DOI: 10.1111/jdv.17433 JEADV

ORIGINAL ARTICLE

Complete clearance and Psoriasis Area and Severity Index response for brodalumab and ustekinumab by previous treatment history in AMAGINE-2 and AMAGINE-3

K. Reich,[1,*] J.B. Hansen,[2] L. Puig,[3] M.P. Konstantinou,[4] R.B. Warren[5]

[1]Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2]LEO Pharma, Ballerup, Denmark
[3]Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, Spain
[4]Service de Dermatologie, Larrey Hospital, Toulouse, France
[5]Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, University of Manchester, Manchester, UK
*Correspondence: K. Reich. E-mail: kreich@jerucon.com

Abstract

Background The pathway for treatment of psoriasis is partly dependent upon disease severity, and patients may experience inadequate response at any point along the treatment pathway. Patients who repeatedly fail therapy represent a population in whom effective and well-tolerated treatment options are limited.

Objectives To investigate and describe patients achieving Psoriasis Area and Severity Index (PASI) 100 and cumulative treatment benefit over time in patients with moderate-to-severe psoriasis receiving brodalumab or ustekinumab by prior treatment.

Methods We conducted a post hoc analysis of data from two phase 3, randomized, controlled, 52-week AMAGINE trials of brodalumab to describe patients who achieved complete clearance as measured by PASI 100 by prior treatment subgroup (naïve to systemic and biologic treatment, systemic-treated but biologic-naïve, biologic-treated without failure, and biologic-treated with failure). A competing risk model was used to assess cumulative incidence over a 52-week period with outcomes of PASI 100 or inadequate response. Cumulative clinical benefit of treatment was determined with an area under the curve analysis.

Results The 52-week cumulative incidence of patients achieving PASI 100 was consistently higher for brodalumab vs. ustekinumab across treatment pathway subgroups (76% vs. 58% in systemic/biologic-naïve patients, 78% vs. 55% in systemic-treated/biologic-naïve patients, 75% vs. 41% in biologic-treated patients without failure, and 70% vs. 30% in biologic-treated patients with failure). Rates of inadequate response were lower with brodalumab compared with ustekinumab across all subgroups. Cumulative treatment benefit was also higher for all subgroups treated with brodalumab compared with those treated with ustekinumab.

Conclusion Treatment with brodalumab was associated with higher levels of complete clearance and greater cumulative benefit over time compared with ustekinumab, in patients with moderate-to-severe psoriasis, regardless of prior treatment experience.

Received: 3 March 2021; revised: 26 April 2021; Accepted: 19 May 2021

Conflicts of interest

KR has been a consultant for and/or has received honoraria and/or investigator fees from AbbVie, Affibody, Almirall, Amgen, Biogen-Idec, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Covagen, Eli Lilly, Forward Pharma, Fresenius Medical Care, Galapagos, GlaxoSmithKline, Janssen, Kyowa Kirin, LEO Pharma, Medac, Merck Sharp & Dohme, Miltenyi, Novartis, Ocean Pharma, Pfizer, Samsung Bioepis, Sandoz, Sanofi, Sun Pharma, Takeda, UCB Pharma, Valeant, XBiotech and XenoPort. JBH is an employee of LEO Pharma. MPK has been a principal and sub-investigator for AbbVie, Boehringer Ingelheim, LEO Pharma, Pfizer and Sanofi, and a speaker and consultant for AbbVie, Janssen and LEO Pharma. LP has received grants/research funding, honoraria or consultation fees from or has served as a speaker or clinical trial investigator for AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, LEO Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Samsung Bioepis, Sandoz, Sanofi and UCB Pharma. RBW has been a consultant for and has received grants from AbbVie, Almirall, Amgen, Avillion, Arena

Pharmaceuticals, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi and UCB Pharma.

Funding source

The brodalumab clinical study programme was sponsored by Amgen and AstraZeneca. This analysis was performed by LEO Pharma.

Introduction

Psoriasis vulgaris is a chronic inflammatory skin disease which affects approximately 3% of the population and is characterized by red plaques with silvery scaling, commonly involving the scalp, elbows, knees and presacral region.[1-3] Psoriasis significantly impacts patients' quality of life (QoL).[1] Severity of psoriasis is partly defined by the total body surface area (BSA) affected, with mild, moderate and severe disease involving <3%, 3–10% and ≥10% of the BSA, respectively.

Mild-to-moderate psoriasis can be adequately controlled in most patients by topical therapies including corticosteroids and vitamin D3 analogs, or phototherapy.[1] In patients with moderate-to-severe disease, non-biologic systemic medications, including methotrexate, retinoids and ciclosporin, are appropriate. Biologic agents are used when there is an inadequate response to conventional systemic agents.[1, 4, 5]

In some patients, biologic treatment of psoriasis may result in a primary failure (initial non-response), which may be influenced by baseline characteristics such as increased body mass index,[6] or secondary failure (loss of efficacy after initial response). Such loss of efficacy may reflect the development of neutralizing antidrug antibodies. Under these circumstances, improved efficacy, safety and/or tolerability may be achieved by switching the patient to a different biologic agent, but there are currently insufficient data to support specific switching recommendations.[1] Moreover, treatment efficacy is less likely to improve for subsequently offered biologics.[7] Consequently, there is an unmet need to establish which, if any, alternative biologic, will be most likely to offer benefit in patients experiencing either a primary or a secondary failure.

Brodalumab is a fully humanized monoclonal antibody with a unique mechanism of action that targets the IL-17 receptor A subunit (IL-17RA).[8] Unlike biologics that target IL-17A such as secukinumab and ixekizumab,[9,10] brodalumab inhibits the downstream signalling of multiple members of the IL-17 family of cytokines involved in the pathogenesis of psoriasis by directly blocking the interaction of several IL-17 isoforms with the IL-17RA subunit of their receptors.[8] Results from phase 3 AMAGINE-2 and AMAGINE-3 clinical trials have shown that high levels of skin clearance in patients with moderate-to-severe psoriasis can be achieved with brodalumab for up to 52 weeks,[11] with longer sustained response and greater cumulative clinical treatment benefits vs. ustekinumab in the overall pooled study population.[12] Furthermore, in an analysis of data from these trials investigating the impact of previous biologic exposure, rates of skin clearance with brodalumab were shown to be similar in biologic-naïve and biologic-experienced patients.[13]

