ORIGINAL ARTICLE

Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis

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ABSTRACT

BACKGROUND

Early clinical studies suggested that the anti–interleukin-17 receptor A monoclonal antibody brodalumab has efficacy in the treatment of psoriasis.

METHODS

In two phase 3 studies (AMAGINE-2 and AMAGINE-3), patients with moderate-to-severe psoriasis were randomly assigned to receive brodalumab (210 mg or 140 mg every 2 weeks), ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg), or placebo. At week 12, patients receiving brodalumab were randomly assigned again to receive a brodalumab maintenance dose of 210 mg every 2 weeks or 140 mg every 2 weeks, every 4 weeks, or every 8 weeks; patients receiving ustekinumab continued to receive ustekinumab every 12 weeks, and patients receiving placebo received 210 mg of brodalumab every 2 weeks. The primary aims were to evaluate the superiority of brodalumab over placebo at week 12 with respect to at least a 75% reduction in the psoriasis area-and-severity index score (PASI 75) and a static physician's global assessment (sPGA) score of 0 or 1 (clear or almost clear skin), as well as the superiority of brodalumab over ustekinumab at week 12 with respect to a 100% reduction in PASI score (PASI 100).

RESULTS

At week 12, the PASI 75 response rates were higher with brodalumab at the 210-mg and 140-mg doses than with placebo (86% and 67%, respectively, vs. 8% [AMAGINE-2] and 85% and 69%, respectively, vs. 6% [AMAGINE-3]; P<0.001); the rates of sPGA scores of 0 or 1 were also higher with brodalumab (P<0.001). The week 12 PASI 100 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001). The PASI 100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 (P=0.08 for the comparison with ustekinumab) and 27% in AMAGINE-3 (P=0.007). Rates of neutropenia were higher with brodalumab and with ustekinumab than with placebo. Mild or moderate candida infections were more frequent with brodalumab than with ustekinumab or placebo. Through week 52, the rates of serious infectious episodes were 1.0 (AMAGINE-2) and 1.3 (AMAGINE-3) per 100 patient-years of exposure to brodalumab.

CONCLUSIONS

Brodalumab treatment resulted in significant clinical improvements in patients with moderate-to-severe psoriasis. (Funded by Amgen; AMAGINE-2 and AMAGINE-3 ClinicalTrials.gov numbers, NCT01708603 and NCT01708629.)

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Psoriasis is an inflammatory skin disease that occurs in 2 to 3% of the worldwide population.[1,2] Despite the availability of several therapies, many patients remain untreated, do not have an adequate response, or have treatment-related toxic effects.[3] Interleukin-17 cytokines have been implicated in the pathogenesis of psoriasis. Genomewide association studies have linked interleukin-17 pathway–related genes with psoriasis,[4,5] and interleukin-17 mRNA levels are higher in psoriatic lesions than in normal skin.[6,7] Numbers of type 17 helper T cells are increased in psoriatic lesions and are stimulated by interleukin-23 to release interleukin-17 cytokines.[8] Interleukin-17 cytokines, which include interleukin-17A, interleukin-17C, interleukin-17F, and interleukin-17A/F, can induce expression of psoriasis-related proinflammatory molecules in keratinocytes.[9-11]

Brodalumab (AMG 827) is a human anti–interleukin-17 receptor A monoclonal antibody. Interleukin-17 receptor A, a common subunit of multiple heterodimeric interleukin-17 receptor complexes, is critical for binding and downstream signaling of interleukin-17 cytokines. Blockade of interleukin-17 receptor A with brodalumab has been shown to result in reversal of the psoriatic phenotype and gene expression patterns, with many keratinocyte-expressed genes responding within 1 week; a return to nonlesional levels of gene expression has been seen by 2 weeks.[12]

To confirm the findings of early clinical studies with brodalumab,[13,14] we conducted the AMAGINE-2 and AMAGINE-3 trials. The AMAGINE-2 and AMAGINE-3 trials were large, replicate, multinational studies involving patients with moderate-to-severe plaque psoriasis; the studies were designed to compare the efficacy and safety of brodalumab with those of ustekinumab, a human IgG1κ monoclonal antibody against the p40 subunit common to interleukin-12 and interleukin-23 that has demonstrated efficacy and is an approved treatment for psoriasis.

