Long-term efficacy and safety of brodalumab in the treatment of psoriasis: 120-week results from the randomized, double-blind, placebo- and active comparator–controlled phase 3 AMAGINE-2 trial

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Background: Randomized controlled trials have shown the efficacy and safety of brodalumab in patients with moderate to severe plaque psoriasis.

Objective: To evaluate the efficacy and safety of brodalumab through 120 weeks of treatment in the AMAGINE-2 trial.

Methods: Patients received ustekinumab through week 52 followed by brodalumab 210 mg every 2 weeks, continuous brodalumab 210 mg every 2 weeks, or any dose of brodalumab. Efficacy data were reported through 120 weeks by using observed data, last observation carried forward, and nonresponder imputation analyses.

Results: Of patients who received brodalumab 210 mg every 2 weeks, 84.4%, 75.6%, and 61.1% achieved 75%, 90%, and 100% improvement from baseline in Psoriasis Area and Severity Index at 120 weeks (observed data analysis), respectively. Patients who received brodalumab 210 mg every 2 weeks after receiving ustekinumab through 52 weeks achieved a similar skin clearance response as patients who received continuous brodalumab 210 mg every 2 weeks. Safety through 120 weeks was comparable to that of the blinded study periods.

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Limitations: A large number of discontinuations toward the end of the study (31% in the final 6 months) were due to early termination and led to differences between observed data and nonresponder imputation results.

Conclusions: Brodalumab is well tolerated and showed robust efficacy for more than 2 years. (J Am Acad Dermatol 2020;82:352-9.)

Key words: AMAGINE-2; brodalumab; efficacy; long-term; psoriasis; safety.

CAPSULE SUMMARY

- Sustained skin clearance is an unmet need in patients with psoriasis.
- Brodalumab showed sustained skin clearance through 120 weeks, with 61.1% of patients achieving 100% improvement from baseline in Psoriasis Area and Severity Index (observed data analysis) and no new safety signals, suggesting that brodalumab is an efficacious long-term treatment.

Despite recent improvements in systemic treatment for psoriasis, there is an unmet need for biologic therapies that do not lose efficacy over time. However, the mechanisms underlying loss of efficacy are multifactorial and not completely understood.[1] Studies reporting skin clearance efficacy of biologics with 2 to 3 years of follow-up have shown maintenance of Psoriasis Area and Severity Index (PASI) of 75% improvement from baseline (PASI 75) in 83.0% to 93.4% of participants.[2-4] With regard to long-term complete skin clearance, open-label extension studies have shown 100% improvement in PASI over baseline (PASI 100) (observed data analysis) in 43.8%, 56.3%, and 42.6% of patients after 160 weeks of ustekinumab, 108 weeks of ixekizumab, and 152 weeks of secukinumab, respectively.[2-4] Drugs associated with increased rates of complete skin clearance over long periods of time may have a long-term positive effect on health-related quality of life in patients with psoriasis.[5]

Brodalumab is a fully human anti–interleukin (IL) 17 receptor A monoclonal antibody approved for the treatment of moderate to severe psoriasis in patients who have inadequate response to other systemic therapies.[6] The efficacy and safety of brodalumab have been shown in 1 phase 2 and 3 phase 3 clinical trials (AMAGINE-1/-2/-3) in which brodalumab showed superior skin clearance efficacy at week 12 compared with placebo (AMAGINE-1/-2/-3) and ustekinumab (AMAGINE-2/-3).[7,8] At week 12, PASI 75 response rates were 83.3%, 86%, and 85% for AMAGINE-1, -2, and -3, respectively, and PASI 100 response rates were 41.9%, 44%, and 37%, respectively.[7,8]

Here, we compare efficacy and safety data from the open-label extension of AMAGINE-2 in patients who received brodalumab 210 mg every 2 weeks after ustekinumab, patients who received only brodalumab 210 mg every 2 weeks, and all patients who received any dose of brodalumab.

