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ORIGINAL ARTICLE

Complete clearance and psoriasis area and severity index response for brodalumab and ustekinumab in AMAGINE-2 and -3

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Abstract

Background Modern biologics achieve complete skin clearance [100% improvement in psoriasis area and severity index (PASI 100)] in 30–45% of psoriasis patients. Cumulative benefit considering rapidity, frequency and sustainability of response has not been thoroughly investigated.

Objectives Compare the frequency, rapidity and sustainability of PASI 90 and 100 response in patients with moderate-to-severe psoriasis treated with brodalumab or ustekinumab.

Methods Integrated analyses of the brodalumab Phase III AMAGINE-2 (NCT01708603) and -3 (NCT01708629) trials were performed to determine proportion of patients achieving PASI response per visit; corresponding odds ratios (OR) were calculated. Cumulative clinical benefit of treatment was determined with area-under-the-curve (AUC) analysis. Cumulative incidence of response was analysed using a competing risk model of PASI response or rescue. Sustained response was evaluated by time to inadequate response using Kaplan–Meier methods. Proportion of time spent in different response states was descriptively analysed. Association between PASI response and health-related quality of life [Dermatology Life Quality Index (DLQI)] was assessed using data from all treatment groups from AMAGINE-1, -2 and -3.

Results A significantly higher proportion of patients treated with brodalumab achieved PASI 100 vs. ustekinumab (Week 52: 51% vs. 28%; OR [95% CI] 2.8 [2.1, 3.7]; $P < 0.0001$), with significant differences observed from Week 4. Cumulative benefit through 52 weeks was 69% higher with brodalumab (AUC ratio: 1.69; $P < 0.001$). Brodalumab patients were also significantly more likely to achieve a PASI 100 at least once over 52 weeks vs. ustekinumab (76% vs. 52%; $P < 0.0001$). Once response was achieved, brodalumab patients had a low likelihood of failure or need for rescue. There was significant positive association between PASI response level and DLQI0/1 achievement ($P < 0.0001$).

Conclusion Brodalumab treatment resulted in significantly higher levels of skin clearance, longer sustained response and greater cumulative treatment benefit vs. ustekinumab.

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Conflicts of interest

JB Hansen is an employee of LEO Pharma. No other conflicts of interest have been declared. Dr Warren 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. Dr Puig 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. Dr Paul has been a consultant for and has received grants from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sandoz and UCB Pharma. Dr. Reich 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,

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Introduction

Psoriasis is a chronic, systemic inflammatory skin disease that affects 2–3% of the worldwide population.[1–3] Management of moderate-to-severe psoriasis may require phototherapy, non-biologic systemic agents and biologics.[4] These agents target cytokines responsible for psoriasis manifestations, including interleukin 17 (IL-17), interleukin 23 (IL-23) and tumour necrosis factor-alpha (TNF-alpha).[4,5]

Brodalumab is a fully human monoclonal antibody that targets the IL-17 receptor A (IL-17 RA), a common subunit of multiple heterodimeric IL-17 receptor complexes.[6] It directly blocks IL-17 by binding to its receptor, thereby inhibiting downstream signalling of multiple IL-17 family cytokines that are involved in the pathogenesis of psoriasis,[6] as opposed to specifically targeting IL-17A like secukinumab and ixekizumab.[7,8] Results from Phase III clinical trials show that brodalumab provides high levels of skin clearance for up to 52 weeks, in patients with moderate-to-severe psoriasis.[9,10]

Despite the availability of numerous therapies, many patients do not achieve complete clearance.[11–14] The Psoriasis Area and Severity Index (PASI) is the most widely used tool for measuring treatment effect of psoriasis medications. PASI 75 response (≥75% reduction from baseline in PASI score) has long been a treatment goal for plaque psoriasis,[15–18] but studies of newer biologics (particularly anti-IL-17 and IL-23 therapies) also include PASI 90 and 100.[9,10,19–23] Complete skin clearance may be the next clinically meaningful treatment goal, as it is associated with substantially reduced psoriasis symptom severity and improved quality of life (QoL).[24–26] Even limited residual skin disease can impact patients' QoL, since incremental improvements in QoL have been observed between PASI 100 and PASI 90.[24–26]

Traditional efficacy end points at fixed time points in clinical trials may not be sufficient for fully understanding treatment benefit over time. The physical, psychological, social and economic burden of psoriasis may cumulatively result in failure to achieve 'full life potential' in some patients, a concept known as 'cumulative life course impairment' (CLCI).[27–29] As the impact of psoriasis is continuous, cumulative treatment benefit using an area-under-the-curve (AUC) analysis should be considered.[30] This estimates total time spent at a particular PASI response level, capturing the rapidity and sustainability of response.

