Celgene, Eli Lilly and Company, Janssen, LEO Pharma, Novartis, Sanofi Genzyme, and UCB Pharma. Dr Gooderham has served as an advisor or clinical investigator, or both, for AbbVie, Amgen, Arcutis, Akros, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coherus, Dermira Inc, Eli Lilly and Company, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO Pharma, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, and Valeant, and as a paid speaker for AbbVie, Amgen, Celgene, Eli Lilly and Company, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, and Sanofi Genzyme. Russel Burge, Baojin Zhu, Karen Huayu Liu, David Shrom, Jiaying Guo, and Alan Brnabic are employees and stockholders of Eli Lilly and Company. Blauvelt has served as a scientific adviser or clinical study investigator, or both, for AbbVie, Aclaris, Almirall, Arena, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Dermira Inc, Eli Lilly and Company, FLX Bio, Forte, Galderma, Janssen, LEO Pharma, Novartis, Ortho, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma, and UCB Pharma, and as a paid speaker for AbbVie.

IRB approval status: Not applicable.

Accepted for publication December 19, 2019.

Correspondence and reprint requests to: Russel Burge, PhD, Eli Lilly and Company, Lilly Corporate Center DC 1532, Indianapolis, IN, 46285. E-mail: burge_russel_thomas@lilly.com.

Published online December 26, 2019.

0190-9622

https://doi.org/10.1016/j.jaad.2019.12.038

Limitations: Recently approved biologics were not included.

Conclusion: Ixekizumab (at 12 weeks and 16 weeks) and brodalumab (at 12 weeks) had greater cumulative clinical benefit than all of other biologics studied. (J Am Acad Dermatol 2020;82:1138-49.)

Key words: area under the curve; biologics; cumulative benefit; ixekizumab; meta-analysis; psoriasis.

CAPSULE SUMMARY

- Network meta-analyses on biologic treatment efficacy at a single time point have been reported. This article reports the cumulative efficacy over time for different biologic treatments.
- Knowledge on the cumulative benefits of treatments, which combines the rapidity and magnitude of efficacy, can help guide clinicians' decision making.

Patients with psoriasis have been shown to have poor quality of life and significant long-term cumulative life course impairment.[1] A quick resolution of psoriasis symptoms is an important feature of an ideal therapy for helping patients alleviate their daily pain, itching, embarrassment, and other effects of the disease.[2-6]

Conventional measures of skin clearance are generally assessed at the end of prespecified end points or fixed time periods (eg, 12 or 16 weeks) in clinical trials[7] but may not fully account for the cumulative benefits of treatment. One of the newer measures used to determine cumulative clinical benefit for assessing psoriasis treatment is the area under the curve (AUC), which can provide discernible differences in the cumulative benefit of responders to treatment.[8] Cumulative clinical benefit can be influenced by variations in response and the speed and persistence of response over time. Although cumulative life course impairment is a theoretical construct referring to the burden of disease over a long period of time,[9] evaluating the cumulative clinical benefit, even over the first 12 to 16 weeks of treatment, can improve understanding of the impact of treatment on the patient.

A number of approved therapies for the treatment of psoriasis are currently available, including several newer biologics with highly targeted mechanisms of action. Ixekizumab is a humanized monoclonal antibody that selectively targets interleukin (IL)-17A.[10,11] Other monoclonal antibodies targeted against IL-17 include secukinumab and brodalumab.[12,13] Therapies targeting IL-23 include guselkumab and tildrakizumab, whereas ustekinumab is an inhibitor of IL-12/IL-23.[14-16] Finally, adalimumab, infliximab, and etanercept are tumor necrosis factor-α (TNF-α) inhibitors.[17-19] In a recent analysis conducted on the use of targeted immunomodulators for the treatment of patients with moderate to severe plaque psoriasis, the anti—IL-17 agents ixekizumab and brodalumab were reported to be the most effective initial treatments.[7]

Because there are many other approved therapies for psoriasis, direct comparisons with all relevant comparators are not feasible. Here, a network meta-analysis (NMA) was used to indirectly compare the relative efficacies of 9 approved biologic therapies (ixekizumab, brodalumab, secukinumab, guselkumab, tildrakizumab, adalimumab, infliximab, etanercept, and ustekinumab) that reported week 12 over the first 12 weeks of treatment and to indirectly compare 5 approved biologic therapies (ixekizumab, secukinumab, guselkumab, adalimumab, and ustekinumab) that reported week 16 data over the first 16 weeks of treatment.

MATERIALS AND METHODS

Data source

A systematic literature review was conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions guidance.[20] The initial search was performed on December 11, 2014 and retrieved relevant literature published since January 1, 1990. Two further update searches were conducted, one on November 18, 2015, and another on November 15, 2018. The 3 searches were performed using the OvidSP platform. The search strategy was designed to identify publications reporting data from phase II to phase IV clinical trials of biologics that are approved or are likely to gain approval soon for treating moderate to severe psoriasis. The search strategy identified publications reporting data on Psoriasis Area and Severity Index ≥75% improvement (PASI 75), ≥90% improvement (PASI 90), and 100% improvement (PASI 100) from phase III clinical trials for this study, including data on 2 new anti—IL-23 agents (guselkumab and tildrakizumab). Because most of the phase III clinical trials for psoriasis used PASI 75 as the primary end point and reported PASI 90 and PASI 100 data as key secondary end points,

Abbreviations used:

AUC:	area under the curve
IL:	interleukin
NMA:	network meta-analysis
PASI:	Psoriasis Area Severity Index
PASI 75:	≥75% improvement in Psoriasis Area and Severity Index
PASI 90:	≥90% improvement in Psoriasis Area and Severity Index
PASI 100:	100% improvement in Psoriasis Area and Severity Index
Q2W:	every 2 weeks
Q4W:	every 4 weeks
Q8W:	every 8 weeks
Q12W:	every 12 weeks
SLR:	systematic literature review
TNF-α:	tumor necrosis factor-α

the objective of this NMA was to compare the cumulative benefits for PASI 75, PASI 90, and PASI 100 among biologics by 12 and 16 weeks.

Two reviewers determined the suitability of abstracts retrieved. After initial screening, full texts of included abstracts were appraised by 2 reviewers to verify relevance. Disputes regarding inclusion were resolved through discussion or involvement of an independent reviewer. All publications on randomized, controlled trials underwent a bias check using the Cochrane Handbook for Systematic Reviews of Interventions checklist to ensure appropriateness for inclusion in the NMA.