METHODS

Study design and patients

AMAGINE-2 (ClinicalTrials.gov identifier NCT01708603) was a randomized, double-blind, placebo- and active comparator–controlled phase 3 trial that has been previously described.[8] Patients were 18 to 75 years of age and had moderate to severe plaque psoriasis diagnosed at least 6 months before the first dose of brodalumab with involved body surface area 10% or greater, PASI score of 12 or greater, and static physician's global assessment (sPGA) score of 3 or greater at screening and at baseline. Patients were randomly assigned to receive brodalumab (140 or 210 mg every 2 weeks), ustekinumab, or placebo during the 12-week induction phase, followed by a maintenance phase through week 52 (Supplemental Fig 1; available at http://dx.doi.org/10.17632/6jghtvc333.1). During the maintenance phase, patients who received brodalumab were randomly reassigned to receive brodalumab 140 mg every 2 weeks, every 4 weeks, or every 8 weeks or 210 mg every 2 weeks; patients receiving ustekinumab continued to receive ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every 2 weeks. Patients receiving brodalumab who experienced inadequate response between weeks 16 and 52 and patients receiving ustekinumab experiencing inadequate response at week 16 were switched to brodalumab 210 mg every 2 weeks (rescue phase), as described previously.[8] At week 52, patients receiving brodalumab continued to receive brodalumab at their maintenance or rescue phase dosage, and patients who were originally assigned to received ustekinumab were switched to brodalumab 210 mg every 2 weeks. Data are shown for patients who

Abbreviations used:

AE:	adverse event
IL:	interleukin
LOCF:	last observation carried forward
NRI:	nonresponder imputation
PASI:	Psoriasis Area and Severity Index
PASI 75:	75% improvement in Psoriasis Area and Severity Index
PASI 90:	90% improvement in Psoriasis Area and Severity Index
PASI 100:	100% improvement in Psoriasis Area and Severity Index
SIB:	suicidal ideation and behavior
sPGA:	static physician's global assessment
TEAE:	treatment-emergent adverse event

received brodalumab 210 mg every 2 weeks after receiving ustekinumab through week 52, patients who received continuous brodalumab 210 mg every 2 weeks, and all patients who received any dose of brodalumab.

All patients provided written informed consent before the initiation of study procedures. AMAGINE-2 study protocols were consistent with the 2008 Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use for Good Clinical Practice and were approved by individual institutional review boards at each participating study center.

Clinical assessments

Skin clearance efficacy was monitored through week 120 by the sPGA and PASI. The percentages of patients achieving PASI 75, 90% improvement in PASI over baseline (PASI 90), or PASI 100 were determined. Efficacy end points during the long-term extension phase focus on week 120 because the study was ended prematurely by the sponsor, and most patients who were continuing to receive treatment had undergone efficacy assessments at that study visit. Safety was assessed by monitoring treatment-emergent adverse events (TEAEs), and serious adverse events (AEs) and were summarized by treatment group. TEAEs are shown as exposure-adjusted event rates per 100 patient-years from the first dose of brodalumab through the end of the study. Rates of depression and suicidal ideation and behavior (SIB) were calculated as follow-up observation time–adjusted rates per 100 patient-years from the first dose of brodalumab through the end of the study, as described previously.[9]

Statistical analysis

Long-term efficacy was analyzed by using observed data for patients who received any dose or interval of brodalumab (140 mg every 2 weeks, every 4 weeks, or every 8 weeks or 210 mg every 2 weeks) in the long-term extension, after receiving either any dose or interval of brodalumab (n = 1790) or ustekinumab (n = 274) in the maintenance phase. Data for patients who received continuous brodalumab 210 mg every 2 weeks during the induction, maintenance, and long-term extension phases (n = 168) were also analyzed by using observed data and imputed data (either using the last observation carried forward [LOCF] method or nonresponder imputation [NRI] method). The observed data analysis included data for patients with a valid measurement at the specified time point, with no steps taken to account for missing data. The LOCF analysis replaced missing data with the most recently observed value. The NRI analysis assumed nonresponse for all missing data.[10]

RESULTS

Patient characteristics

Baseline demographics and disease characteristics are shown in Table I. Patients who were initially randomly assigned to receive ustekinumab had similar demographics and disease characteristics as patients who received continuous brodalumab 210 mg every 2 weeks.

