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Long-term efficacy and safety of brodalumab in psoriasis through 120 weeks and after withdrawal and retreatment: subgroup analysis of a randomized phase III trial (AMAGINE-1)*

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Conflicts of interest
See Appendix.

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Summary

Background Brodalumab is efficacious for the treatment of moderate-to-severe plaque psoriasis through 52 weeks.
Objectives To evaluate the efficacy and safety of brodalumab through 120 weeks, including following withdrawal and retreatment.
Methods At baseline, patients were randomized to brodalumab (n = 222) or placebo (n = 220). At week 12, patients achieving a static Physician's Global Assessment (sPGA) score of 0 or 1 (sPGA 0/1) with brodalumab were rerandomized to brodalumab (n = 83) or placebo (n = 84; later re-treated with brodalumab if sPGA ≥ 3 occurred), and patients receiving placebo switched to brodalumab (n = 208). Safety was assessed by exposure-adjusted rates of treatment-emergent adverse events.
Results Among those who achieved sPGA 0/1 at week 12 and were rerandomized to brodalumab, 96% and 80% using observed data, respectively, and 74% and 61% using nonresponder imputation, respectively, achieved 75% improvement in Psoriasis Area and Severity Index (PASI 75) and PASI 100 at week 120. Following withdrawal from brodalumab, return of disease occurred after a mean ± SD duration of 74·7 ± 50·5 days. Among those who switched from brodalumab to placebo at week 12, PASI 75 rates using observed data and nonresponder imputation were 55% and 51% at week 20, respectively and 94% and 75% at week 120, respectively; PASI 100 rates at week 120 were 75% and 60%, respectively. Efficacy was maintained through week 120 in those receiving brodalumab after placebo. No new safety signals were observed.
Conclusions These findings indicate that brodalumab is efficacious and safe for continuous long-term treatment of psoriasis, and support the potential for response after discontinuation and retreatment.

What is already known about this topic?

- Sustained efficacy and safety of biologics is an unmet need in patients with psoriasis, given that patients frequently discontinue and restart psoriasis therapies.
- Brodalumab is a fully human anti-interleukin-17 receptor A monoclonal antibody approved for the treatment of moderate-to-severe psoriasis in patients who had inadequate responses to other systemic therapies.

What does this study add?

- The current study evaluated the efficacy and safety of brodalumab through 120 weeks in AMAGINE-1, including following withdrawal and retreatment.
- These data indicate that brodalumab is efficacious and safe for continuous long-term treatment of psoriasis, particularly in patients who have experienced a lapse in their treatment.

Sustained skin clearance is an unmet need in patients with psoriasis, given that biological therapies have been shown to lose their effectiveness in a proportion of patients over time.[1] An analysis of long-term persistence of adalimumab, etanercept, infliximab and ustekinumab found that 67% of treatment discontinuations were caused by loss of efficacy.[2] Furthermore, analysis of an international psoriasis registry showed that lack of effectiveness was the most common reason why patients discontinued treatment with these same biologics and that second- and third-line therapies had higher rates of discontinuation than first-line therapy.[3] Many patients with psoriasis stop and restart treatment because of factors including psychological distress, dissatisfaction with treatment, inconvenience, cost, insurance problems and use of therapy only when needed.[4,5] A recent cohort study of patients with long-term plaque psoriasis found that, over a 12-month period, 17·5% of patients switched biological therapies and 2·6% stopped and restarted treatment after a break of ≥ 90 days.[6] To approximate scenarios of real-world discontinuation associated with events such as pregnancy, adherence issues or changes to insurance coverage, multiple studies have used withdrawal and retreatment periods to evaluate the potential for recapture of response following treatment and subsequent retreatment.[7–9] Therefore, inability to achieve sustained skin clearance extends to patients who withdraw from treatment and are subsequently re-treated with the same or a different agent. In contemplating long-term psoriasis therapy (i.e. ≥ 1 year), patients require both sustained symptom control and safety with prolonged use, highlighting the importance of long-term studies.

Studies have reported efficacy of the interleukin (IL)-12/23 inhibitor ustekinumab and the IL-17A inhibitors secukinumab and ixekizumab for skin clearance in psoriasis over 2–4 years of follow-up.[10–12] Among 517 patients who received ustekinumab 45 mg or 90 mg, some of whom were withdrawn from therapy at week 40 and were later re-treated, 63·4% and 72·0%, respectively, achieved 75% improvement from baseline in Psoriasis Area and Severity Index (PASI 75) at week 244, 21·6% and 26·4%, respectively, achieved PASI 100, and 42·5% and 51·0%, respectively, achieved a Physician's Global Assessment (PGA) score of 0 or 1 at week 244.[12]

Among 168 patients receiving secukinumab 300 mg, 83·0% achieved PASI 75 and 42·6% achieved PASI 100 at week 152.[10] Among 385 patients who received ixekizumab 80 mg, 93·4% achieved PASI 75, 56·3% achieved PASI 100 and 82·6% achieved a static PGA (sPGA) score of 0 or 1 at 108 weeks.[11] In studies of tumour necrosis factor-α inhibitors conducted over 2–4 years,[13–15] skin clearance response to adalimumab and infliximab was stable or declined slightly over time,[13,15] while response to etanercept fell more substantially.[14] Of note, many of these studies had maintenance and extension phases in which patients with initial response to therapy (e.g. PASI 75 at week 12) were included; thus, the observed maintenance of response may be attributable to these patients being high responders.[10,12]

Brodalumab is a fully human anti-IL-17 receptor A monoclonal antibody approved for the treatment of moderate-to-severe psoriasis in patients who had inadequate responses to other systemic therapies.[16] Brodalumab has been investigated for the treatment of psoriasis in phase II and three phase III clinical trials (AMAGINE-1/-2/-3).[17–20] In the AMAGINE-1 study, patients were treated for 12 weeks with brodalumab 140 mg every 2 weeks (Q2W), brodalumab 210 mg Q2W or placebo. Patients who achieved sPGA 0/1 after 12 weeks of brodalumab 210 mg were rerandomized to either brodalumab 210 mg or placebo at 12 weeks. Patients who were rerandomized were eligible for rescue treatment with brodalumab 210 mg if they experienced return of disease (defined as an sPGA score ≥ 3).[17] Among 222 patients who received brodalumab 210 mg for 12 weeks, 75·7% achieved sPGA 0/1. Among 83 patients who achieved sPGA 0/1 at week 12 and then continued on brodalumab 210 mg, 83% achieved sPGA 0/1 at week 52.[17] In the group of patients who switched to placebo at week 12 and were then eligible for retreatment with brodalumab 210 mg, 96·9% achieved sPGA 0/1 after 24 weeks.[17]

The objective of this study was to evaluate the efficacy and safety of brodalumab 210 mg Q2W through 120 weeks of treatment in the AMAGINE-1 trial. Patients who underwent withdrawal and retreatment with brodalumab were also included.