Calculations of cumulative clinical benefits

Cumulative clinical benefits for each therapy were estimated as the AUC for each of the 3 clinical measures, PASI 75, PASI 90, and PASI 100, over the 16-week ($AUC_{0\text{-}16wks}$) or 12-week ($AUC_{0\text{-}12wks}$) periods. The AUC and its variance were calculated using each PASI response rate at the same intervals at weeks 2, 4, 8, 12, and 16 for all biologics studied. The total AUC for each PASI response was determined using the trapezoidal rule.[8]

The AUC achieved for each therapy was then normalized to obtain the proportion of the maximum AUC by dividing the $AUC_{0\text{-}12wks}$ or $AUC_{0\text{-}16wks}$ by the maximum AUC for the 12-week period (12 weeks × 100% = 1200% × weeks) or the 16-week period (16 weeks × 100% = 1600% × weeks) for each PASI response. The percentage of maximum AUC was subsequently obtained by multiplying the proportion of maximum AUC by 100%.

Indirect comparison using NMA

The NMA was conducted on the proportion of AUC for each PASI response using Bayesian mixed-treatment comparisons as described in the National Institute for Health and Care Excellence Decision Support Unit Technical Support Documents[21] and Reich et al.[22] The NMA analysis had 2 separate analyses for each PASI response, one using week 12 data only and another using both weeks 12 and 16 data for all clinical trials listed in Table I. The 2 NMA analyses confirmed our assumption that the estimated percentage of maximum AUC probabilities for PASI 75, PASI 90, and PASI 100 for each biologic at week 12 was not affected by including week 16 data in the weeks 12 and 16 NMA analysis (Table II). All of the estimated percentages of maximum AUC from NMA were placebo-adjusted in this study.

The Bayesian-based NMA analyses were performed in JAGS via R software (The R Foundation for Statistical Computing, Vienna, Austria) using the R2jags package. Fixed-effect and random-effect models, as well as a separate baseline model,[46] were fitted to the NMA analyses. The consistency of results between the fixed-effects model and random-effects model was confirmed with 310,000 iterations, which provided satisfactory convergence for all models and end points verified by trace plots as modified by Brooks and Gelman.[47] Results from the fixed-effects models are reported.

RESULTS

The number of records identified by the systematic literature review (SLR) is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Fig 1). The SLRs identified 714 records (245 full-text publications and 469 conference abstracts). Of these, 28 articles with available data were included in all of the NMA analyses. Table I provides baseline characteristics and an overview of reported response rate for PASI 75, PASI 90, and PASI 100 from clinical trials included in the NMA analyses, and Fig 2 provides an example of an NMA diagram using weeks 12 and 16 PASI 75 data. Because all of the studies included in this NMA had similar inclusion/exclusion criteria for the treatment of patients with moderate to severe psoriasis, the baseline characteristics were similar, as provided in Table I.

Proportions of maximum AUC by week 12 on PASI 75, PASI 90, and PASI 100 were presented for all biologics compared (Fig 3 and Table II). Among all of the biologics approved for the treatment of psoriasis, anti—IL-17 biologics showed greater cumulative clinical benefits as measured by the percentage of maximum AUC on PASI 75, PASI 90, and PASI 100 than anti—IL-23 and other biologics. Specifically, anti—IL-17 biologics (ixekizumab and brodalumab) showed a similar proportion of maximum AUC at week 12, and both had greater cumulative benefits

Table I. Overview of studies for the network meta-analysis*

Study	Treatment	No.	Male sex	Age, y	Baseline BSA, %	Baseline PASI score	Response rate observed in study, %		
							PASI 75	PASI 90	PASI 100
							Week 12/16	Week 12/16	Week 12/16
UNCOVER 1	Ixekizumab 80 mg Q2W	433	291 (67.2)	45 ± 12	28 ± 18	20 ± 8	89.1/—	70.9/—	35.3/—
Gordon et al[23] (2016)	Ixekizumab 80 mg Q4W	432	289 (66.9)	46 ± 13	27 ± 16	20 ± 7	82.6/—	64.6/—	33.6/—
	Placebo	431	303 (70.3)	46 ± 13	27 ± 18	20 ± 9	3.9/—	0.5/—	0.0/—
UNCOVER 2	Ixekizumab 80 mg Q2W	351	221 (63.0)	45 ± 13	25 ± 16	19 ± 7	89.7/—	70.7/—	40.5/—
Gordon et al[23] (2016)	Ixekizumab 80 mg Q4W	347	244 (70.3)	45 ± 14	27 ± 17	20 ± 7	77.5/—	59.7/—	30.8/—
	Etanercept 50 mg BIW	358	236 (65.9)	45 ± 13	25 ± 16	19 ± 7	41.6/—	18.7/—	5.3/—
	Placebo	168	120 (71.4)	45 ± 12	27 ± 18	21 ± 8	2.4/—	0.6/—	0.6/—
UNCOVER 3	Ixekizumab 80 mg Q2W	385	254 (66.0)	46 ± 13	28 ± 17	21 ± 8	87.3/—	68.1/—	37.7/—
Gordon et al[23] (2016)	Ixekizumab 80 mg Q4W	386	258 (66.8)	46 ± 13	28 ± 16*	21 ± 8†	84.2/—	65.3/—	35.0/—
	Etanercept 50 mg BIW	382	269 (70.4)	46 ± 14	28 ± 17	21 ± 8	53.4/—	25.7/—	7.3/—
	Placebo	193	137 (71.0)	46 ± 12	29 ± 17	21 ± 8	7.3/—	3.1/—	0/—
RHBP	Ixekizumab 80 mg Q4W	616	398 (64.6)	47 ± 13	26 ± 17	21 ± 8	82.8/—	64.6/—	35.7/—
Langley et al[24] (2018)	Ixekizumab 80 mg Q2W/Q2W	611	412 (67.4)	49 ± 14	27 ± 18	20 ± 8	89.2/91.3	75.3/81.2	46.0/50.9
IXORA-S	Ustekinumab 45/90 mg	166	112 (67.5)	44 ± 13	28 ± 17	20 ± 9	68.7/72.3	42.2/45.2	14.5/18.7
Reich et al[25] (2017)	Ixekizumab 80 mg Q2W/Q4W	136	90 (66.2)	43 ± 13	27 ± 16	20 ± 8	88.2/89.7	72.8/77.9	36.0/41.9
ERASURE	Secukinumab 300 mg	245	169 (69.0)	44.9 ± 13.5	32.8 ± 19.3	22.5 ± 9.2	81.6/—	59.2/—	28.6/—
Langley et al[26] (2014)	Secukinumab 150 mg	245	168 (68.6)	44.9 ± 13.3	33.3 ± 19.2	22.3 ± 9.8	71.6/—	39.1/—	12.8/—
	Placebo	248	172 (69.4)	45.4 ± 12.6	29.7 ± 15.9	21.4 ± 9.1	4.5/—	1.2/—	0.8/—
FIXTURE	Secukinumab 300 mg	327	224 (68.5)	44.5 ± 13.2	34.3 ± 19.2	23.9 ± 9.9	77.1/—	54.2/—	24.1/—
Langley et al[26] (2014)	Secukinumab 150 mg	327	236 (72.2)	45.4 ± 12.9	34.5 ± 19.4	23.7 ± 10.5	67.0/—	41.9/—	14.4/—
	Etanercept 50 mg BIW	326	232 (71.2)	43.8 ± 13.0	33.6 ± 18.0	23.2 ± 9.8	44.0/—	20.7/—	4.3/—
	Placebo	326	237 (72.7)	44.1 ± 12.6	35.2 ± 19.1	24.1 ± 10.5	4.9/—	1.5/—	0.0/—
CLEAR	Secukinumab 300 mg	337	229 (68.0)	45.2 ± 14.0	32.6 ± 17.8	21.7 ± 8.5	91.0/93.1	72.8/79.0	38.9/44.3
Thaci et al[27] (2015)	Ustekinumab 45/90 mg	339	252 (74.3)	44.6 ± 13.7	32.0 ± 16.8	21.5 ± 8.1	79.1/82.7	53.4/57.6	25.7/28.4
FEATURE	Secukinumab 300 mg	59	38 (64.4)	45.1 ± 12.6	33.3 ± 18.0	20.7 ± 8.0	75.9/—	60.3/—	43.1/—
Blauvelt et al[28] (2015)	Secukinumab 150 mg	59	40 (67.8)	46.0 ± 15.1	30.6 ± 16.6	20.5 ± 8.3	69.5/—	45.8/—	8.5/—
	Placebo	59	39 (66.1)	46.5 ± 14.1	32.2 ± 17.4	21.1 ± 8.5	0.0/—	0.0/—	0.0/—
JUNCTURE	Secukinumab 300 mg	60	46 (76.7)	46.6 ± 14.2	26.4 ± 12.8	18.9 ± 6.4	86.7/—	55.0/—	26.7/—
Paul et al[29] (2015)	Secukinumab 150 mg	61	41 (67.2)	43.9 ± 14.4	30.1 ± 16.7	22.0 ± 8.9	71.7/—	40.0/—	16.7/—
	Placebo	61	38 (62.3)	43.7 ± 12.7	25.7 ± 14.7	19.4 ± 6.7	3.3/—	0.0/—	0.0/—
AMAGINE-1	Brodalumab 210 mg Q2W	222	161 (73)	46 ± 12	25.1 ± 15.3	19.4 ± 6.6	83.3/—	70.3/—	41.9/—
Papp et al[30] (2016)	Brodalumab 140 mg Q2W	219	162 (74)	46 ± 13	27.4 ± 17.1	20.0 ± 7.4	60.3/—	42.5/—	23.3/—
	Placebo	220	161 (73)	47 ± 13	26.9 ± 17.1	19.7 ± 7.7	2.7/—	0.9/—	0.5/—