The Psoriasis Area and Severity Index (PASI) 75 (proportion of patients with ≥75% reduction in baseline PASI) was traditionally accepted as the primary treatment endpoint for assessing efficacy in clinical trials and guidelines.[5,14-16] However, more rigorous treatment goals (PASI 90 and PASI 100) have become feasible with the emergence of modern biologics such as the anti-IL-17 and IL-23 therapies.[17] Many patients can achieve complete skin clearance (PASI 100)[11,18] resulting in further improvements in QoL compared with patients with almost clear skin (PASI 90).[19-22] It may also change the natural history of the disease, including long-term disease remission.[23] Additionally, as the impact of psoriasis on patients is continuous, Armstrong *et al.* proposed an integrated analysis of PASI over time using an area under the curve (AUC) analysis.[24]

In this post hoc analysis, we investigated patients achieving complete clearance and the cumulative clinical benefit of treatment with brodalumab vs. ustekinumab over a 52-week period in the AMAGINE-2 and AMAGINE-3 trials according to prior treatment with systemic medications and/or biologic agents. The aim was to compare the rapidity and sustainability of observed treatment responses for the two treatments for patients with different prior treatment histories.

Materials and methods

Trial design and patients

Data were pooled from phase 3, 52-week, placebo- and ustekinumab-controlled trials of brodalumab: AMAGINE-2 (NCT01708603) and AMAGINE-3 (NCT01708629).[11] The study designs are provided in Figure S1 and have previously been described.[11] Briefly, the studies included patients ≥18 years of age, with ≥6 months' duration of moderate-to-severe plaque psoriasis (PASI score ≥12, static Physician's Global Assessment [sPGA] score ≥3 and BSA involvement ≥10%). Patients were randomized 2:2:1:1 to receive brodalumab 210 mg, brodalumab 140 mg, ustekinumab (45 mg for patients with bodyweight ≤100 kg and 90 mg for >100 kg) or placebo, on Day 1, and then on Weeks 1, 2, 4, 6, 8 and 10. At Week 12, patients receiving brodalumab were re-randomized 2:2:2:1 to receive a brodalumab maintenance dose of

210 mg every 2 weeks (Q2W) or 140 mg Q2W, every 4 weeks, or every 8 weeks. Patients receiving ustekinumab continued to receive ustekinumab every 12 weeks and patients receiving placebo switched to brodalumab 210 mg Q2W.

Patients were eligible for rescue treatment at Week 16, if they had an inadequate response (sPGA ≥3, or sPGA ≥2 for ≥4 weeks at, or after, Week 16) and were treated with brodalumab 210 mg Q2W. From Week 16 through Week 52, patients on brodalumab were rescued with brodalumab 210 mg Q2W, while those on ustekinumab remained on ustekinumab. Rescue treatment was blinded, and after ≥12 weeks, patients were evaluated for response and discontinued if they were non-responders.

Trial assessments

PASI, sPGA and Dermatology Life Quality Index (DLQI) scores were used to evaluate disease severity, treatment response and QoL, respectively. Measures were obtained throughout the trials at least once every 2–4 weeks.

Post hoc efficacy analyses

Responder analyses for clearance (PASI 90, PASI 100) and DLQI 0/1 at a given time point (Week 0–52) by prior treatment subgroup These analyses included data from patients randomized to receive constant dosing of the approved dose of either brodalumab (210 mg Q2W) or ustekinumab for the entire 52-week treatment period, subdivided into four subgroups according to prior treatment history: systemic/biologic-naïve; systemic-treated, biologic-naïve; biologic-treated without failure; biologic-treated with failure.

Proportions of patients achieving PASI 100 and DLQI 0/1 responses were presented according to prior treatment history and visits, with comparisons between treatment groups being reported as odds ratios (OR) and 95% confidence intervals (CI) calculated using the Cochran–Mantel–Haenszel method and adjusted for study, baseline total bodyweight group (≤100 kg, >100 kg), geographic region, and within study and subgroup baseline score (≤median, >median). Non-responder imputation (NRI) was used to handle missing data.

Cumulative treatment benefit as integrated AUC for PASI 100 and DLQI 0/1 by prior treatment subgroup Cumulative clinical benefit was assessed as the integrated AUC over the 52-week trial period for the percentage of patients achieving complete clearance and using NRI for missing data. The AUC was calculated using the trapezoidal rule:

$$\text{Total AUC} = \sum_{i}^{N} =_{0}^{1/2} (P_i + P_{i+1})\,(T_{i+1} - T_i)$$

where N = number of assessment time points, 0 = baseline, P_i = percentage of responders, T_i = time point.

Cumulative benefit was calculated as a percentage of the maximum possible nominal AUC of 5200 (based on a 100% response rate over 52 weeks). *P*-values for treatment differences of brodalumab vs. ustekinumab were tested using a *Wilcoxon* test. Ratios of AUC (brodalumab total AUC value divided by ustekinumab total AUC value) were calculated, with values >1.0 indicating a greater clinical benefit for brodalumab vs. ustekinumab. Bootstrapping was used to calculate 95% CIs.

Competing risk model by prior treatment subgroup Cumulative incidence of complete clearance over 52 weeks was analysed by prior treatment subgroup using a competing risk model[25] with outcomes of:

- Achieving PASI 100, or
- Inadequate response defined as sPGA ≥3 or sPGA ≥2 for more than 4 weeks at, or after Week 16.

Comparisons between treatment arms were performed using subdistribution hazard ratios and associated chi-squared tests[26,27] and adjusted for baseline characteristics, as detailed for the responder analyses.

Association between PASI response and QoL Association between PASI and DLQI was examined by all pairs of PASI response category and DLQI 0/1 at the same time point (Weeks 0–52), but if either DLQI or PASI were missing the data could not be included in the analysis. Tests for trend were done using logistic regression.

Proportion of time spent in different response states The proportion of time spent from baseline through Week 52 in PASI <50, 50–<75, 75–<90, 90–<100 and 100 and requirement for rescue treatment were calculated for brodalumab and ustekinumab for each prior treatment group. PASI observed per visit was assumed to apply until the next scheduled visit. A PASI <50 was assumed for all patients for the period from baseline until the Week 1 visit. Missing visits were imputed with PASI <50 and the planned visit date (study start date + 7 × visit week).