Materials and methods

AMAGINE-1 was a phase III, randomized, double-blind, placebo-controlled study (ClinicalTrials.gov NCT01708590) conducted in accordance with applicable country, US Food and Drug Administration, and International Council for Harmonisation Good Clinical Practice regulations/guidelines. All patients provided written informed consent. The independent ethics committee or institutional review board at each study

centre received a copy of the protocol, the patients' informed consent forms and any other patient information and/or recruitment material.

Study design

Detailed methods of the AMAGINE-1 study were previously reported.[17] Enrolled patients were aged 18–75 years with moderate-to-severe plaque psoriasis affecting ≥ 10% of body surface area, PASI ≥ 12 and an sPGA score ≥ 3. Patients were initially randomized 1 : 1 : 1 to brodalumab 140 mg Q2W, brodalumab 210 mg Q2W or placebo (Figure 1). The current analysis includes only patients originally treated with brodalumab 210 mg Q2W or placebo.

Patients who were initially randomized to brodalumab 210 mg Q2W and achieved sPGA 0/1 at week 12 were rerandomized 1 : 1 to brodalumab 210 mg Q2W or placebo. Patients originally randomized to brodalumab who had an sPGA score ≥ 2 at week 12 were not rerandomized and received brodalumab 210 mg Q2W. Beginning at week 16, patients rerandomized to placebo who experienced return of disease qualified for retreatment with their induction doses of brodalumab. Patients receiving placebo during the first 12 weeks of AMAGINE-1 were switched to brodalumab 210 mg Q2W at week 12. The current analysis summarizes data through week 120 for the following three treatment groups: patients receiving continuous brodalumab 210 mg Q2W, patients who received brodalumab and were rerandomized at week 12 to placebo and who subsequently qualified for retreatment with brodalumab 210 mg Q2W, and patients receiving placebo who were switched to brodalumab 210 mg Q2W at week 12. Data are reported through week 120, including the long-term extension starting at week 52 (Figure 1).

Clinical assessments

As previously reported, coprimary objectives of the AMAGINE-1 study were the percentage of patients achieving sPGA 0/1 and PASI 75 at week 12.[17] During the course of the study, sPGA and PASI were assessed at week 1, Q2W from week 2 to week 24 (in addition to week 13), every 4 weeks from week 24 to week 52, and every 12 weeks from week 60 to week 120.

The sPGA scale evaluates severity of induration, scaling and erythema on a 6-point scale, where 0 = clear and 5 = very severe; sPGA scores of 0 (clear) or 1 (almost clear) are considered treatment success. The PASI scale measures the same three plaque qualities together with percentage area of involvement on four body areas.

Safety and immunogenicity

Safety was assessed by exposure-adjusted rates of treatment-emergent adverse events (TEAEs) and adverse events (AEs) of interest. AEs were summarized by treatment group and expressed as exposure-adjusted event rates per 100 patient-years for all patients who received at least one dose of brodalumab at any time. Blood samples were collected from all patients at baseline and weeks 4, 12, 24 and 48 for measurement of brodalumab-binding antibodies. The methods used to quantify the presence of brodalumab-binding antibodies were previously specified.[21]

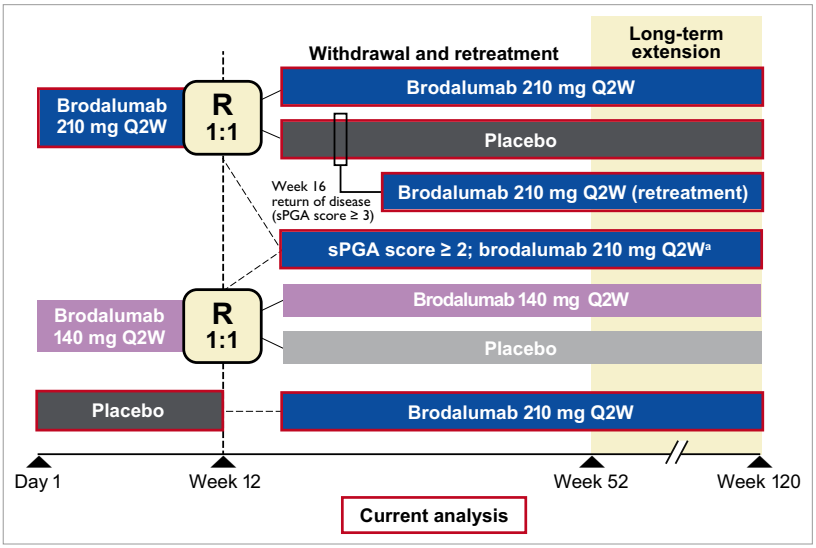

Figure 1 AMAGINE-1 study design. The current analysis reports findings for patients who originally received brodalumab 210 mg Q2W (dosage approved by the US Food and Drug Administration) or placebo during the 12-week induction phase. [a]At week 12, patients originally randomized to brodalumab who had sPGA score ≥ 2 at week 12 received brodalumab 210 mg Q2W. Q2W, every 2 weeks; R, randomized; sPGA, static Physician's Global Assessment.

Table 1 Patient demographics and baseline disease characteristics by treatment group

	Continuous brodalumab 210 mg Q2W (n = 83)	Placebo after brodalumab 210 mg Q2W (n = 84)	Brodalumab 210 mg Q2W after placebo (n = 208)
Age, median (Q1–Q3), years	49·0 (36·0–53·0)	49·0 (36·0–58·5)	47·0 (35·5–56·0)
Male sex	56 (67·5)	63 (75·0)	152 (73·1)
Race			
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Asian	5 (6·0)	5 (6·0)	7 (3·4)
Black (or African American)	0 (0)	2 (2·4)	6 (2·9)
Native Hawaiian/Pacific Islander	0 (0)	2 (2·4)	2 (1·0)
White	77 (92·8)	75 (89·3)	191 (91·8)
Other	1 (1·2)	0 (0)	2 (1·0)
Weight, kg			
Mean ± SD	87·7 ± 20.3	84·5± 18.4	90·9 ± 20.3
Median (Q1–Q3)	86·6 (74·3–98·1)	81·7 (70·4–97·9)	88·2 (78·0–104·1)
Body mass index, kg m^{-2}			
Mean ± SD	30·2 ± 7.1	28·6 ± 5.3	30·4 ± 6.7
Median (Q1–Q3)	29·4 (26·4–33·1)	27·7 (24·5–31·9)	28·7 (25·9–34·0)
Psoriatic arthritis	20 (24·1)	21 (25·0)	60 (28·8)
Duration of psoriasis, mean ± SD, years	19·7 ± 12.0	21·6 ± 14.1	20·4 ± 11.6
PASI, median (Q1–Q3)	17·4 (14·4–21·9)	17·1 (14·9–21·3)	17·5 (14·4–22·4)
BSA involvement, median (Q1–Q3), %	18·0 (14·0–30·0)	20·0 (14·3–31·0)	20·0 (14·0–35·0)
sPGA			
3	54 (65·1)	44 (52·4)	108 (51·9)
4	24 (28·9)	34 (40·5)	86 (41·3)
5 (very severe)	5 (6·0)	6 (7·1)	14 (6·7)

BSA, body surface area; PASI, Psoriasis Area and Severity Index; Q, quartile; Q2W, every 2 weeks; sPGA, static Physician's Global Assessment. Data are provided as n (%) unless otherwise stated.