We report an integrated analysis of the AMAGINE Phase III randomized controlled trials evaluating proportions of patients achieving PASI 100 and PASI 90 with brodalumab vs. ustekinumab [a human immunoglobulin G1κ (IgG1κ) monoclonal antibody targeting the p40 subunit that is common to IL-12 and IL-23] over 52 weeks. We determined the cumulative benefit of brodalumab treatment in patients with moderate-to-severe psoriasis using an AUC analysis and investigated the association between PASI response and QoL.

Methods

Trial design and patients

Data were pooled from a Phase III randomized, double-blind, placebo-controlled, 52-week trial of brodalumab (AMAGINE-1, NCT01708590)[9] and two Phase III randomized, double-blind, placebo- and ustekinumab-controlled 52-week trials of brodalumab (AMAGINE-2, NCT01708603 and AMAGINE-3, NCT01708629).[10] Detailed descriptions of these trial designs were previously published[9,10] and are illustrated in Figure S1. In brief, all three trials enrolled patients ≥18 years of age with moderate-to-severe plaque psoriasis of ≥6 months' duration, defined as a PASI score ≥12, static Physician's Global Assessment (sPGA) score of ≥3, and ≥10% body surface area (BSA) involvement. A description of AMAGINE-1 is provided in the Appendix S1, and the study design is summarized in Figure S1a. Results of AMAGINE-1 were analysed for associations between PASI and Dermatology Life Quality Index (DLQI).

The studies were conducted in accordance with applicable country and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. The institutional review board at each participating centre approved the study protocols. All patients provided written informed consent. Sites maintained compliance with the Health Insurance Portability and Accountability Act or relevant regional regulations.

In AMAGINE-2 and AMAGINE-3 (Figure S1b), patients were randomized 2 : 2 : 1 : 1 to receive brodalumab 210 mg, brodalumab 140 mg, ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg on Day 1, Week 4, and Q12W thereafter) or placebo on Day 1, as well as Weeks 1, 2, 4, 6, 8 and 10. At Week 12, brodalumab patients were re-randomized 2 : 2 : 2 : 1 to receive a brodalumab maintenance

dose of 210 mg Q2W or 140 mg Q2W, Q4W or Q8W, while ustekinumab patients continued to receive ustekinumab Q12W, and placebo patients received 210 mg of brodalumab Q2W.

Patients were eligible for rescue treatment if they had inadequate response (defined as sPGA ≥3 or persistent values of 2 over a ≥4-week period at, or after, Week 16). At Week 16, all patients received rescue treatment with brodalumab 210 mg. After Week 16 and through Week 52, patients on brodalumab were rescued with brodalumab 210 mg Q2W, while those on ustekinumab remained on ustekinumab. Rescue treatment was blinded. After receiving rescue treatment for ≥12 weeks, patients were assessed for non-response and discontinued if they were non-responders.

The primary objectives of AMAGINE-2 and -3 were to evaluate the efficacy of brodalumab vs. placebo at Week 12 with respect to the proportion of patients achieving PASI 75, and sPGA score of 0 or 1, as well as the efficacy of brodalumab vs. ustekinumab at Week 12, with respect to the proportion of patients achieving PASI 100.

Trial assessments

We used PASI, sPGA and DLQI scores, measured throughout the trials at least once every 2–4 weeks, to evaluate disease severity, treatment response and patient-reported outcomes, respectively.

Integrated efficacy analyses

Treatment benefit: skin clearance These analyses included pooled data from AMAGINE-2 and -3 patients randomized to receive the approved dose of brodalumab (210 mg Q2W) or ustekinumab at constant dosing for the entire 52-week treatment period.

The analyses compared the efficacy of brodalumab vs. ustekinumab in terms of the following:

1 Proportion of patients with PASI 90 and PASI 100 at a given time point over Weeks 0–52 and corresponding adjusted odds ratio (OR) using Cochran–Mantel–Haenszel method were determined.
2 Cumulative clinical benefit was assessed as the integrated AUC over 52 weeks for the percentage of patients achieving PASI 90 and 100. The AUC was calculated using the trapezoidal rule:

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

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 *t*-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, and 95% confidence intervals (CIs) were calculated via bootstrapping.