Continued

Table I. Cont'd

Study	Treatment	No.	Male sex	Age, y	Baseline BSA, %	Baseline PASI score	Response rate observed in study, %		
							PASI 75	PASI 90	PASI 100
							Week 12/16	Week 12/16	Week 12/16
AMAGINE-2	Brodalumab 210 mg Q2W	612	421 (69)	45 ± 13	26 ± 16	20.3 ± 8.3	86.3/—	69.9/—	44.4/—
Lebwohl et al[31] (2015)	Brodalumab 140 mg Q2W	610	413 (68)	45 ± 13	27 ± 17	20.5 ± 8.2	66.6/—	49.0/—	25.7/—
	Ustekinumab 45/90 mg	300	205 (68)	45 ± 13	27 ± 19	20.0 ± 8.4	70.0/—	47.0/—	21.7/—
	Placebo	309	219 (71)	44 ± 13	28 ± 17	20.4 ± 8.2	8.1/—	2.9/—	0.6/—
AMAGINE-3	Brodalumab 210 mg Q2W	624	431 (69)	45 ± 13	28 ± 18	20.4 ± 8.3	85.1/—	69.1/—	36.7/—
Lebwohl et al[31] (2015)	Brodalumab140 mg Q2W	629	437 (70)	45 ± 13	29 ± 18	20.1 ± 8.5	69.2/—	52.0/—	27.0/—
	Ustekinumab 45/90 mg	313	212 (68)	45 ± 13	28 ± 18	20.1 ± 8.4	69.3/—	47.9/—	18.5/—
	Placebo	315	208 (66)	44 ± 13	28 ± 17	20.1 ± 8.7	6.0/—	1.9/—	0.3/—
ACCEPT	Ustekinumab 45 mg	209	133 (63.6)	45.1 ± 12.6	26.7 ± 17.8	20.5 ± 9.2	67.5/—	36.4/—	—
Griffiths et al[32] (2010)	Ustekinumab 90 mg	347	234 (67.4)	44.8 ± 12.3	26.1 ± 17.6	19.9 ± 8.4	73.8/—	44.7/—	—
	Etanercept 50 mg BIW	347	246 (70.9)	45.7 ± 13.4	23.8 ± 13.9	18.6 ± 6.2	56.8/—	23.1/—	—
PHOENIX 1	Ustekinumab 45 mg	255	175 (68.6)	44.8 ± 12.5	27.2 ± 17.5	20.5 ± 8.6	67.1/—	41.6/—	—/—
Leonardi et al[33] (2008)	Ustekinumab 90 mg	256	173 (67.6)	46.2 ± 11.3	25.2 ± 15.0	19.7 ± 7.6	66.4/—	36.7/—	—/—
	Placebo	255	183 (71.8)	44.8 ± 11.3	27.7 ± 17.4	20.4 ± 8.6	3.1/—	2.0/—	—/—
PHOENIX 2	Ustekinumab 45 mg	409	283 (69.2)	45.1 ± 12.1	25.9 ± 15.5	19.4 ± 6.8	66.7/—	42.3/—	—/—
Papp et al[34] (2008)	Ustekinumab 90 mg	411	274 (66.7)	46.6 ± 12.1	27.1 ± 17.4	20.1 ± 7.5	75.7/—	50.9/—	—/—
	Placebo	410	283 (69.0)	47.0 ± 12.5	26.1 ± 17.4	19.4 ± 7.5	3.7/—	0.7/—	—/—
PEARL	Ustekinumab 45 mg	61	50 (82.0)	40.9 ± 12.7	41.8 ± 24.4	25.2 ± 11.9	67.2/—	—/—	—/—
Tsai et al[35] (2011)	Placebo	60	53 (88.3)	40.4 ± 10.1	35.8 ± 21.4	22.9 ± 8.6	5.0/—	—/—	—/—
Igarashi et al[36] (2012)	Ustekinumab 45 mg	64	53 (82.8)	45.0	47.0 ± 23.7	30.1 ± 12.9	59.4/—	32.8/—	—/—
	Ustekinumab 90 mg	62	47 (75.8)	44.0	46.6 ± 19.7	28.7 ± 11.2	67.7/—	43.5/—	—/—
	Placebo	32	26 (83.9)	49.0	49.8 ± 22.5	30.3 ± 11.8	6.5/—	3.2/—	—/—
VOYAGE 1	Guselkumab 100 mg	329	240 (72.9)	43.9 ± 12.7	28.3 ± 17.1	22.1 ± 9.5	82.0/91.2	58.3/73.3	21.3/37.4
Blauvelt et al[37] (2017)	Adalimumab 40 mg Q2W	334	249 (74.6)	42.9 ± 12.6	28.6 ± 16.7	22.4 ± 9.0	71.6/73.1	44.2/49.7	13.7/17.1
	Placebo	174	119 (68.4)	44.9 ± 12.9	25.8 ± 15.9	20.4 ± 8.7	5.4/5.7	1.8/2.9	0.0/0.6
VOYAGE 2	Guselkumab 100 mg	496	349 (70.4)	43.7 ± 12.2	28.5 ± 16.4	21.9 ± 8.8	79.8/86.3	57.9/70.0	23.0/34.1
Reich et al[38] (2017)	Adalimumab 40 mg Q2W	248	170 (68.5)	43.2 ± 11.9	29.1 ± 16.7	21.7 ± 9.0	66.0/68.5	40.5/46.8	15.2/20.6
reSURFACE 1	Tildrakizumab 200 mg	308	226 (73)	46.9 ± 13.2	30.9 ± 17.8	20.7 ± 8.5	62.3/—	35.4/—	14.0/—
Reich et al[39] (2017)	Tildrakizumab 100 mg	309	207 (67)	46.4 ± 13.1	29.7 ± 17.4	20.0 ± 7.9	63.8/—	34.6/—	13.9/—
	Placebo	155	100 (65)	47.9 ± 13.5	29.6 ± 17.3	19.3 ± 7.1	5.8/—	2.6/—	1.3/—
reSURFACE 2	Tildrakizumab 200 mg	314	225 (72)	44.6 ± 13.6	31.8 ± 17.2	19.8 ± 7.5	65.6/—	36.6/—	11.8/—
Reich et al[39] (2017)	Tildrakizumab 100 mg	307	220 (72)	44.6 ± 13.6	34.2 ± 18.4	20.5 ± 7.6	61.2/—	38.8/—	12.4/—
	Etanercept 50 mg BIW	313	222 (71)	45.8 ± 14.0	31.6 ± 16.6	20.2 ± 7.4	48.2/—	21.4/—	4.8/—
	Placebo	156	112 (72)	46.4 ± 12.2	31.3 ± 14.8	20.0 ± 7.6	5.8/—	1.3/—	0.0/—
REVEAL	Adalimumab 40 mg Q2W	814	546 (67.1)	44.1 ± 13.2	25.8 ± 15.5	19.0 ± 7.1	68.0/71.0	—/—	—/—
Menter et al[40] (2008)	Placebo	398	257 (64.6)	45.4 ± 13.4	25.6 ± 14.8	18.8 ± 7.1	5.0/7.0	—/—	—/—