Discontinuations in patients who received continuous brodalumab 210 mg every 2 weeks are shown in Supplemental Table I (available at http://dx.doi.org/10.17632/6jghtvc333.1). A notable increase in discontinuations after week 85 was observed, with most of these discontinuations attributed to the early termination of the study by the sponsor. The median duration of exposure in patients who received any dose of brodalumab through the end of study was 24.0 (range, 0.3-35.0) months.

Efficacy

On the basis of the observed data analysis, skin clearance efficacy was maintained from week 52 through week 120 in patients who received continuous brodalumab 210 mg every 2 weeks (Fig 1). Starting at week 52, patients who switched to brodalumab 210 mg every 2 weeks after receiving ustekinumab experienced increased sPGA score of 0 or 1 (sPGA 0/1), PASI 90, and PASI 100 response rates that were maintained through week 120 (Fig 1, *A*). Among patients who switched from ustekinumab to brodalumab, PASI 100 response rates were 43.4% at week 52, had increased to 60.7% by week 56, and remained stable through week 120. Patients who received continuous brodalumab 210 mg every 2 weeks achieved a PASI 100 response rate of 64.8% at week 52, which was maintained through week

120 (Fig 1, *B*). Skin clearance efficacy was also maintained from week 52 through week 120 among patients who received any dose of brodalumab, with a small numeric decrease in efficacy from weeks 96 to 120 (Fig 1, *C*).

For patients who received continuous brodalumab 210 mg every 2 weeks, LOCF analysis showed skin clearance response rates similar to those with observed data analysis (Supplemental Fig 2; available at http://dx.doi.org/10.17632/6jghtvc333.1). However, skin clearance estimates in the NRI analysis were consistently less than corresponding estimates in the observed data analysis after week 52. On the basis of the observed data, LOCF, and NRI analyses, PASI 75 was achieved in 84.4% (76/90), 81.0% (136/168), and 45.2% (76/168) of patients who received continuous brodalumab at week 120, respectively, and PASI 100 was achieved in 61.1% (55/90), 50.0% (84/168), and 32.7% (55/168) of patients, respectively. sPGA 0/1, PASI 75, PASI 90, and PASI 100 response rates based on NRI analysis at week 52 were 11.8%, 12.7%, 11.9%, and 8.8% less than rates based on observed data analysis, respectively. At week 120, sPGA 0/1, PASI 75, PASI 90, and PASI 100 response rates based on NRI analysis were 37.6%, 39.2%, 35.1%, and 28.4% less than response rates based on observed data analysis, respectively. Before week 52, 15 patients in the group receiving continuous brodalumab 210 mg every 2 weeks discontinued treatment.

Patients who received continuous brodalumab 210 mg every 2 weeks had more rapid onset of skin clearance response than patients who received ustekinumab or any dose of brodalumab in the maintenance phase (Supplemental Fig 3; available at http://dx.doi.org/10.17632/6jghtvc333.1). As early as week 2, patients who received continuous brodalumab 210 mg every 2 weeks showed a mean decrease in baseline PASI score of 57.1%, compared with a mean decrease of 29.4% and 41.1% at week 2 in patients who received ustekinumab or any dose of brodalumab in the maintenance phase, respectively. Mean percent decrease in baseline PASI score was maintained at approximately 90% with continuous brodalumab 210 every 2 weeks from week 18 onward.