Pooled data from AMAGINE-2 and AMAGINE-3 were analysed at all time points and by previous treatment subgroups to assess the association between PASI response and the proportion of patients achieving a DLQI score of 0 or 1, as a measure of QoL. The linear trend between DLQI 0/1 and PASI was evaluated using an adjusted generalized estimating equation (GEE) model. Missing data were handled using NRI.

Results

Patients

A total of 929 patients (brodalumab 210 mg, n = 339; ustekinumab, n = 590) from AMAGINE-2 and AMAGINE-3 were included in the analyses of complete clearance and cumulative

Table 1 Demographic and baseline characteristics

Baseline characteristics	Systemic/biologic-naïve		Systemic-treated biologic-naive	
	Brodalumab (*n* = 144, 42.5%)	Ustekinumab (*n* = 249, 42.2%)	Brodalumab (*n* = 99, 29.2%)	Ustekinumab (*n* = 186, 31.5%)
Age, mean (SD)	44.3 (12.8)	44.5 (13.7)	42.2 (13.4)	45.6 (12.8)
Weight, mean (SD)	89.6 (19.1)	89.0 (20.9)	89.0 (23.8)	89.3 (21.7)
Male, *n* (%)	103 (71.5)	171 (68.7)	74 (74.7)	132 (71.0)
Race white, *n* (%)	125 (86.8)	224 (90.0)	92 (92.9)	175 (94.1)
Duration of disease, years (mean [SD])	14.1 (10.5)	17.0 (12.4)	17.2 (11.4)	19.7 (12.3)
BSA, mean (SD)	25.6 (15.3)	26.8 (17.7)	30.3 (17.9)	29.7 (20.2)
PASI, mean (SD)	20.1 (8.1)	19.5 (7.7)	21.7 (8.4)	21.1 (9.8)
DLQI, mean (SD)	13.5 (7.0)	14.5 (7.4)	16.0 (7.2)	15.5 (7.3)
NAPSI, mean (SD)	9.0 (3.0)	10.2 (3.6)	9.6 (4.1)	9.6 (3.6)
PSI, *n*, mean (SD)	127, 17.7 (7.5)	237, 17.8 (6.9)	94, 19.4 (6.4)	175, 18.8 (6.7)
PsA, *n* (%)	17 (11.8)	31 (12.4)	17 (17.2)	30 (16.1)
Baseline characteristics	**Biologic-treated without failure**		**Biologic-treated with failure**	
	Brodalumab (*n* = 50, 14.8%)	Ustekinumab (*n* = 95, 16.1%)	Brodalumab (*n* = 46, 13.6%)	Ustekinumab (*n* = 60, 10.2%)
Age, mean (SD)	49.4 (12.9)	45.1 (13.4)	45.0 (14.8)	46.1 (10.5)
Weight, mean (SD)	92.1 (26.4)	96.9 (27.7)	93.8 (34.9)	95.6 (24.1)
Male, *n* (%)	23 (46.0)	61 (64.2)	30 (65.2)	40 (66.7)
Race white, *n* (%)	48 (96.0)	82 (86.3)	43 (93.5)	51 (85.0)
Duration of disease, years (mean [SD])	23.8 (12.0)	19.2 (11.7)	20.3 (12.4)	21.0 (11.4)
BSA, mean (SD)	25.8 (15.4)	24.7 (16.9)	25.8 (15.4)	29.0 (19.4)
PASI, mean (SD)	19.3 (6.8)	19.1 (7.4)	19.7 (6.7)	20.0 (7.8)
DLQI, mean (SD)	15.1 (7.2)	14.8 (7.3)	15.9 (7.8)	14.8 (7.1)
NAPSI, mean (SD)	9.2 (2.5)	10.4 (3.8)	9.8 (5.0)	9.4 (3.3)
PSI, *n*, mean (SD)	46, 19.9 (7.2)	90, 20.2 (6.9)	44, 21.1 (6.0)	55, 19.5 (7.0)
PsA, *n* (%)	27 (54.0)	30 (31.6)	18 (39.1)	19 (31.7)

BSA, body surface area; DLQI, Dermatology Life Quality Index; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PSI, Psoriasis Symptom Inventory; SD, standard deviation.

treatment benefit (Table 1). Patients were generally well balanced in terms of age and weight. There tended to be fewer males in the biologic-treated with and without failure subgroups. Disease durations ranged from 14 to 24 years. Baseline PASI scores and DLQI scores were similar across the subgroups and ranged from 19 to 22 and from 14 to 16. The proportions of patients with psoriatic arthritis ranged from 12% to 54% (Table 1).

Similar proportions of the brodalumab and ustekinumab patients had received prior biologic treatment, with a slightly higher proportion of brodalumab patients having a treatment failure. This mainly reflects higher rates of failure with infliximab treatment in this group (Table 2). Of note, eight patients with prior ustekinumab use entered into the trials (Table 2); prior ustekinumab exposures were >40 weeks before the baseline visit. Analysis of all efficacy endpoints to exclude these eight subjects yielded no significant changes to the results.

Efficacy analyses

Responder analysis for complete clearance (PASI 100) and DLQI 0/1 at a given time point (Week 0–52) by prior treatment subgroup There was a clear difference in favour of brodalumab in the proportion achieving PASI 100 (Fig. 1a) in each subgroup. Regardless of treatment history, brodalumab was associated with earlier achievement of complete clearance and consistently higher rates of complete clearance vs. ustekinumab. ORs (95% CI) for complete clearance with brodalumab vs. ustekinumab at Week 52 were as follows: systemic/biologic-naïve, OR 2.29 (1.47–3.58, $P = 0.0002$); systemic-treated, biologic-naïve, OR 2.87 (1.71–4.83, $P < 0.0001$); biologic-treated without failure, OR 6.89 (2.64–17.94, $P < 0.0001$); biologic-treated with failure, OR 5.03 (1.54–16.43, $P = 0.0065$).

Similarly, greatest brodalumab treatment benefit vs. ustekinumab was observed for DLQI, with more patients in the biologic-treated subgroup achieving DLQI 0/1 (Fig. 1b).