Methods

Study Population

Adults 18 to 75 years of age who were candidates for biologic therapy for stable moderate-to-severe plaque psoriasis (minimum 6 months' duration) were eligible if they had a psoriasis area-and-severity index (PASI) score of 12 or higher (scores range from 0 to 72, with higher scores indicating more severe disease), a static physician's global assessment (sPGA) score of 3 or higher (scores range from 0 [clear skin] to 5 [severe disease]), and involvement of 10% or more of the body-surface area. Patients with medical conditions that could potentially prevent them from completing the study or that could interfere with the interpretation of results were not included (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Medications with the potential to confound efficacy were prohibited; patients who had received specified drugs could participate after a washout period (Table S2 in the Supplementary Appendix). Negative tuberculosis test results (or receipt of prophylactic treatment) were required. If applicable, women were required to use effective birth control.

Study Oversight

The institutional review board at each participating center approved the study protocols. All patients provided written informed consent. Sites maintained compliance with the Health Insurance Portability and Accountability Act or relevant regional regulations. Amgen funded both studies. Site investigators collected the data, and Amgen conducted the data analyses. All the authors interpreted the data and, after a first draft had been written by the first author, collaborated in the preparation of the manuscript, with support from a professional medical writer who was an employee of Amgen. All the authors made the decision to submit the manuscript for publication and attest to the veracity and completeness of data and analyses for their respective studies, as well as for the fidelity of this report to the study protocols, available at NEJM.org.

Study Design

Both studies, which were identical in design, were multicenter, randomized, double-blind, placebo-controlled and active comparator–controlled, parallel-group, phase 3 trials. The AMAGINE-2 study was conducted at 142 sites worldwide from August 2012 through September 2014 (data cutoff). The AMAGINE-3 study was conducted at 142 sites worldwide (none of which were included in the AMAGINE-2 study) from September 2012 through August 2014 (data cutoff). Each study included a 12-week induction phase and a 40-week maintenance phase (Fig. S1 in the

Supplementary Appendix). Patients were randomly assigned in a 2:2:1:1 ratio to receive brodalumab at a dose of 210 mg or at a dose of 140 mg (subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8, and 10), ustekinumab (subcutaneous injection of 45 mg for patients with a body weight ≤100 kg and 90 mg for patients with a body weight >100 kg, on day 1 and week 4 and every 12 weeks thereafter, in accordance with standard dosing regimens), or placebo (subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8, and 10 as double-blind, double-dummy injections, as appropriate for each randomly assigned study group). Randomization lists were generated with the use of a permuted block design within each stratum based on baseline body weight (≤100 kg or >100 kg), geographic region, and previous use of biologic agents; enrollment of patients with previous biologic use was capped at 50% of each study population.

At week 12, patients who were originally randomly assigned to receive brodalumab underwent repeat randomization, in a 2:2:2:1 ratio, to one of four maintenance regimens: brodalumab at 210 mg every 2 weeks, 140 mg every 2 weeks, 140 mg every 4 weeks, or 140 mg every 8 weeks, stratified according to week 12 body weight (≤100 kg or >100 kg), induction regimen, and week 12 response (sPGA score, 0 or ≥1). Patients who were originally randomly assigned to receive placebo were switched to brodalumab at a dose of 210 mg every 2 weeks. Patients who were originally randomly assigned to receive ustekinumab continued to receive ustekinumab every 12 weeks until week 52, when patients who were still receiving the regimen could receive brodalumab at a dose of 210 mg every 2 weeks in an open-label extension study. The original treatment blinding was maintained during the rerandomization process and through week 52.

Beginning at week 16, patients who were assigned to receive brodalumab in the rerandomization process and who did not have an adequate response (i.e., patients who had a single sPGA score of ≥3 or persistent sPGA scores of 2 over at least a 4-week period) received rescue treatment (210 mg of brodalumab every 2 weeks). Patients receiving ustekinumab who did not have an adequate response continued to receive ustekinumab, except at week 16, when they could receive rescue treatment (210 mg of brodalumab every 2 weeks). For patients who did not have a response to rescue treatment (i.e., patients who had persistent sPGA scores ≥3 over at least a 4-week period while receiving continuous rescue treatment for at least 12 weeks), treatment with the study drug was discontinued. Rescue treatment was blinded through week 52.

ASSESSMENTS AND SAFETY EVALUATIONS

We conducted efficacy assessments throughout each study, with key assessments conducted at week 12 (end of the induction phase) and week 52 (end of the maintenance phase). We assessed disease activity with the use of the PASI and sPGA. Patients performed symptom self-assessment with the Psoriasis Symptom Inventory (PSI) (range, 0 to 32, with higher scores indicating more severe disease), which is a validated instrument for the measurement of psoriasis signs and symptoms.[15] We evaluated safety by monitoring adverse events,[16,17] serious adverse events,[18] adverse events of interest, laboratory assessments, vital signs, and anti-brodalumab antibodies. Major adverse cardiovascular events, which were reviewed by an independent adjudication committee of cardiologists and neurologists, were reported in a blinded manner.

