ORIGINAL RESEARCH

Increased Skin Clearance and Quality of Life Improvement with Brodalumab Compared with Ustekinumab in Psoriasis Patients with Aggravating Lifestyle Factors

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ABSTRACT

Introduction: Obesity, smoking, and alcohol consumption are prevalent in psoriasis patients and have been associated with increased disease severity and reduced treatment adherence and response. This post hoc analysis of pooled data from the phase 3 AMAGINE-2 and -3 trials compared the efficacy of brodalumab versus ustekinumab in psoriasis patients with aggravating and potentially treatment-confounding lifestyle risk factors.

Methods: This post hoc analysis evaluated complete skin clearance, as measured by a 100% reduction of Psoriasis Area and Severity Index (PASI100) and quality of life (QoL), as measured by a Dermatology Life Quality Index (DLQI) score of 0/1, by the presence of risk factors (obesity, tobacco or alcohol use). A competing risk model assessed cumulative incidence over 52 weeks with outcomes of PASI100 or inadequate response.

Results: This analysis included 929 patients (brodalumab 210 mg, $n = 339$; ustekinumab, $n = 590$) with moderate-to-severe psoriasis. At week 52, odds ratios (95% confidence intervals [CIs]) for complete clearance with brodalumab versus ustekinumab were 2.50 (1.14–5.46, $P = 0.0186$), 4.64 (2.80–7.69, $P < 0.0001$), 2.06 (1.25–3.40, $P = 0.0045$), and 2.55 (0.55–11.91, $P = 0.2117$) in patients with no, one, two, or three risk factors, respectively. Corresponding odds ratios (ORs) (95% CIs) for DLQI 0/1 with brodalumab versus ustekinumab were 1.72 (0.78–3.79, $P = 0.1883$), 2.49 (1.54–4.02, $P < 0.0002$), 1.57 (0.97–2.54, $P = 0.0666$), and 2.07 (0.45–9.57, $P = 0.3438$). The 52-week cumulative incidence of patients achieving PASI100 was consistently higher for brodalumab versus ustekinumab, regardless of number of risk factors ($P < 0.0001$ for one or two risk factors and $P = 0.0029$ for three risk factors).

Conclusions: Higher levels of complete skin clearance and QoL were achieved and maintained with brodalumab versus ustekinumab in patients with moderate-to-severe psoriasis, regardless of the presence of lifestyle risk factors.

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Key Summary Points
Why carry out this study?
Obesity, smoking, and alcohol consumption are prevalent in patients with psoriasis.
These lifestyle risk factors have been associated with increased psoriasis severity, limited systemic treatment options, and reduced treatment response.
This analysis compared the efficacy of brodalumab versus ustekinumab in patients with moderate-to-severe psoriasis with or without the presence of at least one of these three aggravating lifestyle risk factors at baseline.
What was learned from the study?
This post hoc analysis of pooled data from the phase 3 AMAGINE-2 and -3 trials found higher levels of complete skin clearance and quality of life were achieved and maintained with brodalumab versus ustekinumab in patients with moderate-to-severe psoriasis, regardless of the presence of lifestyle risk factors.
Brodalumab may offer a good treatment option for psoriasis patients who have a history of aggravating lifestyle risk factors.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease with systemic manifestations that has a substantial impact on quality of life (QoL) [1, 2]. While the influence of genetics in psoriasis is well established [3], the extent to which exogenous lifestyle factors such as smoking, alcohol intake, and body mass index (BMI) influence psoriasis pathogenesis is less clear [4].

Alcohol misuse is common in patients with moderate-to-severe psoriasis [approximately > 10% body surface area (BSA) involvement] [5, 6]. Some patients may use alcohol to manage their psychological distress [5], and a correlation between increased alcohol intake and extent of BSA involvement by psoriasis has been shown [5, 6]. Alcohol use has also been linked to the triggering/worsening of psoriasis and poor response to treatment [7].

Evidence suggests that smoking affects the onset of psoriasis [8, 9]. Nicotine also stimulates innate immune cells, including dendritic cells, macrophages, and keratinocytes, which play key roles in the pathogenesis of psoriasis [8]. Random-effects meta-analysis of 25 prevalence studies identified associations between psoriasis and current smoking, and between psoriasis and former smoking [9]. Three incidence studies showed an association between smoking and the incidence of psoriasis, with a possible dose–effect of smoking intensity and duration on psoriasis incidence [9]. Furthermore, smoking has been linked to the clinical severity of psoriasis and response to treatment [10, 11]. Importantly, there is evidence to suggest that smoking may also negatively impact treatment adherence [12, 13]. A systematic review of treatment adherence in patients with psoriasis assessed the role of smoking and identified two studies that reported greater adherence among non-smokers compared with smokers, while a third study reported no association [12]. More recently, registry data have shown being a current smoker to be a predictor of biologic discontinuation [13].

Meta-analyses have shown that higher BMI and obesity are risk factors for psoriasis [14]. In addition, obesity, defined by the World Health Organization as a BMI of 30 kg/m^2 or above [15], is associated with more severe psoriasis [14].

Moderate-to-severe psoriasis is increasingly treated with biologics that target various cytokines responsible for psoriasis evolution, including interleukin (IL)-17, IL-23, and tumor

necrosis factor (TNF)-α [16, 17]. While biologics are effective for many patients in the short term [18], some patients fail to respond and 13% of patients discontinue treatment within the first year because of ineffectiveness [13]. Furthermore, as the efficacy of these agents may be negatively impacted by lifestyle factors [17], it is important that lifestyle risk factors are screened for and considered when selecting psoriasis medication [19].