Table 2 Summary of prior biologic treatment history for all patients and with respect to specific biologics

Baseline characteristics	Systemic/biologic-naïve		Systemic-treated biologic-naive	
	Brodalumab (n = 144, 42.5%)	Ustekinumab (n = 249, 42.2%)	Brodalumab (n = 99, 29.2%)	Ustekinumab (n = 186, 31.5%)
Prior biologic experience	0 (0)	0 (0)	0 (0)	0 (0)
Prior biologic-failure	0 (0)	0 (0)	0 (0)	0 (0)
Prior biologic use				
Adalimumab	0 (0)	0 (0)	0 (0)	0 (0)
Infliximab	0 (0)	0 (0)	0 (0)	0 (0)
Ustekinumab	0 (0)	0 (0)	0 (0)	0 (0)
Golimumab	0 (0)	0 (0)	0 (0)	0 (0)
Etanercept	0 (0)	0 (0)	0 (0)	0 (0)
Onercept	0 (0)	0 (0)	0 (0)	0 (0)
Abatacept	0 (0)	0 (0)	0 (0)	0 (0)
Alefacept	0 (0)	0 (0)	0 (0)	0 (0)
Briakinumab	0 (0)	0 (0)	0 (0)	0 (0)
Efalizumab	0 (0)	0 (0)	0 (0)	0 (0)
Baseline characteristics	**Biologic-treated without failure**		**Biologic-treated with failure**	
	Brodalumab (n = 50, 14.8%)	Ustekinumab (n = 95, 16.1%)	Brodalumab (n = 46, 13.6%)	Ustekinumab (n = 60, 10.2%)
Prior biologic experience	50 (100.0)	95 (100.0)	46 (100.0)	60 (100.0)
Prior biologic-failure	0 (0)	0 (0)	46 (100.0)	60 (100.0)
Prior biologic use				
Adalimumab	12 (24.0)	16 (16.8)	30 (65.2)	33 (55.0)
Infliximab	6 (12.0)	3 (3.2)	10 (21.7)	11 (18.3)
Ustekinumab	0 (0)	2 (2.1)	2 (4.3)	4 (6.7)
Golimumab	0 (0)	2 (2.1)	0 (0)	0 (0)
Etanercept	25 (50.0)	64 (67.4)	28 (60.9)	47 (78.3)
Onercept	2 (4.0)	0 (0)	0 (0)	0 (0)
Abatacept	0 (0)	0 (0)	1 (2.2)	0 (0)
Alefacept	2 (4.0)	2 (2.1)	2 (4.3)	0 (0)
Briakinumab	5 (10.0)	6 (6.3)	2 (4.3)	4 (6.7)
Efalizumab	1 (2.0)	2 (2.1)	5 (10.9)	4 (6.7)

Cumulative treatment benefit as integrated AUC for PASI 100 and DLQI 0/1 by prior treatment subgroup Brodalumab demonstrated similar cumulative treatment benefit (PASI 100) for all treatment subgroups, except those who previously experienced a treatment failure with a biologic (Fig. 1a; Table 3). The decrease in efficacy in biologic-treated patients was higher with ustekinumab, with greater than two-fold reduction in complete clearance. Treatment escalation with brodalumab was more likely to result in achievement of PASI 100 compared with ustekinumab (AUC ratios ranging from 1.5 [systemic/biologic-naïve] to 2.4 [biologic-treated without failure], all $P < 0.001$) (Table 3). Differences in cumulative treatment benefit favouring brodalumab were also observed for PASI 90. AUC ratios ranged from 1.3 (systemic/biologic-naïve) to 1.9 (biologic-treated with failure) across prior treatment groups with all $P < 0.001$ (Table 3).

Similar findings were observed with respect to achievement of DLQI 0/1. The highest mean AUC was observed for the brodalumab, systemic-treated, biologic-naïve subgroup (2941 units). AUC ratios ranged from 1.3 (systemic/biologic-naïve) to 1.7 (biologic-treated with failure), all $P < 0.01$ with the highest ratio being observed in the brodalumab vs. ustekinumab biologic-treated with failure subgroup (Table 3).

Competing risk model by prior treatment subgroup The 52-week cumulative incidence of patients achieving PASI 100 was consistently higher for brodalumab vs. ustekinumab across prior treatment subgroups (all $P < 0.0001$). In systemic/biologic-naïve patients, 76% [95% CI: 69–84%] of brodalumab patients achieved PASI 100 vs. 58% [52–65%] of ustekinumab patients (Fig. 2a). In the systemic-treated/biologic-naïve subgroup, 78% [70–87%] of brodalumab patients vs. 55% [48–62%] of ustekinumab patients achieved PASI 100 (Fig. 2b). In the biologic-treated without failure