3 Cumulative incidence of skin clearance over 52 weeks, together with adjusted hazard ratios (HR) and 95% confidence intervals, was calculated using a competing risk model with outcomes of the following:
   a Achieving PASI 90/100
   b Inadequate response defined as sPGA ≥3 or persistent values of 2 over at least a 4-week period at or after Week 16.

Different outcomes were used because PASI 90/100 is the most sensitive measure of skin clearance and sPGA is more appropriate for capturing response.

Once PASI 90/100 was achieved, sustained response was evaluated as the time to an inadequate response, using Kaplan–Meier methods. Results were analysed descriptively, as the subpopulations of PASI responders with brodalumab and ustekinumab might be different.

4 Proportions of patients achieving different levels of treatment response (rescue treatment, PASI <50, 50 to <75, 75 to <90, 90 to <100 and 100) and number of days spent in the different levels of response were determined.
5 Association between skin clearance and QoL

Pooled data from all treatment arms in AMAGINE-1, -2 and -3 were analysed at all time points and for all treatment arms to assess the association between PASI response and the proportion of patients achieving a DLQI score of 0 or 1 (no effect at all on patient's life[31,32]), 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 non-responder imputation.

Results

Patients

A total of 929 patients (brodalumab 210 mg, n = 339; ustekinumab, n = 590) from AMAGINE-2 and -3 were included in the analyses of skin clearance and cumulative treatment benefit. Overall, treatment groups were well balanced in terms of patient demographics and baseline characteristics (Table 1).

Pooled data from 4373 patients from all treatment arms of AMAGINE-1, -2 and -3 were included in the analysis of correlation between skin clearance and QoL.

Efficacy analyses

Proportion of patients achieving skin clearance through 52 weeks A consistently higher proportion of brodalumab-

Table 1 Patient demographic and baseline characteristics (pooled data by treatment arm from the AMAGINE-2 and -3 trials)

Baseline characteristic	Brodalumab (n = 339)	Ustekinumab (n = 590)
Age, years	44.5 (13.4)	45.1 (13.0)
Male, n (%)	230 (67.8)	404 (68.5)
Weight, kg	90.4 (24.2)	91.0 (22.9)
Race white, n (%)	308 (90.9)	532 (90.2)
Disease duration, years	17.3 (11.7)	18.6 (12.2)
% BSA involvement	27.0 (16.2)	27.6 (18.6)
PASI score	20.4 (7.9)	20.0 (8.4)
DLQI score	14.8 (7.3)	14.9 (7.3)
NAPSI score	9.3 (3.6)	9.9 (3.6)
PSI score	19.1 (7.0)	18.7 (6.9)
PsA, n (%)	79 (23.3)	110 (18.6)
Systemic/biologic naive, n (%)	144 (42.5)	246 (41.7)
Systemic experienced without biologics, n (%)	99 (29.2)	188 (31.9)
Biologic experienced without failure, n (%)	50 (14.8)	95 (16.1)
Biologic failure, n (%)	46 (13.6)	61 (10.3)

Data are mean (±SD) unless otherwise stated.
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.

treated patients achieved PASI 100 and PASI 90 at any given time point over the 52-week treatment period, compared with ustekinumab-treated patients (Fig. 1). Brodalumab was associated with more rapid achievement of PASI 100 and PASI 90 vs. ustekinumab, with significant differences observed by Week 4: PASI 100 was achieved in 9.4% (95% CI, 6.5, 13.1) of brodalumab patients vs. 0.7% (95% CI, 0.2, 1.7) of ustekinumab patients ($P < 0.0001$), and PASI 90 was achieved in 26.8% of brodalumab patients vs. 3.4% of ustekinumab patients ($P < 0.0001$). Skin clearance rates remained higher with brodalumab throughout the study period, with 51.0% (95% CI, 45.6, 56.5) and 63.1% (95% CI, 57.7, 68.3) of brodalumab patients achieving PASI 100 and PASI 90, respectively, at Week 52 vs. 28.1% (95% CI, 24.5, 32.0) and 42.7% (95% CI, 38.7, 46.8) of ustekinumab patients, respectively (all $P < 0.0001$).