CHAMPION	Adalimumab 40 mg Q2W	108	70 (64.8)	42.9 ± 12.6	33.6 ± 19.9	20.2 ± 7.5	76.9/79.6	48.1/51.9	11.1/16.7
Saurat et al[41] (2008)	Placebo	5 3	35 (66.0)	40.7 ± 11.4	28.4 ± 16.1	19.2 ± 6.9	15.1/18.9	7.5/11.3	0.0/1.9
Papp et al[42] (2005)	Etanercept 50 mg BIW	194	130 (67)	44.5	25.0	16.1	49.5/—	—/—	—/—
	Etanercept 25 mg BIW	196	128 (65)	46.0	23.0	16.9	34.2/—	—/—	—/—
	Placebo	193	124 (64)	44.0	20.0	16.0	3.1/—	—/—	—/—
NCT01646073	Adalimumab 40 mg Q2W	338	254 (75.1)	43.1 ± 11.9	42.6 ± 21.8	28.2 ± 12.0	77.8/—	55.6/—	13.3/—
Cai et al[43] (2017)	Placebo	87	58 (66.7)	43.8 ± 12.5	39.3 ± 22.5	25.6 ± 11.0	11.5/—	3.4/—	1.1/—
EXPRESS II	Infliximab 5 mg/kg	314	204 (65.0)	44.5 ± 13.0	28.7 ± 16.4	20.4 ± 7.5	75.5/—	—/—	—/—
Menter et al[44] (2007)	Placebo	208	144 (69.2)	44.4 ± 12.5	28.4 ± 17.6	19.8 ± 7.7	1.9/—	—/—	—/—
EXPRESS	Infliximab 5 mg/kg	301	207 (69)	42.6 ± 11.7	34.1 ± 19	22.9 ± 9.3	81.3/—	58.6/—	—/—
Reich et al[45] (2005)	Placebo	77	61 (79)	43.8 ± 12.6	33.5 ± 18	22.8 ± 8.7	3.5/—	1.4/—	—/—

BIW, Twice weekly; *BSA*, body surface area; *NMA*, network meta-analysis; *No.*, number; *PASI 75*, ≥75% improvement in Psoriasis Area and Severity Index; *PASI 90*, ≥90% improvement in Psoriasis Area and Severity Index; *PASI 100*, 100% improvement in Psoriasis Area and Severity Index; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; —, no data available.
*Categorical data are presented as the number (%) and continuous data as the mean ± standard deviation.
†Data were available for 383 patients.

than secukinumab, followed by guselkumab, infliximab, adalimumab, ustekinumab, and etanercept. The greater proportion of maximum AUC for ixekizumab and other anti—IL-17 biologics than anti—IL-23 biologics appeared to be attributable to the early rapid improvement in the PASI, which was sustained through the following 12-week study periods.

For studies that continued from week 12 to week 16, the proportion of maximum AUC was estimated for the entire 16-week period. Among the 5 biologics with week 16 data (ixekizumab, secukinumab, guselkumab, ustekinumab, and adalimumab), ixekizumab showed the greatest cumulative clinical benefits compared with all other biologics (Table III). The median proportion of maximum AUC for PASI 75 was 66% for ixekizumab, 80 mg every 2 weeks (Q2W)/every 4 weeks (Q4W); 57% for secukinumab, 300 mg Q4W; 52% for guselkumab, 100 mg every 8 weeks (Q8W); 44% for adalimumab, 40 mg Q2W; and 42% for ustekinumab, combined 45/90 mg doses every 12 weeks (Q12W). The corresponding PASI 90 proportion of maximum AUC estimates (Table III) were 47% for ixekizumab, 39% for secukinumab, 33% for guselkumab, 24% for adalimumab, and 23% for ustekinumab. Similarly, for PASI 100, ixekizumab Q2W/Q4W had a greater proportion of maximum AUC (22%) than secukinumab, 300 mg (19%), followed by guselkumab, 100 mg (12%), ustekinumab (10%), and adalimumab (7%).

The posterior estimate of the median proportion of maximum AUC and its credible intervals for PASI 75, PASI 90, and PASI 100 showed that ixekizumab, 80 mg Q2W and Q4W, was more efficacious and had the highest probability of achieving total cumulative benefits at week 16 for PASI 75, PASI 90, and PASI 100 than the available comparators (Table III).