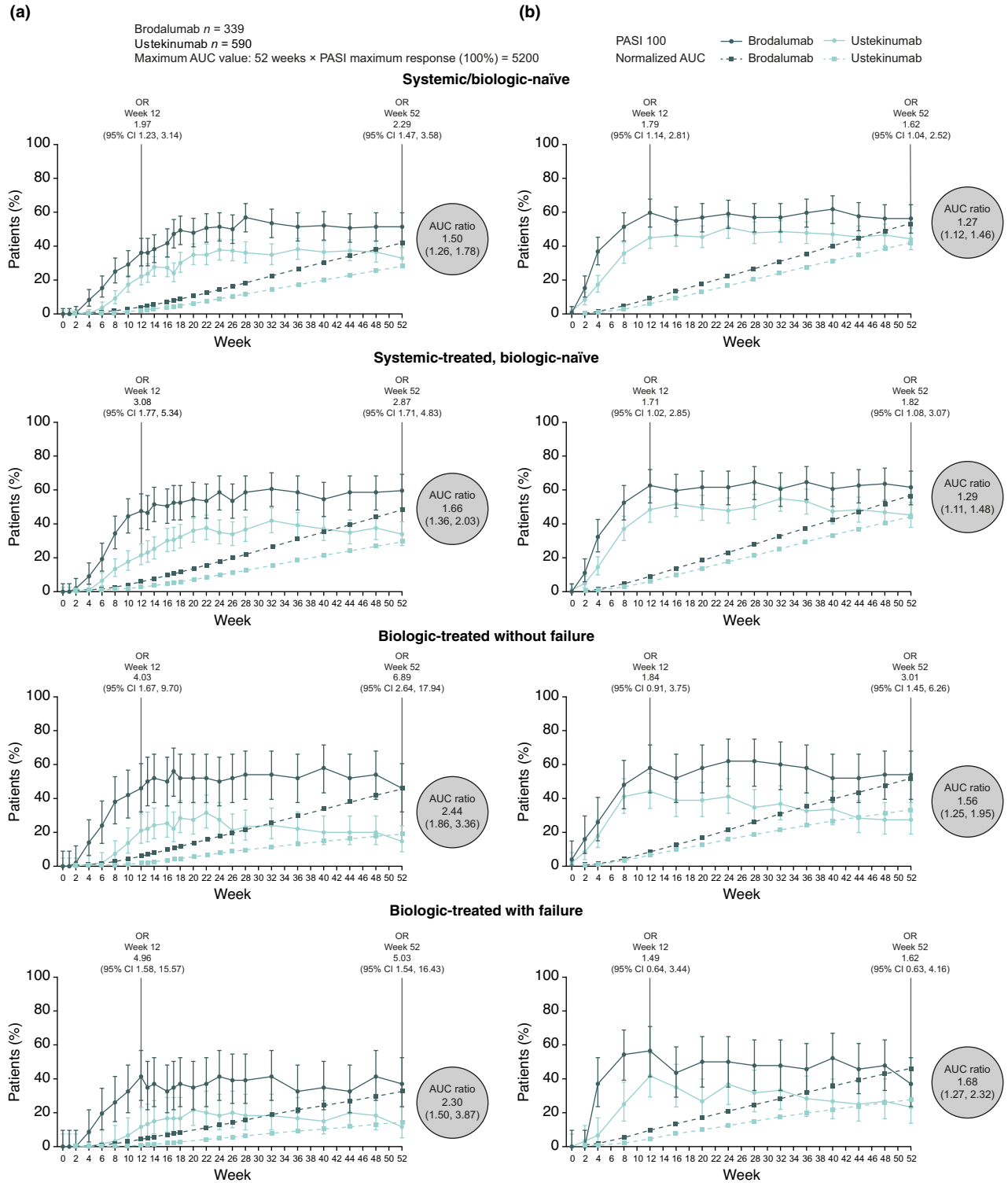

Figure 1 Percentage of patients achieving PASI 100 (a) and DLQI 0/1 (b) and normalized AUC through Week 52 by prior treatment subgroup. Pooled data from the AMAGINE-2 and AMAGINE-3 trials. AUC, area under the curve; CI, confidence interval; DLQI, Dermatology Life Quality Index; OR, odds ratio; PASI, Psoriasis Area and Severity Index.

Table 3 Cumulative treatment benefit of brodalumab and ustekinumab at Week 52 by prior treatment subgroup

	Brodalumab 210 mg			Ustekinumab			Difference (BRO vs. UST)			
	N	AUC mean	Normalized AUC (%)	N	AUC mean	Normalized AUC (%)	Mean	% Normalized AUC difference	AUC ratio	*P*-value
PASI 100										
Systemic/biologic-naïve	144	2198	42.3	249	1469	28.3	729	14.0	1.50 (1.26, 1.78)	<0.0001
Systemic-treated, biologic-naïve	99	2518	48.4	186	1521	29.3	998	19.2	1.66 (1.36, 2.03)	<0.0001
Biologic-treated without failure	50	2391	46.0	95	980	18.9	1411	27.1	2.44 (1.86, 3.36)	<0.0001
Biologic-treated with failure	46	1691	32.5	60	735	14.1	956	18.4	2.30 (1.50, 3.87)	0.0002
PASI 90										
Systemic/biologic-naïve	144	3254	64.6	249	2546	49.0	709	13.6	1.28 (1.14, 1.43)	<0.0001
Systemic-treated, biologic-naïve	99	3362	71.7	186	2403	46.2	959	18.4	1.40 (1.23, 1.60)	<0.0001
Biologic-treated without failure	50	3129	56.0	95	1703	32.8	1426	27.4	1.84 (1.50, 2.28)	<0.0001
Biologic-treated with failure	46	2700	47.8	60	1434	27.6	1266	24.3	1.88 (1.38, 2.64)	0.0003
DLQI 0/1										
Systemic/biologic-naïve	144	2779	53.4	249	2184	42.0	594	11.4	1.27 (1.12, 1.46)	0.0013
Systemic-treated, biologic-naïve	99	2941	56.6	186	2284	43.0	657	12.6	1.29 (1.11, 1.48)	0.0036
Biologic-treated without failure	50	2686	51.7	95	1718	33.0	967	18.6	1.56 (1.25, 1.95)	0.0045
Biologic-treated with failure	46	2380	45.8	60	1420	27.3	960	18.5	1.68 (1.27, 2.32)	0.0077

P = *Wilcoxon* test.

AUC, area under the curve; BRO, brodalumab; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; UST, ustekinumab.

subgroup, 75% [63–89%] of brodalumab patients achieved PASI 100 compared with 41% [32–53%] of ustekinumab patients (Fig. 2c). In the biologic-failure subgroup, 70% [57–86%] of brodalumab patients achieved PASI 100 compared with 30% [20–45%] of ustekinumab patients (Fig. 2d). Moreover, there were fewer inadequate responders to brodalumab compared with ustekinumab (Fig. 2).

The incidence of treatment response and inadequate response was not affected by prior treatment history for brodalumab ($P = 0.709$), unlike for ustekinumab ($P = 0.001$). The median time to achieve complete clearance could not be estimated for ustekinumab patients in the biologic-treated with and without failure subgroups, as <50% of patients achieved complete clearance by Week 52.

Proportion of time spent in PASI response states The proportion of time spent in PASI 100 was consistently higher following treatment with brodalumab (32–47%) compared with ustekinumab (14–29%) across all treatment subgroups (Fig. 3). Further, proportionately less time was spent on rescue treatment for patients treated with brodalumab (13–22%) compared with ustekinumab (21–40%) across treatment groups, with the highest proportion of time spent in rescue treatment in the prior biologic-failure group for both treatments (Fig. 3).

Association between skin clearance and QoL A significant association was observed between the PASI response level and QoL, as measured by achievement of DLQI 0/1, across all treatment subgroups ($P < 0.0001$; Fig. 4).