The likelihood of achieving complete clearance was numerically greater for brodalumab than ustekinumab at all time points assessed, from Week 2, and was significant from Week 4 (OR 15.5; 95% CI, 5.4, 44.4), with ORs at Weeks 12 and 52 of 2.8 (95% CI, 2.1, 3.8) and 2.8 (95% CI, 2.1, 3.7), respectively(all $P < 0.0001$). The likelihood of achieving PASI 90 consistently and significantly favoured brodalumab over ustekinumab from Week 2 (OR 4.8; 95% CI, 1.7, 13.5: $P = 0.001$), with ORs at Weeks 12 and 52 of 2.3 (95% CI 1.8, 3.1) and 2.5 (95% CI 1.9, 3.4), respectively (both $P < 0.0001$).

Cumulative treatment benefit Based on an analysis of the AUC through 52 weeks, brodalumab was associated with a significantly greater cumulative benefit for PASI 100 than ustekinumab (Fig. 1). Cumulative benefit (nominal AUC value) for PASI 100 was 2251 (43.3%) for brodalumab vs. 1332 (25.6%) for ustekinumab, with a treatment difference of 919 (17.7%; $P < 0.0001$). Incremental clinical benefit for PASI 100 with brodalumab was 69% higher than ustekinumab (AUC ratio: 1.69 [95% CI, 1.5, 1.9]; $P < 0.0001$). Cumulative benefit for PASI 90 was 3192 (61.4%) for brodalumab vs. 2252 (43.3%) for ustekinumab, with a treatment difference of 940 (18.1%; $P < 0.0001$) (Fig. 1). Incremental clinical benefit for PASI 90 was 42% higher with brodalumab than ustekinumab (AUC ratio: 1.42 [95% CI, 1.3, 1.5]; $P < 0.0001$).

Competing risk model for achieving skin clearance Cumulative incidence of PASI 100 over 52 weeks showed that brodalumab patients were significantly more likely to achieve PASI 100 at least once over 52 weeks, than ustekinumab patients, with 76% (95% CI, 71–80%) responders on brodalumab vs. 52% (95% CI, 48–56%) on ustekinumab (HR 2.06; 95% CI, 1.74, 2.44; $P < 0.0001$) (Fig. 2). Median time to PASI 100 was 14 weeks with brodalumab vs. 44 weeks with ustekinumab. Cumulative incidence of achieving PASI 90 at least once over 52 weeks was also higher 87.3% (95% CI, 83.3, 90.5) with brodalumab vs. 71.4% (95% CI, 67.6, 74.8) for ustekinumab (HR 2.08; 95% CI, 1.78, 2.43; $P < 0.0001$).

At the end of the maintenance phase, 90.1% (95% CI, 86.2, 94.2%) of patients who achieved PASI 100 with brodalumab had sustained response vs. 76.7% (95% CI, 66.8–88.2%) on ustekinumab. 83.2% (95% CI, 78.9, 87.7) of brodalumab patients and 62.2% (95% CI, 50.9, 75.9) of ustekinumab patients sustained PASI 90.

Proportion of time spent in treatment response Overall, a higher proportion of time was spent in PASI 100 response on brodalumab (42.5%) than ustekinumab (25.2%) (Fig. 3). The mean (SD) number of days spent in PASI 100 response was 154.7 (124.4) days with brodalumab vs. 91.7 (112.4) days with ustekinumab. Additionally, rescue treatment accounted for a greater proportion of time in ustekinumab patients (25.7%) vs. brodalumab patients (15.2%).

Association between skin clearance and QoL A significant association was observed between the PASI response level and QoL measured by achievement of DLQI 0/1, regardless of treatment arm ($P < 0.0001$; Fig. 4). A higher proportion of patients who achieved PASI 100 also achieved DLQI 0/1 (83.5%) vs. PASI 90 to <100 (64.3%).

Discussion

In this integrated analysis of data from the AMAGINE trials, brodalumab rapidly achieved high levels of complete and sustained skin clearance and a greater overall cumulative treatment

