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Efficacy and safety of brodalumab in patients with psoriasis who had inadequate responses to ustekinumab: subgroup analysis of two randomized phase III trials*

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Summary

Background Brodalumab, a fully human anti-interleukin-17 receptor A monoclonal antibody, has demonstrated superior efficacy and safety over ustekinumab as induction therapy for moderate-to-severe psoriasis.

Objectives To evaluate the efficacy and safety of brodalumab through week 52 in patients who had inadequate responses to ustekinumab.

Methods A subgroup analysis of the phase III AMAGINE-2/-3 double-blind randomized controlled trials was performed. Participants were aged 18–75 years and had a Psoriasis Area and Severity Index (PASI) ≥ 12, static Physician's Global Assessment score ≥ 3 and involvement of ≥ 10% body surface area. The studies were registered at ClinicalTrials.gov: AMAGINE-2, NCT01708603; AMAGINE-3, NCT01708629.

Results At baseline, patients with or without prior biologic experience who had an adequate response at week 16 on ustekinumab or brodalumab had lower rates of involved body surface area, PASI, prior biologic use, psoriatic arthritis and body mass index than patients who experienced inadequate response at or after week 16. Among patients who experienced inadequate response to ustekinumab, those rescued with brodalumab had PASI ≥ 75%, ≥ 90% and 100% improvement response rates of 72·6%, 58·1% and 36·3%, respectively, at week 52 compared with 61·7%, 25·5% and 5·4%, respectively, in patients who continued ustekinumab. Exposure-adjusted rates of treatment-emergent adverse events were similar among patients rescued with brodalumab (377·3 adverse events per 100 patient-years) and those who remained on ustekinumab (389·9 adverse events per 100 patient-years).

Conclusions Among patients who experienced inadequate responses to ustekinumab, rescue with brodalumab improved skin clearance outcomes compared with continuing ustekinumab.

What's already known about this topic?

- Among biologics used to treat psoriasis, brodalumab provides a unique mechanism of action by antagonizing interleukin-17 receptor A.

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**Plain language summary available online*

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- In the AMAGINE-2/-3 randomized controlled trials, brodalumab demonstrated superior skin clearance efficacy and safety compared with ustekinumab as induction therapy in patients with psoriasis.
- Brodalumab is approved for the treatment of moderate-to-severe psoriasis in adults who have experienced treatment failure or loss of response on other systemic therapies.

What does this study add?

- In this subgroup analysis of AMAGINE-2/-3, patients who had been rescued with brodalumab at week 16 after experiencing inadequate response to ustekinumab had higher skin clearance rates at week 52 (72·6%, 58·1% and 36·3% achieved Psoriasis Area and Severity Index ≥ 75%, ≥ 90% and 100% improvement, respectively) than patients who continued on ustekinumab (61·7%, 25·5% and 5·4%, respectively).
- Brodalumab may be effective in patients who have inadequate responses to ustekinumab.

Psoriasis is a chronic, systemic, immune-mediated inflammatory disease that affects approximately 1–8·5% of adults worldwide.[1] Psoriatic tissue inflammation is characterized by excess of inflammatory cytokines, particularly overexpression and activation of members of the interleukin (IL)-17 family of cytokines.[2,3] These cytokines, specifically IL-17A, IL-17C and IL-17F, are produced by T helper (Th)17 cells and innate immune cells.[4] IL-23 is an upstream regulatory cytokine that activates and promotes survival of Th17 cells.[5]

Brodalumab is a fully human anti-IL-17 receptor A (IL-17RA) monoclonal antibody that selectively targets IL-17RA and blocks the effects of several IL-17 cytokine family members, including IL-17A, IL-17F, IL-17A/F and IL-25.[2] The efficacy and safety of brodalumab have been established in a clinical trial programme that included three large phase III trials: AMAGINE-1, AMAGINE-2 and AMAGINE-3.[6,7] In AMAGINE-2/-3, both of which included ustekinumab (a monoclonal antibody to the p40 subunit of IL-12 and IL-23) as an active comparator, > 50% of patients receiving brodalumab had complete clearance of psoriasis [i.e. 100% reduction from baseline in Psoriasis Area and Severity Index (PASI 100)] within 1 year of treatment compared with 29–30% for ustekinumab.[6,7] The onset of skin clearance was also faster in patients treated with brodalumab 140 mg or 210 mg every 2 weeks (Q2W) compared with ustekinumab, with differences in speed of efficacy evident by week 1.[8]

Understanding the efficacy and safety of brodalumab in patients with and without prior exposure to biologics is important for clinicians to inform treatment decisions. It is especially useful to determine the efficacy and safety of brodalumab in patients who had inadequate responses to other biologics. Therefore, we undertook this analysis of patients in AMAGINE-2/-3 initially randomized to ustekinumab who were switched to brodalumab 210 mg Q2W at week 16 after experiencing inadequate responses to ustekinumab.

