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## ORIGINAL ARTICLE

# Long-term efficacy and safety of brodalumab in moderate-to-severe plaque psoriasis: a post hoc pooled analysis of AMAGINE-2 and -3

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## Abstract

**Background** Brodalumab is a monoclonal antibody that blocks multiple interleukin (IL)-17 family cytokines by binding to the shared A subunit of the IL-17 receptor. In Phase 3 trials, brodalumab provided high levels of skin clearance through 52 weeks in patients with moderate-to-severe psoriasis and was generally well tolerated.

**Objectives** To assess efficacy response rates and safety outcomes through 120 weeks for patients with moderate-to-severe psoriasis who received brodalumab.

**Methods** Safety and efficacy data were pooled for patients from AMAGINE-2 and -3 who received continuous brodalumab 210 mg every 2 weeks, or brodalumab 210 mg every 2 weeks after receiving either brodalumab 140 mg or placebo through Week 12. Efficacy data are presented using observed data, non-responder imputation (NRI) and a combination of NRI and missing at random assumption to account for missing data. Absolute PASI scores are presented using mixed-effect model repeated measure modelling and multiple imputation.

**Results** Based on observed data at Week 120, 86% of the continuous brodalumab 210 mg group achieved PASI 90 and 74% achieved PASI 100. At Week 12, 58% of this group achieved absolute PASI  $\leq 1$ ; this proportion increased to approximately 80% at Week 52 and persisted through Week 120. Among patients receiving continuous brodalumab 210 mg, median duration of brodalumab exposure was 747 days and the overall exposure-adjusted event rate of treatment emergent adverse events per 100 patient-years was 329. Safety through 120 weeks was comparable to the results of the primary AMAGINE-2 and -3 studies. Patients who switched to brodalumab 210 mg after receiving either brodalumab 140 mg or placebo through Week 12 showed similar skin clearance and safety profiles.

**Conclusions** Brodalumab treatment was well tolerated and resulted in high levels of skin clearance that were rapidly achieved and maintained through Week 120, supporting its long-term efficacy and safety profile.

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## Conflicts of interest

Kristian Reich has served as advisor, paid speaker for and/or participated in clinical trials sponsored by Abbvie, Ammirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Forward Pharma, Gilead, Galderma, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Lilly, Medac, Novartis, Ocean Pharma, Pfizer, Sanofi, and UCB, and is co-founder of Moonlake Immunotherapeutics. Lars Iversen has served as a consultant, paid speaker for and/or participated in clinical trials sponsored by AbbVie, Ammirall, Amgen, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen-Cilag, Kyowa, LEO Pharma, Novartis, Pfizer, Regranion, Samsung-Bioepis, UCB and UNION Therapeutics. Luis Puig has received consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Ammirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Gebro, Janssen, JS BIOCAD, LEO Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanofi and UCB. Jo Lambert has received unrestricted grants from AbbVie, Ammirall, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis and UCB, has acted as a speaker

for AbbVie, Ammirall, BMS, Janssen-Cilag, Pfizer and UCB and has been consultant for AbbVie, BMS, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Novartis and UCB. Ulrich Mrowietz has served as an advisor for, received speaker's hono-  
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Pharma A/S.

### Introduction

Psoriasis is a chronic, immune-mediated disease impacting approximately 125 million people worldwide.<sup>1</sup> Psoriasis is asso-  
ciated with other diseases, including psoriatic arthritis, cardio-  
vascular disease and psychiatric disorders, and has been shown  
to negatively impact patient quality of life (QoL).<sup>1</sup>

Members of the interleukin (IL)-17 family of proinflamma-  
tory cytokines are upregulated in psoriatic skin relative to  
healthy skin and are thought to play a central role in driving  
psoriasis pathogenesis.<sup>2</sup> Brodalumab is a monoclonal antibody  
that blocks multiple IL-17 family cytokines by binding to the  
shared A subunit of the IL-17 receptor. Brodalumab treatment  
normalized gene expression in psoriatic lesions to non-lesional  
levels.<sup>3</sup> In the three AMAGINE Phase 3 trials, brodalumab pro-  
vided high levels of skin clearance for up to 52 weeks in patients  
with moderate-to-severe psoriasis.<sup>4,5</sup> In a recent integrated anal-  
ysis of data from AMAGINE-2 and -3, patients who received  
the approved dose of brodalumab (210 mg every 2 weeks) over  
52 weeks rapidly achieved high levels of complete and sustained  
skin clearance, and showed a greater overall cumulative treat-  
ment benefit than patients who received ustekinumab.<sup>6</sup> In a  
long-term, open-label extension study, which included patients  
with moderate-to-severe psoriasis who completed a 12-week  
Phase 2 dose ranging study, high levels of skin clearance were  
maintained and QoL was improved throughout 5 years of bro-  
dalumab treatment.<sup>7</sup>