Statistical analyses

Baseline demographics and disease characteristics were summarized by treatment group. Long-term efficacy (achievement of sPGA 0/1 or PASI ≥ 75 through 120 weeks) was analysed using observed data, which included data from patients with a valid measurement at the specified timepoint. Data were also analysed using last observation carried forward (LOCF) analysis, which replaced missing data with the most recently observed value, and nonresponder imputation (NRI) analysis, which assumed nonresponse for all missing data.

Results

Patient disposition and baseline characteristics

At baseline, 222 patients were randomized to receive brodalumab 210 mg Q2W and 220 patients were randomized to receive placebo. At week 12, 95·5% (n = 212) of patients remained in the brodalumab 210 mg Q2W group and 95·0% (n = 209) of patients remained in the placebo group. Overall, 83 patients who achieved sPGA 0/1 at week 12 received brodalumab 210 mg Q2W continuously for 120 weeks, 84 patients who achieved sPGA 0/1 with brodalumab 210 mg Q2W were rerandomized to placebo beginning at week 12 (with potential for later retreatment with brodalumab), and 208 patients received brodalumab 210 mg Q2W beginning at week 12 after receiving placebo. Patients originally randomized to brodalumab 210 mg Q2W who had an sPGA score ≥ 2 at week 12 were not rerandomized and continued to receive brodalumab 210 mg Q2W (n = 45).

Patient demographics and baseline disease characteristics were similar among the treatment groups (Table 1). There was a slightly lower proportion of men in the continuous brodalumab 210 mg Q2W group (67·5%) compared with other treatment groups (range 73·1–75·0%). Rates of psoriatic arthritis were similar across treatment groups (range 24·1–28·8%), as were rates of very severe psoriasis (sPGA score of 5; range 6·0–7·1%). The duration of psoriasis was slightly longer in patients who initially received brodalumab 210 mg Q2W and were rerandomized to placebo at week 12 (21·6 years) compared with the other treatment groups (range 19·7–20·4 years).

Reasons for discontinuation during the trial, including the long-term extension, are shown in Table 2. A notable increase in discontinuations was observed following week 108, which were most often attributed to 'administrative decision' or the early termination of the study by the sponsor. An administrative decision was made by the study sponsor to terminate the AMAGINE trials on 22 May 2015, on the basis of suicidal ideation and behaviour events occurring with brodalumab treatment. No causal associations between brodalumab and increased risk of suicidal ideation and behaviour have been

established.[16] Additionally, in 2017, a report synthesizing data from five clinical trials of brodalumab did not indicate a causal relationship between suicidality and brodalumab treatment.[22]

Skin clearance efficacy

Observed data analysis showed that efficacy was maintained from week 12 through week 120 among patients who achieved sPGA 0/1 with brodalumab 210 mg Q2W at week 12 and continued to receive brodalumab 210 mg Q2W (Figure 2). Similar trends were observed with NRI (Figure 2) and LOCF analyses (Figure S1; see Supporting Information), except that skin clearance estimates were consistently lower with NRI analysis, which was expected. Using observed data, LOCF and NRI analysis, PASI 75 was achieved at week 120 in 96% (66 of 69), 92% (76 of 83) and 80% (66 of 83) of patients receiving continuous brodalumab, respectively; PASI 100 was achieved in 74% (51 of 69), 69% (57 of 83) and 61% (51 of 83), respectively. In 45 patients receiving brodalumab 210 mg Q2W who had an sPGA score ≥ 2 at week 12, PASI 75 rates at week 52 were 77% (24 of 31), 60% (27 of 45) and 53% (24 of 45) and PASI 100 rates were 16% (five of 31), 11% (five of 45) and 11% (five of 45) using observed data, LOCF and NRI analyses, respectively.

Among patients who switched from brodalumab 210 mg Q2W to placebo at week 12, 79 (94%) experienced return of disease (defined as an sPGA score ≥ 3) at or after week 16 through week 52. Return of disease occurred after a mean ± duration of 74·7 ± 50.5 days (median 56·0) following the start of placebo treatment. From observed data analysis, skin clearance improved in patients re-treated with brodalumab after week 16 (Figure 3). PASI 75 response rates reached 100% (84 of 84) at week 12, fell to 55% (43 of 78) at week 20 after the switch to placebo, then reached 95% (72 of 76) at week 52 and 94% (63 of 67) at week 120. PASI 100 response rates were 55% (46 of 84) at week 12, 13% (10 of 78) at week 20, 68% (52 of 76) at week 52, and 75% (50 of 67) at week 120. Using NRI analysis, rates of PASI 75 and PASI 100 at week 120 were 75% (63 of 84) and 60% (50 of 84), respectively (Figure 3). Similar data were seen with LOCF analysis (Figure S2; see Supporting Information).

Among patients who switched from placebo to brodalumab 210 mg Q2W at week 12, skin clearance improved rapidly and was maintained from week 24 onwards (Figure 4). At week 120, 88·3% (144 of 163), 95·7% (156 of 163), 87·1% (142 of 163) and 65·6% (107 of 163) of patients achieved sPGA 0/1, PASI 75, PASI 90 and PASI 100, respectively (observed data analysis). Using NRI analysis, rates of sPGA 0/1,

Table 2 Study discontinuation by treatment group

	≤ 51 weeks	52–60 weeks	61–72 weeks	73–84 weeks	85–96 weeks	97–108 weeks	> 108 weeks
Continuous brodalumab 210 mg Q2W (n = 83)	5	0	2	2	1	2	71
Administrative decision[a]	0	0	0	0	0	0	66
Adverse event	2	0	0	0	0	1	0
Death	1	0	0	0	0	0	0
Full consent withdrawn	1	0	2	1	0	0	1
Lost to follow-up	1	0	0	0	0	1	3
Requirement for alternative therapy	0	0	0	0	0	0	1
Other/unspecified	0	0	0	1	1	0	0
Placebo after brodalumab 210 mg Q2W (n = 84)	6	1	3	1	1	3	69
Administrative decision[a]	1	0	0	0	0	0	67
Adverse event	1	0	1	0	0	1	0
Death	1	0	1	0	0	0	0
Full consent withdrawn	2	0	0	0	0	1	0
Lost to follow-up	1	0	0	0	0	0	2
Pregnancy	0	1	0	0	0	0	0
Requirement for alternative therapy	0	0	0	1	1	0	0
Other/unspecified	0	0	1	0	0	1	0
Brodalumab 210 mg Q2W after placebo (n = 208)	18	4	3	1	7	10	165
Administrative decision[a]	1	1	0	0	1	2	154
Adverse event	4	0	1	0	1	1	1
Death	1	1	0	0	1	0	0
Full consent withdrawn	3	1	1	0	3	2	1
Ineligibility determined	1	0	0	0	0	0	0
Lost to follow-up	1	0	0	0	0	2	8
Nonadherence	0	0	0	1	0	1	0
Requirement for alternative therapy	4	1	0	0	0	0	1
Other/unspecified	3	0	1	0	1	2	0

Q2W, every 2 weeks. [a]Patients who discontinued because of the early termination of the AMAGINE-1 trial. Values provided indicate the number of patients who discontinued.