OBJECTIVES AND END POINTS

The primary objectives were to compare the two brodalumab doses with placebo, with regard to the coprimary end points of the proportion of patients who had a 75% or greater reduction from baseline in PASI score (PASI 75) and the proportion of patients who had an sPGA score of 0 or 1 at week 12, as well as to compare brodalumab (in the group that received 210 mg every 2 weeks and in the weight-based analysis group) with ustekinumab with regard to the primary end point of the proportion of patients who had a 100% reduction in PASI score (PASI 100) at week 12. The weight-based analysis group was a prespecified subgroup that included patients with a body weight of 100 kg or less who were in the group that received 140 mg of brodalumab every 2 weeks and patients with a body weight greater than 100 kg who were in the group that received 210 mg of brodalumab every 2 weeks; therefore, this was not an independent treatment group, but it was based on the randomly assigned treatment groups, because weight was a randomization stratification factor.

The key secondary efficacy end points at

week 12 were the superiority of the two brodalumab doses over placebo with respect to PASI 100, an sPGA score of 0, and PSI response (defined as a total score ≤8, with no item scores >1); the superiority of brodalumab at a dose of 140 mg every 2 weeks over ustekinumab with respect to PASI 100; and the superiority of brodalumab, in the group that received 210 mg every 2 weeks and in the weight-based analysis group, over ustekinumab with respect to PASI 75. The key maintenance end point was an sPGA score of 0 or 1 among the four brodalumab maintenance regimens at week 52.

STATISTICAL ANALYSIS

Primary analyses were conducted after all patients completed the week 52 visit or discontinued participation in the study. Efficacy was analyzed according to the patients' randomly assigned treatment group and consisted of two sets of primary and key secondary end points (one for the comparison with placebo and one for the comparison with ustekinumab); analyses of efficacy were performed with a combination of parallel, sequential, and Bonferroni-based recycling testing procedures at an alpha level of 0.01 (vs. placebo) or 0.04 (vs. ustekinumab) to maintain a 5% two-sided type I error rate (see the Supplementary Appendix). Dichotomous variables were tested with the use of the Cochran–Mantel–Haenszel test, with missing data imputed as indicating no response (see the Supplementary Appendix). P values for the primary and key secondary comparisons were adjusted for multiplicity; all other P values were nominal. The safety-analysis set included all randomly assigned patients who received one or more doses of a study drug.

Table 1. Demographics and Baseline Clinical Characteristics of the Patients.*

Characteristic	AMAGINE-2 (N=1831)	AMAGINE-3 (N=1881)
Age — yr	45±13	45±13
Male sex — no. (%)	1258 (69)	1288 (68)
White race — no. (%)†	1652 (90)	1708 (91)
Weight — kg	91±23	89±22
Body-mass index‡	30.6±7.2	30.1±6.9
Duration of psoriasis — yr	19±12	18±12
Psoriatic arthritis — no. (%)	340 (19)	384 (20)
Body-surface area involved — %	27±17	28±18
PASI score§	20.3±8.2	20.2±8.4
sPGA score — no. (%)¶		
3	994 (54)	1169 (62)
4	723 (39)	634 (34)
5	114 (6)	78 (4)
PSI score‖	18.8±6.9	18.5±7.0
Previous systemic treatment or phototherapy — no. (%)	1395 (76)	1287 (68)
Previous biologic therapy — no. (%)	530 (29)	468 (25)

* Plus–minus values are means ±SD. Further details and comparison of baseline characteristics according to randomized groups are available in the Supplementary Appendix.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Scores on the psoriasis area-and-severity index (PASI) range from 0 to 72, with higher scores indicating more severe disease.
¶ Scores on the static physician's global assessment (sPGA) range from 0 (clear skin) to 5 (very severe disease); a score of 3 indicates moderate disease.
‖ Scores on the Psoriasis Symptom Inventory (PSI) range from 0 to 32, with higher scores indicating more severe disease.

RESULTS

PATIENTS

The demographic and clinical characteristics of the patients at baseline were balanced across the treatment groups (Table 1, and Table S3 in the Supplementary Appendix). In the AMAGINE-2 study, 1831 patients underwent randomization, 1776 (97%) completed the 12-week induction phase, and 1601 (87%) completed the 52-week induction–maintenance phases (Tables S4 and S5 in the Supplementary Appendix). In the AMAGINE-3 study, 1881 patients underwent randomization, 1816 (97%) completed the 12-week induction phase, and 1656 (88%) completed the 52-week induction–maintenance phases (Tables S4 and S6 in the Supplementary Appendix).