DISCUSSION

In the study reported here, anti—IL-17 biologics showed greater cumulative clinical benefits than other classes of biologics for the treatment of moderate to severe psoriasis. The cumulative benefits for PASI 75 were consistently higher for ixekizumab and brodalumab compared with other biologics at 12 weeks and were higher for ixekizumab compared with any biologic at 16 weeks. Corresponding cumulative benefits for PASI 90 and PASI 100 generally followed similar patterns, with ixekizumab and brodalumab having higher cumulative benefits than other biologics at 12 weeks and ixekizumab having higher cumulative benefits at 16 weeks than secukinumab, guselkumab, adalimumab, and ustekinumab.

Table II. Estimated median proportion of maximum area under the curve and 95% credible interval at week 12 for the Psoriasis Area and Severity Index

	Proportion of maximum area under the curve, median (95% credible interval)					
	PASI 75		PASI 90		PASI 100	
Treatment	Method 1*	Method 2†	Method 1*	Method 2†	Method 1*	Method 2†
Placebo	0.02 (0.02, 0.02)	0.02 (0.02, 0.02)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Ixekizumab 80 mg Q2W	0.59 (0.57, 0.61)	0.59 (0.57, 0.61)	0.37 (0.35, 0.38)	0.37 (0.35, 0.38)	0.17 (0.15, 0.18)	0.17 (0.15, 0.18)
Ixekizumab 80 mg Q4W	0.55 (0.53, 0.57)	0.55 (0.53, 0.57)	0.33 (0.32, 0.35)	0.33 (0.32, 0.35)	0.14 (0.13, 0.16)	0.14 (0.13, 0.16)
Adalimumab 40 mg Q2W	0.36 (0.34, 0.37)	0.35 (0.34, 0.37)	0.18 (0.16, 0.20)	0.18 (0.16, 0.20)	0.05 (0.04, 0.05)	0.05 (0.04, 0.06)
Guselkumab 100 mg Q8W	0.42 (0.39, 0.44)	0.41 (0.39, 0.44)	0.23 (0.21, 0.25)	0.23 (0.20, 0.25)	0.07 (0.05, 0.08)	0.07 (0.05, 0.08)
Secukinumab 300 mg Q4W	0.47 (0.45, 0.50)	0.47 (0.45, 0.50)	0.27 (0.25, 0.29)	0.27 (0.25, 0.29)	0.11 (0.10, 0.12)	0.11 (0.10, 0.12)
Secukinumab 150 mg Q4W	0.37 (0.34, 0.39)	0.37 (0.34, 0.39)	0.16 (0.15, 0.18)	0.16 (0.15, 0.18)	0.05 (0.04, 0.06)	0.05 (0.04, 0.06)
Ustekinumab 45/90 mg Q12W	0.32 (0.30, 0.35)	0.32 (0.30, 0.35)	0.17 (0.15, 0.18)	0.17 (0.15, 0.18)	0.06 (0.05, 0.07)	0.06 (0.05, 0.07)
Ustekinumab 45 mg Q12W	0.33 (0.31, 0.35)	0.33 (0.31, 0.35)	0.16 (0.14, 0.17)	0.16 (0.14, 0.17)	…	…
Ustekinumab 90 mg Q12W	0.36 (0.34, 0.37)	0.36 (0.34, 0.37)	0.17 (0.16, 0.19)	0.17 (0.16, 0.19)	…	…
Etanercept 25 mg BIW	0.13 (0.10, 0.17)	0.13 (0.10, 0.17)	…	…	…	…
Etanercept 50 mg BIW	0.21 (0.20, 0.23)	0.21 (0.20, 0.23)	0.07 (0.06, 0.08)	0.07 (0.06, 0.08)	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)
Tildrakizumab 100 mg Q12W	0.28 (0.25, 0.31)	0.28 (0.25, 0.31)	0.13 (0.11, 0.15)	0.13 (0.11, 0.15)	0.04 (0.03, 0.06)	0.04 (0.03, 0.06)
Tildrakizumab 200 mg Q12W	0.28 (0.25, 0.31)	0.28 (0.25, 0.31)	0.13 (0.11, 0.15)	0.13 (0.11, 0.15)	0.05 (0.03, 0.06)	0.05 (0.03, 0.06)
Brodalumab 210 mg Q2W	0.59 (0.57, 0.60)	0.59 (0.57, 0.60)	0.39 (0.37, 0.40)	0.39 (0.37, 0.40)	0.19 (0.18, 0.20)	0.19 (0.18, 0.20)
Brodalumab 140 mg Q2W	0.46 (0.44, 0.48)	0.46 (0.44, 0.48)	0.28 (0.27, 0.30)	0.28 (0.27, 0.30)	0.14 (0.14, 0.15)	0.14 (0.14, 0.15)
Infliximab 5 mg/kg	0.45 (0.42, 0.48)	0.45 (0.42, 0.47)	0.28 (0.24, 0.32)	0.28 (0.25, 0.32)	…	…

AUC, Area under the curve; *BIW*, twice weekly; *PASI 75*, ≥75% improvement in Psoriasis Area and Severity Index; *PASI 90*, ≥90% improvement in Psoriasis Area and Severity Index; *PASI 100*, 100% improvement in Psoriasis Area and Severity Index; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks; *Q12W*, every 12 weeks.

*Method 1: Network meta-analysis estimation of percent of maximum AUC using both week 12 and 16 data available for each drug.

†Method 2: Network meta-analysis estimation of percent of maximum AUC using only week 12 data for each drug.