Brodalumab is a fully human monoclonal antibody that binds with high affinity to the IL-17 receptor subunit A (IL-17RA) [20]. By binding to IL-17RA, brodalumab inhibits downstream signaling of multiple IL-17 family cytokines involved in the pathogenesis of psoriasis [20], in contrast to biologics such as secukinumab and ixekizumab, which specifically target IL-17A [21, 22]. In phase 3 trials in patients with moderate-to-severe psoriasis, brodalumab provided high levels of skin clearance for up to 52 weeks [23, 24].

In this post hoc analysis, we evaluated skin clearance and impact on patient QoL over 52 weeks in the phase 3 AMAGINE-2 and -3 studies according to the presence of obesity, tobacco use, and alcohol use. The aims were to compare the efficacy of brodalumab versus ustekinumab in patients with psoriasis with aggravating lifestyle risk factors and to identify lifestyle risk factors that could affect response to therapy.

METHODS

Study Design and Patients

Data were pooled from two phase 3, randomized, double-blind, placebo- and ustekinumab-controlled, 52-week studies of brodalumab (AMAGINE-2 [NCT01708603] and AMAGINE-3 [NCT01708629]). The AMAGINE-2 and -3 study designs have previously been described [24] and are provided in Supplementary Fig. 1. In brief, patients aged $\geq$ 18 years with moderate-to-severe plaque psoriasis (defined as a Psoriasis Area and Severity Index [PASI] score $\geq$ 12, static Physician's Global Assessment [sPGA] score of $\geq$ 3 and $\geq$ 10% BSA involvement

of $\geq$ 6 months duration) were enrolled in the trials. Patients were randomized 2:2:1:1 to receive brodalumab 210 mg, brodalumab 140 mg, or placebo on day 1 and weeks 1, 2, 4, 6, 8 and 10; or ustekinumab (45 mg for patients $\leq$ 100 kg and 90 mg for patients $>$ 100 kg) on day 1, week 4 and every 12 weeks (Q12W) thereafter. At week 12, brodalumab patients 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 (Q4W) or every 8 weeks (Q8W). Ustekinumab patients continued to receive ustekinumab Q12W, and placebo patients received 210 mg of brodalumab Q2W.

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

The study protocols were approved by the institutional review boards at each participating center, and the studies were conducted in accordance with the International Conference on Harmonization guideline for Good Clinical Practice, the Declaration of Helsinki, and the Health Insurance Portability and Accountability Act of 1996 or relevant regional regulations. All subjects provided informed consent to participate in the study.

Assessments

Lifestyle Risk Factors

Tobacco and alcohol use were self reported. Patients were categorized as "yes" (current user or stopped within the last year) or "no" (former user/no use). Patients were categorized as obese if they had a BMI of $\geq$ 30 kg/m^2.

Table 1 Demographic and baseline characteristics

Characteristic	No risk factors		One risk factor		Two risk factors		Three risk factors	
	Brodalumab ($n = 51$)	**Ustekinumab** ($n = 76$)	**Brodalumab** ($n = 140$)	**Ustekinumab** ($n = 221$)	**Brodalumab** ($n = 122$)	**Ustekinumab** ($n = 236$)	**Brodalumab** ($n = 26$)	**Ustekinumab** ($n = 57$)
Male, n (%)	34 (66.7)	48 (63.2)	93 (66.4)	144 (65.2)	82 (67.2)	170 (72.0)	21 (80.8)	42 (73.7)
Age, years	47.2 (14.7)	40.8 (13.9)	44.7 (13.4)	45.9 (12.9)	43.3 (13.2)	46.4 (12.7)	44.3 (11.9)	42.6 (12.6)
Weight, kg	75.5 (10.8)	75.8 (12.0)	88.0 (23.9)	85.7 (19.8)	96.7 (26.9)	96.9 (23.8)	102.5 (12.3)	107.5 (23.3)
BMI, kg/m^2	25.7 (2.8)	25.6 (2.7)	29.6 (7.7)	29.3 (6.4)	32.0 (8.2)	32.2 (7.6)	34.0 (3.1)	35.3 (5.4)
White, n (%)	48 (94.1)	64 (84.2)	127 (90.7)	200 (90.5)	110 (90.2)	216 (91.5)	23 (88.5)	52 (91.2)
Duration of disease, years	17.4 (10.6)	18.7 (13.2)	18.0 (12.0)	18.5 (11.8)	16.9 (12.0)	19.0 (12.6)	15.2 (11.7)	17.6 (11.1)
BSA, %	26.5 (14.2)	29.8 (18.9)	27.6 (16.0)	27.1 (18.6)	27.3 (17.4)	27.7 (18.8)	23.6 (15.6)	25.9 (17.7)
PASI score	20.7 (8.4)	20.2 (8.3)	20.2 (7.2)	20.0 (8.3)	20.8 (8.5)	20.0 (8.5)	19.2 (7.3)	20.1 (8.2)
DLQI score	16.2 (6.5)	15.8 (7.1)	14.4 (7.3)	14.6 (7.5)	14.9 (7.7)	14.7 (7.1)	13.8 (6.4)	15.6 (7.4)
NAPSI score	8.4 (3.3)	7.9 (3.3)	9.4 (3.2)	9.9 (3.4)	9.5 (4.3)	9.9 (3.6)	9.7 (2.9)	11.4 (3.8)
sPGA score	3.4 (0.6)	3.5 (0.6)	3.4 (0.6)	3.5 (0.6)	3.6 (0.6)	3.5 (0.6)	3.6 (0.6)	3.6 (0.6)
PSI score	19.6 (7.2)	18.6 (7.1)	18.4 (6.9)	18.4 (7.1)	19.6 (7.4)	18.5 (6.7)	18.8 (5.6)	20.5 (6.3)

