



Dermatology Life Quality Index in Patients with Moderate-to-Severe Plaque Psoriasis Treated with Brodalumab or Ustekinumab

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Received: January 29, 2021 / Accepted: April 29, 2021 / Published online: May 14, 2021
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ABSTRACT

Introduction: Targeted biological therapies for psoriasis have resulted in significant benefits, with therapeutic goals such as clear or almost clear skin accompanied by improvements in health-related quality of life (HRQoL). The objective of this study was to compare the effects of 52 weeks of treatment with brodalumab or ustekinumab on HRQoL in patients with moderate-to-severe plaque psoriasis.

Methods: Data were pooled from two randomised controlled phase 3 trials (AMAGINE-2 and -3) which included patients with moderate-to-severe plaque psoriasis treated with brodalumab 210 mg or ustekinumab 45 or 90 mg for 52 weeks. HRQoL outcomes were measured using the Dermatology Life Quality Index (DLQI) as well as the DLQI-Relevant (DLQI-R) version which excludes ‘not relevant’ responses.

Results: A total of 929 patients were included, 339 in the brodalumab group and 590 in the

ustekinumab group. A significantly greater reduction (improvement) in DLQI score from baseline was observed in the brodalumab group compared with the ustekinumab group at weeks 4 [least-squares (LS) mean difference -2.9 , 95% confidence interval [CI] -3.6 to -2.2 ; $p < 0.001$], 12 (LS mean difference -0.85 , 95% CI -1.5 to -0.2 ; $p = 0.01$) and 52 (LS mean difference -0.94 , 95% CI -1.6 to -0.2 ; $p = 0.009$]. Significantly greater proportions of patients treated with brodalumab achieved a DLQI score of 0 at weeks 4 (15.0 vs. 5.4%; $p < 0.0001$), 12 (37.5 vs. 28.0%; $p = 0.0140$) and 52 (46.3 vs. 30.3%; $p < 0.0001$), or of ≤ 1 [DLQI (0/1): 33.9 vs. 15.4%, 59.9 vs. 45.6% and 54.9 vs. 39.8%, respectively; all $p < 0.0001$]. Similar results were observed using the DLQI-R scoring system. Significantly more patients achieved a ≥ 4 or ≥ 5 improvement in DLQI with brodalumab compared to ustekinumab at weeks 4 and 52. Treatment with brodalumab was associated with significantly more patients achieving a DLQI of 0 compared to ustekinumab for all domains after 4 and 52 weeks.

Conclusion: Brodalumab was associated with a significantly greater improvement in HRQoL compared to ustekinumab in patients with moderate-to-severe psoriasis.

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Keywords: Brodalumab; Pharmacology;
Psoriasis; Quality of life; Ustekinumab

Key Summary Points

Both ustekinumab and brodalumab have been associated with significantly improved health-related quality of life in patients with moderate-to-severe psoriasis, as measured by the Dermatology Life Quality Index (DLQI). Brodalumab has also been shown to provide superior skin clearance to ustekinumab in patients with moderate-to-severe plaque psoriasis in randomised controlled trials.

In an analysis of data pooled from two randomised, controlled, phase 3 trials of patients with moderate-to-severe plaque psoriasis, a significantly greater reduction (improvement) in DLQI score from baseline was observed with brodalumab compared to ustekinumab at weeks 4, 12 and 52.

More patients treated with brodalumab than ustekinumab achieved a DLQI score of 0 or 0/1.

Brodalumab was associated with a significantly greater improvement in HRQoL compared to ustekinumab in patients with moderate-to-severe psoriasis.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14501088>.

INTRODUCTION

Psoriasis can have a substantial negative impact on the health-related quality of life (HRQoL) of patients, affecting emotional well-being and interfering with daily activities, including home

life, social activity and work functioning. The use of targeted biological therapies has resulted in significant improvements in the treatment of psoriasis with therapeutic goals, such as clear or almost clear skin, attainable for many patients. These improvements in clinical efficacy have been associated with significant benefits in the self-reported HRQoL of patients [1].

Biological treatments include ustekinumab, which targets the interleukin (IL)-12/23 pathway and, more recently, IL-17 inhibitors, including secukinumab and ixekizumab, which bind to the IL-17 ligand, and brodalumab, which binds to the IL-17 receptor A and inhibits the action of multiple pro-inflammatory IL-17 family cytokines. Both ustekinumab and brodalumab have been associated with significantly improved HRQoL in patients with moderate-to-severe psoriasis, as measured by the Dermatology Life Quality Index (DLQI) [2–5]. Previous studies have suggested that IL-17 inhibition with secukinumab or ixekizumab is associated with greater improvements in skin clearance and HRQoL than ustekinumab [6–8]. Brodalumab has also been shown to provide superior skin clearance to ustekinumab in patients with moderate-to-severe plaque psoriasis in two 1-year randomised controlled trials (AMAGINE-2 and AMAGINE-3) [9]. However, the comparative effects of brodalumab and ustekinumab on HRQoL from these trials have not previously been reported.