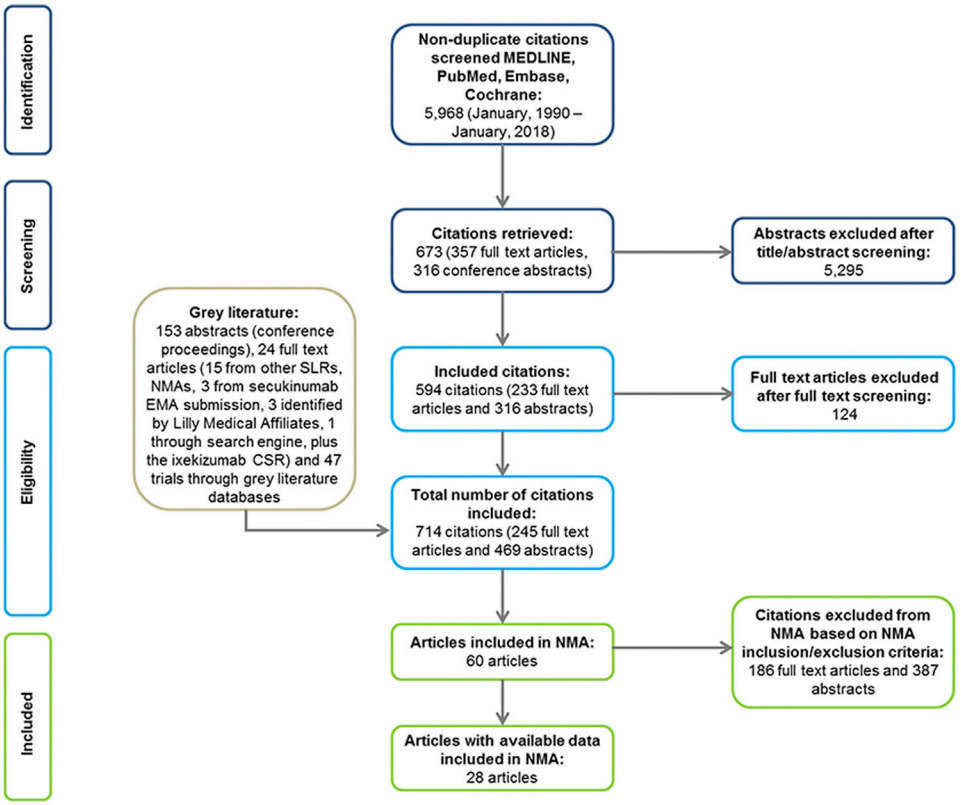

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for the systematic literature review (*SLR*). *CSR*, Clinical study report; *EMA*, European Medicines Agency; *NMA*, network meta-analysis.

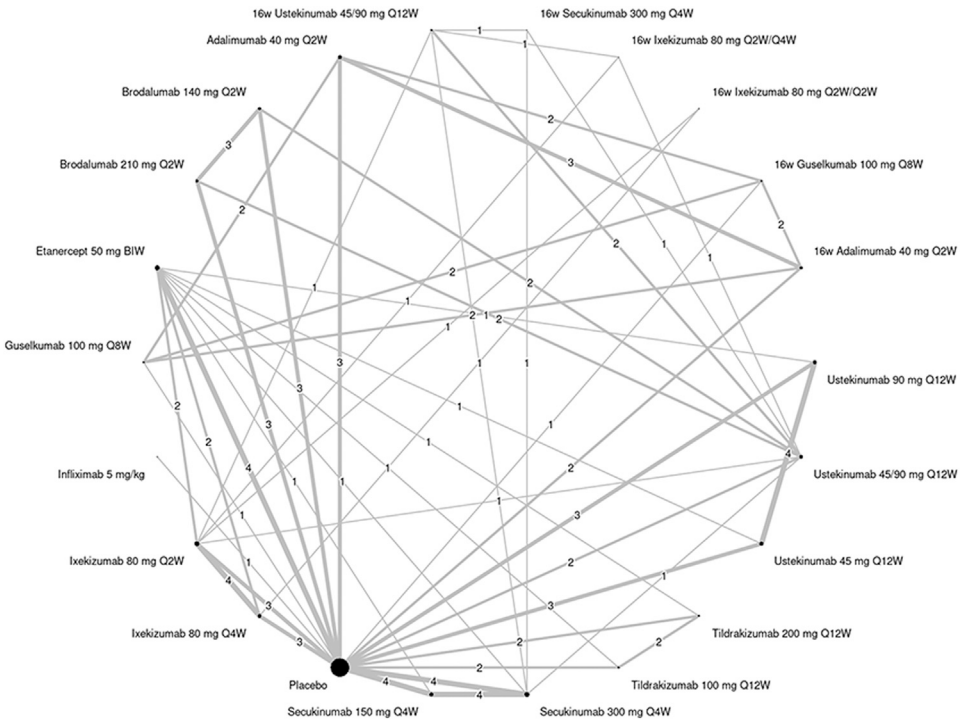

Fig 2. Network meta-analysis diagram for Psoriasis Area Severity Index ≥75% improvement. *BIW*, Every other week; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *Q12W*, every 12 weeks.

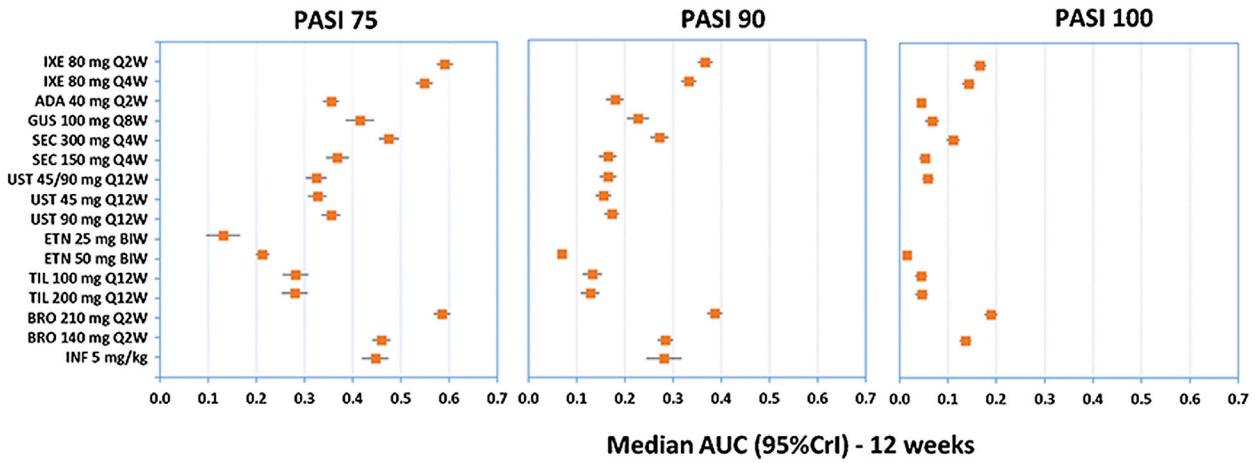

Fig 3. Proportion of the maximum area under the curve (*AUC*) for Psoriasis Area Severity Index ≥75% improvement (*PASI 75*), ≥90% improvement (*PASI 90*), and 100% improvement (*PASI 100*) at week 12 among biologics. *ADA*, Adalimumab; *BIW*, every other week; *BRO*, brodalumab; *CrI*, credible interval; *ETN*, etanercept; *GUS*, guselkumab; *INF*, infliximab; *IXE*, ixekizumab; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks; *Q12W*, every 12 weeks; *SEC*, secukinumab; *TIL*, tildrakizumab; *UST*, ustekinumab.