Discussion

With the emergence of modern biologic therapies such as brodalumab and ustekinumab, achievement of PASI 100 (complete skin clearance) becomes a viable treatment endpoint. Here, we assessed the cumulative attainment of different levels of PASI or requirement for rescue treatment to better understand the rapidity and sustainability of any observed treatment responses, with patients being subdivided into four subgroups according to prior treatment history. We found that, regardless of prior treatment history, proportionately more patients treated with brodalumab compared with ustekinumab achieved PASI 100 and proportionately fewer of them required rescue treatment. We also demonstrated that complete clearance was achieved more rapidly in more patients treated with brodalumab compared with ustekinumab, consistent with findings of a previous analysis of AMAGINE-2 and AMAGINE-3 trial data; rates of complete clearance at Week 12 were equivalent in patients treated with brodalumab with (40.9%) or without (39.5%) prior exposure to biologics, including whether (41.7%) or not (32.0%) they were responsive to prior biologics.[13] Furthermore, our analyses showed that response rates with brodalumab were consistent across four subgroups in the treatment pathway (systemic/biologic-naïve, systemic-treated/biologic-naïve, biologic-treated without failure, biologic-treated with failure). These findings are particularly promising with respect to the latter group. In addition to intolerance/side-effects, or even commercial withdrawal, a substantial number of patients discontinue biologic treatment because of primary or secondary treatment failure.

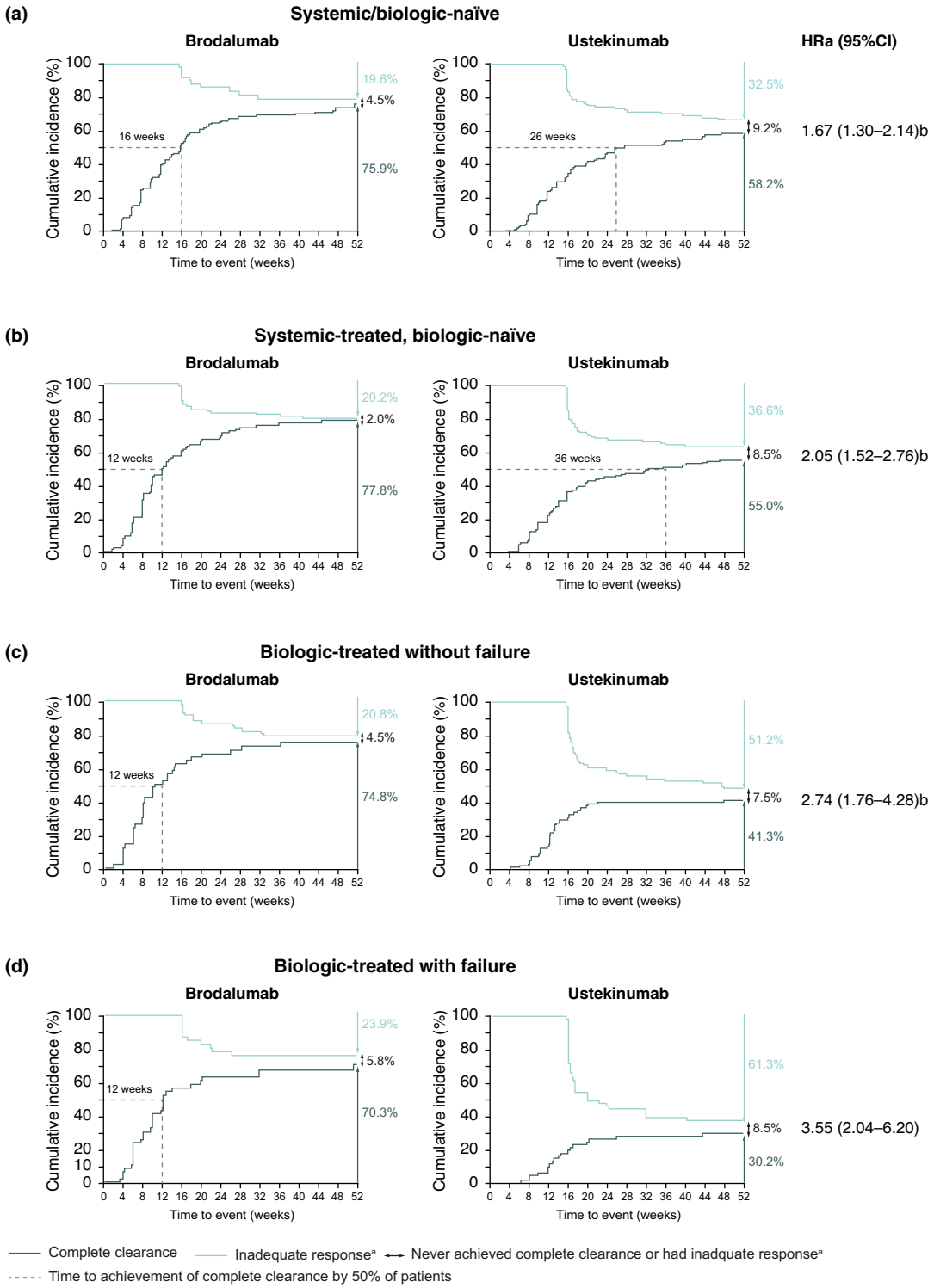

Figure 2 Cumulative incidence of patients in AMAGINE-2 and AMAGINE-3 trials achieving PASI 100 at least once at any given time point (competing risk analysis). [a]Defined as a static Physician's Global Assessment >3 or persistent values of 2 over at least a 4-week period at or after Week 16. [b]HR of complete clearance cumulative incidence. CI, confidence interval; HR, hazard ratio; PASI, Psoriasis Area and Severity Index.