Data are mean (SD) unless otherwise stated

BMI body mass index, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *n* number of patients, *NAPSI* Nail Psoriasis Severity Index, *PASI* Psoriasis Area and Severity Index, *PSI* Psoriasis Symptom Inventory, *SD* standard deviation, *sPGA* static Physician's Global Assessment

Table 2 Distribution of lifestyle factors at baseline, by treatment

Lifestyle risk factor, n (%)	Brodalumab (n = 339)		Ustekinumab (n = 590)	
None	51 (15.0)		76 (12.9)	
1	140 (41.3)		221 (37.5)	
2	122 (36.0)		236 (40.0)	
3	26 (7.7)		57 (9.7)	

	Brodalumab (n = 339)		Ustekinumab (n = 590)	
	Yes	**No**	**Yes**	**No**
Alcohol (current or stopped within last year)	201 (59.3)	138 (40.7)	383 (64.9)	207 (35.1)
Smoking (current or stopped within last year)	111 (32.7)	228 (67.3)	209 (35.4)	381 (64.6)
Obesity (BMI $\geq$ 30 kg/m^2)	147 (43.4)	192 (56.6)	271 (45.9)	319 (54.1)
Weight > 100 kg	93 (27.4)	246 (72.6)	166 (28.1)	424 (71.9)

BMI body mass index, *n* number of patients

Disease Severity, Response, and QoL

Disease severity was evaluated using three instruments: the PASI, the Psoriasis Symptom Inventory (PSI), and the sPGA. The PASI is the most commonly used tool for measuring disease activity and treatment effect in clinical trials of biologics to treat psoriasis. While PASI75 (a 75% reduction in the PASI score with respect to baseline) has historically been considered the treatment goal for moderate-to-severe psoriasis [25], studies of newer biologics have included PASI90 and PASI100 as endpoints [23, 24, 26–30]. Patients who achieve PASI100 are more likely to have improved QoL scores and a reduction in the signs and symptoms of psoriasis [24, 31].

The PSI is a patient-reported outcome instrument (developed by Amgen) that measures the severity of psoriasis signs and symptoms. The eight-point questionnaire assesses signs and symptoms of itch, redness, scaling, burning, stinging, cracking, flaking, and pain. Each item is scored on a scale of 0 (not at all severe) to 4 (very severe), giving a total score ranging from 0 (best) to 32 (worst). Response on the PSI is defined as attaining a total score of $\leq$ 8, with each symptom rated as either 0 (not at

all severe) or 1 (mild) [32]. The sPGA, which assesses erythema, induration, and scaling on a scale from 0 to 5, where 0 indicates clear and 5 indicates severe disease [33], was also used to measure response to treatment. QoL was assessed using the Dermatology Life Quality Index (DLQI). A DLQI score of 0 or 1 indicates no effect at all on patient's life [34]. PASI, PSI, and DLQI scores were measured at least once every 2–4 weeks throughout the trials.

Responder Analyses for Clearance (PASI100), DLQI 0/1, and PSI $\leq$ 8 at a Given Time Point by Risk Factor History

This analysis included data from patients randomized to receive constant dosing of either the approved dose of brodalumab (210 mg Q2W) or ustekinumab for the entire 52-week treatment period, subdivided according to risk factor history (none, one risk factor, two risk factors, or three risk factors).

Proportions of patients achieving PASI100, PSI $\leq$ 8 responder status, and DLQI 0/1 are presented according to risk factor history and visit (weeks 0–52 for PASI100 and DLQI 0/1; weeks 0–24 and 48–52 for PSI $\leq$ 8 responder),
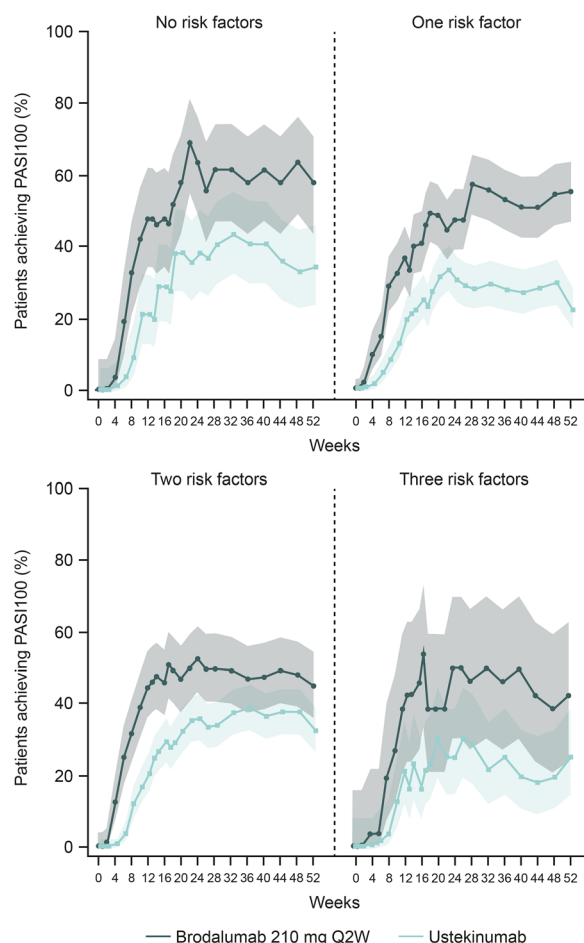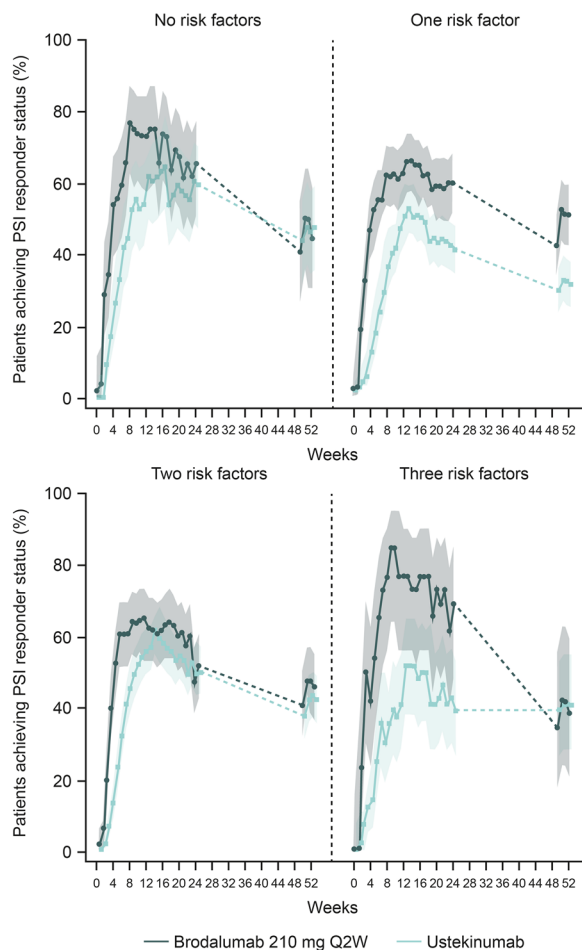
Fig. 1 Percentage of patients achieving PASI100, by visit, treatment, and history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. Shading indicates 95% confidence interval. *PASI* Psoriasis Area and Severity Index, *Q2W* every 2 weeks