Here, we report the effects of 1-year of treatment with brodalumab or ustekinumab on the HRQoL in patients with moderate-to-severe plaque psoriasis enrolled in the AMAGINE-2 and AMAGINE-3 phase 3 trials.

METHODS

AMAGINE-2 and AMAGINE-3 were two multi-centre, randomised, double-blind, placebo-controlled and active comparator-controlled phase 3 trials [9]. In both trials, patients were randomised (2:2:1:1) to brodalumab 210 mg or 140 mg, ustekinumab (45 mg for patients with a body weight \leq 100 kg and 90 mg for patients $>$ 100 kg) or placebo. At week 12, patients originally randomised to brodalumab

underwent repeat randomisation (2:2:2:1) to brodalumab 210 mg every 2 weeks, 140 mg every 2 weeks, 140 mg every 4 weeks or 140 mg every 8 weeks. Full details of these studies have been previously reported [9]. The present analysis was focused on the on-label dosages for brodalumab so only those patients randomised to brodalumab 210 mg for the entire 52 weeks were included.

Patients eligible for enrolment were aged 18–75 years and candidates for biologic therapy for stable moderate-to-severe plaque psoriasis (minimum disease duration of 6 months) with a psoriasis area and severity index (PASI) score of ≥ 12 , a physician's global assessment (PGA) score of ≥ 3 , and involvement of $\geq 10\%$ of body surface area. The institutional review board (IRB) at each participating centre approved the study protocols (list of IRBs is given in the Acknowledgements). Both studies were conducted in accordance with the Helsinki Declaration of 1964, and its later amendments and all relevant regional regulations. All patients provided written informed consent.

HRQoL was assessed using the DLQI, a ten-item measure assessing a patient's self-assessment of their quality of life and problems associated with dermatological disease. DLQI total scores range from 0 to 30, with lower scores indicating better dermatology-specific quality of life and a score of 0 or 1 both representative of no disease effect at all on HRQoL. In the present study, the DLQI questionnaire was completed by patients at baseline and every 4 weeks during the 52-week treatment period. Endpoints included changes in mean DLQI and changes in the six individual domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment), percentage of patients achieving DLQI total scores of 0 and ≤ 1 (0/1) at weeks 12 and 52, patients achieving a ≥ 4 - or ≥ 5 -point improvement in DLQI from baseline and area-under-the-curve (AUC) for DLQI 0/1.

Of the ten items of the DLQI, eight include 'not relevant' as a possible response, meaning patients do not consider that the item is applicable to their lifestyle. In the original DLQI, a 'not relevant' response (NRR) is scored as having no impact on the patient's HRQoL. High rates of

NRRs have previously been observed among patients with psoriasis, and concerns have been raised regarding the potential for NRRs to lead to a lower DLQI and thus the patient being categorised as having a higher quality of life than may be the case [10]. An adjusted scoring system for the DLQI that is intended to correct for bias in the NRR option (DLQI-R) has been proposed [11]. The DLQI-R was also used to determine proportions of patients achieving DLQI 0/1 in a post-hoc analysis.

Statistical Analysis

All binary endpoints were analysed and compared between treatments by odds ratios (ORs) and 95% confidence intervals (CIs) calculated using a Cochran-Mantel-Haenszel Chi-squared test stratified by total body weight at baseline (\leq or $>$ 100 kg), prior biologic use, geographic region and baseline DLQI score (\leq or $>$ median). Missing data for binary endpoints were accounted for by non-responder imputation (NRI).

For continuous outcomes, an analysis of covariance model adjusting for total body weight at week 12 (\leq or $>$ 100 kg), week 12 static PGA (sPGA) response (0, ≥ 1), study and treatment was used. Last observation carried forward (LOCF) method was used to impute missing data.

The full analysis set included all patients randomly assigned to treatment with at least one efficacy assessment after randomisation.

All statistical analyses were performed using SAS version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 929 patients were included in the present analysis, 339 in the brodalumab 210 mg group and 590 in the ustekinumab group. Baseline demographic and clinical characteristics were similar across both groups (Table 1). DLQI at baseline was similar in both treatment groups, with mean [\pm standard deviation (SD)] scores of 14.8 ± 7.3 in the brodalumab group and 14.9 ± 7.3 in the ustekinumab group.