Although biologics generally demonstrate high short-term  
efficacy and good long-term tolerability, several studies suggest  
that many biologics lose efficacy over time.<sup>8</sup> The rate of efficacy  
loss over time can vary based on patient sex, body mass index  
(BMI), previous biologic use and between biologics, although  
the reasons for this are not clear.<sup>8,9</sup> Sustained treatment efficacy,  
particularly complete skin clearance, is important and may have  
meaningful positive impact on patient QoL.<sup>10</sup> Several studies  
suggest a positive association between improvement in psoriasis

area severity index (PASI) and health-related QoL, including  
meaningful improvement in QoL scores in patients achieving  
100% improvement of PASI over baseline (PASI 100) relative to  
those achieving PASI 90.<sup>6,10,11</sup>

There is a need for biologics with sustained high efficacy over  
time. Here, we used pooled data from the Phase 3 AMAGINE-2  
and -3 studies to assess response rates and safety outcomes  
through 120 weeks for patients with moderate-to-severe psoria-  
sis who received brodalumab 210 mg every 2 weeks.

### Materials and methods

#### Study design

Details of the AMAGINE-2 (NCT01708603) and AMAGINE-3  
(NCT01708629) studies have been described previously.<sup>4</sup> Briefly,  
AMAGINE-2 and -3 included a 12-week induction phase, fol-  
lowed by a 40-week maintenance phase and a long-term exten-  
sion (Fig. S1). All patients provided written informed consent.  
Study protocols were approved by the institutional review board  
at each participating centre. All study sites maintained compli-  
ance with the Health Insurance Portability and Accountability  
Act or appropriate regional regulations. AMAGINE-2 and -3  
were terminated during the long-term extension phase by the  
sponsor (Amgen; 22 May 2015).

The current efficacy and safety analyses include patients ran-  
domized to receive the approved dose of brodalumab (210 mg  
every 2 weeks). These patients fall into three groups, as  
highlighted in Fig. S1: those who received continuous brodal-  
umab 210 mg every 2 weeks from Week 0 (referred to as the  
'210 mg Constant' group), those who switched to brodalumab  
210 mg every 2 weeks after receiving brodalumab 140 mg  
through Week 12 (referred to as the '140 mg Switch' group) and  
those who switched to brodalumab 210 mg every 2 weeks after  
receiving placebo through Week 12 (referred to as the 'Placebo  
Switch' group).

### Efficacy and safety endpoints

Disease activity was assessed using PASI. Absolute PASI (score 0 to 72) was calculated as a combined score for head, arms, trunk and legs; assessments were made at least once every 2–4 weeks. Safety was assessed by monitoring treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) and was summarized by treatment group. Safety data are reported as number of events per 100 subject-years for subjects receiving the actual treatment over time.

### Statistical analysis

The proportion of patients achieving PASI 75, PASI 90 and PASI 100 at given timepoints through 120 weeks was determined. Results from the long-term extension phase are presented using observed data and two different imputation methods to account for missing data. Observed data analysis includes data for patients with a valid measurement at the indicated timepoint, without any adjustment for missing data. The non-responder imputation (NRI) method imputed all patients with missing data, as well as those receiving rescue medication, as non-responders at the indicated timepoint. However, as the trials were stopped prematurely by the sponsor, it may be unfair to assume that unobserved outcomes are uniformly non-responders.

When the probability of missingness is independent of the unobserved data after conditioning on observed data, the mechanism is said to be missing at random (MAR). Appropriate analyses that assume MAR include extensions of generalized estimating equations (GEEs) model. For these analyses (referred to as NRI/MAR), patients with missing data and patients eligible for rescue treatment or withdrawing prior to study termination were treated as non-responders throughout the trial. If patients had missing data, were withdrawn, or were eligible for rescue treatment after the date of study termination, their data were imputed using the MAR method utilizing a GEE model, with a logit link function, unstructured working correlation matrix and with treatment group, total body weight group ( $\leq 100$  kg,  $>100$  kg), prior biologic treatment (yes, no), geographic region, baseline PASI score and study (AMAGINE-2 vs -3) as fixed effects.

Additionally, absolute PASI scores were analysed using mixed-effect model repeated measure (MMRM) modelling with and without multiple imputation (MI) at given timepoints through 120 weeks. The MMRM model used fixed terms for baseline PASI score, total body weight group ( $\leq 100$  kg,  $>100$  kg), geographic region, prior biologic treatment (yes, no), treatment group and a treatment group by visit interaction. A random effect for subject with an autoregressive AR(1) correlation structure was also included.