PRIMARY EFFICACY END POINTS

Brodalumab was superior to placebo and to ustekinumab with respect to the primary end points in both studies. At week 12, PASI 75 response rates were significantly higher with brodalumab at a dose of 210 mg and at a dose of 140 mg than with placebo (AMAGINE-2, 86% and 67%, respectively, vs. 8%; AMAGINE-3, 85% and 69%, vs. 6%; P<0.001) (Table 2). Rates of sPGA scores of 0 or 1 at week 12 were also significantly higher with the two doses of brodalumab than with placebo (AMAGINE-2, 79% and

58%, vs. 4%; AMAGINE-3, 80% and 60%, vs. 4%; P<0.001) (Table 2). PASI 100 response rates at week 12 were significantly higher with 210 mg of brodalumab than with ustekinumab (AMAGINE-2, 44% vs. 22%; AMAGINE-3, 37% vs. 19%; P<0.001) (Table 2); similar results were seen in the weight-based analysis (AMAGINE-2, 34% vs. 22%; AMAGINE-3, 30% vs. 19%; P<0.001) (Table S7 in the Supplementary Appendix).

KEY SECONDARY END POINTS AND OTHER EFFICACY RESULTS

In both studies, the two brodalumab doses were superior to placebo with regard to all key secondary end points (PASI 100, sPGA score of 0, and PSI response at week 12) (P<0.001) (Table 2). Response rates for a 90% reduction in PASI (PASI 90) were significantly higher with both brodalumab doses than with placebo (P<0.001) (Fig. S2 in the Supplementary Appendix) and were significantly higher with 210 mg of brodalumab than with ustekinumab (P<0.001) (Fig. S2 in the Supplementary Appendix). In analyses of PASI 100, the 140-mg dose of brodalumab was superior to ustekinumab in the AMAGINE-3 study (P=0.007) (Table 2) but not in the AMAGINE-2 study (P=0.08). PASI 75 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab in the AMAGINE-3 study (P=0.007) (Table 2) but not in the AMAGINE-2 study, on the basis of the sequential testing procedure (P=0.08); however, the nominal P value was significant (P<0.001). Similarly, in the weight-based analysis of PASI 75, brodalumab was superior to ustekinumab in the AMAGINE-3 study (P=0.007) (Table S6 in the Supplementary Appendix) but not in the AMAGINE-2 study (P=0.08). The median time to a response in both studies was significantly shorter with either brodalumab dose than with ustekinumab (P<0.001) (Fig. 1, and Table S8 in the Supplementary Appendix). With respect to patient-reported severity of symptoms, both brodalumab doses were superior to placebo, as indicated by the significantly higher proportions of patients with a PSI response at week 12 in both studies (P<0.001) (Table 2).

MAINTENANCE

At week 12, patients receiving brodalumab underwent rerandomization to receive one of four brodalumab maintenance regimens, patients receiving ustekinumab continued to receive therapy, and patients receiving placebo switched to 210 mg of brodalumab every 2 weeks (Tables S5 and S6 in the Supplementary Appendix). In the AMAGINE-2 study, 1174 patients were assigned in the rerandomization process to receive brodalumab, and 297 switched from placebo; 1331 patients (90%) remained in the study at week 52 (Table S5 in the Supplementary Appendix). In the AMAGINE-3 study, 1200 patients were assigned in the rerandomization process to receive brodalumab, and 298 patients switched from placebo, with 1370 patients (91%) remaining in the study at week 52 (Table S6 in the Supplementary Appendix). In the AMAGINE-2 study, 55 of 300 patients (18%) assigned to receive ustekinumab were given rescue therapy with brodalumab at week 16 (Table S5 in the Supplementary Appendix); 69 of 313 patients (22%) received rescue therapy in the AMAGINE-3 study (Table S6 in the Supplementary Appendix).