Table III. Estimated median proportion of maximum area under the curve and 95% credible interval at week 16 for the Psoriasis Area and Severity Index*

Treatment	PASI 75	PASI 90	PASI 100
Adalimumab 40 mg Q2W	0.44 (0.42, 0.46)	0.24 (0.22, 0.26)	0.07 (0.06, 0.09)
Guselkumab 100 mg Q8W	0.52 (0.50, 0.55)	0.33 (0.31, 0.35)	0.12 (0.11, 0.14)
Ixekizumab 80 mg Q2W/Q4W	0.66 (0.61, 0.71)	0.47 (0.41, 0.53)	0.22 (0.18, 0.27)
Secukinumab 300 mg Q4W	0.57 (0.53, 0.60)	0.39 (0.36, 0.43)	0.19 (0.16, 0.22)
Ustekinumab 45/90 mg Q12W	0.42 (0.39, 0.46)	0.23 (0.20, 0.26)	0.10 (0.07, 0.12)

PASI 75, ≥75% improvement in Psoriasis Area and Severity Index; *PASI 90*, ≥90% improvement in Psoriasis Area and Severity Index; *PASI 100*, 100% improvement in Psoriasis Area and Severity Index; *Q2W*, every 2 weeks; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks; *Q12W*, every 12 weeks.
*16-week data shown.

Conventionally, measures of skin clearance, such as PASI 75, PASI 90, and PASI 100, were often measured at the end of prespecified end points or fixed time periods (eg, 12 or 16 weeks). As such, several NMA studies have been conducted on PASI response rates at weeks 12 and 16 from SLRs.[22,48-54] The findings from these NMAs showed a consistent pattern of greater efficacy for anti—IL-17 biologics than anti-TNF inhibitors and other biologics.

More recently, the Institute for Clinical and Economic Review published an update on NMA using PASI response rates at weeks 12 to 16 for biologics,[7] which showed that ixekizumab had the highest efficacy in PASI 50-100 responses, followed by (in order) risankizumab, brodalumab, infliximab, guselkumab, secukinumab, ustekinumab, adalimumab, and others. The results using cumulative benefits from the current study are consistent with the previous work using one-time PASI responses. The cumulative benefit of treatment is the total time spent at a certain PASI response level.[8] By comparing the normalized percentage maximum AUC on PASI 75 at week 16 (ixekizumab, 66%; secukinumab, 57%; guselkumab, 52%; adalimumab, 44%; ustekinumab, 42%), for example, the data provide the relative clinical efficacy for different biologics, and more importantly, the data show the different gaps left by these relatively efficacious biologics for reaching the maximum benefits possible.

A noticeable exception in comparing one-time clinical response with cumulative benefits are the anti—IL-23 biologics, which did not rank as well from the NMA using cumulative benefits as the NMA using one-time PASI response rates. In the analyses reported here, the anti—IL-17 biologics achieved the largest cumulative benefits compared with the anti—IL-23 biologic guselkumab. One reason for this difference is that anti—IL-23 biologics may have

slower clinical responses in the first few weeks of treatment than anti—IL-17 biologics. Studies have shown that the maintenance of IL-17—producing Th17 cells is dependent on IL-23 in psoriasis and other diseases. Thus, it is possible that anti—IL-23 therapies are more delayed in improving psoriasis because they work indirectly to affect IL-17, leading to slower onset of action and lack of rapidity even though they could have sustainability similar to anti—IL-17 biologics in long-term treatment responses.

Evaluating cumulative clinical benefits—which captures both speed and magnitude of efficacy onset—can help identify therapies that could have the greatest impact on disease burden (ie, cumulative life course impairment). For instance, PASI response rates in clinical trials may appear similar at fixed time points (eg, 12 or 16 weeks), but cumulative clinical benefit can help to differentiate therapies with rapid and sustained improvement on measures of efficacy, which may be particularly impactful for therapies that help patients achieve clear or nearly clear skin (ie, PASI 100 or PASI 90). Ultimately, improving our understanding of factors that influence cumulative life course impairment helps clinicians make more informed decisions for patients with psoriasis.[55,56]

The analyses included all major biologic therapies for psoriasis, including anti—IL-23 agents approved for the treatment of moderate to severe psoriasis at the time of this study. This NMA was performed using Bayesian methodology, which is recommended by the National Institute for Health and Care Excellence.[57] The NMA models the relationship between true parameters rather than using observed measures. The nodes in the NMA were clearly defined and focused on the labeled doses of approved biologics. Using an AUC approach allows for an assessment of benefits, which considers both speed of onset and overall magnitude of improvement over a given treatment period. These analyses also reflect the value of rapid onset of efficacy.

This study has some limitations. The NMA combines both direct and indirect evidence and therefore requires several strong assumptions for the treatment comparisons to be valid, whereas direct head-to-head comparisons do not require such assumptions.[58] The percentage maximum AUC from indirect comparison and from the observed percentage of cumulative clinical benefit in each study were checked to ensure consistency from NMA.

The NMA that was used was limited by availability of data at week 16, which limited certain biologics (such as brodalumab) from being included in this analysis. AUC numbers should be extracted from PASI response rates at the same visits during the week 16 period from the published data. Thus, measurement errors during data extraction could exist, which was estimated by the credible intervals of NMA. Week 1 results were not used in the estimation of the percentage of maximum AUC for all biologics, which may bias against ixekizumab and other anti—IL-17 biologics that demonstrate more rapid treatment responses.

The common correlation structure, which was obtained from the individual patient-level data of the pooled treatment arms from 5 ixekizumab studies, was applied to the estimation of the variance of the AUC for all biologics with the assumption that the correlation structures were similar among all biologics compared in this study. Although cumulative benefit is shown only over a period of 12 to 16 weeks and provides insight into the effect of speed of onset of treatment, longer-term data are ideal for the AUC and would allow for a more meaningful connection to cumulative life course impairment.

Finally, only clinical efficacy measurement (PASI) was evaluated, whereas other important outcomes such as quality of life and safety were not.

CONCLUSIONS

Relative efficacy comparisons reported here revealed that anti—IL-17 biologics, specifically, ixekizumab and brodalumab, had the largest cumulative benefits achieved for PASI 75, 90, and 100 over the first 12 to 16 weeks of treatment. Of note, the cumulative benefits of 12 and 16 weeks of ixekizumab treatment exceeded the benefits accumulated over the same period of treatment with secukinumab, guselkumab, ustekinumab, and TNF inhibitors for all PASI response thresholds studied. Maximum cumulative clinical benefit percentage achieved is a useful metric for capturing the speed and magnitude of clinical responses for psoriasis biologics and may help clinicians differentiate among treatment choices for their patients.