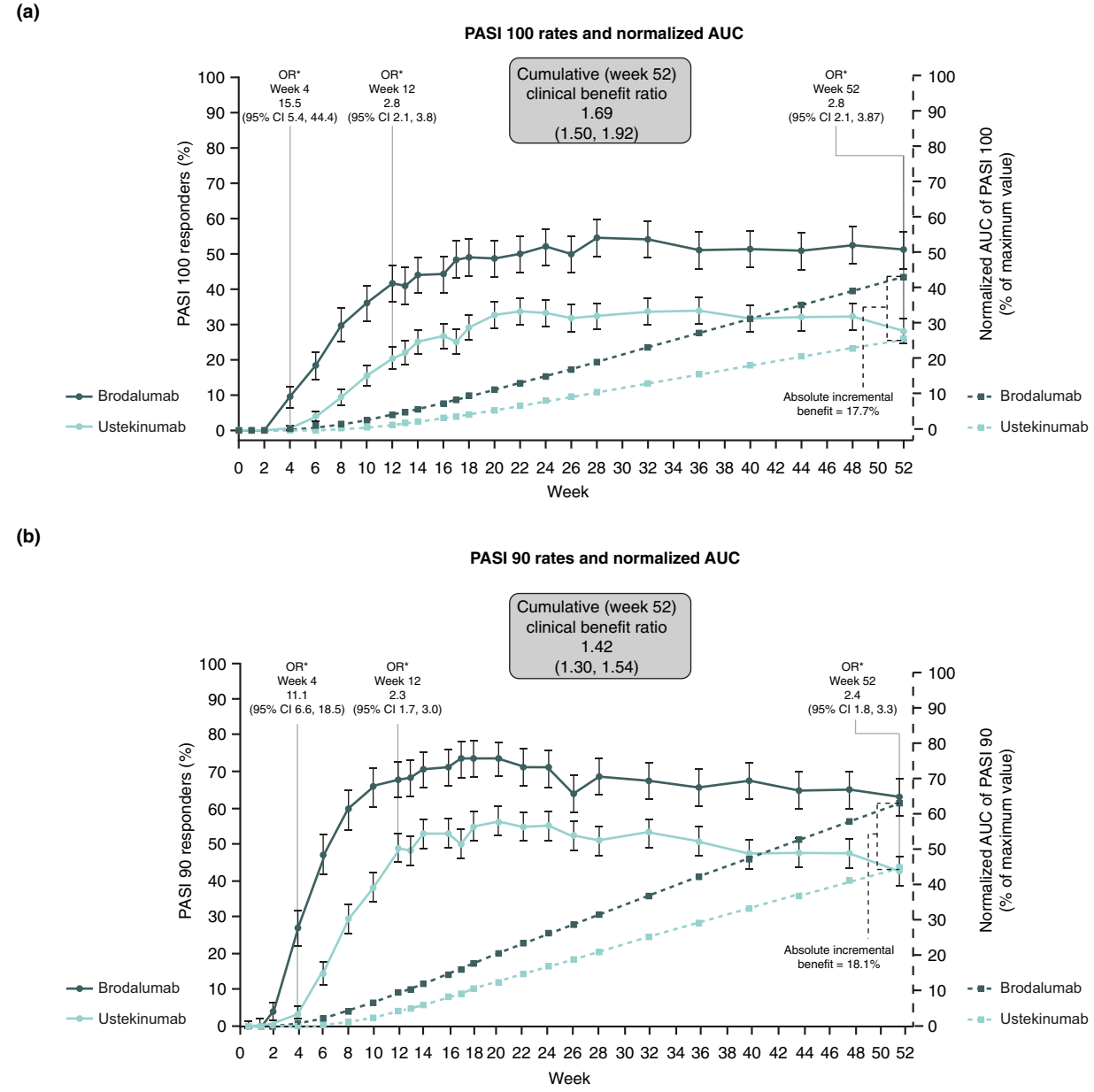

Figure 1 Percentage of patients achieving (a) PASI 100 and cumulative benefit (AUC as % of maximum AUC value) and (b) PASI 90 and cumulative benefit (AUC as % of maximum AUC value) at each time point. Pooled data from the AMAGINE-2 and -3 trials. Brodalumab $n = 339$; Ustekinumab $n = 590$; Maximum AUC value: 52 weeks × PASI maximum response (100%) = 5200. *OR values apply to percentage of patients achieving PASI response. AUC, area under the curve; CI, confidence interval; NRI, non-responder imputation; OR, odds ratio; Q2W, every 2 weeks.

benefit in patients with moderate-to-severe psoriasis through 52 weeks vs. ustekinumab.