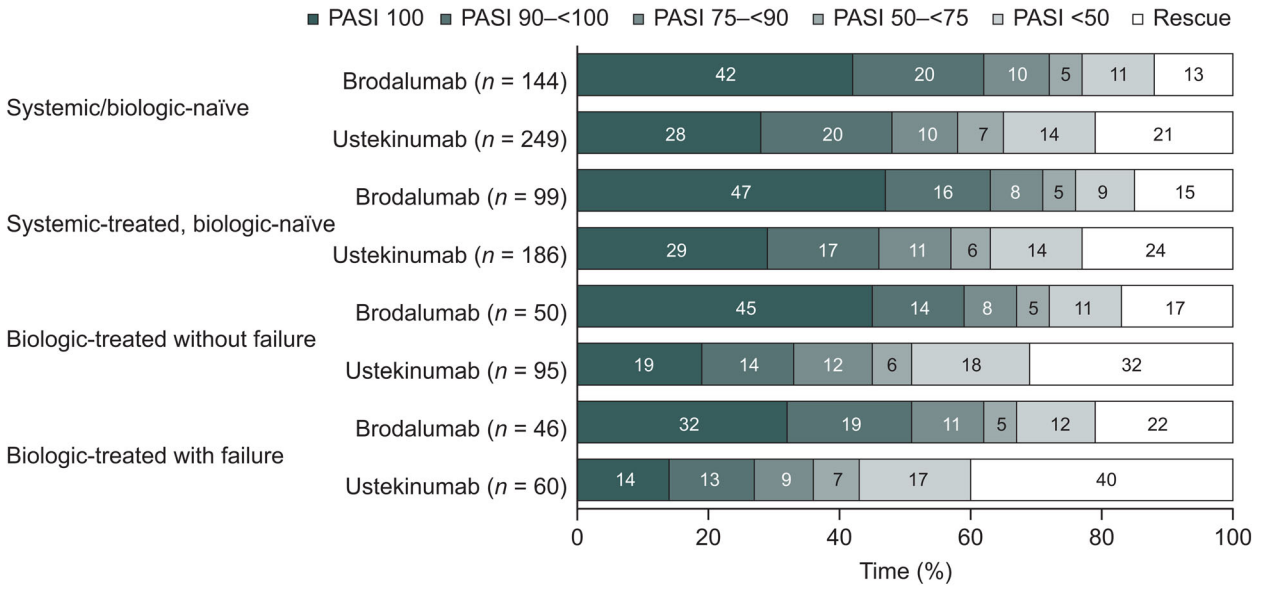

Figure 3 Proportion of time spent in different response states. PASI, Psoriasis Area and Severity Index.

Furthermore, in subsequent biologic treatment, the second agent typically offers reduced benefit compared with the first treatment.[7]

AUC analyses which capture the sustainability of treatment response over time[24] suggested the cumulative benefit of brodalumab was greater than with ustekinumab over 52 weeks for each of the treatment pathway subgroups. Our analyses further suggest that unlike ustekinumab, response to brodalumab was not dependent on prior treatment history.

Improvement in QoL as measured by DLQI has been shown to associate with achievement of PASI in patients treated with brodalumab,[12] with patients achieving PASI 100 being more likely to also achieve DLQI 0/1 than those with PASI 90. These findings are analogous to earlier observations of Revicki *et al.* who showed that the PASI 90 or 100 responders among 1469 patients in two adalimumab clinical trials had greater improvements in their DLQI total score than the PASI 75 responders.[28] To achieve clinically meaningful benefit for patients affected by plaque psoriasis, it is clearly important to target the rigorous treatment goals of PASI 90 or ideally, PASI 100. Recent data suggest that PASI 100 is associated with substantially reduced physical burden of psoriasis, increased treatment satisfaction, and improved QoL in both the clinical trial and real-world settings.[19-21,28-30]

The achievement of complete clearance may be of particular importance for patients who have failed multiple prior therapies. These patients have had a longer disease duration, negatively impacting on QoL with a consequent higher disease burden. The patients are also the ones least likely to respond to any new treatment. The data from this study suggest switching to brodalumab may offer a viable treatment strategy for some of these patients since consistent rates of complete clearance were observed even in the patients who had previously failed to respond to biologics.

There are a number of limitations to this study. Firstly, the data analysed were from a clinical trial population with strict entry criteria and as such findings may not be generalizable to broader populations. Secondly, four patients previously treated with ustekinumab with failure were retreated with ustekinumab. This may have contributed to the lack of efficacy in this subgroup. Thirdly, these were post hoc efficacy analyses of data from trials not specifically statistically powered to assess the endpoints of interest here. The analyses were also restricted to patients in constant treatment arms, thus reducing the number of patients available for inclusion. This particularly affected the subgroup analyses. Finally, the determination of PASI assessment response is subjective, as minor psoriatic lesions may be missed during examination.

In conclusion, the results of these analyses suggest higher rates of complete clearance are achieved and maintained with brodalumab compared with ustekinumab regardless of prior treatment history. Furthermore, these excellent response rates remain high over time. Brodalumab, with its unique mechanism of action, may offer a good treatment option for patients who have failed previous therapies.

Acknowledgements

RBW is supported by the Manchester NIHR Biomedical Research Centre. Medical writing support provided by Susan Dyas, MSc, from Adelphi Communications Ltd, Bollington, UK,

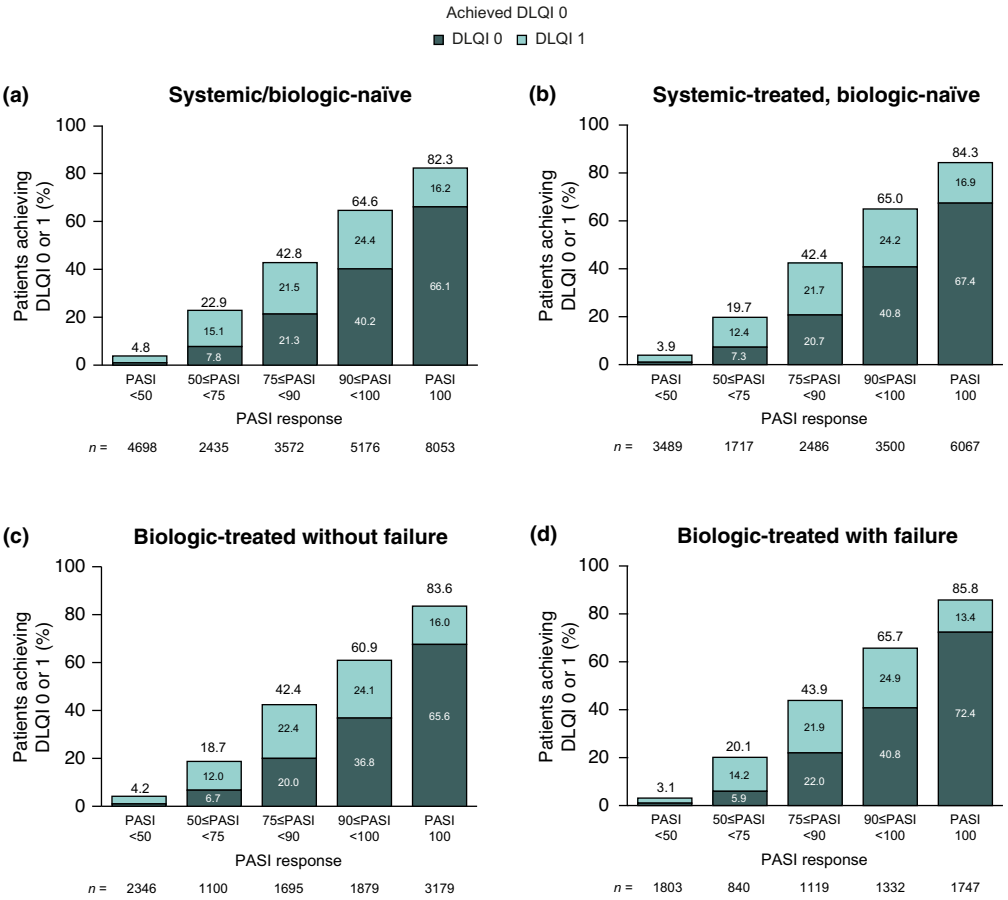

Figure 4 Association between PASI response and QoL. Pooled data from the AMAGINE-2 and AMAGINE-3 trials. DLQI, Dermatology Life Quality Index; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; QoL, quality of life.