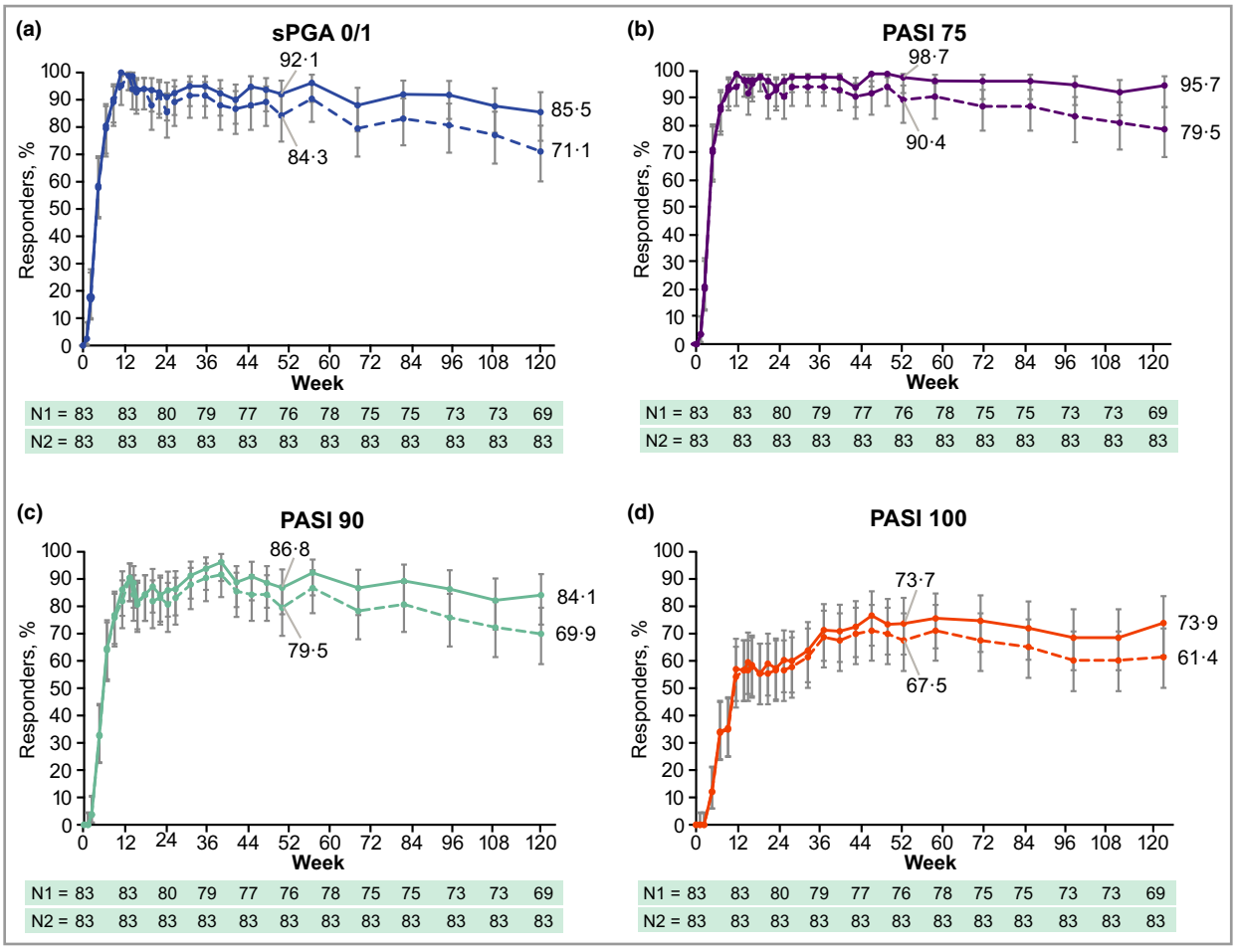

Figure 2 (a) sPGA 0/1, (b) PASI 75, (c) PASI 90 and (d) PASI 100 response rates through week 120 in patients who achieved sPGA 0/1 at week 12 and received continuous brodalumab 210 mg Q2W (n = 83). Solid lines indicate observed data analyses and broken lines indicate nonresponder imputation (NRI) analyses. Error bars show the 95% confidence interval. N1, number of patients with a valid measurement at the specified week (observed data analysis); N2, number of patients with a valid measurement at the specified week (NRI analysis); PASI, Psoriasis Area and Severity Index; PASI 75, 75% improvement in PASI; PASI 90, 90% improvement in PASI; PASI 100, 100% improvement in PASI; Q2W, every 2 weeks; sPGA 0/1, static Physician's Global Assessment score of 0 or 1.

PASI 75, PASI 90 and PASI 100 at week 120 were 69·2% (144 of 208), 75·0% (156 of 208), 68·3% (142 of 208) and 51·4% (107 of 208), respectively (Figure 4). Findings were similar when using LOCF analysis (Figure S3; see Supporting Information).

A large proportion of patients regained response after retreatment. More than 90% of patients who achieved PASI 75, 90 or 100 after 12 weeks of brodalumab 210 mg Q2W treatment, who were subsequently withdrawn from brodalumab and were then eligible for retreatment with brodalumab achieved PASI 75 within 6 weeks of initiation of brodalumab retreatment (Figure 5a). Of patients who achieved PASI 75, 90 and 100 at week 12, 84% (27 of 32), 90% (27 of 30), and 95% (20 of 21) achieved PASI 100 24 weeks after initiation of retreatment, respectively (Figure 5c). During retreatment, most patients experienced the level of response achieved with initial treatment; of PASI 75, PASI 90 and PASI 100 responders at week 12, 100% (32 of 32), 97% (29 of 30) and 95% (20 of 21) achieved PASI 75, PASI 90 and PASI 100 again after 24 weeks of retreatment, respectively.

Safety

Among patients who received any dose of brodalumab during AMAGINE-1 and its long-term extension, TEAEs occurred at an exposure-adjusted event rate of 255·8 per 100 patient-years (Table 3). Common TEAEs included headache (7·8 per 100 patient-years), arthralgia (7·5 per 100 patient-years) and diarrhoea (3·4 per 100 patient-years). Serious TEAEs occurred at a rate of 9·1 per 100 patient-years (Table 4). Myocardial infarction (0·4 per 100 patient-years), appendicitis (0·3 per 100 patient-years) and cellulitis (0·3 per 100 patient-years) were the most common serious TEAEs.