The proportion of patients with an sPGA score of 0 or 1 at week 52 was significantly higher among those who had received 210 mg or 140 mg of brodalumab every 2 weeks than among those who had received the other brodalumab maintenance regimens (P<0.001) (Table 3). The PASI response-over-time curves for patients who received brodalumab at a dose of 210 mg throughout the study or ustekinumab throughout the study showed that response rates increased through week 12 and stabilized during weeks 16 through 52 (Fig. S3 in the Supplementary Appendix). Most of the patients who were switched to brodalumab after placebo had PASI 75 and sPGA 0 or 1 responses, and the majority had PASI 100 responses at week 52 (Table S9 in the Supplementary Appendix). Most of the patients who were given rescue therapy with brodalumab after ustekinumab treatment had PASI 75 and sPGA 0 or 1 responses, and more than 40% had PASI 100 responses (Table S9 in the Supplementary Appendix).

SAFETY

During the induction phase, the proportion of patients with at least one adverse event was higher with brodalumab and with ustekinumab than with placebo (Table 4). The most common adverse events were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. With the exception of upper respiratory tract infection, these events were more frequent with

Table 2. Clinical Responses and Patient-Reported Outcomes at Week 12.*

Outcome	AMAGINE-2				AMAGINE-3			
	Placebo (N=309)	Ustekinumab (N=300)	Brodalumab, 140 mg every 2 wk (N=610)	Brodalumab, 210 mg every 2 wk (N=612)	Placebo (N=315)	Ustekinumab (N=313)	Brodalumab, 140 mg every 2 wk (N=629)	Brodalumab, 210 mg every 2 wk (N=624)
PASI 75 — no.	25	210	406	528	19	217	435	531
% (95% CI)	8 (5–12)	70 (65–75)	67 (63–70)	86 (83–89)	6 (4–9)	69 (64–74)	69 (65–73)	85 (82–88)
P value vs. placebo†‡	—	—	<0.001	<0.001	—	—	<0.001	<0.001
P value vs. ustekinumab	—	—	0.33	0.08†	—	—	0.95	0.007†
sPGA score of 0 or 1 — no.	12	183	354	481	13	179	377	497
% (95% CI)	4 (2–7)	61 (55–67)	58 (54–62)	79 (75–82)	4 (2–7)	57 (52–63)	60 (56–64)	80 (76–83)
P value vs. placebo†‡	—	—	<0.001	<0.001	—	—	<0.001	<0.001
P value vs. ustekinumab	—	—	0.49	<0.001	—	—	0.44	<0.001
PASI 100 — no.	2	65	157	272	1	58	170	229
% (95% CI)	1 (0–2)	22 (17–27)	26 (22–29)	44 (41–49)	0.3 (0–2)	19 (14–23)	27 (24–31)	37 (33–41)
P value vs. placebo†	—	—	<0.001	<0.001	—	—	<0.001	<0.001
P value vs. ustekinumab†	—	—	0.08	<0.001§	—	—	0.007	<0.001§
sPGA score of 0 — no.	2	65	157	274	1	58	170	229
% (95% CI)	1 (0–2)	22 (17–27)	26 (22–29)	45 (41–49)	0.3 (0–2)	19 (14–23)	27 (24–31)	37 (33–41)
P value vs. placebo†	—	—	<0.001	<0.001	—	—	<0.001	<0.001
P value vs. ustekinumab	—	—	0.17	<0.001	—	—	0.004	<0.001
PSI response — no.¶	21	166	314	414	20	162	336	382
% (95% CI)	7 (4– 0)	55 (50–61)	51 (47–56)	68 (64–71)	6 (4–10)	52 (46–57)	53 (49–57)	61 (57–65)
P value vs. placebo†	—	—	<0.001	<0.001	—	—	<0.001	<0.001

* In the statistical analysis, missing data were imputed as nonresponses. PASI 75 and PASI 100 responses indicate reductions from baseline in the PASI score of 75% or more and 100%, respectively. N values are the numbers of patients who were randomly assigned to a study regimen and had a valid measurement value at week 12, after imputation. All P values were nominal except as noted otherwise. P values were not calculated for the comparison of brodalumab and ustekinumab for the PSI response definition.
† P values were calculated by means of Bonferroni-based recycling testing (a multiple testing procedure; additional details are provided in the Supplementary Appendix), which includes all primary and key secondary end point comparisons with placebo and ustekinumab, at a significance level of 0.05.
‡ P values in this row are for the coprimary end points in the comparison of brodalumab with placebo.
§ The P value is for the primary end point in the comparison of brodalumab with ustekinumab.
¶ A PSI response was defined as a total score of up to 8, with no item having a score greater than 1.