Safety

The overall exposure-adjusted event rate of TEAEs among all patients who received any dose of brodalumab in the long-term extension was 306.9 per 100 patient-years from the first dose of

Table I. Patient demographics and baseline disease characteristics*

Demographics and characteristics	Brodalumab 210 mg every 2 weeks after ustekinumab (n = 274)	Continuous brodalumab 210 mg every 2 weeks (n = 168)	All patients who received any dose of brodalumab (n = 1790)
Age in years, mean ± SD	45.7 ± 12.9	43.7 ± 13.5	44.6 ± 12.8
Sex, n (%)			
Male	189 (69.0)	116 (69.0)	1233 (68.9)
Female	85 (31.0)	52 (31.0)	557 (31.1)
Race, n (%)			
American Indian or Alaska Native	1 (0.4)	1 (0.6)	7 (0.4)
Asian	12 (4.4)	4 (2.4)	68 (3.8)
Black (or African American)	4 (1.5)	4 (2.4)	50 (2.8)
Multiple	3 (1.1)	1 (0.6)	10 (0.6)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.6)	9 (0.5)
White	248 (90.5)	153 (91.1)	1615 (90.2)
Other	6 (2.2)	4 (2.4)	31 (1.7)
Psoriatic arthritis, n (%)			
No	228 (83.2)	130 (77.4)	1459 (81.5)
Yes	46 (16.8)	38 (22.6)	331 (18.5)
Duration of psoriasis in years, mean ± SD	19.3 ± 12.8	16.9 ± 11.6	18.6 ± 12.2
PASI, mean ± SD	19.9 ± 8.2	20.2 ± 8.0	20.3 ± 8.2
% BSA, mean ± SD	27.0 ± 19.6	25.4 ± 15.3	26.8 ± 17.25
sPGA, n (%)			
3	136 (49.6)	92 (54.8)	971 (54.2)
4	124 (45.3)	65 (38.7)	707 (39.5)
5	14 (5.1)	11 (6.5)	112 (6.3)

BSA, Body surface area; *PASI*, Psoriasis Area and Severity Index; *SD*, standard deviation; *sPGA*, static physician's global assessment.
*Treatment groups are as treated after first dose of active brodalumab.