Table 1 Baseline characteristics of patients

Baseline characteristic	Brodalumab (<i>n</i> = 339)	Ustekinumab (<i>n</i> = 590)
Age, years	44.5 (13.4)	45.1 (13.0)
Male, <i>n</i> (%)	230 (67.8)	404 (68.5)
Weight, kg	90.4 (24.2)	91.0 (22.9)
Race, white, <i>n</i> (%)	308 (90.9)	532 (90.2)
Disease duration, years	17.3 (11.7)	18.6 (12.2)
Body surface area involvement, %	27.0 (16.2)	27.6 (18.6)
Psoriasis area and severity index (PASI) score	20.4 (7.9)	20.0 (8.4)
Dermatology Life Quality Index (DLQI) score	14.8 (7.3)	14.9 (7.3)
Nail Psoriasis Severity Index (NAPSI) score	9.3 (3.6)	9.9 (3.6)
Psoriasis Symptom Inventory (PSI) score	19.1 (7.0)	18.7 (6.9)
Psoriatic arthritis, <i>n</i> (%)	79 (23.3)	110 (18.6)
Systemic treatment-naïve, <i>n</i> (%)	144 (42.5)	246 (41.7)
Previous non-biologic systemic treatment, <i>n</i> (%)	99 (29.2)	188 (31.9)
Previous biologic without failure, <i>n</i> (%)	50 (14.8)	95 (16.1)
Previous biologic failure, <i>n</i> (%)	46 (13.6)	61 (10.3)

All data are presented as the mean with the standard deviation (SD) in parentheses unless otherwise indicated

Mean individual domain scores were also similar between groups at baseline.

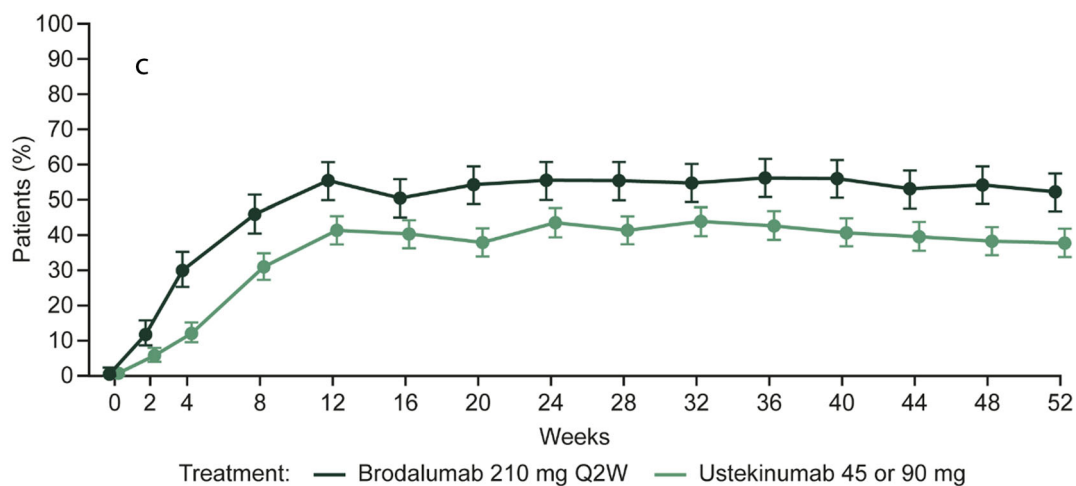
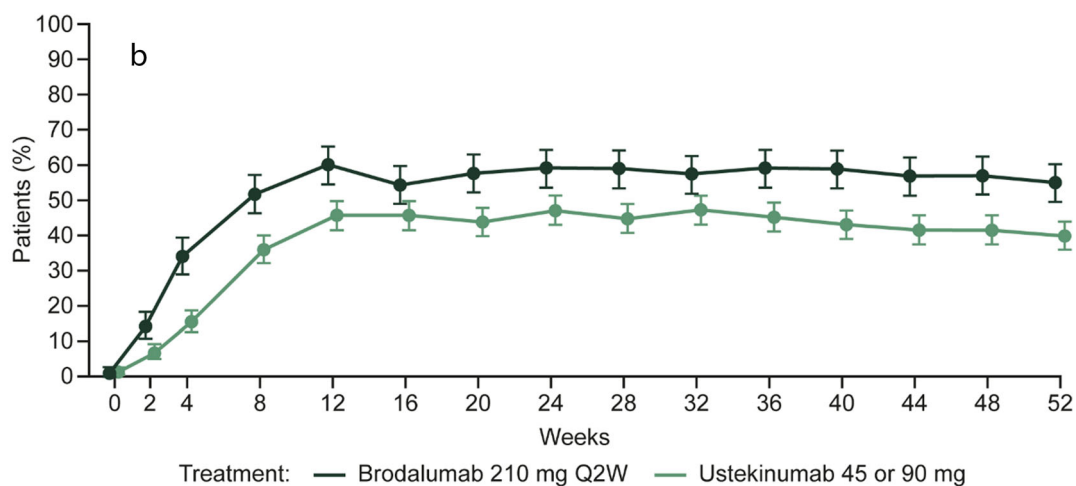
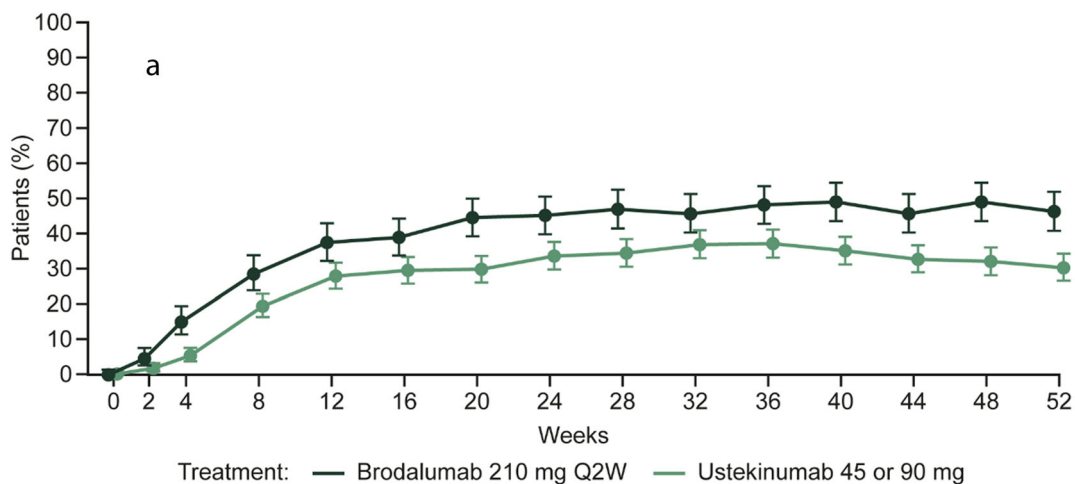
A significantly greater reduction (improvement) in DLQI score from baseline was observed in the brodalumab group compared with the ustekinumab group at weeks 4 [mean \pm SD –