The MI approach used a pattern mixture model where missing data was imputed within the treatment group. This was done separately for two subgroups: patients who fulfilled the rescue

criterion and those who did not fulfil the rescue criterion. This was done as per the following:

- Intermittent missing values were imputed in each group using a Markov Chain Monte Carlo method to obtain a monotone missing data pattern, and five copies of the dataset were generated.
- For each of the five copies of the dataset, an ANCOVA model was fitted to the absolute PASI value at Week 1 in each treatment group. The model included effect of baseline PASI score as a covariate and weight group ( $\leq 100$  kg,  $>100$  kg), geographic region and prior biologic treatment (yes, no) as factors.
- Missing data at other subsequent weeks were imputed similarly including the data from previous weeks.
- For each of the five imputed datasets, the absolute PASI was analysed using the MMRM model described above.

The proportion of patients occupying given PASI score categories over time was determined. Patients receiving rescue therapy are not included in this calculation.

Following the early termination of the studies by the sponsor during the long-term extension phase, there was an increase in discontinuations and therefore an increase in missing data beginning around Week 96 (Table S1). In the 210 mg Constant group, 61% of the participants had missing data at Week 120, which was adjusted to 19% missing data by applying NRI/MAR imputation for statistical analysis. Therefore, we focused our analyses on data up to Week 120.

## Results

### Baseline demographic and clinical characteristics

The demographic and clinical characteristics of patients at baseline are shown in Table 1. Patients randomized to the 210 mg Constant group had similar characteristics to those assigned to the 140 mg Switch or Placebo Switch groups (Table 1). The median duration of exposure in patients in the 210 mg Constant, 140 mg Switch and Placebo Switch groups were 2.05, 2.03 and 2.08 years, respectively (Table 2).

### Efficacy analyses

**Improvement in psoriasis area severity index over baseline** Assessment of improvement in PASI over baseline showed that patients in the 210 mg Constant group had treatment response rates that rapidly increased through the induction period and were largely stable once they reached their peak (Fig. 1a,b). Based on analysis of observed data, 96% of patients in the 210 mg Constant group achieved PASI 90 and 77% achieved PASI 100 at Week 52 (Fig. 1a,b). These high response rates were largely maintained through to Week 120, when 86% of patients



**Table 1** Baseline demographic and clinical characteristics (pooled data by treatment arm from the AMAGINE-2 and -3 trials)

	<b>210 mg Constant (N = 339)</b>	<b>140 mg Switch (N = 337)</b>	<b>Placebo Switch (N = 595)</b>
Age (years) – mean ± SD	44.5 ± 13.4	44.0 ± 13.1	44.0 ± 12.7
Sex – n (%)			
Male	230 (67.8)	222 (65.9)	406 (68.2)
Female	109 (32.2)	115 (34.1)	189 (31.8)
Ethnicity – n (%)			
Hispanic or Latino	40 (11.8)	37 (11.0)	62 (10.4)
Not Hispanic or Latino	299 (88.2)	300 (89.0)	533 (89.6)
Race – n (%)			
Asian	7 (2.1)	12 (3.6)	21 (3.5)
Black (or African American)	10 (2.9)	12 (3.6)	19 (3.2)
White	308 (90.9)	308 (91.4)	540 (90.8)
BMI (kg/m <sup>2</sup> ) – mean ± SD	30.22 ± 7.48	30.40 ± 7.18	30.22 ± 6.88
Psoriatic arthritis – n (%)			
No	260 (76.7)	266 (78.9)	492 (82.7)
Yes	79 (23.3)	71 (21.1)	103 (17.3)
Disease duration of psoriasis (years) – mean ± SD	17.3 ± 11.7	17.0 ± 11.1	17.8 ± 12.1
PASI – mean ± SD	20.42 ± 7.88	19.84 ± 7.80	20.08 ± 8.32
BSA involvement (%) – mean ± SD	27.02 ± 16.17	26.92 ± 17.23	27.68 ± 17.13
sPGA – n (%)			
3	194 (57.2)	215 (63.8)	349 (58.7)
4	129 (38.1)	110 (32.6)	217 (36.5)
5	16 (4.7)	12 (3.6)	29 (4.9)
Prior treatment – n (%)			
Biologics	95 (28.0)	86 (25.5)	154 (25.9)
Other systemic†	194 (57.2)	194 (57.6)	329 (55.3)

BMI, body mass index; BSA, body surface area; n, number of patients; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician's Global Assessment.