Patients and methods

Study design

AMAGINE-2 and AMAGINE-3 are two phase III trials comparing the efficacy and safety of brodalumab and ustekinumab in patients with moderate-to-severe plaque psoriasis.[6] Patients in these identically designed, double-blinded studies were aged 18–75 years with PASI ≥ 12, static Physician's Global Assessment (sPGA) score ≥ 3 and involvement of ≥ 10% of body surface area. Patients were randomized during the induction phase (12 weeks) to receive brodalumab 210 mg or 140 mg Q2W (subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8 and 10), ustekinumab or placebo (Fig. 1). Ustekinumab was dosed, in accordance with the product label, as subcutaneous injections of 45 mg in patients weighing ≤ 100 kg and 90 mg in patients weighing > 100 kg, with the first dose followed by a second dose 4 weeks later, then doses every 12 weeks after that.[9] Placebo injections were given as needed to maintain blinding throughout the study.

At week 12, patients who had been randomized to one of the brodalumab regimens in the induction phase were pooled and rerandomized (2 : 2 : 2 : 1) to receive maintenance therapy with brodalumab 210 mg Q2W, brodalumab 140 mg Q2W, brodalumab 140 mg every 4 weeks (Q4W) or brodalumab 140 mg every 8 weeks (Q8W). Starting at week 16, patients who had inadequate response to their randomized treatment (i.e. one sPGA score ≥ 3 or persistent sPGA scores of 2 over a ≥ 4-week period) were rescued with brodalumab 210 mg Q2W. Patients who had been randomized to any of the brodalumab regimens and qualified for rescue treatment at any point between week 16 and week 52 received rescue treatment with brodalumab 210 mg Q2W. Patients on ustekinumab who qualified for rescue after week 16 remained on

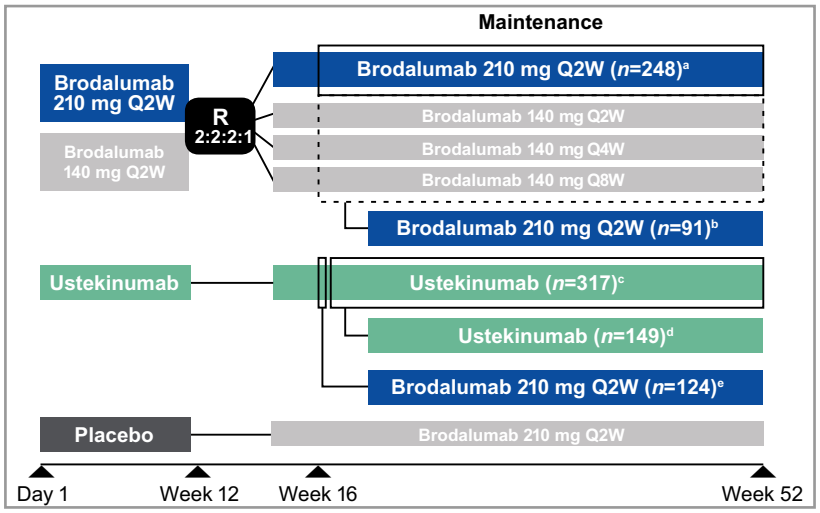

Fig 1. Study design for AMAGINE-2/-3. Treatment arms in grey boxes were not included in this analysis. [a]Patients who were not rescued because of adequate response at week 16. [b]Patients who continued on brodalumab 210 mg Q2W following inadequate response after week 16. [c]Patients who were not rescued because of adequate response at week 16. [d]Patients who continued on ustekinumab following inadequate response after week 16. [e]Patients who were rescued with brodalumab 210 mg Q2W following inadequate response at week 16. Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; R, randomization.

ustekinumab until week 52. After receiving rescue treatment for ≥ 12 weeks, patients were assessed for nonresponse (i.e. sPGA score ≥ 3 for ≥ 4 weeks after continuous treatment for ≥ 12 weeks) and discontinued from the investigational product if they had not responded to rescue treatment. All treatment assignments, including rescue treatments, were double blinded from randomization to week 52 or discontinuation from the study.

The primary objective in this post hoc analysis was to compare at week 52 the efficacy of brodalumab rescue treatment in patients with inadequate response to ustekinumab at week 16 vs. ustekinumab continuation in patients with inadequate responses to ustekinumab after week 16, using PASI 75, PASI 90 and PASI 100. Furthermore, we assessed patient-reported health outcomes in these patients using the Dermatology Life Quality Index (DLQI) and Psoriasis Symptom Inventory (PSI).

The institutional review board at each participating centre approved the study protocols. The study protocols were consistent with the 2008 Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practice. All patients provided informed written consent prior to study procedures. The trials were registered with ClinicalTrials.gov (AMAGINE-2, NCT01708603; AMAGINE-3, NCT01708629).

Patient population

In AMAGINE-2, 55 of 300 patients (18·3%) randomized to ustekinumab received rescue therapy with brodalumab 210 mg Q2W at week 16.[6] In AMAGINE-3, 69 of 313 patients (22·0%) received rescue therapy with brodalumab 210 mg Q2W at week 16.[6] Among patients receiving brodalumab 210 mg Q2W during both the induction and maintenance phases in AMAGINE-2 (n = 168) and AMAGINE-3 (n = 171), a total of 91 patients (26·8%) had inadequate responses at or after week 16 but continued on the same regimen.