Fig. 1 Proportions of patients achieving DLQI score of 0 (a) or 0/1 (b) or a DLQI-R score of 0/1 (c) per visit with brodalumab or ustekinumab (full analysis set, non-responder imputation). *DLQI* Dermatology Life Quality Index, *DLQI-R* adjusted DLQI correcting for bias in the ‘not relevant’ response (NRR), *Q2W* once every 2 weeks

10.4 \pm 7.0 vs. – 7.5 \pm 6.3; least-squares (LS) mean difference – 2.9, 95% CI – 3.6 to – 2.2; $p < 0.001$], 12 [– 11.7 \pm 7.8 vs. – 10.9 \pm 7.2; LS mean difference – 0.85, 95% CI – 1.5 to – 0.2; $p = 0.01$] and 52 [– 12.1 \pm 8.1 vs. – 11.2 \pm 7.7; LS mean difference – 0.94, 95% CI – 1.6 to – 0.2; $p = 0.009$].

Significantly greater proportions of patients treated with brodalumab achieved a DLQI score of 0 at week 4 compared with ustekinumab-treated patients (15.0 vs. 5.4%; OR 2.95, 95% CI 1.82–4.79; $p < 0.0001$) and this difference remained significant at weeks 12 (37.5 vs. 28.0%; OR 1.45, 95% CI 1.08–1.95; $p = 0.0140$) and 52 (46.3 vs. 30.3%; OR 2.08, 95% CI 1.55–2.78; $p < 0.0001$) (Fig. 1a). Similarly, among patients with a DLQI score > 1 at baseline, more patients in the brodalumab group than ustekinumab group achieved a DLQI score of 0/1 at weeks 4 (33.9 vs. 15.4%; OR 2.82, 95% CI 2.01–3.95; $p < 0.0001$), 12 (59.9 vs. 45.6%; OR 1.74, 95% CI 1.32–2.31; $p < 0.0001$) and 52 (54.9% vs. 39.8%; OR 1.90, 95% CI 1.43–2.53; $p < 0.0001$) (Fig. 1b). The AUC for patients achieving DLQI 0/1 was significantly higher for those receiving brodalumab than for those on ustekinumab (53.1 vs. 39.7%; AUC ratio 1.34; $p < 0.0001$) (Fig. 2).