with comparisons between treatment groups reported as odds ratios (ORs) and 95% confidence intervals (95% CIs) calculated using the Cochran–Mantel–Haenszel method and adjusted for study, baseline total body weight group (≤ 100 or > 100 kg), geographic region, and within-study and subgroup baseline score ($\leq$ or $>$ median). Non-responder imputation was used to handle missing data.

Competing Risk Model by Risk Factor History
The cumulative incidence of complete clearance over 52 weeks was analyzed by risk factor

history using a competing risk model [35] with the outcomes of:

(a) Achieving PASI100, or
(b) Inadequate response (defined as sPGA ≥ 3, or sPGA ≥ 2 for > 4 weeks at or after week 16)

Comparisons between treatment arms were performed using subdistribution hazard ratios and associated chi-squared tests [36, 37] and adjusted for baseline characteristics, as detailed for the responder analyses.

RESULTS

Patients

A total of 929 patients (brodalumab 210 mg, $n = 339$; ustekinumab, $n = 590$) were included in this analysis. Baseline characteristics were generally balanced across treatment and risk groups (Table 1). Baseline PASI, PSI, and DLQI scores were similar across the subgroups.

Lifestyle Risk Factors

At baseline, approximately 85% of patients had a history of one or more lifestyle risk factors. In the brodalumab and ustekinumab groups, respectively, 41.3% and 37.5% had a history of one risk factor, 36.0% and 40.0% had a history of two risk factors, and 7.7% and 9.7% had a history of three risk factors (Table 2).

Alcohol use was the most common risk factor: 59.3% and 64.9% of patients in the brodalumab and ustekinumab groups, respectively, had a history of alcohol use. Almost half of the patients in both groups were obese (43.4% and 45.9% in the brodalumab and ustekinumab groups, respectively, Table 2). Further details of tobacco and alcohol use (i.e., light, moderate, or heavy use) are provided in Supplementary Table 1.

Table 3 Overview of patients with PASI100, PSI response, and DLQI 0/1 at weeks 12 and 52, according to lifestyle risk factors and treatment

	No risk factors			One risk factor			Two risk factors			Three risk factors		
	Brodalumab (n = 51)	Ustekinumab (n = 76)	OR (95% CI)	Brodalumab (n = 140)	Ustekinumab (n = 221)	OR (95% CI)	Brodalumab (n = 122)	Ustekinumab (n = 236)	OR (95% CI)	Brodalumab (n = 26)	Ustekinumab (n = 57)	OR (95% CI)
PASI100 week 12	24 (47.1)	16 (21.1)	3.54 (1.41–8.87)**	51 (36.4)	44 (19.9)	2.54 (1.52–4.25)***	56 (45.9)	49 (20.8)	3.59 (2.09–6.17)***	10 (38.5)	12 (21.1)	1.53 (0.45–5.22)
PASI100 week 52	29 (56.9)	26 (34.2)	2.50 (1.14–5.46)*	77 (55.0)	49 (22.2)	4.64 (2.80–7.69)***	56 (45.9)	76 (32.2)	2.06 (1.25–3.40)**	11 (42.3)	15 (26.3)	2.55 (0.55–11.91)
PSI response week 12	37 (72.5)	47 (61.8)	2.11 (0.80–5.53)	89 (63.6)	117 (52.9)	1.57 (0.95–2.60)	76 (62.3)	134 (56.8)	1.11 (0.66–1.88)	20 (76.9)	30 (52.6)	2.37 (0.62–9.03)
PSI response week 52	23 (45.1)	36 (47.4)	1.09 (0.48–2.43)	70 (50.0)	69 (31.2)	2.56 (1.55–4.22)***	57 (46.7)	100 (42.4)	1.45 (0.86–2.45)	10 (38.5)	23 (40.4)	1.03 (0.28–3.85)
DLQI 0/1 week 12	30 (58.8)	36 (47.4)	1.75 (0.75–4.10)	84 (60.0)	89 (40.3)	2.20 (1.37–3.54)***	69 (56.6)	120 (50.8)	1.14 (0.71–1.81)	20 (76.9)	24 (42.1)	3.54 (0.84–14.92)
DLQI 0/1 week 52	32 (62.7)	36 (47.4)	1.72 (0.78–3.79)	76 (54.3)	73 (33.0)	2.49 (1.54–4.02)***	67 (54.9)	108 (45.8)	1.57 (0.97–2.54)	11 (42.3)	18 (31.6)	2.07 (0.45–9.57)