REFERENCES

1. Mattei PL, Corey KC, Kimball AB. Cumulative life course impairment: evidence for psoriasis. *Curr Probl Dermatol*. 2013;44:82-90.
2. Fairchild AO, Reed SD, Johnson FR, et al. What is clearance worth? Patients' stated risk tolerance for psoriasis treatments. *J Dermatolog Treat*. 2017;28(8):709-715.
3. Leonardi CL, Blauvelt A, Sofen H, et al. Rapid improvements in health-related quality of life and itch with ixekizumab treatment in randomized phase 3 trials: results from UNCOVER-2 and UNCOVER-3. *J Eur Acad Dermatol Venereol*. 2017;31(9):1483-1490.
4. Gottlieb AB, Chaudhari U, Mulcahy LD, Li S, Dooley LT, Baker DG. Infliximab monotherapy provides rapid and

sustained benefit for plaque-type psoriasis. *J Am Acad Dermatol*. 2003;48:829-835.
5. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc*. 2011;86(4):304-314.
6. Goold SD, Lipkin M. The doctor-patient relationship. *J Gen Intern Med*. 1999;14(Supp. 1):S26-S33.
7. Institute for Clinical and Economic Review. Targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: effectiveness and value. Condition update: evidence report. Available at: https://icer-review.org/wp-content/uploads/2017/11/ICER_Psoriasis_Update_Draft_Report_04272018.pdf; 2018. Accessed June 21, 2018.
8. Armstrong AW, Feldman SR, Korman NJ, et al. Assessing the overall benefit of a medication: cumulative benefit of secukinumab over time in patients with moderate-to-severe plaque psoriasis. *J Dermatolog Treat*. 2017;28(3):200-205.
9. Augustin M, Mayer A, Goepel LM, et al. Cumulative Life Course Impairment (CLCI): a new concept to characterize persistent patient burden in chronic wounds. *Wound Med*. 2013;1:2-6.
10. Taltz [prescribing information]. Indianapolis, IN: Eli Lilly and Company; 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125521s000lbl.pdf. Accessed June 21, 2018.
11. European Medicines Agency. Taltz: EPAR summary for the public. London, UK: EMA; 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003943/WC500205807.pdf. Accessed June 21, 2018.
12. Cosentyx [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/cosentyx.pdf. Accessed October 8, 2019.
13. Siliq [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf. Accessed October 8, 2019.
14. Tremfya [prescribing information]. Horsham, PA: Janssen Biotech, Inc; 2017. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/TREMFYA-pi.pdf. Accessed October 8, 2019.
15. Ilumya [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; 2018. Available at: https://ypd57my3oo168lx16fbexdxu-wpengine.netdna-ssl.com/wp-content/uploads/sites/9/Sun_Pharma_ILUMYA_US_Prescribing_Information.pdf. Accessed October 8, 2019.
16. Stelara [prescribing information]. Horsham, PA: Janssen Biotech, Inc; 2017. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/STELARA-pi.pdf. Accessed October 8, 2019.
17. Humira [prescribing information]. North Chicago, IL: Abbott Laboratories; 2011. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125057s0276lbl.pdf. Accessed October 8, 2019.
18. Remicade [prescribing information]. Horsham, PA: Janssen Biotech, Inc: 2017. Available at: http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf. Accessed October 8, 2019.
19. Enbrel [prescribing information]. Thousand Oaks, CA: Immunex Corporation; 2017. Available at: https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/enbrel/enbrel_pi.pdf. Accessed October 8, 2019.
20. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. Baltimore, MD: Cochrane Collaboration; 2011. Available at: http://handbook-5-1.cochrane.org/. Accessed June 21, 2018.
21. National Institute for Health and Care Excellence Decision Support Unit. Evidence synthesis TSD series. Available at: http://nicedsu.org.uk/technical-support-documents/evidence-synthesis-tsd-series/. Accessed June 21, 2018.
22. Reich K, Burden AD, Eaton JN, et al. Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials. *Br J Dermatol*. 2012;166(1):179-188.
23. 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.
24. Langley RG, Papp K, Gooderham M, et al. Efficacy and safety of continuous every 2-week dosing of ixekizumab over 52 weeks in patients with moderate-to-severe plaque psoriasis in a randomized phase 3 trial (IXORA-P). *Br J Dermatol*. 2018;178(6):1315-1323.
25. Reich K, Pinter A, Lacour JP, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol*. 2017;177(4):1014-1023.
26. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. *N Engl J Med*. 2014;371(4):326-338.
27. Thaci 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(3):400-409.
28. 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(2):484-493.
29. 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(6):1082-1090.
30. Papp KA, Reich K, Paul 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(2):273-286.
31. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med*. 2015;373(14):1318-1328.
32. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med*. 2010;362(2):118-128.
33. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371(9625):1665-1674.
34. Papp KA, Langley RG, Lebwohl M, et al. 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(9625):1675-1684.
35. Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J Dermatol Sci*. 2011;63(3):154-163.
36. Igarashi A, Kato T, Kato M, et al. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe

plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. *J Dermatol*. 2012;39(3):242-252.
37. 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(3):405-417.
38. 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(3):418-431.
39. 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(10091):276-288.
40. 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(1):106-115.
41. 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(3):558-566.
42. 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(6):1304-1312.
43. Cai L, Gu J, Zheng J, 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(1):89-95.
44. 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(1):31.e31-15.
45. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet*. 2005;366(9494):1367-1374.
46. Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making*. 2013;33(5):607-617.
47. Brooks SP, Gelman A. Alternative methods for monitoring convergence of iterative simulations. *J Comput Graph Stat*. 1998;7:434-455.
48. Signorovitch JE, Betts KA, Yan YS, et al. Comparative efficacy of biological treatments for moderate-to-severe psoriasis: a network meta-analysis adjusting for cross-trial differences in reference arm response. *Br J Dermatol*. 2015;172:504-512.
49. Jabbar-Lopez ZK, Yiu ZZN, Ward V, et al. Quantitative evaluation of biologic therapy options for psoriasis: a systematic review and network meta-analysis. *J Invest Dermatol*. 2017;137(8):1646-1654.
50. Gómez-García F, Epstein D, Isla-Tejera B, et al. Short-term efficacy and safety of new biological agents targeting the interleukin-23-T helper 17 pathway for moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis. *Br J Dermatol*. 2017;176(3):594-603.
51. Lin VW, Ringold S, Devine EB. Comparison of ustekinumab with other biological agents for the treatment of moderate to severe plaque psoriasis: a Bayesian network meta-analysis. *Arch Dermatol*. 2012;148:1403-1410.
52. Bansback N, Sizto S, Sun HY, et al. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. *Dermatology*. 2009;219:209-218.
53. Sbidian E, Chaimani A, Garcia-Doval I, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev*. 2017;12:CD011535.
54. Sawyer L, Fotheringham I, Wright E, et al. The comparative efficacy of brodalumab in patients with moderate-to-severe psoriasis: a systematic literature review and network meta-analysis. *J Dermatolog Treat*. 2018;29:1-12.
55. Warren RB, Kleyn CE, Gulliver WP. Cumulative life course impairment in psoriasis: patient perception of disease-related impairment throughout the life course. *Br J Dermatol*. 2011;164(Suppl 1):1-14.
56. Ros S, Puig L, Carrascosa JM. Cumulative life course impairment: the imprint of psoriasis on the patient's life. *Actas Dermosifiliogr*. 2014;105(2):128-134.
57. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. London, UK: National Institute for Health and Clinical Excellence; 2011.
58. Schacht A, Dyachkova Y, Walton RJ. Critical evaluation of mixed treatment comparison meta-analyses using examples assessing antidepressants and opioid detoxification treatments. *Int J Methods Psychiatr Res*. 2013;22(2):166-174.