Complete skin clearance (PASI 100) is associated with substantially reduced physical burden of psoriasis, improved treatment satisfaction and QoL in both clinical trial and real-world settings.[24–26,33,34] In our analysis, level of PASI response was closely associated with degree of QoL improvement, as measured by DLQI 0/1. PASI 100 responders appeared more likely to

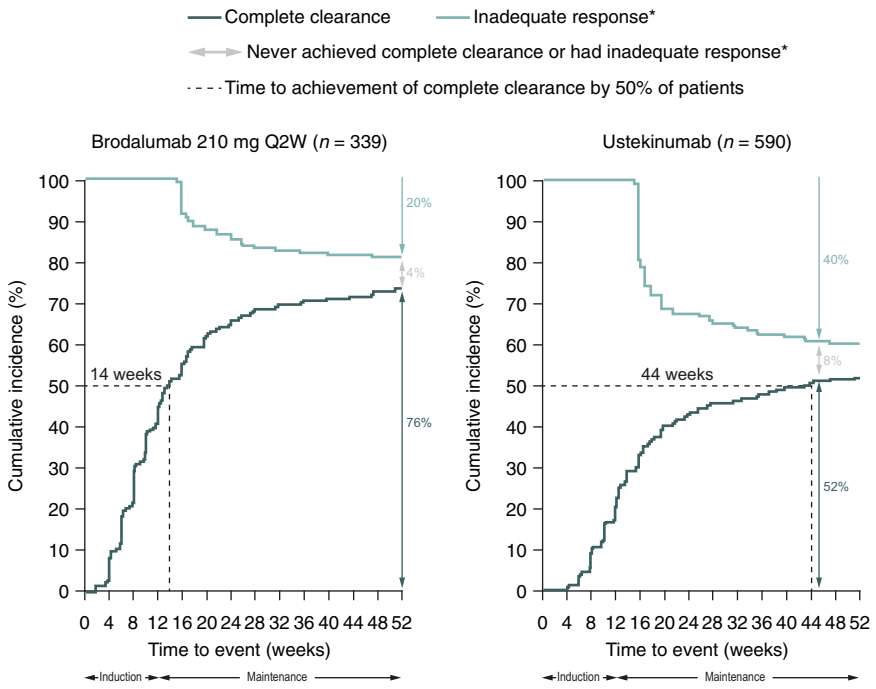

Figure 2 Cumulative incidence of patients achieving PASI 100 at least once at any given time point (competing risk analysis). *Defined as a static Physician's Global Assessment ≥3 or persistent values of 2 over at least a 4-week period at or after week 16. Q2W, every 2 weeks.

achieve DLQI 0/1 than those with PASI 90. These findings reflect those reported by Armstrong *et al.*,[35] showing that the PASI 90 or 100 responders among 1829 patients in two guselkumab clinical trials had greater improvements in their DLQI total score than PASI 75 to <PASI 90 responders, further supporting the suggestion of a clinically meaningful benefit in raising the treatment goal in plaque psoriasis to at least PASI 90, and ideally PASI 100.

We assessed frequency, speed and sustainability of PASI 100 response using data from AMAGINE-2 and -3. These trials previously showed significantly higher PASI 75, 90 and 100 response rates with brodalumab vs. ustekinumab.[10] In the current integrated analysis, a consistently higher proportion of brodalumab-treated than ustekinumab-treated patients achieved rapid and consistent complete clearance over the 52-week treatment period, with significant differences observed from Week 4 onwards.

Another recent proposal is that cumulative treatment benefit should be measured as an outcome in clinical trials to understand therapeutic effect over time.[30] In this analysis, brodalumab was associated with a significantly greater cumulative benefit than ustekinumab, with 69% added benefit over 52 weeks of treatment in patients achieving PASI 100 and 42% added benefit in patients achieving PASI 90. A greater cumulative benefit over 52 weeks was also recently observed with the anti-IL-17A monoclonal antibody, secukinumab, when compared with the TNF-alpha inhibitor, etanercept, in patients with moderate-to-severe psoriasis.[30] In this study, the cumulative clinical benefit for PASI 100 through 52 weeks was 1677 (32.3%), 979 (18.8%) and 453 (8.7%) with secukinumab 300 mg, secukinumab 150 mg and etanercept, respectively. Armstrong *et al.* (2017) propose that measuring cumulative treatment benefit over time may be highly clinically relevant for chronic diseases such as psoriasis, where the impact on patients is continuous. Two therapies producing similar PASI 75 response rates after 52 weeks' treatment do not necessarily confer the same clinical benefit; for example, across the treatment period, one medication may achieve PASI 75 more quickly and/or for a longer sustained time. In our cumulative incidence analysis, PASI 100 was achieved at least once with brodalumab more frequently than ustekinumab (specifically 76% vs. 52%, respectively, over 52 weeks of study) and also, more rapidly (as early as 2–4 weeks, with a median response time of 14 weeks vs. 44 weeks with ustekinumab). This is important to patients, as shown by a qualitative study which found that patients want a rapid cure of their psoriasis,[36] and the World Health

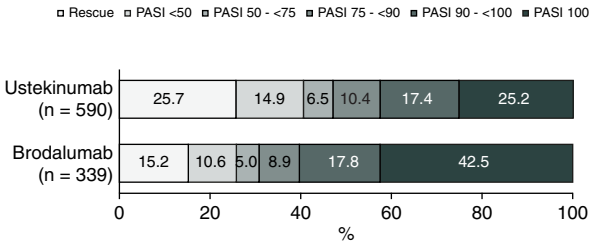

Figure 3 Proportion of time spent in treatment response. PASI, Psoriasis Area and Severity Index.