The current analyses focused on the following treatment groups during the maintenance phase of AMAGINE-2/-3: (i) patients receiving brodalumab 210 mg Q2W during both the induction and maintenance phases who maintained adequate response through week 52; (ii) patients receiving brodalumab 210 mg Q2W during both the induction and maintenance phases who demonstrated inadequate responses between weeks 16 and 52 but continued the same regimen after week 16; (iii) patients receiving ustekinumab during both the induction and maintenance phases who were rescued with brodalumab 210 mg Q2W at week 16; (iv) patients receiving ustekinumab during both the induction and maintenance phases who demonstrated inadequate responses after week 16 but continued the same ustekinumab regimen after week 16; and (v) patients receiving ustekinumab during both the induction and maintenance phases who maintained an adequate response on ustekinumab through week 52.

Patients receiving ustekinumab who were rescued with brodalumab 210 mg Q2W at week 16 were administered an additional loading dose of brodalumab 210 mg 1 week after the initiation of brodalumab. Of these patients, 82 inadvertently received a placebo loading dose at week 17 instead of brodalumab 210 mg as planned. Correct treatments were administered at all subsequent time points, and the missed dose was determined to have no significant effect on patient safety or the study analyses. Rescue treatment assignments were blinded through week 52: individuals continued to receive brodalumab or matching placebo, or ustekinumab or matching placebo according to the maintenance-phase dosing schedule.

Statistical analyses

Statistical analyses carried out in the primary reports of AMAGINE-2/-3 are described elsewhere.[6] All primary efficacy analyses were performed adjusting for the following covariates: baseline total bodyweight group (≤ 100 kg or > 100 kg), prior biologic use (yes or no), geographical region and baseline value group (PASI-related end points: ≤ median, > median; sPGA-related end points: baseline sPGA score of 3, 4 or 5). Missing values for dichotomous end points were imputed by nonresponder imputation, which imputed missing values as nonresponse, and continuous variables were imputed using the last observation carried forward method.

For each treatment group, baseline demographics and disease characteristics were summarized descriptively, with counts and percentages for categorical variables and with descriptive statistics for continuous variables. Percentages of responders for each efficacy end point were reported in each treatment group (as described previously; post hoc P-values were not calculated). PASI 75, PASI 90 and PASI 100 responses were also assessed on the basis of prior biologic therapy and history of psoriatic arthritis. For safety analyses, the patient incidence and exposure-adjusted event rates were summarized for all types of adverse events (AEs). These were defined as treatment emergent, grade ≥ 2, serious, treatment related, serious treatment related, those leading to withdrawal of investigational product, those leading to study discontinuation, fatal and those of special interest.

Results

Patient characteristics

Baseline demographics and disease characteristics are shown in Table 1. Regardless of whether they had been assigned to receive ustekinumab or brodalumab, patients with adequate response at week 16 had similar demographic and clinical baseline characteristics. Patients who had an adequate response tended to have lower weight and body mass index, fewer occurrences of psoriatic arthritis, a lower rate of involved body surface area, lower baseline PASI score and lower rates of prior biologic use compared with patients who experienced inadequate response at or after week 16. However, the clinical implications of these trends were not studied. Across treatment groups, between 18·6% and 36·2% of patients had received at least one prior biologic therapy (Fig. 2).

Efficacy at week 12

PASI 75, PASI 90 and PASI 100 response rates by rescue status are shown in Figure 3. These responses occurred before any rescue therapy was instituted at week 16. At week 12, PASI 75, PASI 90 and PASI 100 response rates for both brodalumab and ustekinumab were lower in patients who were eventually rescued or who remained on maintenance therapy after week 16 following inadequate responses compared with response rates in those who were not rescued.

Furthermore, among patients initially treated with ustekinumab who had inadequate responses at or after week 16, responses were much lower at week 12 in the patients rescued with brodalumab at week 16 than in patients who remained on ustekinumab after week 16 following inadequate responses at later visits (Fig. 3). This may be because patients rescued with brodalumab at week 16 had inadequate responses by week 16, whereas those who remained on ustekinumab after week 16 maintained adequate responses at week 16 and only had inadequate responses at a later point. PASI 75, PASI 90 and PASI 100 response rates prior to rescue in patients rescued with brodalumab 210 mg Q2W at week 16 were 22·6%, 4·8% and 0%, respectively, and response rates in patients who remained on ustekinumab were 66·4%, 33·6% and 11·4%, respectively.

Efficacy at week 52

In patients with inadequate responses to ustekinumab who were rescued with brodalumab at week 16, PASI 75 and PASI 90 rates increased from week 12 to week 52 by three times (24·2% to 72·6%) and 11 times (4·8% to 58·1%), respectively, while PASI 100 rates increased from 0% to 36·3%. Similar improvement was observed in rates of sPGA score of 0 or 1 (data not shown). In ustekinumab-treated patients who continued ustekinumab therapy after week 16 following inadequate responses, and in brodalumab-treated patients with inadequate responses at week 16 who continued brodalumab, PASI response rates from week 12 to week 52 were generally consistent. DLQI and PSI response rates decreased by 16·2% and 32·4%, respectively, from week 12 to week 52 in ustekinumab-treated patients who continued ustekinumab following inadequate responses after week 16, while DLQI rates increased by 3·6% and PSI rates increased by 76·5% over the same period in ustekinumab-treated patients who were rescued with brodalumab following inadequate response at week 16 (Fig. 4).