and additional editorial support by Grace Jeong, PhD, from Alphabet Health, New York, NY, USA, were funded by LEO Pharma in accordance with Good Publication Practice (GPP3) guidelines. All authors participated in interpreting the results and writing the manuscript and approved the final version for submission. AstraZeneca was not involved in the decision to publish these analyses and did not participate in the preparation of this manuscript.

References

1 Menter A, Strober BE, Kaplan DH *et al*. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol* 2019; **80**: 1029–1072.
2 Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol* 2014; **70**: 512–516.
3 World Psoriasis Day Consortium, 2020.
4 Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. *Can Fam Physician* 2017; **63**: 278–285..
5 Pathirana D, Ormerod AD, Saiag P *et al*. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; **23**(Suppl 2): 1–70.
6 Edson-Heredia E, Sterling KL, Alatorre CI *et al*. Heterogeneity of response to biologic treatment: perspective for psoriasis. *J Invest Dermatol* 2014; **134**: 18–23.
7 Karczewski J, Poniedziałek B, Rzymski P, Adamski Z. Factors affecting response to biologic treatment in psoriasis. *Dermatol Ther* 2014; **27**: 323–330.
8 Russell CB, Rand H, Bigler J *et al*. Gene expression profiles normalized in psoriatic skin by treatment with brodalumab, a human anti-IL-17 receptor monoclonal antibody. *J Immunol* 1950; **2014**(192): 3828–3836.
9 Frieder J, Kivelevitch D, Menter A. Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis. *Therap Adv Chronic Dis* 2018; **9**: 5–21.
10 Syed YY. Ixekizumab: a review in moderate to severe plaque psoriasis. *Am J Clin Dermatol* 2017; **18**: 147–158.
11 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.

12 Warren RB, Hansen JB, Reich K, Paul C, Puig L. Complete clearance and psoriasis area and severity index response for brodalumab and ustekinumab in AMAGINE-2 and -3. *J Eur Acad Dermatol Venereol* 2021; **35** (2): 450–457.
13 Papp KA, Gordon KB, Langley RG *et al*. Impact of previous biologic use on the efficacy and safety of brodalumab and ustekinumab in patients with moderate-to-severe plaque psoriasis: integrated analysis of the randomized controlled trials AMAGINE-2 and AMAGINE-3. *Br J Dermatol* 2018; **179**: 320–328.
14 Alwawi EA, Mehlis SL, Gordon KB. Treating psoriasis with adalimumab. *Ther Clin Risk Manag* 2008; **4**: 345–351.
15 Farhi D. Ustekinumab for the treatment of psoriasis: review of three multicenter clinical trials. *Drugs of Today* 2010; **46**(4): 259–264.
16 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**: 1367–1374.
17 Manalo IF, Gilbert KE, Wu JJ. Time to raise the bar to psoriasis area severity index 90 and 100. *J Drugs Dermatol* 2015; **14**: 1086–1088.
18 Blauvelt A, Reich K, Tsai T-F *et al*. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. *J Am Acad Dermatol* 2017; **76**: 60–69.e69.
19 Strober B, Papp KA, Lebwohl M *et al*. Clinical meaningfulness of complete skin clearance in psoriasis. *J Am Acad Dermatol* 2016; **75**(1): 77–82.e7.
20 Takeshita J, Callis Duffin K, Shin DB *et al*. Patient-reported outcomes for psoriasis patients with clear versus almost clear skin in the clinical setting. *J Am Acad Dermatol* 2014; **71**: 633–641.
21 Viswanathan HN, Chau D, Milmont CE *et al*. Total skin clearance results in improvements in health-related quality of life and reduced symptom severity among patients with moderate to severe psoriasis. *J Dermatol Treat* 2015; **26**: 235–239.
22 Puig L, Thom H, Mollon P, Tian H, Ramakrishna GS. Clear or almost clear skin improves the quality of life in patients with moderate-to-severe psoriasis: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2017; **31**: 213–220.
23 Girolomoni G, Griffiths CEM, Krueger J *et al*. Early intervention in psoriasis and immune-mediated inflammatory diseases: a hypothesis paper. *J Dermatol Treat* 2015; **26**: 103–112.
24 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 Dermatol Treat* 2017; **28**: 200–205.
25 Aalen OO, Johansen S. An empirical transition matrix for non-homogeneous markov chains based on censored observations. *Scan J Stat* 1978; **5**: 141–150.
26 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**: 496–509.
27 Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; **16**: 1141–1154.
28 Revicki DA, Willian MK, Menter A, Saurat JH, Harnam N, Kaul M. Relationship between clinical response to therapy and health-related quality of life outcomes in patients with moderate to severe plaque psoriasis. *Dermatology* 2008; **216**: 260–270.
29 Feldman SR, Bushnell DM, Klekotka PA *et al*. Differences in psoriasis signs and symptom severity between patients with clear and almost clear skin in clinical practice. *J Dermatol Treat* 2016; **27**: 224–227.
30 Lacour J-P, Bewley A, Hammond E *et al*. Association between patient- and physician-reported outcomes in patients with moderate-to-severe plaque Psoriasis treated with Biologics in Real Life (PSO-BIO-REAL). *Dermatol Ther* 2020; **10**: 1099–1109.

Supporting information

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

Figure S1. Study designs for the phase 3 randomized, controlled AMAGINE-2 and AMAGINE-3 trials of brodalumab in patients with moderate-to-severe psoriasis. R, randomized; Q2W, every 2 weeks; Q4W, every 4 weeks.