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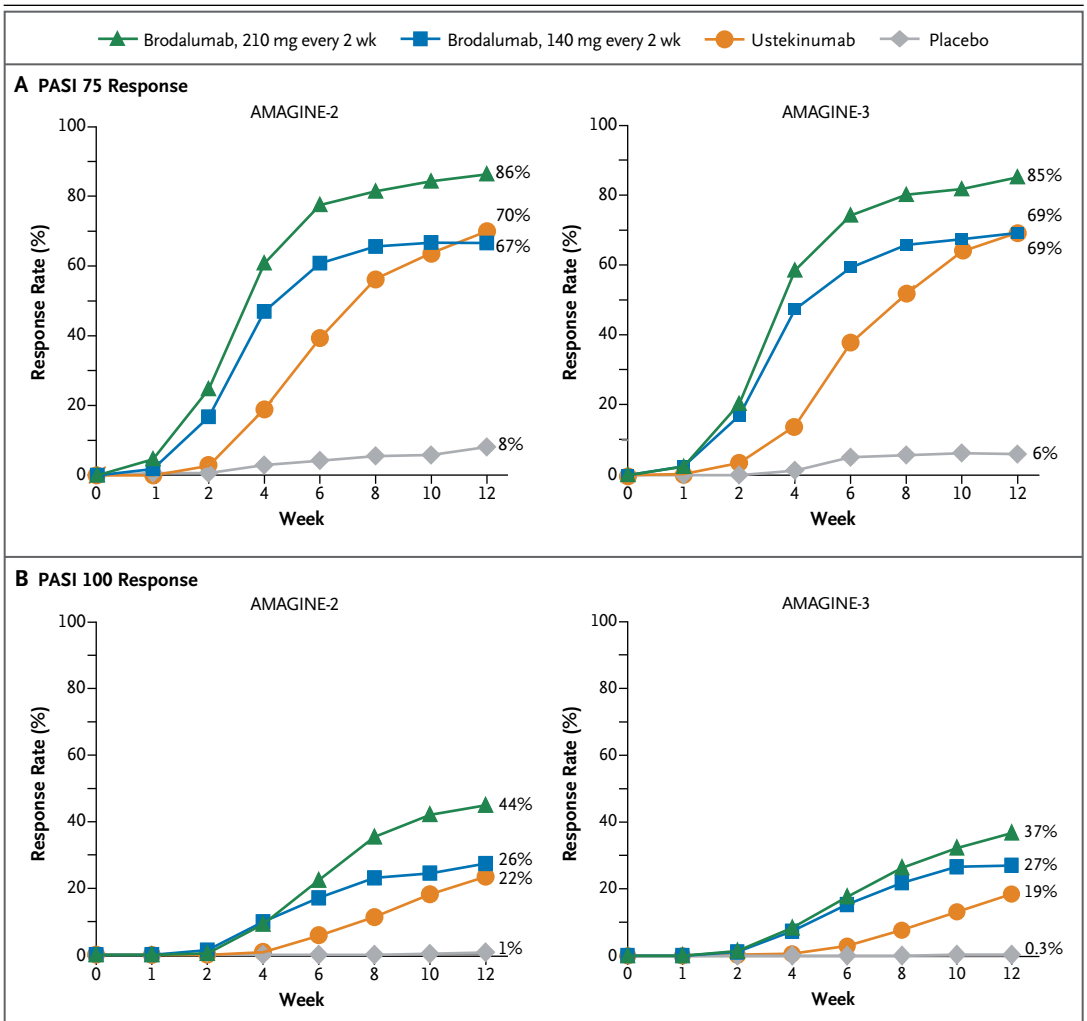

Figure 1. PASI 75 and PASI 100 Response Rates over Time.

Shown are the proportions of patients in each treatment group who had reductions in the psoriasis area-and-severity index (PASI) score of 75% or more (PASI 75) or of 100% (PASI 100) from baseline through the 12-week induction phase in the AMAGINE-2 and AMAGINE-3 studies. PASI scores range from 0 to 72, with higher scores indicating more severe disease. Missing values were imputed as indicating a lack of response.

brodalumab than with placebo or ustekinumab in the AMAGINE-2 study; arthralgia was more frequent with brodalumab in the AMAGINE-3 study (Table S10 in the Supplementary Appendix). The rates of serious adverse events per 100 patient-years through week 52 were 8.3 with brodalumab and 13.0 with ustekinumab in the AMAGINE-2 study (Tables S11 and S15 in the Supplementary Appendix) and 7.9 and 4.0, respectively, in the AMAGINE-3 study (Tables S12 and S16 in the Supplementary Appendix). There were no clinically apparent differences in the types of serious adverse events among study groups (Tables S13 and S14 in the Supplementary Appendix).