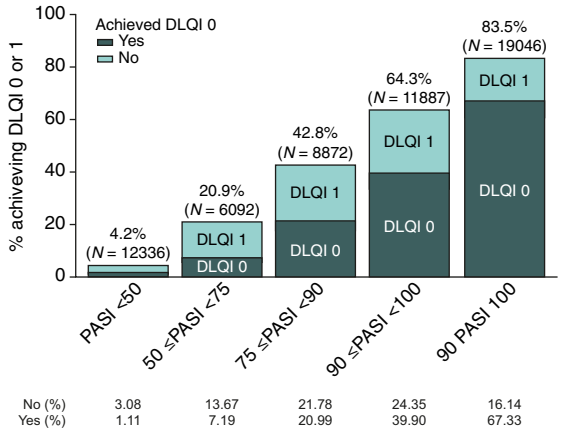

Figure 4 Association between PASI response and QoL (pooled data on 4373 patients from the AMAGINE-1, -2 and -3 trials). Test for trend: $P < 0.001$ (logistic GEE model of the association between PASI response category and DLQI 0/1). DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; QoL, quality of life.

Organization global report on psoriasis found that getting better skin quickly was the highest rated (in 94.2% of responses) patient need from psoriasis treatment.[37,38] Furthermore, response was more likely to be sustained over time, time spent in complete clearance was much higher, and time spent in rescue treatment was lower with brodalumab vs. ustekinumab, demonstrating brodalumab treatment benefit through time.

The introduction of biologics targeting IL-17 has increased the ability of patients to achieve complete or almost complete clearance of psoriasis.[39] While not necessarily a cure, achieving complete skin clearance may represent a clinically meaningful goal for patients in the real world. Other studies show that patients with complete clearance report no impairment in health-related QoL, while having even minimal residual disease activity may continue to negatively affect QoL.[26,34] In an analysis of 188 patients with moderate-to-severe psoriasis in Phase II placebo-controlled trials of brodalumab, those with residual disease (sPGA 1) had a DLQI of 2.5 and experienced more severe scaling, redness, itching and flaking than those who were clear (PGA 0).[26] In this study, PASI 100 responders were more likely to have DLQI scores of 0/1 (67%) than those with PASI 90 to <100 (40%), implying that a substantial benefit can be achieved by aiming for complete clearance. For those patients achieving <PASI 50, the likelihood of achieving DLQI 0/1 was very low (1%).

There are limitations to this study. Firstly, the data analysed were from a clinical trial population with strict entry criteria and may not be generalizable to broader populations. Notably, AMAGINE-2 and -3 excluded patients who had prior ustekinumab experience, resulting in a high number of biologic-naïve patients in this dataset. This may have resulted in better response rates than would be observed in the general population.[40] Secondly, analyses were of pooled data from clinical trials not designed and statistically powered to assess these specific end points. Analyses were also restricted to patients in constant treatment arms, reducing the number of available patients that could be included. Finally, study conclusions rely on assessment of PASI. This is a subjective measure, and while a clinician may judge the patient to have achieved PASI 100, it is possible for minor papules to be missed during examination.

In conclusion, this analysis demonstrated that treatment with brodalumab results in very high levels of complete and sustained skin clearance and greater overall cumulative treatment benefit in patients with moderate-to-severe psoriasis than ustekinumab. Our findings further demonstrated that complete skin clearance is achievable with biologics in many patients with plaque psoriasis, suggesting that this outcome could be the new standard for which to aim.