†Including: methotrexate, cyclosporine, acitretin, apremilast, folic acid, and hydroxyzine.

achieved PASI 90 and 74% of patients achieved PASI 100 (Fig. 1a,b).

However, response rates from observed data should be interpreted with caution due to the high numbers of missing data. Using either NRI or NRI/MAR imputation methods to account for missing data showed a lower percentage of patients achieving PASI 90 and 100 compared to analysis of observed data. Response rates were largely maintained over time, with a drop off after Week 96 based on NRI analysis but maintenance of efficacy after Week 96 based on NRI/MAR analysis (Fig. 1a,b). Response rates at Week 120 were approximately 33% (NRI) and 49% (NRI/MAR) for PASI 90, and 29% (NRI) and 40% (NRI/MAR) for PASI 100.

Patients in the 140 mg Switch group (Fig. 1c,d) had lower response rates at Week 12 compared to those in the 210 mg Constant group (Fig. 1a,b) but reached similar response levels by Week 20 (as observed). Both groups maintained comparable high response rates through to Week 120 (Fig. 1). Response rates at Week 120 for the 140 mg Switch group were 86% (as observed), 29% (NRI) and 43% (NRI/MAR) for PASI 90, and

74% (as observed), 25% (NRI) and 38% (NRI/MAR) for PASI 100 (Fig. 1c,d). In both the 210 mg Constant and 140 mg Switch groups, PASI 75 was reached by approximately 95% of patients based on observed data, with reduced rates calculated using either NRI or NRI/MAR imputation methods, comparable to what was seen for PASI 90 and PASI 100 (Fig. S2).

**Absolute psoriasis area severity index** We used MMRM modelling to estimate absolute PASI scores of patients who received brodalumab 210 mg after receiving placebo, brodalumab 140 mg or brodalumab 210 mg for 12 weeks (Fig. 2a). Patients in the 210 mg Constant group showed more rapid reduction in absolute PASI during the induction phase than patients in the 140 mg Switch group (Fig. 2a). Patients in the Placebo Switch group showed rapid response after starting brodalumab 210 mg at Week 12 (Fig. 2a). All three treatment groups achieved absolute PASI < 2, and largely maintained this level of skin clearance throughout the study period (Fig. 2a).

Analysis of absolute PASI scores over time using MMRM modelling with MI (Fig. 2b) showed similar results to the

**Table 2** Summary of treatment emergent adverse events from baseline until rescue, discontinuation, or Week 120

	<b>210 mg Constant (N = 339)</b>	<b>140 mg Switch (N = 337)</b>	<b>Placebo Switch (N = 595)</b>
<b>Total Patient-years of Exposure (Median)</b>	646.0 (2.05)	625.7 (2.03)	1152.2 (2.08)
<b>All TEAEs</b>	2089 (323.4)	1877 (300.0)	3722 (323.0)
Serious	61 (9.4)	48 (7.7)	91 (7.9)
Fatal	0	0	1 (0.1)
Grade 3	87 (13.5)	85 (13.6)	133 (11.5)
Grade 4	13 (2.0)	6 (1.0)	8 (0.7)
Grade 5	0	0	1 (0.1)
Leading to discontinuation of study	13 (2.0)	6 (1.0)	10 (0.9)
Leading to discontinuation of study drug	19 (2.9)	19 (3.0)	12 (1.0)
<b>TEAEs of special interest</b>			
All infections	684 (105.9)	527 (84.2)	1145 (99.4)
Serious infections	10 (1.5)	4 (0.6)	12 (1.0)
<i>Candida</i> infections	29 (4.5)	20 (3.2)	42 (3.6)
Crohn's disease	1 (0.2)	0	0
Neutropenia	25 (3.9)	15 (2.4)	12 (1.0)
Suicidal behaviour and ideation	7 (1.1)	2 (0.3)	3 (0.3)
Adjudicated MACE	1 (0.2)	3 (0.5)	5 (0.4)
Adjudicated malignancies	7 (1.1)	5 (0.8)	8 (0.7)
SEER malignancies	4 (0.6)	1 (0.2)	3 (0.3)
Non-Melanoma Skin Cancer	3 (0.5)	4 (0.6)	5 (0.4)
Hypersensitivity	115 (17.8)	101 (16.1)	260 (22.6)
Injection Site Reactions	12 (1.9)	23 (3.7)	56 (4.9)

Data are presented as number of events (exposure-adjusted rate per 100 patient-years), unless otherwise stated.