Efficacy by prior biologic use or by history of psoriatic arthritis

PASI 75, PASI 90 and PASI 100 responses were approximately 1·5-, 1·5- and 1·6-fold higher, respectively, in patients without prior biologic use compared with those with prior biologic use among ustekinumab-treated patients rescued with brodalumab. PASI 75, PASI 90 and PASI 100 scores increased from week 12 to week 52 among ustekinumab-treated patients rescued with brodalumab, but not among patients who continued receiving ustekinumab following inadequate response, regardless of prior biologic exposure (Table 2). Prior use of biologics use did not affect responses in brodalumab-treated patients rescued with brodalumab. Presence or absence of a history of psoriatic arthritis appeared to have no effect on efficacy because PASI 75, PASI 90 and PASI 100

Table 1 Baseline demographics and disease characteristics of patients in AMAGINE-2/-3

	Ustekinumab/ustekinumab[a]			Brodalumab/brodalumab[a]	
	Rescued with brodalumab 210 mg Q2W (n = 124)[b]	Continued on ustekinumab (n = 149)[b]	Not rescued (n = 317)[c]	Continued on brodalumab 210 mg Q2W (n = 91)[b]	Not rescued (n = 248)[c]
Weight (kg), mean ± SD	95·0 ± 23·9	94·1 ± 22·8	88·0 ± 22·2	103·1 ± 30·1	85·7 ± 19·7
BMI (kg m^{-2}), mean ± SD	32·0 ± 8·0	31·5 ± 7·0	29·6 ± 6·4	34·1 ± 9·0	28·8 ± 6·3
Duration of psoriasis (years), mean ± SD	18·2 ± 11·3	17·4 ± 11·4	19·3 ± 12·9	16·8 ± 11·5	17·5 ± 11·8
Psoriatic arthritis, n (%)	35 (28)	26 (17)	49 (15)	24 (26)	55 (22)
BSA (%), mean ± SD	32·5 ± 23·0	27·3 ± 17·2	25·8 ± 16·9	31·3 ± 20·3	25·5 ± 14·1
PASI, mean ± SD	23·1 ± 10·9	19·3 ± 7·3	19·1 ± 7·4	21·8 ± 8·6	19·9 ± 7·5
Prior biologic therapy, n (%)	42 (34)	54 (36)	59 (19)	32 (35)	64 (26)
Anti-TNF biologics	39 (31)	47 (32)	50 (16)	31 (34)	54 (22)
Ustekinumab	2 (2)	2 (1)	2 (1)	2 (2)	0
Other biologics	7 (6)	12 (8)	14 (4)	8 (9)	16 (6)

BMI, body mass index; BSA, body surface area; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; TNF, tumour necrosis factor. [a]Ustekinumab/ustekinumab includes those patients who received ustekinumab in the induction and maintenance phases. Brodalumab/brodalumab includes those who were randomized to brodalumab 210 mg Q2W in the induction phase and were rerandomized to brodalumab 210 mg Q2W in the maintenance phase. [b]Following inadequate response at week 16. [c]Because of adequate response at week 16.

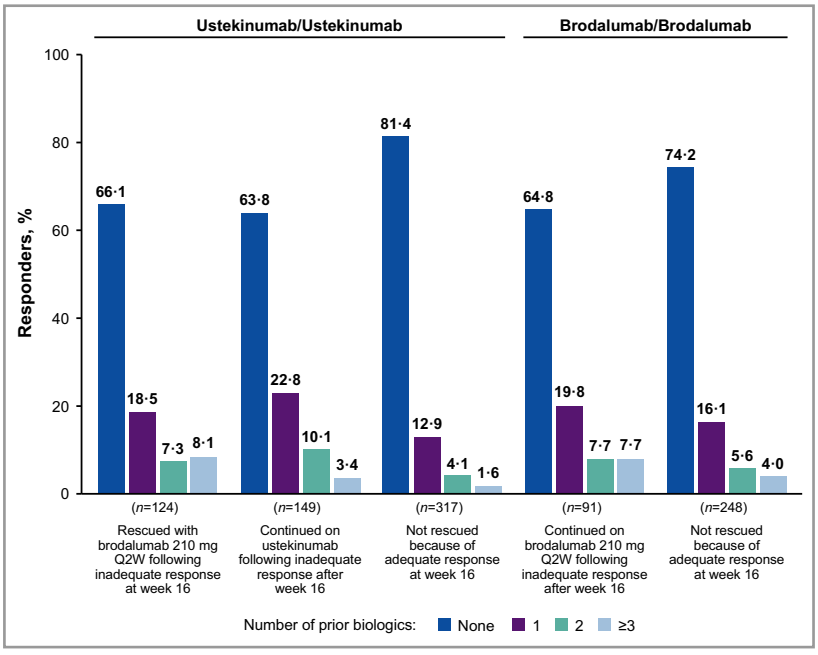

Fig 2. Rates of prior biologic use. Ustekinumab/ustekinumab includes those patients who received ustekinumab in the induction and maintenance phases. Brodalumab/brodalumab includes those who were randomized to brodalumab 210 mg every 2 weeks (Q2W) in the induction phase and were rerandomized to brodalumab 210 mg Q2W in the maintenance phase.

responses were similar in patients within each treatment group regardless of psoriatic arthritis history (Table 3).