Gastrointestinal TEAEs occurring at an exposure-adjusted event rate of ≥ 1 per 100 patient-years included diarrhoea (3·4 per 100 patient-years), nausea (2·5 per 100 patient-

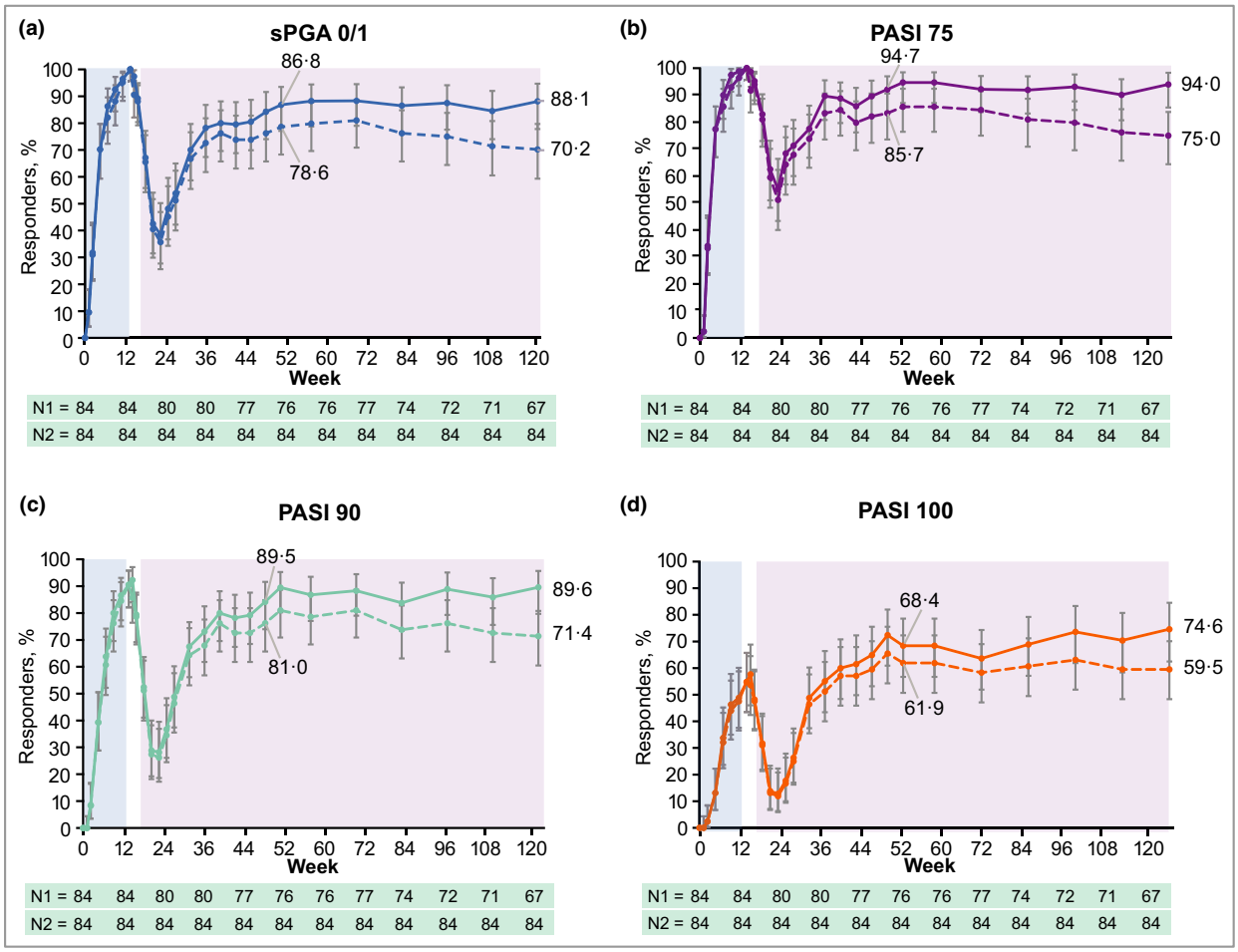

Figure 3 (a) sPGA 0/1, (b) PASI 75, (c) PASI 90 and (d) PASI 100 response rates through week 120 in patients who achieved sPGA 0/1 at week 12 and switched from brodalumab 210 mg Q2W to placebo at week 12 (n = 84). Solid lines indicate observed data analyses and broken lines indicate NRI analyses. Error bars show the 95% confidence interval. Blue background shading indicates the time period when patients were receiving brodalumab 210 mg Q2W (baseline to week 12), white background indicates the time period when patients were receiving placebo (week 12 to week 16) and purple background shading indicates the time period when patients could qualify for retreatment (week 16 to week 120). N1, number of patients with a valid measurement at the specified week (observed data analysis); N2, number of patients with a valid measurement at the specified week (NRI analysis); NRI, nonresponder imputation; PASI, Psoriasis Area and Severity Index; PASI 75, 75% improvement in PASI; PASI 90, 90% improvement in PASI; PASI 100, 100% improvement in PASI; Q2W, every 2 weeks; sPGA 0/1, static Physician's Global Assessment score of 0 or 1.

years), toothache (1·7 per 100 patient-years), dyspepsia (1·6 per 100 patient-years), gastro-oesophageal reflux disease (1·2 per 100 patient-years), vomiting (1·1 per 100 patient-years) and upper abdominal pain (1·0 per 100 patient-years). Across all years, one patient experienced inflammatory bowel disease (preferred term); no patients experienced ulcerative colitis or Crohn disease (preferred terms).

Across all years, 41 patients experienced an AE in the system organ class capturing benign, malignant and unspecified neoplasms (including cysts and polyps), most commonly skin papilloma (exposure-adjusted event rate 0·7 per 100 patient-years), basal cell carcinoma (0·4 per 100 patient-years), fibroma (0·2 per 100 patient-years), lipoma (0·2 per 100 patient-years) and melanocytic naevus (0·2 per 100 patient-years).

Two patients rerandomized to placebo in the planned withdrawal period had positive brodalumab-binding antibodies at week 24; none were positive for brodalumab-neutralizing antibodies. Technical issues concerning sensitivity of antibody detection are discussed in File S1 (see Supporting Information).

Five patients experienced fatal TEAEs across all study years in AMAGINE-1, including one completed suicide. This patient received brodalumab 210 mg Q2W; onset occurred 58 days after the last active dose and 329 days after the first dose of brodalumab. There was also one patient receiving brodalumab 210 mg Q2W who had a fatal intentional overdose reported as suicide that was later adjudicated as indeterminate; onset occurred 14 days after the last active dose and 97 days after the first dose.[22] On the basis of follow-up observation time-adjusted analysis across clinical studies of brodalumab in psoriasis, completed suicides were reported at a rate of 0·04 per 100 patient-years. There was no evidence of increased risk of