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. The severity of adverse events was graded in accordance with CTCAE version 4.0 or 4.03. Treatment groups are defined as actual treatment. Subject-years of exposure is based on planned treatment and period definition is to be found in the statistical analysis plan. Adverse events were coded using the MedDRA version 18.1. Suicidal behaviour includes suicide attempt and complete suicide. Causality is based on investigator's assessment.

CTCAE, common terminology criteria for adverse events; TEAE, treatment-emergent adverse event; MACE, major adverse cardiac events; SEER, Surveillance, Epidemiology, and End Results.

MMRM modelling estimates without MI. The reduction in absolute PASI over the first 12 weeks was greater for patients in the 210 mg Constant group and delayed for patients in the Placebo Switch group (Fig. 2b). The absolute PASI scores achieved for all groups were not as low as the scores estimated by the MMRM method. All groups maintained an absolute PASI <5 to Week 120 (Fig. 2b).

Approximately 60% of patients in the 210 mg Constant group achieved absolute PASI scores  $\leq 1$  by Week 12 (Fig. 2c). This proportion increased to 78% at Week 52 and was largely maintained through Week 120 (Fig. 2c). Patients in the 140 mg Switch group responded more gradually, with 43% of patients achieving absolute PASI scores  $\leq 1$  at Week 12, when the switch to 210 mg occurred. By Week 52, this proportion increased to 78%, consistent with the 210 mg Constant group and was largely steady through Week 120 (Fig. 2d).