All data are n (%); ORs are brodalumab versus ustekinumab

CI confidence interval, DLQI Dermatology Life Quality Index, n number of patients, OR odds ratio, PASI Psoriasis Area and Severity Index, PSI Psoriasis Symptom Inventory

*P < 0.05; **P < 0.01; ***P < 0.001

Fig. 2 Percentage of patients achieving PSI responder status (≤ 8) by visit, treatment, and history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. Shading indicates 95% confidence interval. Data were not collected between weeks 24 and 48; indicated by a broken line. *PSI* Psoriasis Symptom Inventory, *Q2W* every 2 weeks

Fig. 3 Percentage of patients with DLQI 0/1 by visit, treatment, and history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. Shading indicates 95% confidence interval. *DLQI* Dermatology Life Quality Index, *Q2W* every 2 weeks

Responder Analysis for Complete Clearance (PASI100), PSI ≤ 8, and DLQI 0/1 by Number of Lifestyle Risk Factors

Regardless of the presence of risk factors, brodalumab treatment was associated with earlier achievement of complete clearance and consistently higher proportions of complete clearance versus ustekinumab (Fig. 1); differences between the brodalumab and ustekinumab groups were statistically significant for subgroups with no, one, or two baseline risk factors, but did not reach statistical significance in

the subgroup with three risk factors. At week 12, PASI100 was achieved by 47.1% of patients on brodalumab versus 21.1% on ustekinumab with no risk factors (OR 3.54, 95% CI 1.41–8.87, $P = 0.0073$), 36.4% versus 19.9% with one risk factor (OR 2.54, 95% CI 1.52–4.25, $P = 0.0004$), 45.9% versus 20.8% with two risk factors (OR 3.59, 95% CI 2.09–6.17, $P < 0.0001$), and 38.5% versus 21.1% with three risk factors (OR 1.53, 95% CI 0.45–5.22, $P = 0.5127$) (Fig. 1, Table 3). At week 52, the proportions of patients in the brodalumab and ustekinumab groups achieving complete clearance were 56.9% versus 34.2% (OR 2.50, 95% CI 1.14–5.46, $P = 0.0186$), 55.0%

(a) No risk factors
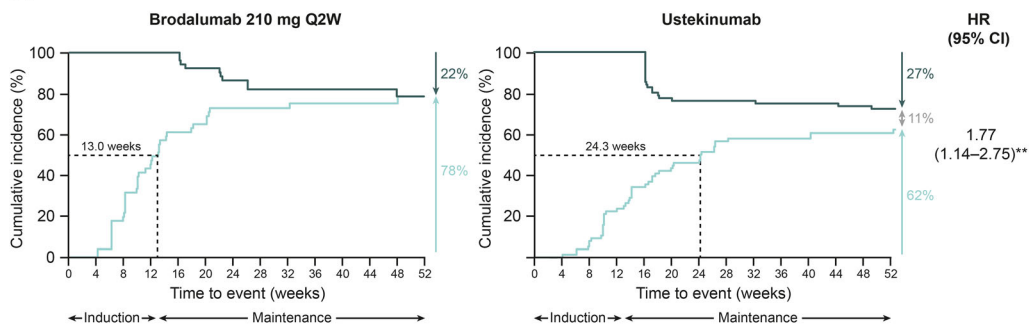
(b) One risk factor
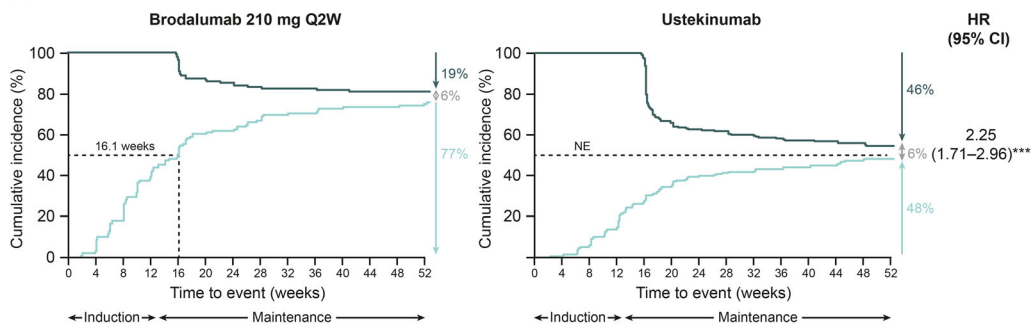
(c) Two risk factors
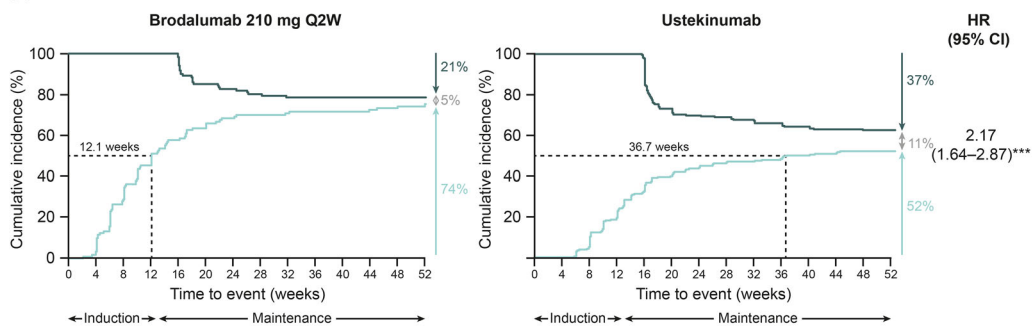
(d) Three risk factors
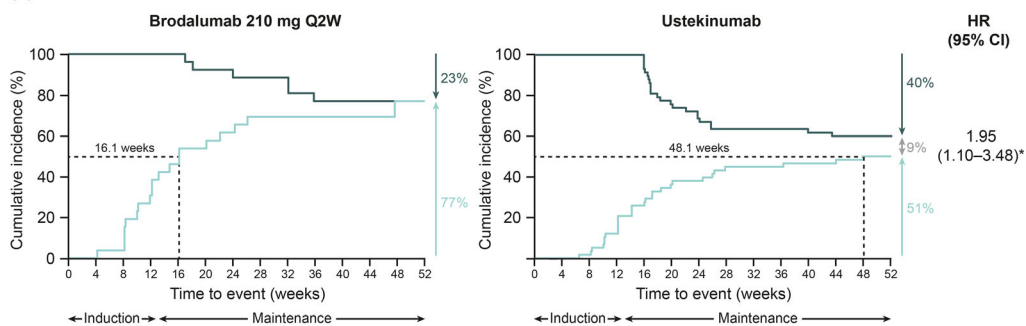
—— Complete clearance   —— Inadequate response[a]   ←→ Never achieved complete clearance[a]