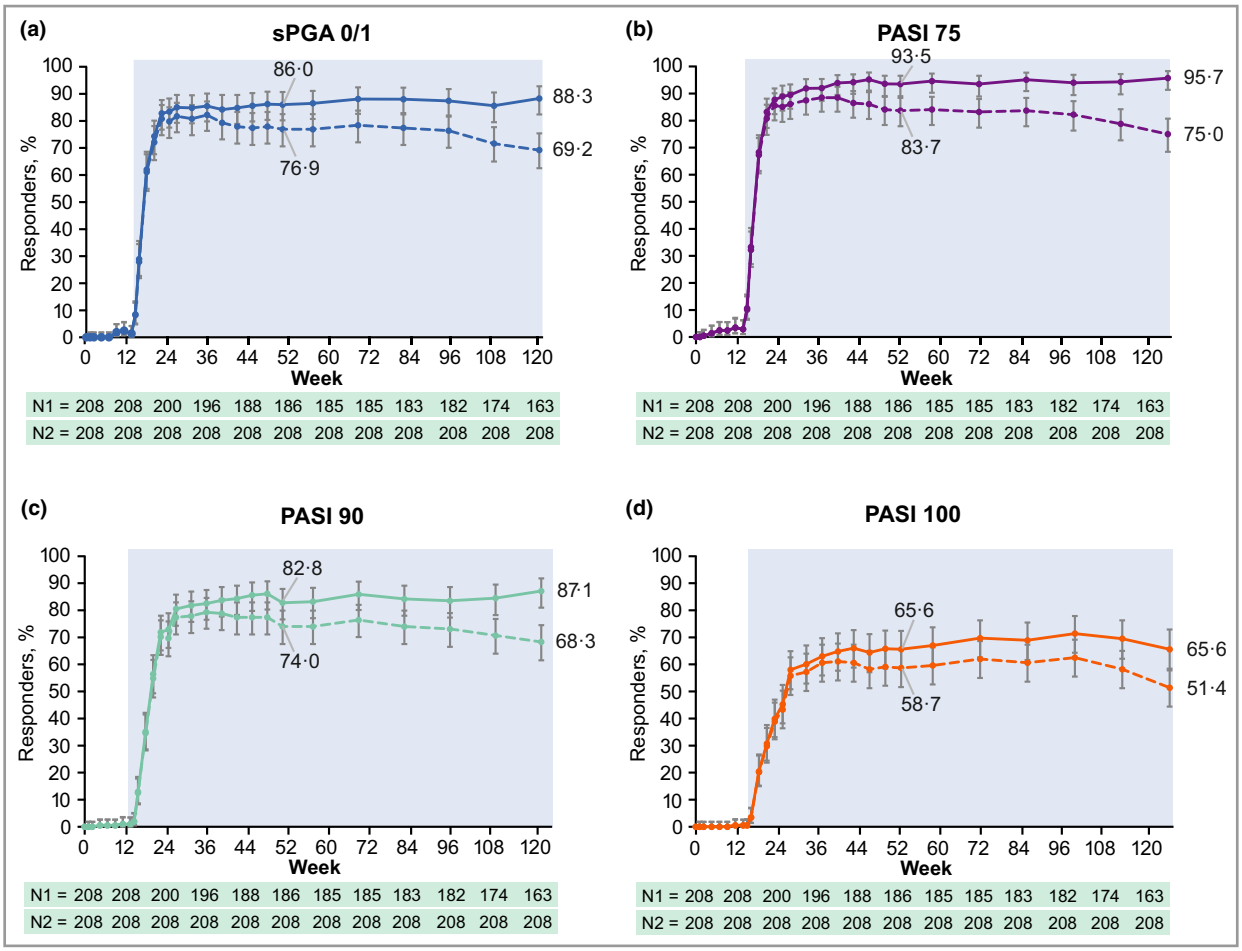

Figure 4 (a) sPGA 0/1, (b) PASI 75, (c) PASI 90 and (d) PASI 100 response rates through week 120 in patients who switched from placebo to brodalumab 210 mg Q2W at week 12 (n = 208). Solid lines indicate observed data analyses and broken lines indicate NRI analyses. Error bars show the 95% confidence interval. White background indicates the time period when patients were receiving placebo (baseline to week 12) and blue background shading indicates the time period when patients were receiving brodalumab 210 mg Q2W (week 12 to week 120). N1, number of patients with a valid measurement at the specified week (observed data analysis); N2, number of patients with a valid measurement at the specified week (NRI analysis); NRI, nonresponder imputation; PASI, Psoriasis Area and Severity Index; PASI 75, 75% improvement in PASI; PASI 90, 90% improvement in PASI; PASI 100, 100% improvement in PASI; Q2W, every 2 weeks; sPGA 0/1, static Physician's Global Assessment score of 0 or 1.

suicidal ideation and behaviour with increasing patient-years of brodalumab exposure.

Discussion

In AMAGINE-1, 75·7% of patients with moderate-to-severe psoriasis treated with brodalumab 210 mg Q2W achieved sPGA 0/1 at week 12. PASI 75 response was 83·3% and PASI 100 response was 41·9% at week 12.[17] In the long-term extension, skin clearance efficacy was maintained through week 120 among patients who achieved sPGA 0/1 at week 12 who continued on brodalumab 210 mg Q2W. Of these 83 patients, 92% achieved sPGA 0/1 at week 52 and 86% achieved sPGA 0/1 at week 120. PASI 75 response was achieved by 99% of patients at week 52 and 96% of patients at week 120, and PASI 100 response was achieved by 74% of patients at week 52 and 74% of patients at week 120. Similarly, skin clearance was achieved within 12 weeks of active treatment and maintained through week 120 among 208 patients who switched from placebo to brodalumab 210 mg Q2W at week 12. Although cross-trial comparisons are complicated by variations in parameters, similar observations were seen in the long-term analysis of brodalumab in the open-label extension period of AMAGINE-2, with 84·4%, 75·6% and 61·1% of patients who received brodalumab 210 mg Q2W achieving PASI 75, PASI 90 and PASI 100 at week 120 (observed data analysis), respectively.[23] Long-term rates of skin clearance efficacy in this study were greater than rates observed at similar timepoints in studies of ustekinumab and secukinumab, which included patients with initial response to therapy (e.g. PASI 75 at week 12) using matching statistical analyses.[10,12] Real-world studies are needed to provide a full characterization of the long-term efficacy and safety of these treatments.