An analysis using the adjusted DLQI-R scoring system showed generally similar results for the proportions of patients achieving DLQI-R 0/1, although there was a slightly lower proportion of patients achieving DLQI-R 0/1 compared to DLQI 0/1 (Fig. 1c). NRRs were most frequent for the sport (13.5%), working/studying (11.6%) and sexual difficulties (10.1%) items, with other items having 1.2–3.6% NRRs. As with the unadjusted DLQI, a significantly higher proportion of patients achieved DLQI-R 0/1 with brodalumab than ustekinumab at weeks 4 (30.1 vs. 12.2%; OR 3.00, 95% CI 2.10–4.29; $p < 0.0001$), 12 (55.5 vs. 41.4%; OR



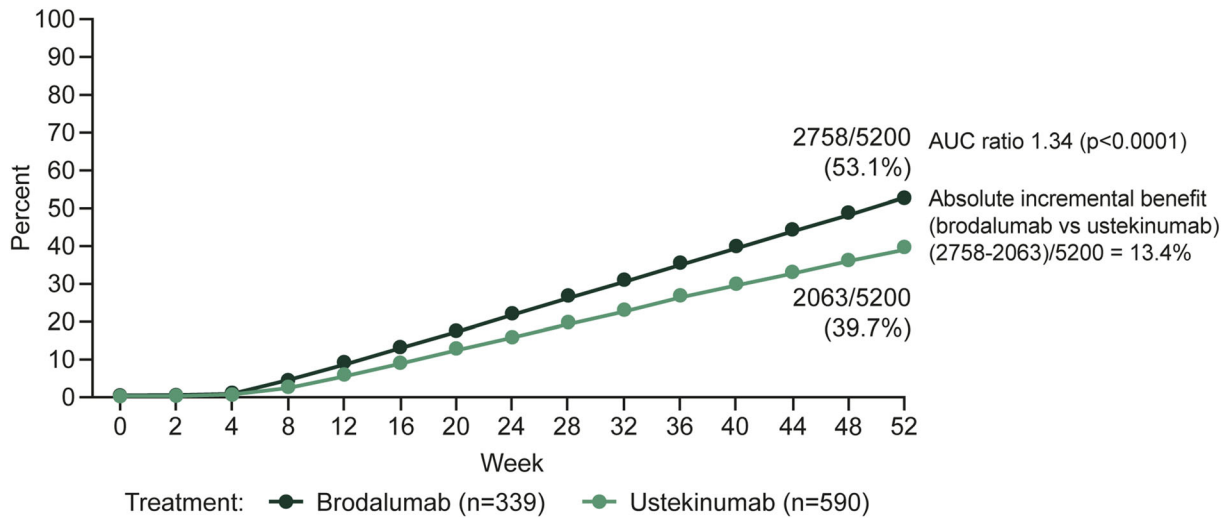


Fig. 2 The AUC for DLQI score 0/1 with brodalumab or ustekinumab. AUC = 100% would mean 100% of patients achieve and maintain DLQI 0/1 from week 0 to week 52 (ideal response). AUC Area-under-the-curve

1.75, 95% CI 1.32–2.32; $p < 0.0001$) and 52 (52.2 vs. 37.8%; OR 1.88, 95% CI 1.41–2.50; $p < 0.0001$).

Among patients with baseline DLQI ≥ 4 , significantly more achieved a ≥ 4 -point improvement with brodalumab compared with ustekinumab at week 4 and week 52, although not at week 12 (Fig. 3). A similar pattern was seen among patients with baseline DLQI ≥ 5 at

weeks 4 (83.6 vs. 67.7%; OR 2.73, 95% CI 1.87–3.99; $p < 0.0001$), 12 (88.2 vs. 86.4%; OR 1.24, 95% CI 0.80–1.92; $p = 0.3384$) and 52 (62.8 vs. 48.5%; OR 1.88, 95% CI 1.40–2.54; $p < 0.0001$).

Treatment with brodalumab was associated with significantly more patients achieving DLQI 0 compared to ustekinumab for the domains of symptoms and feelings, daily activities, leisure