----- Time to achievement of complete clearance by 50 % of patients

◀**Fig. 4** Cumulative incidence of patients achieving PASI100 by visit, treatment, and history of lifestyle risk factors (competing risk analysis). *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$. ªDefined as static Physician's Global Assessment ≥ 3 or persistent values of 2 over at least a 4-week period or after week 16. *CI* confidence interval, *HR* hazard ratio, *NE* not estimable, *PASI* Psoriasis Area and Severity Index, *Q2W* every 2 weeks

versus 22.2% (OR 4.64, 95% CI 2.80–7.69, $P < 0.0001$), 45.9% versus 32.2% (OR 2.06, 95% CI 1.25–3.40, $P = 0.0045$), and 42.3% versus 26.3% (OR 2.55, 95% CI 0.55–11.91, $P = 0.2117$) in the corresponding risk factor groups, respectively.

More patients achieved a PSI response (total PSI ≤ 8) with brodalumab treatment versus ustekinumab, regardless of risk factor history, at week 12 (Fig. 2). At week 12, 72.5% of patients on brodalumab versus 61.8% on ustekinumab with no risk factors (OR 2.11, 95% CI 0.80–5.53, $P = 0.1252$), 63.6% versus 52.9% with one risk factor (OR 1.57, 95% CI 0.95–2.60, $P = 0.0742$), 62.3% versus 56.8% with two risk factors (OR 1.11, 95% CI 0.66–1.88, $P = 0.6979$), and 76.9% versus 52.6% with three risk factors (OR 2.37, 95% CI 0.62–9.03, $P = 0.2091$) achieved a PSI response (Table 3).

Higher proportions of patients in the brodalumab group achieved DLQI 0/1 compared with the ustekinumab group, independent of baseline risk factors (Fig. 3). At week 12, 58.8% of patients on brodalumab versus 47.4% on ustekinumab with no risk factors (OR 1.75, 95% CI 0.75–4.10, $P = 0.2082$), 60.0% versus 40.3% with one risk factor (OR 2.20, 95% CI 1.37–3.54, $P = 0.0006$), 56.6% versus 50.8% with two risk factors (OR 1.14, 95% CI 0.71–1.81, $P = 0.5905$), and 76.9% versus 42.1% with three risk factors (OR 3.54, 95% CI 0.84–14.92, $P = 0.0608$) achieved DLQI 0/1 (Table 3). At week 52, the proportions of patients in the brodalumab and ustekinumab groups achieving DLQI 0/1 were 62.7% versus 47.4% (OR 1.72, 95% CI 0.78–3.79, $P = 0.1883$), 54.3% versus 33.0% (OR 2.49, 95% CI 1.54–4.02, $P = 0.0002$), 54.9% versus 45.8% (OR 1.57, 95% CI 0.97–2.54, $P = 0.0666$), and 42.3% versus 31.6% (OR 2.07,

95% CI 0.45–9.57, $P = 0.3438$) in the corresponding risk factor groups.

Competing Risk Model by Number of Risk Factors

The 52-week cumulative incidence of patients achieving PASI100 was higher for brodalumab versus ustekinumab regardless of the number of risk factors ($P < 0.0001$ for one and two risk factors; $P = 0.0229$ for three risk factors; Fig. 4).

The median time to achievement of PASI100 in brodalumab patients was not affected by baseline risk factors (Fig. 4). The median time to achieve complete clearance could not be estimated for ustekinumab patients in the one risk factor subgroup, as fewer than 50% of patients achieved complete clearance by week 52.

Responder Analysis for Complete Clearance and DLQI 0/1 by Visit by Various Lifestyle Risk Factors

A higher proportion of brodalumab-treated patients achieved PASI100 in each subgroup through week 52, independent of risk factor (Fig. 5). The ORs (95% CIs) for complete clearance with brodalumab versus ustekinumab at week 52 were: smoking OR 3.59 (2.47–5.20, $P < 0.0001$), alcohol use OR 2.87 (1.75–4.71, $P < 0.0001$), and obesity OR 3.44 (2.33–5.07, $P < 0.0001$). Similarly, a higher proportion of patients in the brodalumab group achieved DLQI 0/1 (Fig. 5) or a PSI response (data not shown) in each risk factor subgroup through week 52. Figure 6 compares ORs and 95% CIs for achieving complete clearance and DLQI 0/1 at weeks 12 and 52, by lifestyle risk factors.