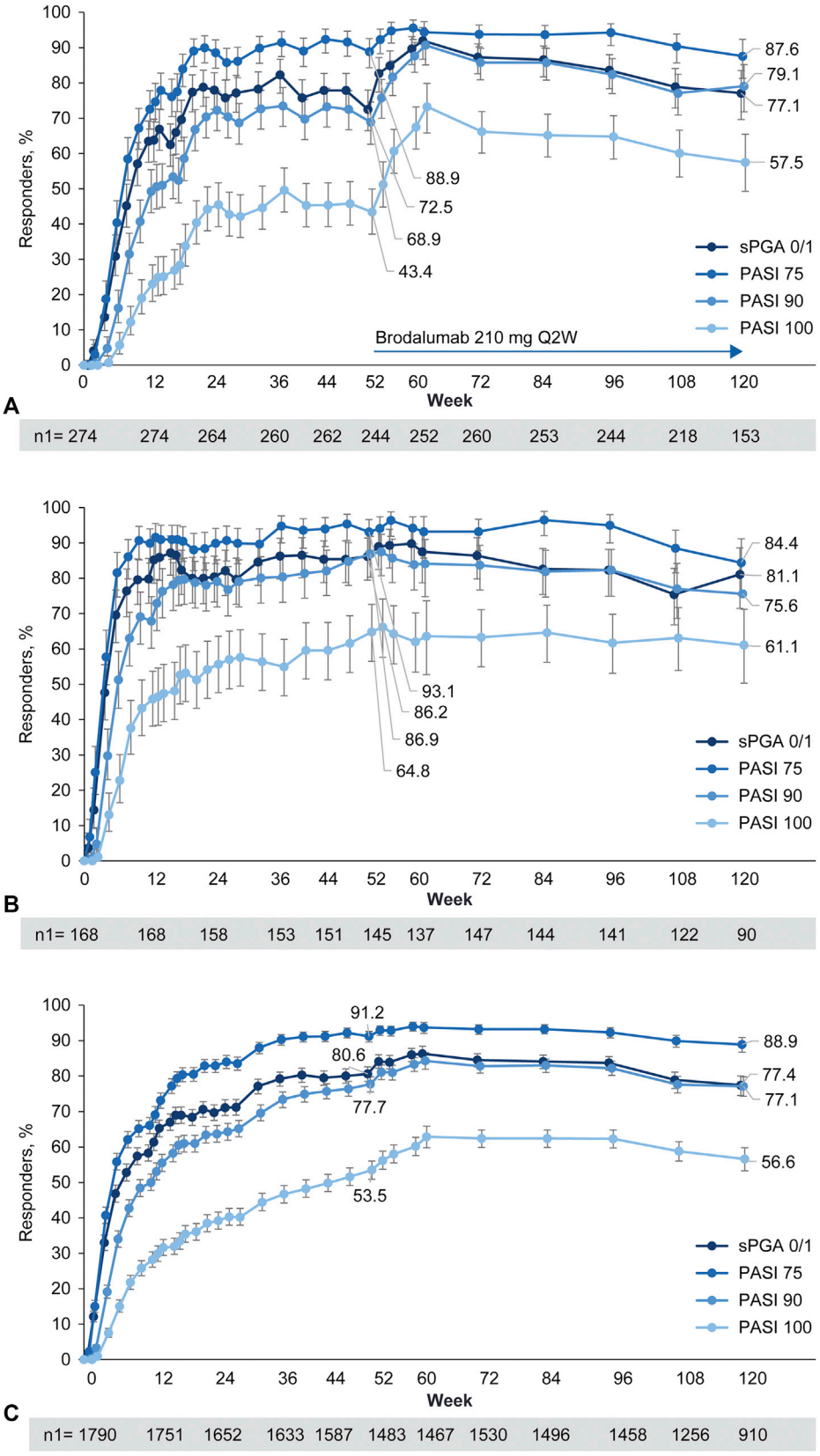

Fig 1. Rates of sPGA 0/1, PASI 75, PASI 90, and PASI 100 response through week 120 among (**A**) patients who received brodalumab 210 mg every 2 weeks after ustekinumab at week 52,

Table II. Exposure-adjusted event rates of adverse events from the first dose of brodalumab through the end of the study*

Exposure and AEs	Brodalumab 210 mg every 2 weeks after ustekinumab (n = 274)	Continuous brodalumab 210 mg every 2 weeks (n = 168)	All patients who received any dose of brodalumab (n = 1790)
Total PY of exposure	343.1	339.1	3228.5
Number of AEs (exposure-adjusted event rate per 100 PY)†			
All TEAEs	908 (264.7)	1084 (319.7)	9909 (306.9)
Grade ≥2	558 (162.6)	659 (194.3)	5601 (173.5)
Grade ≥3	29 (8.5)	43 (12.7)	395 (12.2)
Serious	22 (6.4)	30 (8.8)	247 (7.7)
Leading to discontinuation of brodalumab	17 (5.0)	15 (4.4)	103 (3.2)
Leading to discontinuation from study	5 (1.5)	9 (2.7)	61 (1.9)
Fatal	0 (0)	0 (0)	1 (0)‡

AE, Adverse event; *TEAE*, treatment-emergent adverse event; *PY*, patient-years.
*Multiple occurrences of the same event for a patient are counted as multiple events.
†Exposure-adjusted event rate per 100 PY calculated as n/total PY of exposure through end of study × 100.
‡One death occurred during the exposure period.