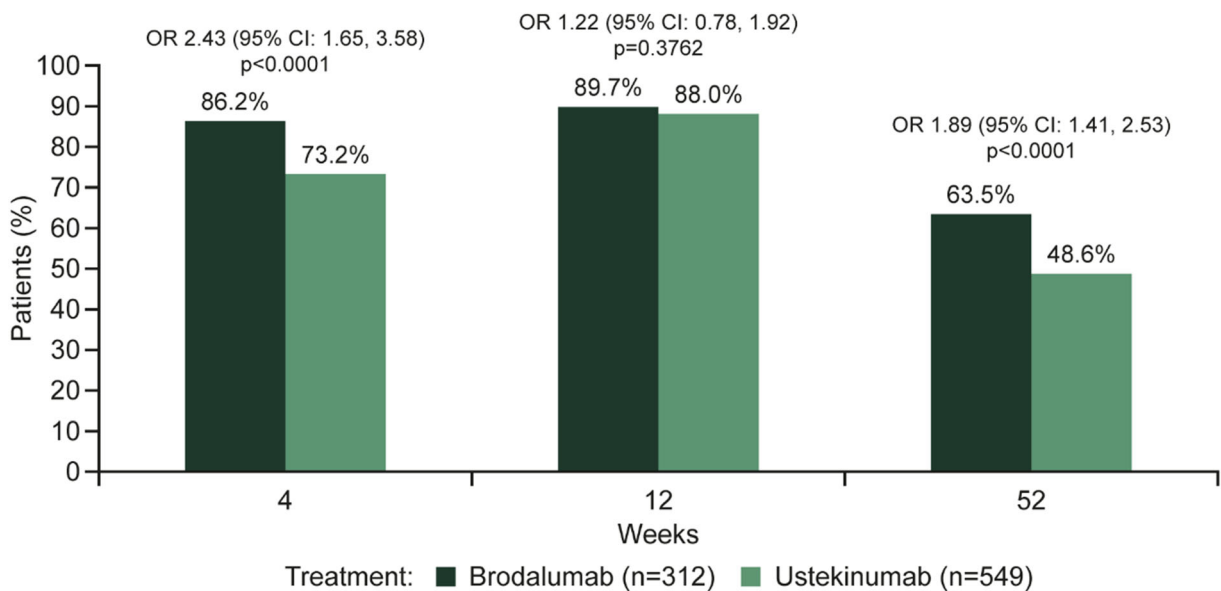


Fig. 3 Patients achieving an improvement in DLQI of ≥ 4 points with brodalumab and ustekinumab at 4, 12 and 52 weeks (full analysis set, non-responder imputation). CI Confidence interval, OR odds ratio