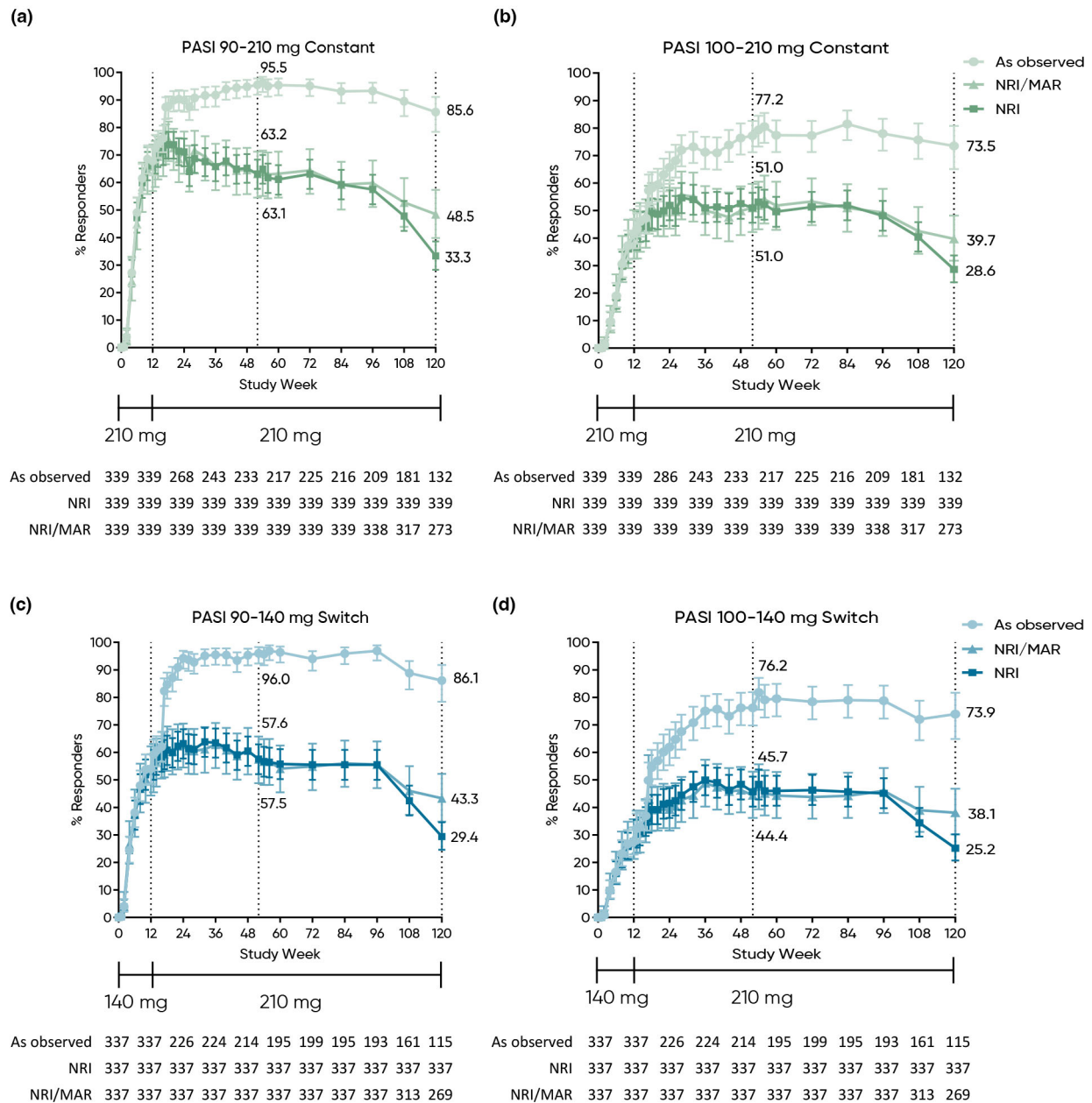
## Safety

The overall exposure-adjusted event rate of TEAEs among patients in the 210 mg Constant, 140 mg Switch and Placebo Switch groups, were 323.4, 300 and 323 events per 100 patient-years, respectively (Table 2). Rates of SAEs were 9.4, 7.7 and 7.9 events per 100 patient-years; rate of adverse events (AEs) leading to discontinuation were 2.9, 3 and 1 events per 100 patient-years (Table 2). Rates of serious infections, suicidal behaviour and ideation, major adverse cardiac events (MACE) and malignancies were  $\leq 1.5$  events per 100 patient-years and similar across treatment groups (Table 2). Exposure-adjusted rates of neutropenia among patients in the 210 mg Constant, 140 mg Switch and Placebo Switch groups were 3.9, 2.4 and 1.0 events per 100 patient-years. One event of enteritis that mapped to Crohn's disease occurred in the 210 mg Constant group; no patients who received brodalumab 210 mg experienced new-onset Crohn's disease or inflammatory bowel disease. Exposure-adjusted rates of *Candida* infections were relatively low: 4.5, 3.2 and 3.6 events per 100 patient-years among patients in the 210 mg Constant, 140 mg Switch and Placebo Switch group, respectively.

## Discussion

This study assessed the efficacy and safety of brodalumab over two years, and further supports primary results which demonstrated a treatment benefit for brodalumab 210 mg through 52 weeks in the AMAGINE-2 and -3 studies<sup>4</sup> and through 120 weeks in the AMAGINE-2 study.<sup>12</sup> High levels of skin clearance, as determined by absolute and relative PASI scores, were achieved, and largely maintained, from Week 52 through Week 120. Additionally, brodalumab was generally well tolerated for over 2 years; rates of SAEs were low and similar to those observed through Week 52 during the AMAGINE-2 and -3 trials.<sup>4</sup>