brodalumab through the end of the study (Table II). Corresponding rates in patients who received brodalumab 210 mg every 2 weeks after receiving ustekinumab and continuous brodalumab 210 mg every 2 weeks were 264.7 and 319.7 events per 100 patient-years, respectively. Similar rates of serious AEs and AEs leading to discontinuation were observed across all treatment groups. Among all patients who received any dose of brodalumab in the long-term extension, the exposure-adjusted rate of all TEAEs was highest in the first year of treatment and decreased in subsequent years (Supplemental Table II; available at http://dx.doi.org/10.17632/6jghtvc333.1). Among the most frequent TEAEs in all brodalumab treatment groups throughout the duration of the study were arthralgia, headache, diarrhea, oropharyngeal pain, and *Candida* species infections. The exposure-adjusted event rate of arthralgia of at least grade 2 and at least grade 3 throughout the duration of the study was 4.0 and 0.2 per 100 patient-years, respectively. Consistent with the yearly rates of all TEAEs, the rates for the most frequent TEAEs and other TEAEs of interest generally declined over time. Furthermore, exposure-adjusted event rates of other psoriasis phenotypes, including erythrodermic, guttate, nail, and pustular psoriasis, were relatively low throughout the study (0.0, 0.1, 0.1, and 0.2 per 100 patient-years, respectively), with these AEs occurring 1, 2, 3, and 8 times throughout the study, respectively.

Rates of depression and SIB were calculated separately as follow-up observation time–adjusted rates. The rates of depression and suicidal ideation and behavior AEs were 3.0 and 0.58 per 100 patient-years, respectively, in patients who received any dose of brodalumab. Rates of self-injury, attempted suicide, and completed suicides were 0.03, 0.15, and 0.06, respectively.

Supplemental data are available at http://dx.doi.org/10.17632/6jghtvc333.1.

DISCUSSION

Skin clearance, as determined by sPGA 0/1, PASI 75, PASI 90, and PASI 100 response rates, was increased after week 52 and maintained through week 120 in patients who received brodalumab 210 mg every 2 weeks after receiving ustekinumab and was maintained from weeks 52 to 120 in patients who received continuous brodalumab 210 mg every 2 weeks and in all patients who received any dose of brodalumab, with a slight decrease from week 96 to week 120. Many patients who received ustekinumab until week 52 achieved better skin clearance response rates after switching to brodalumab 210

(**B**) continuous brodalumab 210 mg every 2 weeks, or (**C**) any dose of brodalumab. All analyses are as observed. Error bars show the 95% confidence intervals. Arrow in panel (**A**) indicates rates after the switch to brodalumab 210 mg every 2 weeks. *n1*, Number of patients who had a valid measurement value at the specified week; *PASI 75*, 75% improvement in Psoriasis Area and Severity Index; *PASI 90*, 90% improvement in Psoriasis Area and Severity Index; *PASI 100*, 100% improvement Psoriasis Area and Severity Index; *Q2W*, every 2 weeks; *sPGA 0/1*, static physician's global assessment score of 0 or 1.

every 2 weeks during the long-term extension. Notably, 57.5% of these patients achieved PASI 100 after 120 weeks, suggesting that brodalumab may be efficacious in patients who received ustekinumab. Patients who received continuous brodalumab 210 mg every 2 weeks experienced a greater percent change from baseline in PASI score at week 2 compared with patients in other treatment groups.

Although cross-trial comparisons are complicated by variability in many parameters, long-term rates of skin clearance efficacy (as determined by PASI 75 response) in this open-label extension were greater than the rates observed at similar time points in trials of ustekinumab and similar to rates observed in long-term trials of secukinumab, an anti−IL-17A biologic.[2,4,11] using matching statistical analysis methodology. Rates of complete skin clearance (determined by PASI 100 response and using matching statistical analysis methodology) were greater than corresponding estimates at similar time points in trials of ustekinumab and secukinumab and similar to rates observed in long-term trials of ixekizumab.[2,4,12] Studies have shown that patients who achieve complete skin clearance have improved symptom- and quality-of-life−related outcomes than patients who do not.[5] The increased likelihood of achieving complete skin clearance associated with brodalumab may allow improvement of patient quality of life relative to other biologics associated with a lesser rate of achieving complete skin clearance. The observed numerically greater efficacy rates with brodalumab versus rates with other biologics may be due to the inhibition of IL-17 receptor instead of upstream components of the IL-17 pathway.