Safety

The exposure-adjusted rate of treatment-emergent AEs (TEAEs) was generally similar between those patients who were rescued with brodalumab and those who remained on ustekinumab (Table S1; see Supporting Information). The most frequent TEAEs (≥ 10 per 100 patient-years among any group) were upper respiratory tract infection, nasopharyngitis, arthralgia, headache and fatigue. A higher exposure-adjusted event rate of serious AEs per 100 patient-years through week 52 was observed in patients continuing ustekinumab therapy after week 16 following inadequate responses compared with ustekinumab-treated patients rescued with brodalumab.

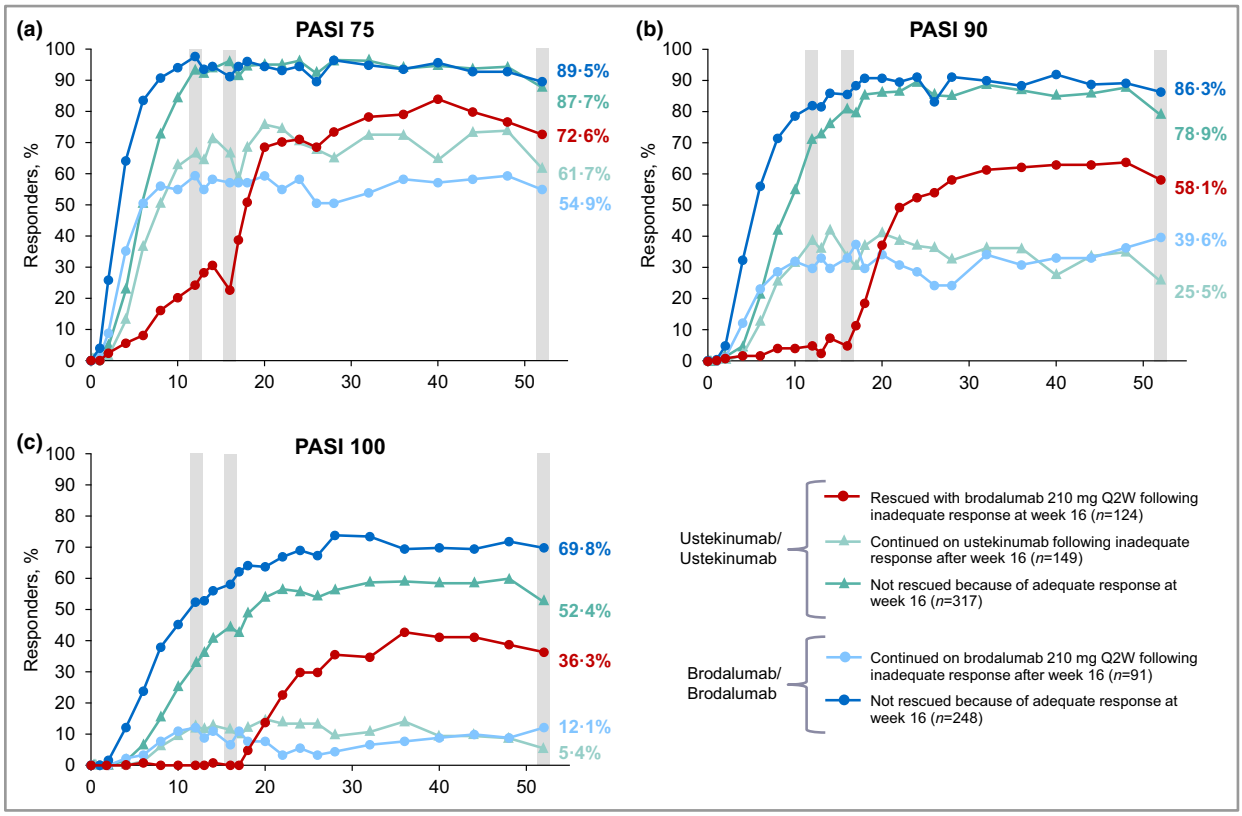

Fig 3. Proportions of responders with (a) PASI 75, (b) PASI 90 and (c) PASI 100 responses by study visit week through week 52. Shaded areas indicate the response rates at weeks 12, 16 and 52. No patients rescued with brodalumab 210 mg every 2 weeks (Q2W) following inadequate response to ustekinumab at week 16 achieved PASI 100 at week 12 or week 16. Ustekinumab/ustekinumab includes those patients who received ustekinumab in the induction and maintenance phases. Brodalumab/brodalumab includes those who were randomized to brodalumab 210 mg Q2W in the induction phase and were rerandomized to brodalumab 210 mg Q2W in the maintenance phase. PASI 75, 90 and 100 indicate ≥ 75%, ≥ 90% and 100% improvement in Psoriasis Area and Severity Index.