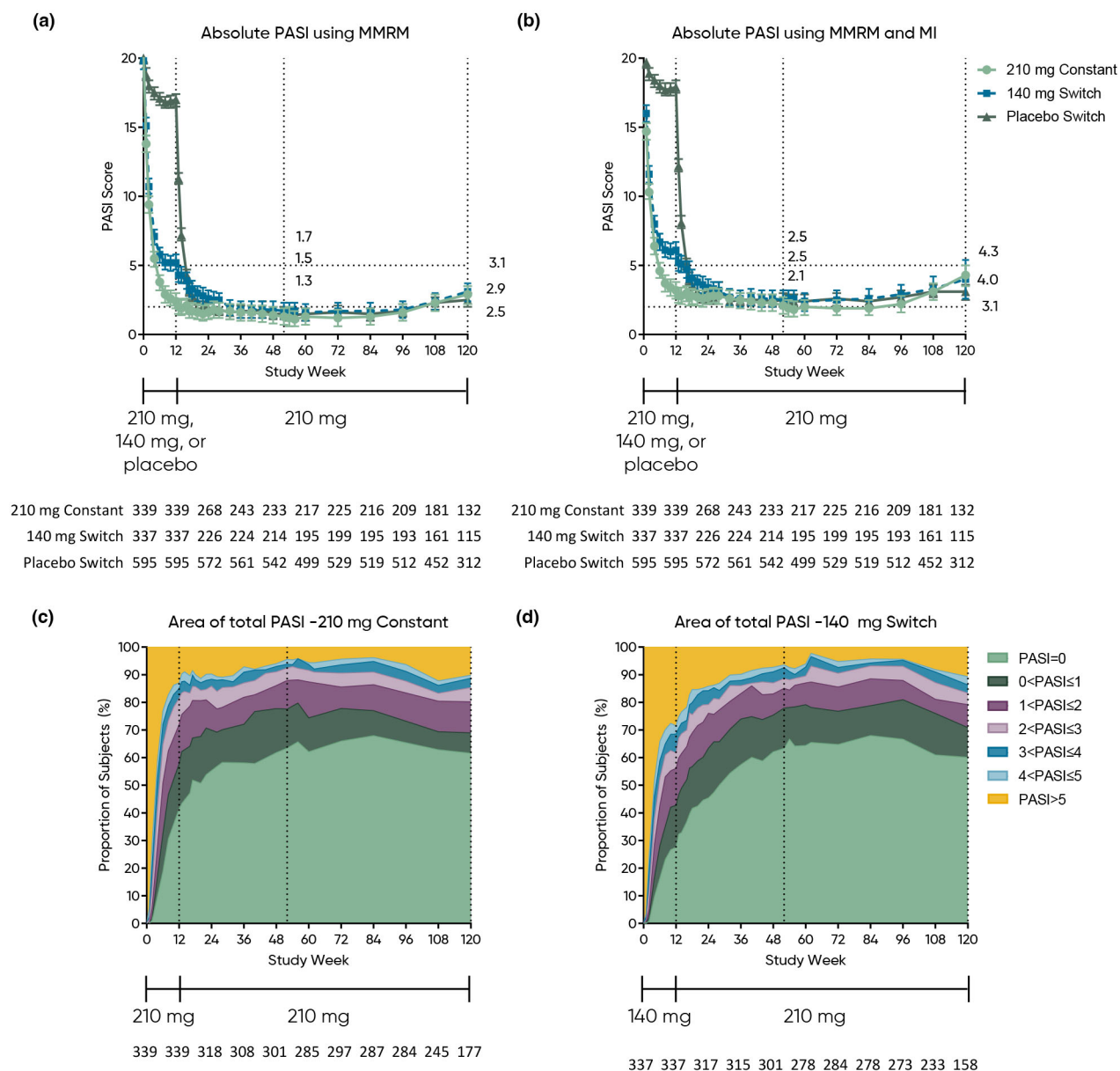
Based on observed data, 86% of patients in the 210 mg Constant group maintained PASI 90 and 74% maintained PASI 100 at Week 120. As expected, using imputation methods to account for missing data showed a lower percentage of responders compared to observed data; at Week 120, 49% of the 210 mg Constant group maintained PASI 90 and 40% maintained PASI 100 using the NRI/MAR imputation method. Rates of AEs of special interest in the 210 mg Constant group, including serious infections (1.5 per 100 patient-years), Crohn's disease (0.2 per 100



**Figure 1** Proportion of subjects achieving PASI 90 and PASI 100 through 120 weeks in brodalumab treatment groups using observed or imputed data. Rates of PASI 90 (a, c) and PASI 100 (b, d) response through Week 120 among (a, b) patients who received continuous brodalumab 210 mg every 2 weeks, or (c, d) patients who received brodalumab 210 mg every 2 weeks after brodalumab 140 mg to Week 12. Data presented are as observed, using NRI, or using NRI/MAR, as indicated. Error bars show 95% confidence intervals. Tables show the number of patients who had a valid measurement value at the specified week. PASI 90, 90% improvement in Psoriasis Area and Severity Index; PASI 100, 100% improvement Psoriasis Area and Severity Index; NRI, non-responder imputation; MAR, missing at random.

patient-years) and MACE (0.2 per 100 patient-years), were low and similar to rates in a pooled analysis of five brodalumab trials<sup>13</sup>; rates of serious infections and MACE were similar to those

observed with secukinumab.<sup>14</sup> Rates of *Candida* infections were relatively low (4.5 per 100 patient-years in the 210 mg Constant group), but slightly higher than those observed with



**Figure 2** Absolute PASI responses through 120 weeks in brodalumab treatment groups. (a, b) Absolute PASI response through Week 120 among patients who received continuous brodalumab 210 mg every 2 weeks, patients who received brodalumab 210 mg every 2 weeks after receiving brodalumab 140 mg to Week 12, or patients who received brodalumab 210 mg every 2 weeks after receiving placebo to Week 12, as indicated. Different treatment groups are presented together to highlight response patterns. Data are presented as LS means using (a) MMRM or (b) MMRM with MI. (c,d) Proportion of patients achieving indicated absolute PASI scores through Week 120 who received (c) continuous brodalumab 210 mg every 2 weeks and (d) brodalumab 210 mg every 2 weeks after receiving brodalumab 140 mg to Week 12. Error bars show 95% confidence intervals. Horizontal dashed lines indicate absolute PASI = 2 or PASI = 5. Tables show the number of patients who had a valid measurement value at the specified week. LS, least squares; PASI, Psoriasis Area and Severity Index; MMRM, mixed-effect model repeated measure; MI, multiple imputation.



secukinumab (1.3 per 100 patient-years).<sup>14</sup> Patients in the 140 mg and Placebo Switch groups showed similar skin clearance and safety profiles to those in the 210 mg Constant group.