Efficacy and safety evaluations of monoclonal antibodies that target IL-23 show PASI 100 response rates of 32% at 28 weeks (observed data analysis) and 50% at 100 weeks (observed data analysis) in patients who received tildrakizumab and guselkumab, respectively, compared with 58% and 63% at 28 and 108 weeks, respectively (all observed data analysis) in patients who received continuous brodalumab.[13,14] Real-world studies are needed to fully characterize the long-term efficacy and safety of these treatments.

A study evaluating loss of efficacy of biologic agents including etanercept, adalimumab, ustekinumab, and infliximab long-term (0.8-3.9 years) has shown that 20%-32% of patients lose PASI 75 response throughout the duration of treatment.[1] This observed decrease in efficacy over time is usually associated with formation of antidrug antibodies that can inactivate therapeutic effects.[1] Our findings show that 91.2% and 88.9% of patients who received brodalumab during the open-label extension achieved PASI 75 at weeks 52 and 120, respectively. The maintenance of efficacy observed with brodalumab may be related to the lack of neutralizing antidrug antibodies detected in any samples in AMAGINE-2 (data not shown).

Point estimates for skin clearance efficacy based on NRI analysis were generally less than the corresponding estimates in the observed data analysis from weeks 52 to 120, with differences ranging from 8.8% to 12.7% at week 52 and 28.4% to 39.2% at week 120. Prior studies evaluating secukinumab have shown differences between PASI 90 response rates at week 52 based on NRI estimates and observed data analyses to be less than 10%.[10] Similar observations were seen in studies evaluating ixekizumab, where PASI 75, PASI 90, and PASI 100 response rates based on modified NRI analysis were 16.7%, 20.7 %, and 18.8% less than rates based on observed data analysis at week 156.[12] Discontinuation may explain the difference between NRI and observed data analyses in our study.[10] Decreases in NRI point estimates beginning at week 96 may have resulted from the increased withdrawal rate beginning at approximately week 96 with the public announcement of study termination. The median duration of brodalumab exposure through the end of the study was 24 months, but it is possible that external factors rather than treatment-related factors influenced NRI analyses, resulting in decreased skin clearance efficacy rates relative to observed data analyses after week 52.

The safety profile of brodalumab during long-term follow-up was similar to that observed during the blinded study periods, and no new safety signals were observed during the long-term extension. Rates of overall TEAEs decreased over time relative to preceding years. The most common AEs were also consistent with those observed in other brodalumab psoriasis clinical trials.[15,16] Relatively low rates of AEs of special interest, such as *Candida* infection (3.9 per 100 patient-years), were observed with long-term brodalumab treatment, similar to rates with secukinumab.[4] The overall rate of AEs associated with brodalumab was similar to that observed during long-term ustekinumab studies, where ustekinumab was associated with 305.9 events per 100 patient-years after 3 years.[17] Common AEs associated with brodalumab, including headache and arthralgia, were similar to those observed in long-term studies evaluating ustekinumab and secukinumab.[4,17]

In conclusion, long-term data show sustained efficacy and consistent safety profile with brodalumab for more than 2 years. Most patients who received brodalumab 210 mg every 2 weeks after ustekinumab treatment achieved complete skin

clearance after 120 weeks, suggesting that brodalumab may be well suited for long-term treatment of moderate to severe psoriasis in patients who received prior systemic therapy. Although cross-trial comparisons are complicated by the variability of many parameters, compared with other biologics used to treat psoriasis, brodalumab was associated with greater rates of complete skin clearance at comparable time points, which may result in greater improvements in quality of life.

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