Acknowledgements

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References

1 Gupta R, Debbaneh MG, Liao W. Genetic epidemiology of psoriasis. *Curr Dermatol Rep* 2014; **3**: 61–78.
2 Menter A, Gottlieb A, Feldman SR *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol* 2008; **58**: 826–850.
3 Goff KL, Karimkhani C, Boyers LN *et al.* The global burden of psoriatic skin disease. *Br J Dermatol* 2015; **172**: 1665–1668.
4 Kim HJ, Lebwohl MG. Biologics and psoriasis: the beat goes on. *Dermatol Clin* 2019; **37**: 29–36.
5 Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. *J Allergy Clin Immunol* 2017; **140**: 645–653.
6 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* 2014; **192**: 3828–3836.
7 Frieder J, Kivelevitch D, Menter A. Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis. *Ther Adv Chronic Dis* 2018; **9**:5–21.

8 Syed YY. Ixekizumab: a review in moderate to severe plaque psoriasis. *Am J Clin Dermatol* 2017; **18**:147–158.
9 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**: 273–286.
10 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.
11 Lebwohl MG, Bachelez H, Barker J *et al*. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol* 2014; **70**: 871–881.e871–830.
12 Armstrong AW, Robertson AD, Wu J *et al*. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003–2011. *JAMA Dermatol* 2013; **149**: 1180–1185.
13 Kaushik SB, Lebwohl MG. Review of safety and efficacy of approved systemic psoriasis therapies. *Int J Dermatol* 2019; **58**: 649–658.
14 Maza A, Richard MA, Aubin F *et al*. Significant delay in the introduction of systemic treatment of moderate to severe psoriasis: a prospective multicentre observational study in outpatients from hospital dermatology departments in France. *Br J Dermatol* 2012; **167**: 643–648.
15 Alwawi EA, Mehlis SL, Gordon KB. Treating psoriasis with adalimumab. *Ther Clin Risk Manag* 2008; **4**: 345–351.
16 Farhi D. Ustekinumab for the treatment of psoriasis: review of three multicenter clinical trials. *Drugs Today (Barc)* 2010; **46**: 259–264.
17 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.
18 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.
19 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.
20 Papp KA, Leonardi CL, Blauvelt A *et al*. Ixekizumab treatment for psoriasis: integrated efficacy analysis of three double-blinded, controlled studies (UNCOVER-1, UNCOVER-2, UNCOVER-3). *Br J Dermatol* 2018; **178**: 674–681.
21 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.
22 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.
23 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.
24 Strober B, Papp KA, Lebwohl M *et al*. Clinical meaningfulness of complete skin clearance in psoriasis. *J Am Acad Dermatol* 2016; **75**: 77–82 e77.
25 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.
26 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 Dermatolog Treat* 2015; **26**: 235–239.
27 Kimball AB, Gieler U, Linder D *et al*. Psoriasis: is the impairment to a patient's life cumulative? *J Eur Acad Dermatol Venereol* 2010; **24**: 989–1004.
28 Linder MD, Piaserico S, Augustin M *et al*. Psoriasis – the life course approach. *Acta Derm Venereol* 2016; **96**: 102–108.
29 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.
30 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**: 200–205.
31 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)–a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–216.
32 Basra MK, Fenech R, Gatt RM *et al*. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**: 997–1035.
33 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 Dermatolog Treat* 2016; **27**: 224–227.
34 Revicki DA, Willian MK, Menter A *et al*. 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.
35 Armstrong AW, Reich K, Foley P *et al*. Improvement in patient-reported outcomes (dermatology life quality index and the psoriasis symptoms and signs diary) with guselkumab in moderate-to-severe plaque psoriasis: results from the phase III VOYAGE 1 and VOYAGE 2 studies. *Am J Clin Dermatol* 2019; **20**: 155–164.
36 Uhlenhake EE, Kurkowski D, Feldman SR. Conversations on psoriasis—what patients want and what physicians can provide: a qualitative look at patient and physician expectations. *J Dermatolog Treat* 2010; **21**: 6–12.
37 World Health Organization. Global report on psoriasis. 2016. URL https://apps.who.int/iris/handle/10665/204417 (last accessed: 31 March 2020).
38 Blome C, Augustin M, Behechtnejad J, Rustenbach SJ. Dimensions of patient needs in dermatology: subscales of the patient benefit index. *Arch Dermatol Res* 2011; **303**: 11–17.
39 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.
40 Karczewski J, Poniedziałek B, Rzymski P, Adamskiet Z. Factors affecting response to biologic treatment in psoriasis. *Dermatol Ther* 2014; **27**: 323–330.

Supporting information

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

Figure S1. Study designs for the Phase III randomized controlled trials of brodalumab in patients with moderate-to-severe psoriasis (a) AMAGINE-1 and (b) AMAGINE-2 and AMAGINE-3.