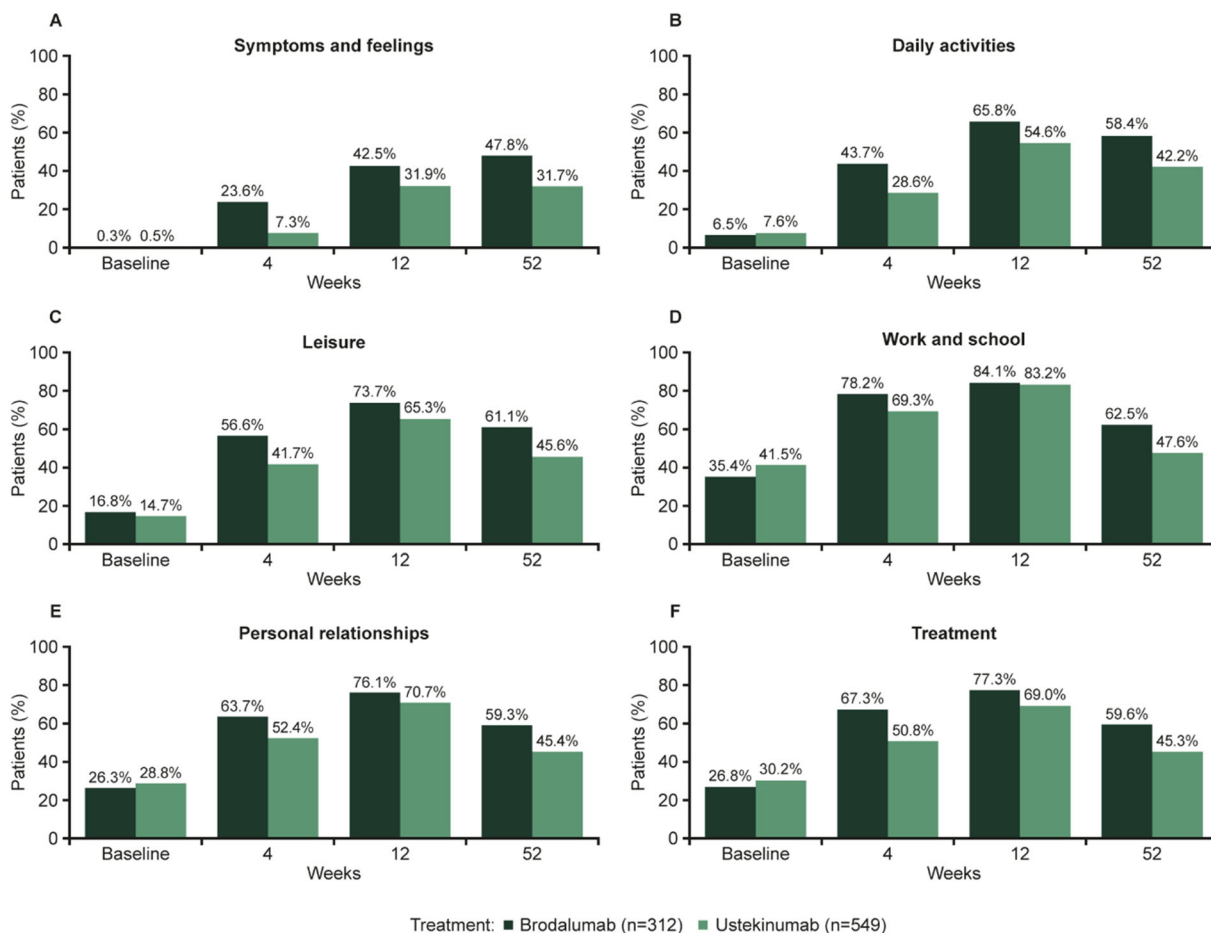


Fig. 4 Patients achieving DLQI 0 for individual domains with brodalumab and ustekinumab at 4, 12 and 52 weeks (full analysis set, non-responder imputation)

and treatment after 4, 12 and 52 weeks (Fig. 4). Proportions of patients achieving DLQI 0 were also significantly higher with brodalumab versus ustekinumab for work and school and personal relationships at weeks 4 and 52 but were not significantly different between groups at week 12.

DISCUSSION

Psoriasis represents a considerable burden for patients, often resulting in feelings of embarrassment and anxiety and poor self-esteem and limiting daily, social and work-related activities [12, 13]. Biological treatments such as brodalumab and ustekinumab have resulted in significant improvements in outcomes for

patients with moderate-to-severe psoriasis, with complete or near complete skin clearance now a realistic treatment goal. However, patients with psoriasis and their physicians may differ regarding how much importance they place on different treatment outcomes [14]. To be clinically meaningful for patients, objective improvements in symptoms, such as those reported by PASI, need to be accompanied by improvements in subjective self-reported HRQoL measures, including the DLQI.

Several studies have previously reported that both brodalumab and ustekinumab improve HRQoL. In a phase II, randomised, placebo-controlled clinical study of 198 patients with moderate-to-severe psoriasis, clinically meaningful improvements in DLQI were observed as early as week 4 following initiation of treatment

with brodalumab [4]. DLQI scores were significantly improved across all domains at week 12. In a 5-year open-label extension of this study, treatment with brodalumab resulted in substantial improvements in HRQoL, with over two-thirds of patients achieving DLQI 0/1 from week 12 through to week 264 [15]. Ustekinumab has also been associated with significant improvements in HRQoL as measured by the DLQI [2, 3], which have been reported to be maintained for up to 3 years of treatment [16]. Ustekinumab was also associated with a sustained improvement in DLQI among 489 patients with psoriasis after transitioning from methotrexate [17]. However, DLQI improvements with ustekinumab have been reported to be less than those with the IL-17 inhibitors secukinumab or ixekizumab [7, 8].

In the present study, improvements in HRQoL were significantly greater with brodalumab than with ustekinumab. Also, mean DLQI scores were lower, and more patients achieved a DLQI of 0 or 0/1 with brodalumab at weeks 4, 12 and 52, indicating a more rapid improvement in HRQoL with the difference being maintained over 1 year of treatment. More patients also achieved a ≥ 4 -point improvement with brodalumab compared with ustekinumab, which is the recommended minimal clinically important difference of the DLQI [18]. The cumulative benefit of brodalumab over ustekinumab regarding HRQoL was confirmed by the AUC ratio for DLQI 0/1 of 1.34. Improvements were also seen in each individual DLQI domain.

Improvement in quality of life tends to be associated with high skin clearance scores [15]. PASI and DLQI are closely correlated, with a substantial improvement in clinical efficacy associated with improved HRQoL in patients with moderate-to-severe psoriasis, and a significant difference in DLQI score of 0/1 between PASI 75 and PASI < 90 responders ($\geq 75\%$ and <90% reduction in PASI scores from baseline, excellent to even better disease improvement, respectively) and PASI 90 responders [1]. In a separate analysis of the AMAGINE-2 and -3 trials, a significant association was observed between the PASI response level and achievement of DLQI 0/1, regardless of treatment arm.

More patients who achieved PASI 100 (complete resolution of all disease) than PASI 90 to < 100 also achieved DLQI 0/1 (83.5 vs. 64.3%) [19]. In the previous phase II trial of brodalumab, patients who achieved total skin clearance (PASI 100) reported greater HRQoL improvements than those who were responders but were not clear of disease (PASI 75 to < 100) [20]. In addition, more patients achieved a DLQI score of 0 in the PASI 90 to < 100 and PASI 100 groups compared with the PASI 75 to < 90 group [21]. However, Abrouk et al. reported no significant differences in DLQI between patients achieving PASI 75 or PASI 90 in an analysis of two ustekinumab clinical trials [22]. In a real-world setting, improvements in PASI were observed to be only weakly to moderately associated with improvements in DLQI in patients treated with ustekinumab [23]. Similarly, data from the Danish National Registry also suggested that the correlation between PASI and DLQI is weak to moderate and varies over time [24]. More research is needed to confirm the correlation between PASI and DLQI outcomes, especially outside of clinical trials.