Adverse events of neutropenia during the induction phase were more frequent with brodalumab and with ustekinumab than with placebo (Table S10 in the Supplementary Appendix). The cases of neutropenia were not associated with serious infections, and most cases were mild (absolute neutrophil count, >1000 per cubic millimeter), transient, and reversible. The exposure-adjusted event rates of neutropenia per 100 patient-years of exposure to brodalumab through week 52 were 0.2 in the AMAGINE-2 study and

Table 3. Maintenance of Clinical Response to Brodalumab at Week 52.*

Variable	AMAGINE-2				AMAGINE-3			
	140 mg every 8 wk (N=168)	140 mg every 4 wk (N=335)	140 mg every 2 wk (N=337)	210 mg every 2 wk (N=334)	140 mg every 8 wk (N=174)	140 mg every 4 wk (N=341)	140 mg every 2 wk (N=343)	210 mg every 2 wk (N=342)
sPGA score of 0 or 1 — no.	8	30	144	209	10	53	154	208
% (95% CI)	5 (2–9)	9 (6–13)	43 (37–48)	63 (57–68)	6 (3–10)	16 (12–20)	45 (40–50)	61 (55–66)
Adjusted P value†								
vs. 140 mg every 8 wk	—	—	<0.001	<0.001	—	—	<0.001	<0.001
vs. 140 mg every 4 wk	—	—	<0.001	<0.001	—	—	<0.001	<0.001
vs. 140 mg every 2 wk	—	—	—	<0.001	—	—	—	<0.001

* In the statistical analysis, missing data and data from patients who did not have an adequate response (i.e., who had an sPGA score ≥3 or persistent sPGA scores of 2 over at least a 4-week period) through week 52 were imputed as nonresponses at the time at which the judgment regarding an inadequate response was made. N values are the numbers of patients who underwent rerandomization and had a valid measurement value at week 52, after imputation.

† We calculated the adjusted P value by applying the sequential testing procedure for multiplicity adjustment at a significance level of 0.05.

1.5 in the AMAGINE-3 study; the corresponding rates with ustekinumab were 0.8 and 0.8 (Tables S11 and S12 in the Supplementary Appendix). Candida infections occurred more frequently with brodalumab than with ustekinumab or placebo during the induction phase (Table S10 in the Supplementary Appendix); all the infections were graded as mild or moderate, and none were systemic. This trend continued through week 52 (Tables S11 and S12 in the Supplementary Appendix). One case of Crohn's disease occurred during the maintenance phase (Tables S11 and S12 in the Supplementary Appendix). The rates of serious infectious episodes per 100 patient-years of exposure to brodalumab through week 52 were 1.0 in the AMAGINE-2 study and 1.3 in the AMAGINE-3 study; the corresponding rates with ustekinumab were 0.8 and 1.2 (Tables S11 and S12 in the Supplementary Appendix).

One death (from stroke) occurred during the induction phase (in the AMAGINE-2 study, in a patient in the 210-mg brodalumab group, 20 days after the last dose), and five deaths occurred through week 52: in the AMAGINE-2 study, one from cardiac arrest (in a patient who received 210 mg of brodalumab continuously throughout the study) and one each from cardiac arrest and pancreatic carcinoma (in patients in the ustekinumab group), and in the AMAGINE-3 study, one from cardiac arrest (in a patient who had received 140 mg of brodalumab every 2 weeks followed by 210 mg) and one from accidental death in a motor vehicle accident (in a patient who had received 210 mg of brodalumab followed by 140 mg every 2 weeks). Three deaths occurred after exposure: in the AMAGINE-2 study, one from completed suicide (in a patient who had received placebo followed by 210 mg of brodalumab, 27 days after the last dose), and in the AMAGINE-3 study, one from the hematophagic histiocytosis syndrome (in a patient who had received 140 mg of brodalumab every 2 weeks followed by 140 mg every 4 weeks and rescue therapy, 41 days after the last dose) and one from cardiomyopathy (in a patient who had received 210 mg of brodalumab followed by 140 mg every 4 weeks and rescue therapy, 87 days after the last dose). There was one additional suicide after week 52 during the open-label extension (in the AMAGINE-2 study, in a patient who had received 210 mg of brodalumab every 2 weeks, 19 days after the last dose).

IMMUNOGENICITY

Anti-brodalumab antibodies (nonneutralizing) were detected during the period from baseline through week 52 in 28 brodalumab-treated patients (1.8%) in the AMAGINE-2 study and in 37 brodalumab-treated patients (2.3%) in the AMAGINE-3 study. None were associated with a loss of efficacy or adverse events. No patient had neutralizing antibodies. Nonneutralizing anti-brodalumab antibodies were detected in 4 patients at baseline. Among the patients who were randomly assigned to ustekinumab, samples from 6 patients after the initiation of ustekinumab

Table 4. Adverse Events during the Induction Phase.