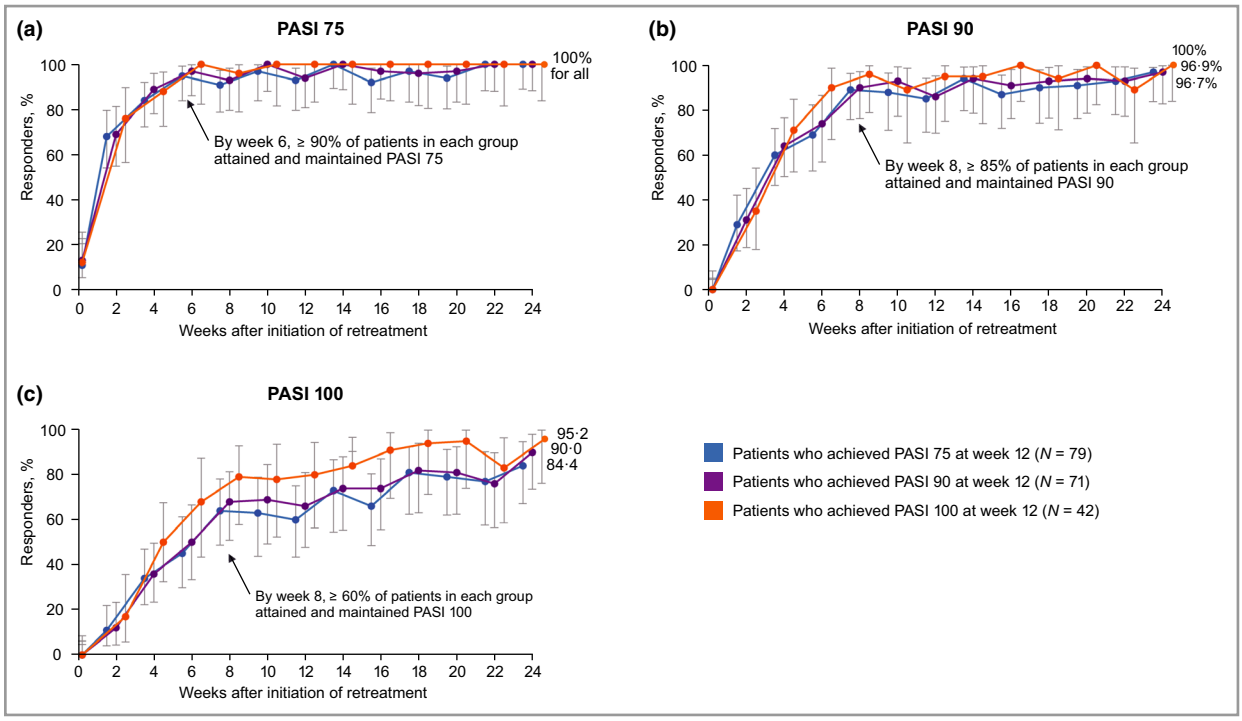

Figure 5 (a) PASI 75, (b) PASI 90 and (c) PASI 100 following retreatment with brodalumab 210 mg Q2W. Observed data analysis. Error bars show the 95% confidence interval. N, number of patients who entered the retreatment phase; PASI, Psoriasis Area and Severity Index; PASI 75, 75% improvement in PASI; PASI 90, 90% improvement in PASI; PASI 100, 100% improvement in PASI; Q2W, every 2 weeks.

Table 3 Exposure-adjusted rates of treatment-emergent adverse events (TEAEs) by year[a]

Preferred term	Year 1 (n = 648; 594·6 PYs)	Year 2 (n = 550; 526·3 PYs)	Year 3 (n = 501; 217·9 PYs)	All years (n = 648; 1338·8 PYs)
All TEAEs	2156 (362·6)	935 (177·7)	334 (153·3)	3425 (255·8)
Arthralgia	69 (11·6)	22 (4·2)	9 (4·1)	100 (7·5)
Headache	84 (14·1)	17 (3·2)	3 (1·4)	104 (7·8)
Fatigue	11 (1·8)	0 (0)	0 (0)	11 (0·8)
Diarrhoea	33 (5·5)	12 (2·3)	1 (0·5)	46 (3·4)
Oropharyngeal pain	18 (3·0)	10 (1·9)	1 (0·5)	29 (2·2)
Nausea	33 (5·5)	1 (0·2)	0 (0)	34 (2·5)
Myalgia	15 (2·5)	2 (0·4)	0 (0)	17 (1·3)
Injection site reactions	19 (3·2)	4 (0·8)	1 (0·5)	24 (1·8)
Influenza	16 (2·7)	12 (2·3)	4 (1·8)	32 (2·4)
Neutropenia	7 (1·2)	0 (0)	0 (0)	7 (0·5)
Tinea infections	12 (2·0)	6 (1·1)	2 (0·9)	20 (1·5)
Conjunctivitis	18 (3·0)	3 (0·6)	1 (0·5)	22 (1·6)
Candida infections	16 (2·7)	14 (2·7)	3 (1·4)	33 (2·5)

PYs, total patient-years of exposure. Values are the number of adverse events [exposure-adjusted event rate per 100 PYs (number of adverse events/PY × 100)]. [a]Multiple occurrences of the same event for a patient are counted as multiple events. Rates are calculated from first dose of brodalumab through end of study.

Importantly, this study analysed 84 patients who achieved sPGA 0/1 at 12 weeks and were then switched to placebo and qualified for retreatment with brodalumab 210 mg Q2W once the disease returned. Skin clearance deteriorated within 12 weeks, with return of disease occurring after a mean ± duration of 74·7 ± SD 50·5 days following withdrawal from brodalumab, and was rapidly restored after retreatment (Figure 3). Overall, 88% of these patients achieved sPGA 0/1 at week 120 and 94% achieved PASI 75. Among patients who achieved PASI 75 during initial treatment, 95% achieved PASI 75 again after 6 weeks of retreatment and 84% achieved PASI 100 after 24 weeks of retreatment (Figure 5). A similar pattern of findings was reported by Kimball *et al.* in a study of ustekinumab treatment for psoriasis; ~50·0% of patients

Table 4 Exposure-adjusted rates of serious treatment-emergent adverse events (TEAEs) by year[a]

Preferred term	Year 1 (n = 648; 594·6 PYs)	Year 2 (n = 550; 526·3 PYs)	Year 3 (n = 501; 217·9 PYs)	All years (n = 648; 1338·8 PYs)
All serious TEAEs	56 (9·4)	48 (9·1)	18 (8·3)	122 (9·1)
Serious TEAEs occurring in more than two patients				
Myocardial infarction	2 (0·3)	3 (0·6)	0 (0·0)	5 (0·4)
Appendicitis	1 (0·2)	3 (0·6)	0 (0·0)	4 (0·3)
Cellulitis	3 (0·5)	1 (0·2)	0 (0·0)	4 (0·3)
Arthritis	0 (0·0)	2 (0·4)	1 (0·5)	3 (0·2)
Inguinal hernia	1 (0·2)	1 (0·2)	1 (0·5)	3 (0·2)
Intervertebral disc protrusion	3 (0·5)	0 (0·0)	0 (0·0)	3 (0·2)
Pneumonia	1 (0·2)	1 (0·2)	1 (0·5)	3 (0·2)
Suicidal ideation	0 (0·0)	3 (0·6)	0 (0·0)	3 (0·2)
Urinary tract infection	1 (0·2)	2 (0·4)	0 (0·0)	3 (0·2)

PYs, total patient-years of exposure. Values are the number of adverse events [exposure-adjusted event rate per 100 patient-years (number of adverse events/PY × 100)]. [a]Multiple occurrences of the same event for a patient are counted as multiple events. Rates are calculated from first dose of brodalumab through end of study.

experienced loss of PASI 75 response within ~16 weeks of treatment withdrawal and > 80·0% regained PASI 75 response within 12 weeks of ustekinumab retreatment.[24] Similar studies evaluating response to withdrawal and retreatment of secukinumab and ixekizumab reported that 93·8% (multiple imputation analysis) and 87·0% (observed data analysis) of patients recaptured their PASI 75 response following 16 weeks and 24 weeks of retreatment, respectively.[9,25]

