Improvements in Lesional Pain and Itch Symptoms With Brodalumab in Psoriasis Studies

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INTRODUCTION

- The interleukin-17 receptor A (IL-17RA) antagonist brodalumab has demonstrated efficacy and safety for the treatment of moderate-to-severe plaque psoriasis in phase 3 clinical studies[1,2]
  - AMAGINE-1: adult patients were randomized to receive placebo, brodalumab 140 mg, or brodalumab 210 mg every 2 weeks (Q2W)[1]
  - AMAGINE-2/-3: patients were randomized to receive placebo, brodalumab (140 or 210 mg Q2W), or ustekinumab (45 or 90 mg depending on body weight)[2]
  - Brodalumab demonstrated superior efficacy at week 12 vs placebo and ustekinumab
    - AMAGINE-1: brodalumab 140 mg Q2W and 210 mg Q2W vs placebo as measured by static physician's global assessment (sPGA) success (0 or 1) and psoriasis area and severity index (PASI) 75
    - AMAGINE-2/-3: brodalumab 210 mg Q2W vs ustekinumab as measured by PASI 100
  - The most common adverse events across the 3 trials included nasopharyngitis, upper respiratory tract infections, and headache[1,2]
- The psoriasis symptom inventory (PSI) is a validated, 8-item, patient-reported outcome instrument designed to assess pain, itch, cracking, scaling, redness, flaking, burning, and stinging in psoriasis[3-5]
  - The PSI assesses signs and symptoms that contribute to disease burden and are considered key measures of patient improvement[3]
  - Two items assessed by the PSI, pain and itch, have been identified by patients as separate psoriasis symptoms that may contribute to diminished health-related quality of life[3]
  - Itch is of particular interest because the itch-scratch cycle can increase inflammation, intensify original itch, traumatize skin, and expand psoriatic lesions through Koebnerization[6]

OBJECTIVE

- The effect of brodalumab on lesional pain and itch, as measured within the PSI, was assessed in patients with moderate-to-severe psoriasis from three phase 3, multicenter, randomized, double-blind, placebo- and active-comparator–controlled studies (AMAGINE-1/-2/-3)

METHODS

Procedures

- Patients in the AMAGINE-1/-2/-3 studies were randomized to receive treatment during the 12-week induction phase as follows: AMAGINE-1: brodalumab (140 or 210 mg Q2W) or placebo; AMAGINE-2: brodalumab (140 or 210 mg Q2W), placebo, or ustekinumab; AMAGINE-3: brodalumab (140 or 210 mg Q2W), placebo, or ustekinumab
- Patients used a daily electronic diary to rate the severity of symptoms during the previous 24 hours on a PSI scale of 0 (not at all severe) to 4 (very severe)
  - In addition to visual assessments of redness, scaling, cracking, and flaking symptoms, which were also included in PASI and sPGA evaluations, the PSI assessed pain, itch, burning, and stinging symptoms

Statistical analysis

- Daily assessments of pain and itch symptoms were analyzed as weekly PSI item average scores. At each study visit (including the baseline assessment), the PSI responder status of patients was assessed; a responder for the pain and itch items was defined as having a weekly PSI item average score ≤1
- Statistical comparisons were based on Cochran-Mantel-Haenszel or analysis of covariance models stratified by total body weight at baseline (≤100 kg, >100 kg), prior biologic use (yes, no), geographic region, study, and adjusting for baseline PSI score (≤ median, > median). There was no adjustment for multiplicity

RESULTS

Patient demographics

- Baseline demographics and disease characteristics, including mean overall PSI scores, were similar across treatment groups (Table 1)

Table 1. Patient Baseline Demographics and Clinical Characteristics (Integrated AMAGINE-1/-2/-3 Induction Phase Analysis Set)