Discussion

The results herein demonstrate that brodalumab is efficacious in treating moderate-to-severe psoriasis in patients who do not achieve adequate responses with ustekinumab. In this pooled subgroup analysis of AMAGINE-2/-3, around 50% of patients initially receiving ustekinumab had inadequate responses (defined as a single sPGA score of ≥ 3 or persistent sPGA scores of 2 for at least a 4-week period) at or after week 16, whereas around 30% of patients receiving brodalumab 210 mg Q2W had inadequate responses at or after week 16. Patients with inadequate responses to ustekinumab at week 16 who were rescued with brodalumab 210 mg Q2W experienced increased response rates in PASI 75 (72·6% vs. 61·7%), PASI 90 (58·1% vs. 25·5%), PASI 100 (36·3% vs. 5·4%), DLQI (69·1% vs. 61·1%) and PSI (55·6% vs. 33·6%) at week 52 compared with patients who continued ustekinumab treatment after inadequate responses at later visits. Patients initially receiving brodalumab or ustekinumab who did not require rescue therapy experienced sustained or improved PASI 75, PASI 90 and PASI 100 response rates from week 12 to week 52.

Rescue with brodalumab in ustekinumab-treated patients was efficacious in both those with and those without prior biologic use, although higher response rates were observed in those without prior biologic use. A higher percentage of patients requiring rescue in this study (regardless of initial and rescue therapies received) had prior exposure to multiple biologics than patients who did not require rescue. This suggests that prior use of multiple biologics may have adversely affected response to psoriasis treatment. Notably, among ustekinumab-treated patients, proportions of patients attaining PASI 75, PASI 90 and PASI 100 increased from week 12 to week 52 in those rescued with brodalumab following inadequate response, but not in those who continued receiving ustekinumab. This pattern was observed regardless of prior exposure to biologics, suggesting that any differences in the proportion of biologic-experienced patients among those who were rescued with brodalumab or who remained on ustekinumab were not clinically important. Moreover, this may support the use of brodalumab in biologic-experienced patients, who may face challenges and poor outcomes with psoriasis therapy, as well as biologic-naive patients.

The results of this analysis are similar to those in a prior study assessing the efficacy and safety of guselkumab (a human IgG1γ monoclonal antibody that inhibits IL-23-specific intracellular and downstream signalling) in patients