Immunogenicity is one of several factors that may contribute to a loss of clinical response with biological therapies.[21] Prior studies of biological therapies for psoriasis have shown decreasing response rates over time, which may be related to the emergence of neutralizing antidrug antibodies.[1] In this analysis, two patients rerandomized to placebo had brodalumab-binding antibodies at week 24, whereas none had brodalumab-neutralizing antibodies. In observed data analyses in this study, response rates generally did not decrease between week 52 and week 120, which may be related to the lack of neutralizing antidrug antibodies. This low incidence of immunogenicity observed with brodalumab may have contributed to the high rate of recapture of efficacy observed upon retreatment with brodalumab 210 mg Q2W. In addition to antidrug antibodies, other reasons for loss of response include inability to tolerate medication, nonadherence, or changes in disease severity.[1]

No new safety signals emerged during the long-term analysis. Across all study years, one patient experienced inflammatory bowel disease (preferred term) and none experienced ulcerative colitis or Crohn disease (preferred terms), which are conditions associated with cutaneous manifestations including psoriasis.[26] There were five fatalities among patients who received brodalumab 210 mg Q2W, including one oesophageal varices haemorrhage, one cerebrovascular incident, one sudden death, one completed suicide and one intentional overdose (which was later adjudicated as indeterminate). The overall exposure-adjusted rate of AEs associated with brodalumab throughout the entire study period (255·8 events per 100 patient-years) was similar to that observed in long-term ustekinumab studies, where ustekinumab was associated with 305·9 events per 100 patient-years after 3 years.[27] Common AEs associated with brodalumab, including headache and arthralgia, were similar to those observed in long-term studies evaluating ustekinumab and secukinumab.[10,27]

Potential limitations of this study include the relatively small numbers of patients in the groups originally treated with brodalumab 210 mg Q2W. However, despite this, baseline characteristics suggest that this cohort adequately reflected the general psoriasis population receiving therapy with biologics. In addition, analyses in patients initially treated with brodalumab 210 mg Q2W included only patients who achieved sPGA 0/1 at week 12, which may limit general conclusions regarding long-term efficacy and response to retreatment. A further limitation is that our analyses extend only to 120 weeks of treatment; longer follow-up (e.g. 5 years) of both efficacy and safety outcomes is desirable because agents 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.[28]

Overall, our findings support the use of brodalumab for continuous long-term treatment of patients with moderate-to-severe psoriasis. We also demonstrated the strong potential for recovery of response among patients who initially responded to brodalumab but subsequently had a lapse in treatment. These results are relevant to real-life clinical practice, because it is relatively common for patients to stop and restart their medications for a number of different reasons.

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Supporting Information

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

File S1 Details and sensitivity of antibody assays.

Figure S1 (a) Static Physician's Global Assessment 0/1, (b) 75% improvement in Psoriasis Area and Severity Index (PASI 75), (c) PASI 90, and (d) PASI 100 response rates through week 120 in patients who achieved sPGA 0/1 at week 12 and received continuous brodalumab 210 mg every two weeks (Q2W) (n = 83).

Figure S2 (a) Static Physician's Global Assessment 0/1, (b) 75% improvement in Psoriasis Area and Severity Index (PASI 75), (c) PASI 90, and (d) PASI 100 response rates through week 120 in patients who achieved sPGA 0/1 at week 12 and switched from brodalumab 210 mg every two weeks (Q2W) to placebo at week 12 (n = 84).

Figure S3 (a) Static Physician's Global Assessment 0/1, (b) 75% improvement in Psoriasis Area and Severity Index (PASI

75), (c) PASI 90, and (d) PASI 100 response rates through week 120 in patients who switched from placebo to brodalumab 210 mg every two weeks (Q2W) at week 12 (n = 208).
Powerpoint S1 Journal Club Slide Set.

Appendix

Conflicts of interest: K.P. has served as a consultant, scientific officer or member of a speaker's bureau, advisory board or steering committee for or received research grants or honoraria from AbbVie, Akesis Pharmaceuticals, Akros, Allergan, Alza Corporation, Amgen, Anacor Pharmaceuticals, Artax Biopharma, Astellas Pharma, AstraZeneca, Bausch Health, Baxter, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Can-Fite BioPharma, Celgene Corporation, Celtic Pharma, Cipher Pharmaceuticals, Dermira, Dow Pharma, Eli Lilly and Company, Ferring Pharmaceuticals, Formycon AG, Forward Pharma A/S, Fujisawa Pharmaceuticals Co, Funxional Therapeutics, Galderma SA, Genentech, Genexion SA, Genzyme Corporation, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Kyowa Hakko Kirin Co, LEO Pharma, MedImmune, Meiji Seika Pharma Co, Merck & Co (MSD), Merck Serono, Mitsubishi Tanabe Pharma, Mylan, Novartis Pharmaceuticals Corporation, NovImmune SA, Pan-Genetics Pharmaceutical Corporation, Pfizer, Regeneron Pharmaceuticals, Roche, Sanofi-Aventis US LLC, Stiefel Laboratories, Takeda Pharmaceuticals, UCB and Vertex Pharmaceuticals. A.M. has received compensation from or served as an investigator, consultant, advisory board member, or speaker for AbbVie, Allergan, Amgen, Anacor Pharmaceuticals, Boehringer Ingelheim, Celgene Corporation, Dermira, Eli Lilly and Company, Galderma, Janssen Biotech, LEO Pharma, Merck & Co, Neothetics, Novartis AG, Pfizer, Regeneron Pharmaceuticals, Symbio/Maruho, Vitae and Xenoport. C.L. has served as an investigator, consultant, advisory board member, or speaker for AbbVie, Actavis, Allergan, Amgen, Boehringer Ingelheim, Celgene Corporation, Cellceutix, Coherus, Corrona, Dermira, Eli Lilly and Company, Galderma, Glenmark, Janssen Pharmaceuticals, LEO Pharma, Merck & Co, Novartis, Novella, Pfizer, Sandoz, Sienna, Stiefel Laboratories, Sun Pharma, UCB, Vitae and Wyeth. J.S. has received compensation from or served as an investigator, consultant, advisory board member, or speaker for AbbVie, Amgen, Bausch Health, Boehringer Ingelheim, Celgene Corporation, Dermira, Eli Lilly and Company, Galderma, GlaxoSmithKline, Janssen Pharmaceuticals, Kyowa Kirin, LEO Pharma, Medimmune, Menlo, Merck & Co, Novan, Novartis, Pfizer, Roche, Regeneron, Sun Pharma, Sanofi Genzyme, Cassiopeia and UCB. S.W. has received compensation from or served as a consultant, advisory board member or speaker for AbbVie, Almirall, Amgen, Boehringer Ingelheim, CivaTech Oncology, Dermasenor, Dermira, DermTech, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceuticals, Ortho Dermatologics, Scynexis and Stiefel Laboratories. R.P. is an employee of Bausch Health US, LLC and may hold stock and/or stock options in its parent company. A.J. is an employee of Bausch Health US, LLC and may hold stock and/or stock options in its parent company.