	Placebo (N=844)	Brodalumab 140 mg Q2W (N=1458)	Brodalumab 210 mg Q2W (N=1458)
Age, mean (SD), y	44.7 (12.9)	44.8 (13.0)	45.1 (12.9)
Male, n (%)	588 (69.7)	1012 (69.4)	1013 (69.5)
White, n (%)	769 (91.1)	1322 (90.7)	1319 (90.5)
Weight, mean (SD), kg	90.2 (22.0)	90.4 (21.6)	90.7 (23.1)
Body mass index, mean (SD), kg/m^2	30.2 (6.8)	30.4 (7.0)	30.5 (7.3)
Duration of psoriasis, mean (SD), y	18.5 (12.0)	18.1 (11.9)	18.7 (12.4)
Psoriatic arthritis (yes), n (%)	173 (20.5)	319 (21.9)	299 (20.5)
BSA, mean (SD), %	27.6 (17.1)	27.8 (17.8)	26.8 (16.8)
PASI score, mean (SD)	20.1 (8.2)	20.2 (8.2)	20.2 (8.0)
sPGA score, n (%)			
3	473 (56.0)	899 (61.7)	810 (55.6)
4	324 (38.4)	489 (33.5)	567 (38.9)
5 (very severe)	47 (5.6)	70 (4.8)	81 (5.6)
PSI score, mean (SD)	18.8 (6.9)	18.7 (7.1)	18.7 (7.0)
Prior biologic therapy (yes), n (%)	267 (31.6)	438 (30.0)	439 (30.1)

BSA, psoriasis body surface area involvement; PASI, psoriasis area and severity index; PSI, psoriasis symptom inventory; Q2W, every 2 weeks; SD, standard deviation; sPGA, static physician's global assessment.

Mean PSI item scores for pain and itch

- At baseline, average pain and itch scores were comparable between placebo-treated and brodalumab-treated patients (Table 2)
  - At week 1, mean scores (standard deviation [SD]) for symptoms of pain (placebo, 1.9 [1.1]; brodalumab 140 mg Q2W, 1.6 [1.1]; brodalumab 210 mg Q2W, 1.5 [1.1]) and itch (placebo, 2.5 [0.9]; brodalumab 140 mg Q2W, 2.2 [0.9]; brodalumab 210 mg Q2W, 2.2 [0.9]) were significantly lower with both doses of brodalumab vs placebo (all $P<0.001$)

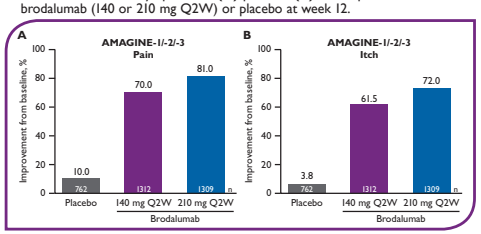
Table 2. Summary of PSI Item Scores (As Observed) by Treatment Group at Baseline and Week 12 in AMAGINE-1/-2/-3

PSI item	Placebo (N=844)[a]	Brodalumab 140 mg Q2W (N=1458)[a]	Brodalumab 210 mg Q2W (N=1458)[a]
Pain			
Mean baseline score (SD)	2.0 (1.2)	2.0 (1.2)	2.1 (1.2)
Mean score at week 12 (SD)	1.8 (1.3)	0.6 (1.0)	0.4 (0.8)
LS mean treatment difference vs placebo (95% CI)		-1.1 (-1.2, -1.0)	-1.3 (-1.4, -1.3)
P value		<0.001	<0.001
Itch			
Mean baseline score (SD)	2.6 (0.9)	2.6 (0.9)	2.5 (0.9)
Mean score at week 12 (SD)	2.5 (1.1)	1.0 (1.1)	0.7 (0.9)
LS mean treatment difference vs placebo (95% CI)		-1.4 (-1.5, -1.3)	-1.7 (-1.8, -1.6)
P value		<0.001	<0.001

CI, confidence interval; LS, least squares; PSI, psoriasis symptom inventory; Q2W, every 2 weeks; SD, standard deviation. [a]Number of patients at baseline. At baseline, the number of evaluable patients was as follows: placebo, n=790; brodalumab 140 mg Q2W, n=1357; brodalumab 210 mg Q2W, n=1368. At week 12, the number of evaluable patients was 762, 1312, and 1309, respectively.

- Mean pain and itch scores remained significantly lower with brodalumab vs placebo through week 12 (Table 2 and Figure 1)

Figure 1. Percent improvement from baseline in observed PSI item mean scores at week 12 in symptoms of **(A)** pain and **(B)** itch in patients treated with brodalumab (140 or 210 mg Q2W) or placebo at week 12.

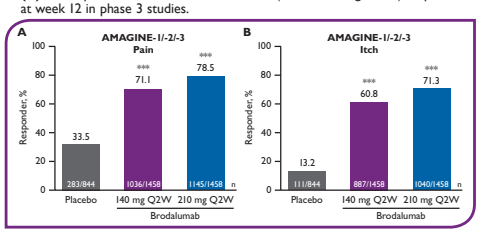


PSI, psoriasis symptom inventory; Q2W, every 2 weeks.