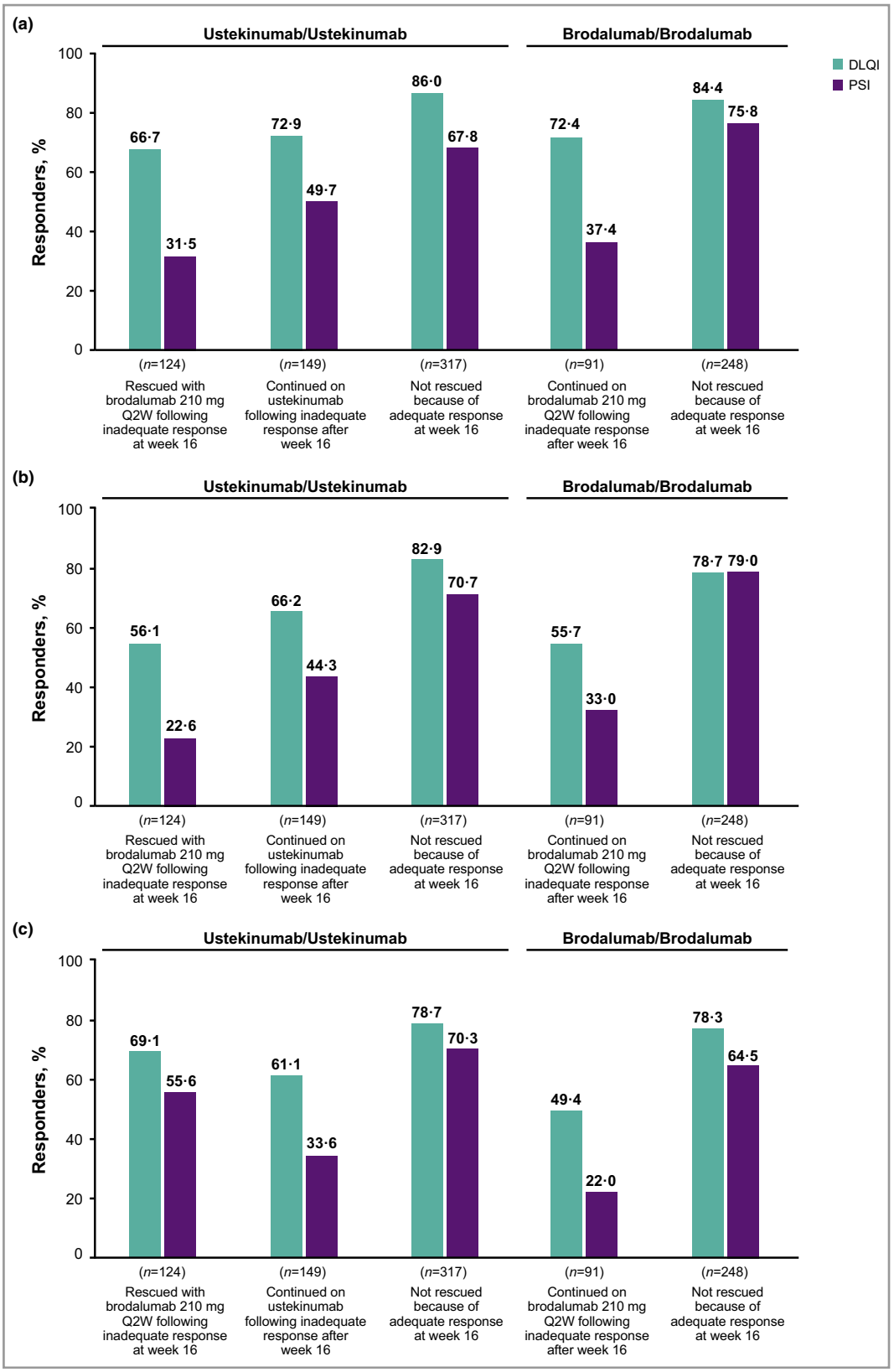

Fig 4. Dermatology Life Quality Index (DLQI) and Psoriasis Symptom Inventory (PSI) responses at (a) week 12, (b) week 16 and (c) week 52. Ustekinumab/ustekinumab includes those who received ustekinumab in the induction and maintenance phases. Brodalumab/brodalumab includes those patients who were randomized to brodalumab 210 mg every 2 weeks (Q2W) in the induction phase and were rerandomized to brodalumab 210 mg Q2W in the maintenance phase.

Table 2 PASI 75, PASI 90 and PASI 100 responses by treatment group and prior biologic use in AMAGINE-2/-3

	Ustekinumab/ustekinumab[a]			Brodalumab 210 mg Q2W/ brodalumab 210 mg Q2W[a]	
Responders (%), week 12/week 52	Rescued with brodalumab 210 mg Q2W (n = 124)[b]	Continued on ustekinumab (n = 149)[b]	Not rescued (n = 317)[c]	Continued on brodalumab 210 mg Q2W (n = 91)[b]	Not rescued (n = 248)[c]
PASI 75					
Biologic naive	26·8/81·7	67·4/65·3	93·4/89·1	57.6/57.6	97·3/91·8
Prior biologic use	19·0/54·8	64·8/55·6	94·9/81·4	62.5/50.0	98·4/82·8
PASI 90					
Biologic naive	6·1/65·9	38·9/28·4	69·0/83·3	30.5/40.7	80·4/89·1
Prior biologic use	2·4/42·9	38·9/20·4	79·7/59·3	28.1/37.5	85·9/78·1
PASI 100					
Biologic naive	0/41·5	14·7/7·4	31·4/56·2	11.9/13.6	50·0/72·3
Prior biologic use	0/26·2	9·3/1·9	37·3/35·6	12.5/9.4	59·4/62·5

PASI 75, 90 and 100; ≥ 75%, ≥ 90% and 100% improvement in Psoriasis Area and Severity Index; Q2W, every 2 weeks. [a]Ustekinumab/ustekinumab includes those patients who received ustekinumab in the induction and maintenance phases. Brodalumab 210 mg Q2W/ 210 mg Q2W includes those who were randomized to brodalumab 210 mg Q2W in the induction phase and were rerandomized to brodalumab 210 mg Q2W in the maintenance phase. [b]Following inadequate response at week 16. [c]Because of adequate response at week 16.

Table 3 PASI 75, PASI 90 and PASI 100 responses by treatment group and history of psoriatic arthritis (PsA) at week 52 in AMAGINE-2/-3

	Ustekinumab/ustekinumab[a]			Brodalumab 210 mg Q2W/ brodalumab 210 mg Q2W[a]	
Responders, %	Rescued with brodalumab 210 mg Q2W (n = 124)[b]	Continued on ustekinumab (n = 149)[b]	Not rescued (n = 317)[c]	Continued on brodalumab 210 mg Q2W (n = 91)[b]	Not rescued (n = 248)[c]
PASI 75					
No history of PsA	74·2	61·8	87·3	53.7	90·2
History of PsA	68·6	61·5	89·8	58.3	87·3
PASI 90					
No history of PsA	58·4	26	78·7	38.8	87
History of PsA	57·1	23·1	79·6	41.7	83·6
PASI 100					
No history of PsA	34·8	5·7	52·2	10.4	72
History of PsA	40	3·8	53·1	16.7	61·8

PASI 75, 90 and 100; ≥ 75%, ≥ 90% and 100% improvement in Psoriasis Area and Severity Index; Q2W, every 2 weeks. [a]Ustekinumab/ustekinumab includes those patients who received ustekinumab in the induction and maintenance phases. Brodalumab 210 mg Q2W/ 210 mg Q2W includes those who were randomized to brodalumab 210 mg Q2W in the induction phase and were rerandomized to brodalumab 210 mg Q2W in the maintenance phase. [b]Following inadequate response at week 16. [c]Because of adequate response at week 16.

with psoriasis who had inadequate responses to ustekinumab.[10] In the phase III NAVIGATE trial, patients with inadequate responses to ustekinumab at week 16 (Investigator's Global Assessment score ≥ 2) were randomized to continue ustekinumab (45 mg in patients weighing ≤ 100 kg and 90 mg in patients weighing > 100 kg) at week 16 and every 12 weeks thereafter or to receive guselkumab 100 mg at weeks 16 and 20 and every 8 weeks thereafter. Greater proportions of guselkumab-treated patients than randomized ustekinumab-treated patients achieved PASI 90 (51·1% vs. 24·1%, $P < 0·001$) and PASI 100 (20·0% vs. 7·5%, $P = 0·003$) at week 52.