These trials (AMAGINE-2 and -3) did not exclude patients with a history of psychiatric disorders and baseline depression data were not captured. Previous work has demonstrated a lack of evidence for a causal relationship between suicidality and brodalumab treatment.<sup>15</sup> While not the focus of these trials, rates of suicidal behaviour and ideation were rare ( $\leq 1.5$  events per 100 patient-years). The latest 2- and 3-year US Pharmacovigilance Reports show no completed suicides and only one suicide attempt in total (the sole instance occurring in an individual with a history of depression).<sup>16,17</sup>

Although relative improvement in PASI scores is commonly used in clinical trials, absolute PASI values represent a particularly relevant measure for clinical practice. Absolute PASI  $\leq 2$  has been suggested as an attainable goal for most patients with moderate-to-severe plaque psoriasis that is likely to reflect meaningful improvement in patient QoL,<sup>18</sup> and correlates with PASI 90 response.<sup>19</sup> The PASI  $\leq 2$  target was achieved by 80% of patients in the 210 mg Constant group at Week 120.

Overall patient satisfaction with existing treatment options remains modest, though patients on biologics generally report higher satisfaction levels than patients receiving oral systemic treatments, topical treatments and phototherapy.<sup>20</sup> Studies have found that treatment efficacy is the most important factor influencing patient satisfaction, which is highly correlated with adherence and resulting treatment success.<sup>20</sup> Probability of benefit, risk of AEs and duration of treatment benefit are among the most important factors impacting patient preference for biologic treatments; duration of treatment benefit was more important for patients with higher PASI scores and greater QoL impairment.<sup>20</sup>

In previous studies, loss of biologic efficacy over time was often associated with the presence of antidrug antibodies.<sup>21</sup> No patients in the AMAGINE-2 or -3 trials had neutralizing antibodies against brodalumab, and non-neutralizing anti-drug antibodies were rare (about 2% of patients through Week 52) and not associated with loss of efficacy at Week 52.<sup>4</sup> This may contribute to the sustained efficacy of brodalumab observed over the course of this study, in which, based on observed data, 74% of patients in the 210 mg Constant group achieved PASI 100 at Week 120. This finding is comparable to previous long-term extension studies, which have demonstrated achievement of PASI 100 (based on observed data analysis) in approximately 56% of patients after 108 weeks of ixekizumab,<sup>22</sup> 43% of patients after 152 weeks of secukinumab<sup>14</sup> and 26% of patients after 244 weeks of ustekinumab.<sup>23</sup>

One limitation of this analysis is the early termination of the AMAGINE-2 and -3 trials based on the sponsor's decision and the resulting missing data. Generally, observed data analysis is likely to overestimate treatment efficacy if patients drop out of a

study due to lack of efficacy. NRI analysis accounts for this case, but is likely to underestimate treatment efficacy if patients drop out for other reasons (e.g. the sponsor terminating the trial).<sup>24</sup> For this study, we highlight NRI/MAR as the most appropriate method to account for the large amount of missing data since the sponsor's decision to stop the trial was not related to an individual patient's ability to respond to the drug. One caveat is that the MAR approach depends on the assumption that the missing data can be appropriately estimated based on data from patients with similar baseline values, which may not always be true. Further, MMRM is less likely to overestimate treatment efficacy than the traditional last observation carried forward (LOCF) approach for imputing missing data in clinical trials.<sup>25</sup> A more conservative approach is applied when using MMRM with MI in controlling type 1 error rate and avoiding underestimation of the variance when imputing. With MI, the original data is copied 5 times and missing values are replaced by randomly generated values and analysed using MMRM.

Another limitation is that the AMAGINE-2/3 trials included high proportions of biologic-naïve patients, who may have better response rates than biologic-experienced patients,<sup>26</sup> although previous analyses found no difference in brodalumab 210 mg efficacy through up to 52 weeks between biologic-experienced and biologic-naïve patients.<sup>27,28</sup> A further limitation is that these are post hoc analyses; therefore, the trials were not designed and statistically powered to measure the specific endpoints of the current analysis.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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### Supporting information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Increasing missing data over time in AMAGINE-2 and -3.

**Figure S1.** Trial design for AMAGINE-2 and -3.

**Figure S2.** Proportion of subjects achieving PASI 75 through 120 weeks in brodalumab treatment groups using observed or imputed data.