PSI item responders

- At baseline, the percentages of patients with pain and itch with an average weekly score ≤1 (classified as responders) were 24.2% and 5.5%, respectively, for the placebo group, 23.4% and 6.7% for the brodalumab 140-mg group, and 23.4% and 6.2% for the brodalumab 210-mg group, respectively
  - At week 1, the proportion of responders for pain and itch had significantly increased from baseline with both doses of brodalumab vs placebo
    - Pain: placebo, 25.4%; 140 mg Q2W, 34.9% ($P<0.0001$); 210 mg Q2W, 37.4% ($P<0.0001$)
    - Itch: placebo, 5.8%; 140 mg Q2W, 10.4% ($P=0.0002$); 210 mg Q2W, 11.9% ($P<0.0001$)
  - At week 12, for both pain and itch, a significantly greater proportion of patients treated with either dose of brodalumab vs placebo were PSI item responders (Figure 2)

Figure 2. Percentage of PSI item responders for symptoms of **(A)** pain and **(B)** itch in patients treated with brodalumab (140 or 210 mg Q2W) or placebo at week 12 in phase 3 studies.

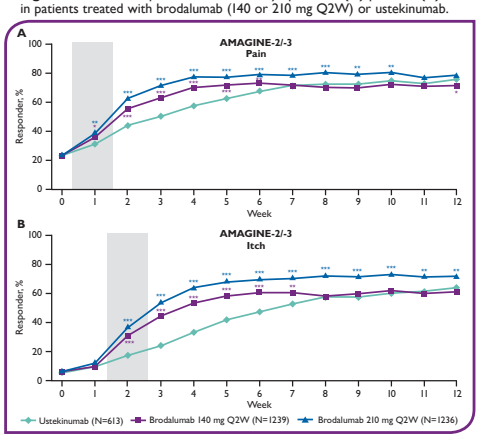


Nonresponder imputation was used to impute missing data. PSI item responders were defined as having a PSI item weekly average score ≤1. PSI, psoriasis symptom inventory; Q2W, every 2 weeks. ***$P<0.0001$ vs placebo.

Pain and itch response over time

- In AMAGINE-1/-2/-3, percentage-point increases from baseline for pain and itch at week 12 were 9.3% and 7.7% for the placebo group, 47.7% and 54.1% for the brodalumab 140-mg Q2W group, and 55.1% and 65.1% for the brodalumab 210-mg group, respectively (all $P<0.0001$ vs placebo)
- In a combined analysis of the two phase 3 studies with ustekinumab as the active comparator (AMAGINE-2/-3), treatment with brodalumab demonstrated rapid and significant improvement vs ustekinumab starting with week 1 for pain (ustekinumab, 31.3%; brodalumab 140 mg Q2W, 35.8% [$P=0.0207$]; brodalumab 210 mg Q2W, 38.3% [$P=0.0007$]) and with week 2 for itch (ustekinumab, 17.1%; brodalumab 140 mg Q2W, 30.9% [$P<0.0001$]; brodalumab 210 mg Q2W, 36.4% [$P<0.0001$]; Figure 3)
  - Significant treatment differences in response rates were observed with brodalumab 210 mg Q2W vs ustekinumab through week 10 for pain ($P<0.01$) and week 12 for itch ($P<0.01$; Figure 3)

Figure 3. PSI item response over time for symptoms of **(A)** pain and **(B)** itch in patients treated with brodalumab (140 or 210 mg Q2W) or ustekinumab.



Shaded portion of figure highlights significant increase in responders observed with brodalumab vs ustekinumab at week 1 for pain and week 2 for itch. Nonresponder imputation was used to impute missing data. PSI, psoriasis symptom inventory; Q2W, every 2 weeks. *$P<0.05$ vs ustekinumab. **$P<0.01$ vs ustekinumab. ***$P<0.0001$ vs ustekinumab.

CONCLUSIONS

- **Brodalumab demonstrated significant improvement in patient-reported pain and itch symptoms of psoriasis vs placebo and ustekinumab, as measured by the PSI, in three phase 3 controlled clinical trials**
  - **Significant improvement in pain was observed at week 1 and persisted through week 10 in patients treated with brodalumab 210 mg Q2W compared with ustekinumab**
  - **Significant improvement in itch was observed at week 2 and persisted through week 12 in patients treated with brodalumab 210 mg Q2W compared with ustekinumab**

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