Of the ten questions of the DLQI, eight offer an NRR option that is scored as if the item had no impact on patients, as a value of 0 is counted for an NRR response. This can mean it is more difficult for these patients to fulfil the DLQI > 10 criterion required to access biologic treatment in some clinical guidelines. Female gender, older age and more severe disease have previously been associated with more NRRs [10]. To address this, a new scoring formula (DLQI-R) that adjusts the total score for the number of NRRs has been proposed [11]. In our analysis, the use of DLQI-R did not have a major effect on the proportions of patients achieving DLQI 0/1. For both treatments, the proportions of patients achieving DLQI 0/1 was slightly lower using DLQI-R than DLQI, which is the opposite effect to that previously reported [10]. Most NRRs occurred in the sport, sexual difficulties and working/studying items of the DLQI, which is consistent with previous findings. However, the proportions of reported NRRs were lower in our analysis than previously reported; for example, the domain with the highest proportion of NRRs, sport, had 13.5%

NNRs compared with 28.4% reported by Rencz et al. [10]. The model was originally developed based on data collected in cross-sectional analyses and it is possible that patients enrolled in clinical trials may be less likely to include 'not relevant' as a response. If this is the case, the use of DLQI-R may be less useful in a clinical trial setting than when used to help guide treatment decisions in clinical practice. Further validation in clinical trials and clinical practice is required.

One possible limitation of this analysis is that the original AMAGINE-2 and -3 studies were conducted between 2012 and 2014. Advances in treatment and greater disease awareness among patients in the ensuing years may have resulted in increased expectations of complete skin clearance and improvements in HRQoL. This may need to be taken into consideration if comparing these DLQI results with those of more recent studies. However, this would not have impacted on the comparative aspect of this trial.

In conclusion, brodalumab treatment provided significant improvement in self-reported HRQoL in patients with moderate-to-severe psoriasis compared with ustekinumab.

ACKNOWLEDGEMENTS

Funding. This analysis and manuscript development, including Rapid Service Fee, was funded by Leo Pharma A/S.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Medical Writing and Editorial Assistance. Medical writing and editorial assistance were provided by Andy Bond of Spirit Medical Communications Group Ltd., funded by Leo Pharma A/S.

Disclosures. Anne Sohr and Jes Birger Hansen are employees of Leo Pharma A/S. Jo

Lambert has received consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, ArgenX, Celgene, Janssen, BIOCAD, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi, and UCB. Lluís Puig has received consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, JS BIOCAD, LEO Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanofi, and UCB.

Compliance with Ethics Guidelines. An institutional review board approved the study protocol for each participating center. These were: Research Review Board, Inc. Richmond Hill, ON, Canada; Health Research Ethics Board of Alberta Clinical Trials Committee, Edmonton, AB, Canada; Eticka Komise Fakultni nemocnice Kralovske Vinohrady, Praha, Czech Republic; Eticka Komise Fakultni nemocnice Kralovske Vinohrady, Brno, Czech Republic; Eticka Komise Fakultni nemocnice, Praha Czech Republic; Eticka Komise Fakultni nemocnice Kralovske Vinohrady, Usti nad Labem, Czech Republic; Eticka Komise Fakultni nemocnice, Novy Jicin, Czech Republic; Eticka Komise Fakultni nemocnice, Jihlava, Czech Republic; Comité de Protection des Personnes Ile de France IV - Hôpital Saint Louis, Paris, France; Egeszsegugyi Tudományok Tanács, Klinikai Farmakológiai Etikai Bizottsága, Budapest, Hungary; Academisch Medisch Centrum, Amsterdam, the Netherlands; Komisja Bioetyczna przy Okregowej Izbie Lekarskiej w Lodzi, Lodz, Poland; Comissao de Etica para a Investigacao Clinica (CEIC), Lisboa, Portugal; CEIC Fundacio de Gestio Sanitaria Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; University of California Davis Institutional Review Board, Sacramento, CA, USA; Schulman Associates IRB, Cincinnati, OH, USA; Oregon Health and Science University Research Integrity Office, Portland, OR, USA; Western Institutional Review Board, Puyallup, WA, USA; Northwestern University IRB, Chicago, IL, USA; University of Michigan Medical School IRB, Ann Arbor, MI, USA; Partners Human Research

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Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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