DISCUSSION

Obesity, smoking, and alcohol use are lifestyle risk factors associated with increased psoriasis severity, limited systemic treatment options, and reduced treatment response [6, 7, 10–12, 15]. Obesity may predict biologic treatment discontinuation and lead to lower efficacy of anti-TNF-α agents [15, 38]. Smoking and obesity have been associated with non-response to anti-TNF-α therapies, and in a retrospective study of 110 patients with psoriasis
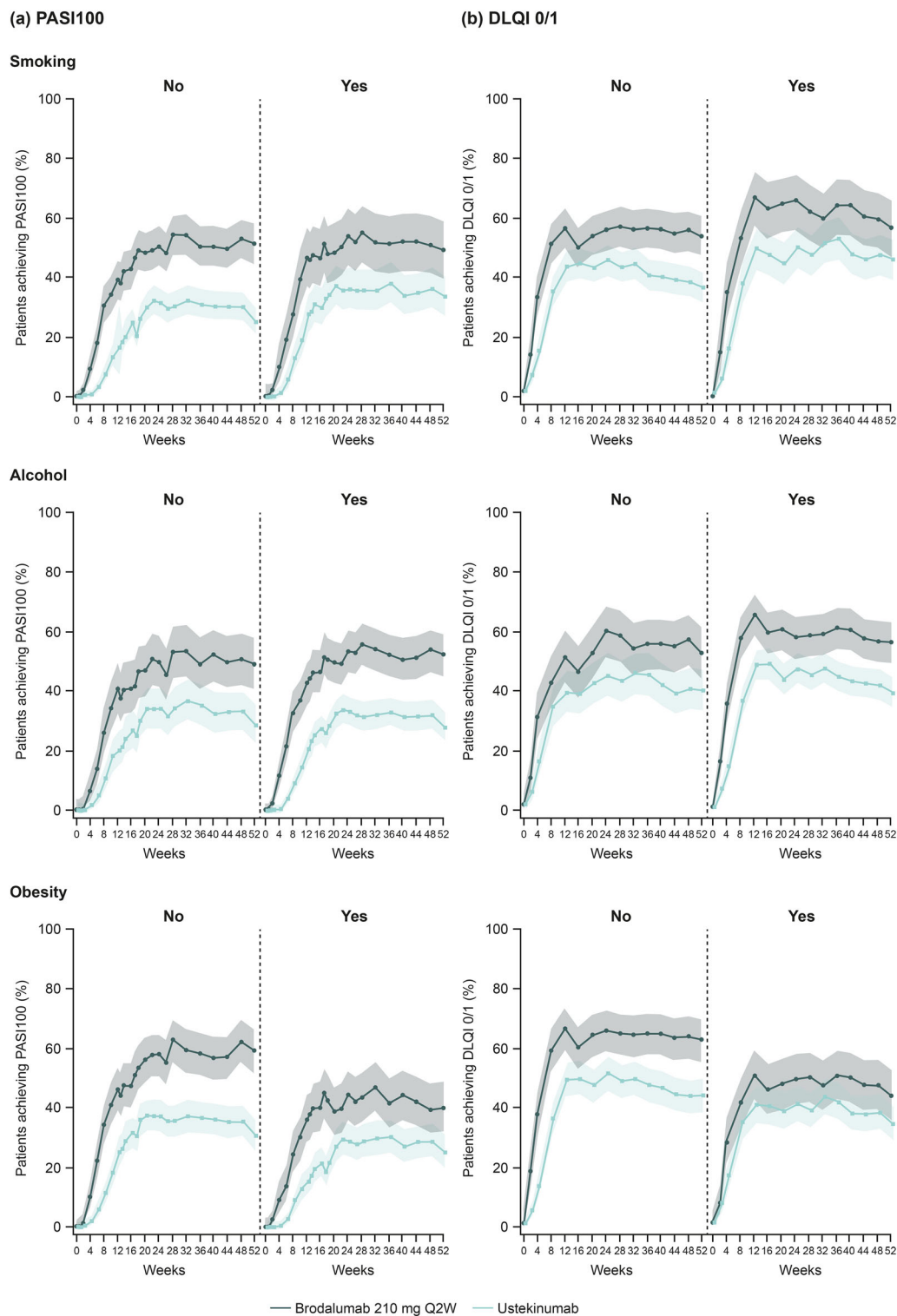
Fig. 5 Percentage of patients achieving **a** PASI100 and **b** DLQI 0/1 at weeks 4, 12, and 52 by history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. Shading indicates 95% confidence interval. *DLQI* Dermatology Life Quality Index, *PASI* Psoriasis Area and Severity Index, *Q2W* every 2 weeks
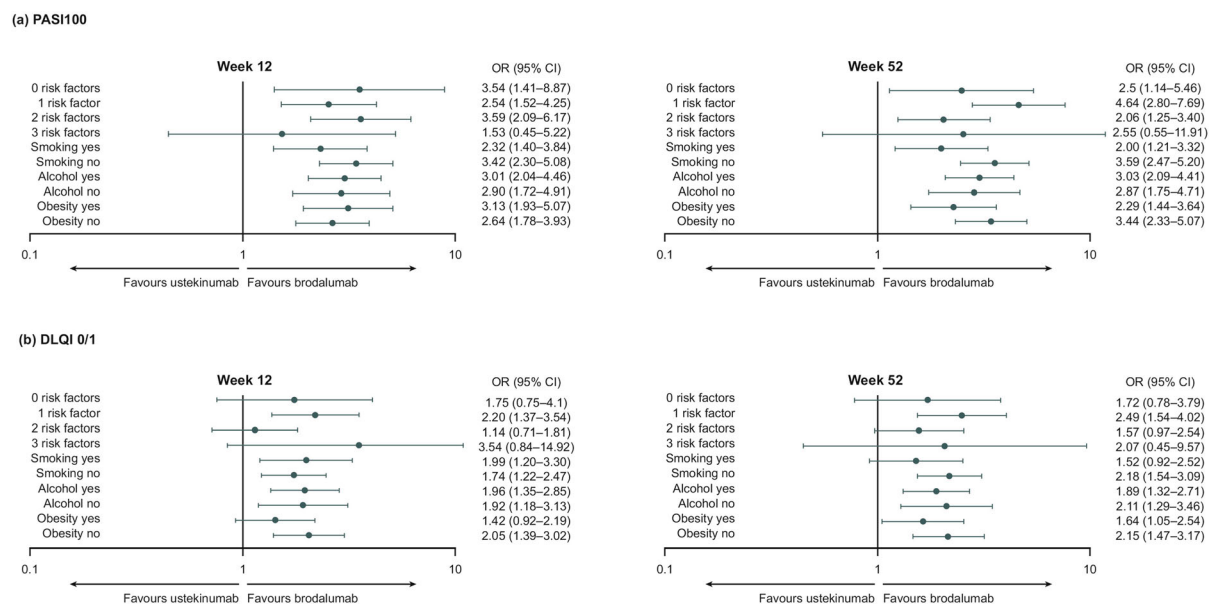
Fig. 6 Forest plots comparing the odds ratios and 95% confidence intervals for achieving **a** PASI100 and **b** DLQI 0/1 at weeks 12 and 52 by history of lifestyle risk factors. Pooled data from the AMAGINE-2 and -3 trials. *CI* confidence interval, *DLQI* Dermatology Life Quality Index, *OR* odds ratio, *PASI* Psoriasis Area and Severity Index