Event	AMAGINE-2				AMAGINE-3			
	Placebo (N = 309)	Ustekinumab (N = 300)	Brodalumab, 140 mg every 2 wk (N = 607)	Brodalumab, 210 mg every 2 wk (N = 612)	Placebo (N = 313)	Ustekinumab (N = 313)	Brodalumab, 140 mg every 2 wk (N = 626)	Brodalumab, 210 mg every 2 wk (N = 622)
	number of patients (percent)							
Any	165 (53.4)	177 (59.0)	365 (60.1)	354 (57.8)	152 (48.6)	168 (53.7)	329 (52.6)	353 (56.8)
Serious*	8 (2.6)	4 (1.3)	13 (2.1)	6 (1.0)	3 (1.0)	2 (0.6)	10 (1.6)	9 (1.4)
Fatal†	0	0	0	1 (0.2)	0	0	0	0
Leading to discontinuation of study	0	2 (0.7)	8 (1.3)	6 (1.0)	2 (0.6)	1 (0.3)	3 (0.5)	5 (0.8)
Leading to discontinuation of study drug	1 (0.3)	4 (1.3)	7 (1.2)	6 (1.0)	3 (1.0)	2 (0.6)	5 (0.8)	7 (1.1)
Grade 3, 4, or 5‡	10 (3.2)	11 (3.7)	29 (4.8)	25 (4.1)	8 (2.6)	8 (2.6)	25 (4.0)	23 (3.7)

* A serious adverse event was defined as an event that was fatal or life-threatening, led to inpatient hospitalization or prolongation of existing hospitalization, caused persistent or substantial disability or incapacity, caused a congenital anomaly or birth defect, or was considered by the investigator to be medically important. Additional details on adverse events are provided in the Supplementary Appendix.

† The fatal event was cerebral infarction (20 days after the last dose).

‡ The severity of adverse events was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

therapy were positive for nonneutralizing antibrodalumab antibodies.

DISCUSSION

These phase 3 studies validate the important role of the interleukin-17 receptor in moderate-to-severe psoriasis. Brodalumab was shown to have efficacy superior to that of placebo and ustekinumab with respect to all the primary end points: PASI 75 and an sPGA score of 0 or 1 in a comparison of two brodalumab doses with placebo and PASI 100 in a comparison of 210 mg of brodalumab every 2 weeks with ustekinumab and in the weight-based analysis comparing brodalumab with ustekinumab. PASI 100 was selected as the primary end point for the comparison of brodalumab with ustekinumab because it is an unambiguous end point and because complete clearance of skin disease is a goal of treatment in several guidelines.[19,20] The dose of 210 mg of brodalumab every 2 weeks was superior to the other doses used, with regard to the maintenance of clinical responses, which indicated that less frequent or lower dosing is not sufficient to maintain skin clearance. PASI 100 responses were sustained in the majority of patients who continued treatment with 210 mg of brodalumab every 2 weeks.

Brodalumab treatment resulted in a rapid reduction in the signs and symptoms of psoriasis. The median time to a PASI 75 response with 210 mg of brodalumab every 2 weeks was 4 weeks — approximately twice as fast as the median time to a response with ustekinumab. These results suggest that interleukin-17 receptor A plays a central role in psoriasis by directly driving downstream signaling in keratinocytes and inducing expression of proinflammatory molecules.[9-11] Ustekinumab, in contrast, acts upstream by targeting interleukin-23.[8]

Investigator-assessed reductions in disease activity were accompanied by reductions in the patient-reported PSI scores; this indicates that brodalumab may provide a benefit with regard to the established preferences of patients for more complete clinical responses.[21,22] Some patients with a response to therapy still have residual disease activity that continues to negatively affect health-related quality of life.[21,22]

The increases in candida infections are consistent with the role of interleukin-17A in host

defense, specifically involving mucocutaneous microbial surveillance.[23-25] Disparities in the patient-years of exposure among groups during the 52-week treatment period limited interpretations of potential dosage effects on exposure-adjusted adverse-event rates. The sizes of the study populations, which were sufficient for the assessments of efficacy and common adverse events, may have been inadequate for the detection of rare adverse events, which would require longer follow-up of large numbers of patients to provide a full understanding of the safety profile of brodalumab.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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