Keeping in mind the limitations of comparing efficacy data between trials, our results show that patients receiving brodalumab had greater PASI 90 and PASI 100 responses at week 52 (58·1% and 36·3%, respectively) than patients receiving guselkumab who had previously received ustekinumab in the prior study. In contrast, the relative proportions of patients in the ustekinumab group achieving PASI 90 and PASI 100 response at week 52 in the prior study were similar to those in the current study (25·5% for PASI 90 and 5·4% for PASI 100).

The overall exposure-adjusted AE rate was similar between treatment groups; however, rates of grade ≥ 3 and serious AEs were higher in patients receiving continuous ustekinumab

therapy than the corresponding rates in ustekinumab-treated patients rescued with brodalumab. The most frequent TEAEs were similar across treatment groups. However, interpretation of the AE reporting patterns in this analysis and how they relate to the different therapy sequences represented by the treatment groups may be limited by disparities in the numbers of patients in the treatment groups through week 52. It should be noted that this post hoc analysis was not planned as part of the study protocol, and the results should be interpreted accordingly. Studies designed and powered specifically to examine the efficacy of brodalumab in patients who have inadequate response to ustekinumab may be warranted.

This post hoc analysis of subgroups from the AMAGINE-2 and AMAGINE-3 randomized trials suggests that brodalumab is efficacious in patients who have experienced inadequate response to ustekinumab treatment. The skin clearance efficacy associated with switching to brodalumab was greater than that associated with continued ustekinumab treatment among patients with inadequate response to ustekinumab. Brodalumab may be an effective treatment in patients with psoriasis who do not respond to other systemic therapies, especially therapies with a different mechanism of action than brodalumab, such as ustekinumab. These results may be useful to clinicians seeking alternatives to ustekinumab therapy for efficacy-related reasons.

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Appendix

Conflicts of interest. R.G.L. has been a consultant, advisory board member and/or paid speaker for AbbVie, Inc.; Amgen; Boehringer Ingelheim; Celgene; Centocor; Eli Lilly; LEO; Novartis; Pfizer and Sun Pharma. A.W.A. has served as a consultant for AbbVie, Inc; Janssen; Eli Lilly; Novartis Pharmaceuticals Corporation and Pfizer, Inc. and has served as an investigator for AbbVie, Inc.; Janssen and Eli Lilly & Co and as a member of the speaker's bureau for AbbVie, Inc.; Eli Lilly and Janssen. M.G.L. is an employee of Mount Sinai, which receives research funds from AbbVie, Inc.; Amgen; Boehringer Ingelheim; Celgene; Eli Lilly; Janssen/Johnson & Johnson; Kadmon; Medimmune/AstraZeneca; Novartis; Pfizer; Valeant and Vidac, and is also a consultant for Allergan, Aqua, LEO Pharma and Promius. A.B. has served as a scientific adviser and clinical study investigator for AbbVie, Inc.; Aclaris; Allergan; Almirall; Amgen; Boehringer Ingelheim; Celgene; Dermavant; Dermira; Eli Lilly; Genentech/Roche; GlaxoSmithKline; Janssen; LEO; Meiji; Merck Sharp & Dohme; Novartis; Pfizer; Purdue Pharma; Regeneron; Sandoz; Sanofi Genzyme; Sienna Pharmaceuticals; Sun Pharma; UCB; Valeant and Vidac, and as a paid speaker for Eli Lilly, Janssen, Regeneron and Sanofi Genzyme. S.H. has served as an investigator, consultant or advisory board member for Centocor Biotech; Abbott Laboratories; Eli Lilly; Genentech; Janssen Biotech; AbbVie, Inc.; Sun Pharma/Ranbaxy; Medicis Pharmaceutical; Galderma; Promius Pharma; Dermik; Biogen; Amgen; Novartis; Regeneron; Sanofi and Valeant Pharmaceuticals North America LLC. S.T. has received payments and research funding from LEO Pharma. S.R. is an employee of Ortho Dermatologics and holds stocks and/or stock options in Valeant Pharmaceuticals. R.P. is an employee of Dow Pharmaceutical Sciences (a division of Valeant Pharmaceuticals North America LLC) and holds stock and/or stock options in the company. R.I. is an employee of Valeant Pharmaceuticals North America LLC and holds stock and/or stock options in the company.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Summary of exposure-adjusted adverse event rates through week 52 in subgroup analysis of AMAGINE-2/-3.

Powerpoint S1 Journal Club Slide Set.