treated with anti-TNF-α therapies, smoking in combination with high BMI and a high baseline PASI score was a risk factor for lack of response [39]. Thus, there is a need for therapeutic strategies that remain effective in patients with aggravating and potentially treatment-confounding lifestyle factors.

In this analysis, which included 929 patients with moderate-to-severe psoriasis from the AMAGINE-2 and -3 studies, approximately 85% of patients had one or more risk factors (obesity or tobacco or alcohol use) at baseline.

We assessed the reduction in disease severity (PASI100 and PSI response) and impact on patient QoL, as estimated by the DLQI 0/1, through 52 weeks by obesity (< 30 versus ≥ 30 kg/m^2), and/or tobacco use (yes/no), and/or alcohol use (yes/no) per risk group (no risk factors, one risk factor, two risk factors, or three risk factors). We found that complete clearance (PASI100) was achieved more rapidly in more patients treated with brodalumab versus ustekinumab in the subgroups with no, one, or two baseline risk factors.

More patients achieved PSI response (total PSI ≤ 8) or DLQI 0/1 with brodalumab than with ustekinumab through to week 52, but these differences did not reach statistical significance. Thus, while Q12W administration of ustekinumab may be more convenient for patients, these data suggest a trend towards improvements in the severity of psoriasis signs and symptoms with brodalumab treatment.

Responder analysis for complete clearance or DLQI 0/1 by lifestyle risk factors showed a higher proportion of patients achieving PASI100 and DLQI through week 52 with brodalumab treatment in the alcohol use subgroup only. While a trend was observed in the smoking and obesity subgroups, statistical significance was not reached, most likely due to the smaller number of patents in these subgroups compared with the alcohol use subgroup (alcohol use was by far the most common risk factor at baseline).

These findings are similar to those of a previous analysis of AMAGINE-2 and -3 data showing that treatment with brodalumab resulted in rapid and higher proportions of

patients achieving complete skin clearance, rapid improvement in QoL, and a greater cumulative benefit for complete skin clearance versus ustekinumab and across subgroups with a history of alcohol and tobacco use [40]. It is possible that lifestyle factors may negatively impact the efficacy of any therapy for patients with psoriasis. However, they had no impact on the demonstrated benefits of brodalumab over ustekinumab in this analysis.

The body of evidence regarding the effects of lifestyle modifications, including weight-loss and smoking-cessation programs as well as trigger-factor elimination, in the management of psoriasis is limited. However, some studies suggest that lifestyle changes, such as a low-calorie diet, may supplement the pharmacologic treatment of obese psoriasis patients [41, 42]. More recently, a systematic review, which included ten randomized controlled trials with 1163 participants, found that dietary intervention may reduce psoriasis severity in obese patients and improve QoL compared with standard care [43].

There are several limitations to this study. The data analyzed were from a clinical trial population with strict entry criteria and may not be representative of real-world patient populations. Notably, AMAGINE-2 and -3 excluded patients who had prior ustekinumab experience, resulting in a high number of biologic-naïve patients, and this may have resulted in better response than would be observed in a real-world population [44]. Analyses were of pooled data from clinical trials that were not designed or statistically powered to assess these specific endpoints. Analyses were also restricted to patients in constant treatment arms, reducing the number of available patients that could be included. Finally, PASI is a subjective measure of disease severity. However, participating sites were encouraged to maintain the same rater for each patient to diminish between-rater bias.

CONCLUSIONS

The results of these analyses suggest that higher proportions of patients achieve complete skin clearance, PSI response, and QoL improvement with brodalumab compared with ustekinumab, regardless of history of risk factors, which are extremely common in real-world practice. Furthermore, these higher proportions of response are sustained over time. Thus, brodalumab may offer a good treatment option for psoriasis patients who have a history of aggravating lifestyle risk factors.

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