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Safety and Efficacy of Bimekizumab in Patients With Active Ankylosing Spondylitis: Three-Year Results From a Phase IIb Randomized Controlled Trial and Its Open-Label Extension Study

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Objective. To assess the long-term safety, tolerability, and efficacy of bimekizumab in patients with active ankylosing spondylitis (AS).

Methods. Patients with active AS who completed the dose-ranging, 48-week BE AGILE randomized controlled trial were eligible to participate in an open-label extension (OLE) study, in which patients received 160 mg of bimekizumab every 4 weeks. We present the safety and efficacy results through 156 weeks. Missing efficacy data were imputed using nonresponder imputation analysis for binary outcomes and multiple imputation for continuous outcomes.

Results. From weeks 0–156, 280 of 303 patients (exposure-adjusted incidence rate 141.0 per 100 patient-years) experienced ≥1 treatment-emergent adverse event; the most frequent adverse events were nasopharyngitis (8.1 per 100 patient-years) and upper respiratory tract infection (5.0 per 100 patient-years). Additionally, 67 of 303 patients (9.8 per 100 patient-years) had mild to moderate localized fungal infections (28 of 303 patients had *Candida* infections [3.7 per 100 patient-years] and 23 of 303 patients had oral candidiasis [3.0 per 100 patient-years]), 10 patients had serious infections (1.3 per 100 patient-years), and no cases of active tuberculosis were reported. Active inflammatory bowel disease (1.1 per 100 patient-years), anterior uveitis (0.7 per 100 patient-years), and adjudicated major adverse cardiovascular events (0.3 per 100 patient-years) were infrequent. The efficacy of bimekizumab treatment demonstrated at week 48 was sustained in the OLE study. At week 156, nonresponder imputation analysis showed that 53.7% of patients (72.6% of observed cases) met the Assessment of SpondyloArthritis international Society criteria for 40% improvement and 28.0% of patients (37.9% of observed cases) achieved partial remission; Ankylosing Spondylitis Disease Activity Scores were reduced from baseline (mean ± SEM 3.9 ± 0.1) to week 48 (2.1 ± 0.1) and week 156 (1.9 ± 0.1) (multiple imputation). Patients showed sustained improvements in pain, fatigue, physical function, and health-related quality of life.

Conclusion. The safety profile of bimekizumab was found to be consistent with previously demonstrated findings, and no new safety signals were identified. The efficacy of bimekizumab in patients with AS was sustained through 3 years of treatment.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, immune-mediated inflammatory disease that mainly affects the axial skeleton (1). Falling within the axial spondyloarthritis (SpA) spectrum, patients with AS (also known as radiographic axial SpA) show definitive structural damage of the sacroiliac joints on pelvic radiographs (2). Due to the significant and lasting impact of AS on patients

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(3–7), it is crucial to assess the long-term safety and efficacy of treatments.

Interleukin-17 (IL-17) cytokines are key mediators of inflammation in SpA and have been targeted by new monoclonal antibody therapies (8,9), including the currently approved IL-17A inhibitors secukinumab and ixekizumab (9–11). In AS patients, safety and efficacy have been reported for up to 5 years for secukinumab, up to 2 years for ixekizumab (12–15), and up to 16 weeks for brodalumab, an anti–IL-17 receptor antibody (16).

Bimekizumab is a monoclonal IgG1 antibody that inhibits IL-17F in addition to IL-17A. These 2 cytokines, which have ~50% structural homology, form homodimers and heterodimers that signal via the same receptor complex (17,18). Despite similarities, IL-17A and IL-17F have distinct proinflammatory features and can independently synergize with tumor necrosis factor (TNF) to drive and amplify the inflammatory response (18–20). Preclinical evidence has demonstrated that inhibition of both cytokines suppresses gene expression and cytokine production to a greater extent than inhibition of IL-17A alone (11,12). The independent roles of IL-17A and IL-17F in pathological bone formation have also been identified in preclinical studies, indicating that dual inhibition of these cytokines may modulate osteoblast activity to a greater extent than only IL-17A inhibition (21,22).

Clinical studies have shown that the dual inhibition of IL-17A and IL-17F with bimekizumab results in rapid and lasting clinical improvements in patients with plaque psoriasis (with superiority demonstrated against secukinumab, ustekinumab, and adalimumab), psoriatic arthritis (PsA), and AS (23–29). In summary, the body of preclinical and clinical evidence suggests that the additional inhibition of IL-17F with bimekizumab may provide an improved therapeutic approach with further potential benefits relative to existing IL-17A inhibitors.

In the phase IIb dose-ranging BE AGILE study of bimekizumab in adults with active AS, a rapid and significant reduction in disease activity was demonstrated at week 12, which was sustained through week 48 (29). Bimekizumab was well tolerated and provided substantial improvements across various domains, including patient-reported symptoms, physical function, and health-related quality of life, as well as objective signs of inflammation such as C-reactive protein (CRP) levels and features of inflammation visible on magnetic resonance imaging (MRI) (29). Here, we report the safety and efficacy of treatment with bimekizumab for up to 156 weeks in adult patients with active AS. The primary objective of this study was to assess the long-term safety and tolerability of bimekizumab in patients with active AS, and secondarily to assess its long-term efficacy.

PATIENTS AND METHODS

Study design and participants. The BE AGILE study (ClinicalTrials.gov identifier NCT02963506) was a 48-week randomized, parallel-group, phase IIb, dose-ranging study that was double-blind to week 12 and then dose-blind to week 48. From the beginning of the trial to week 48, it was conducted at 74 sites across 10 countries in Europe and the US (29). Patients who completed 48 weeks of treatment were eligible to enroll in the open-label extension (OLE) study (ClinicalTrials.gov identifier NCT03355573) for an additional 204 weeks of treatment, with a subsequent safety visit 20 weeks after the last dose (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42282). The OLE study was conducted at 50 sites across the same 10 countries in Europe and the US that participated in the BE AGILE study. Inclusion and exclusion criteria have been reported previously (29). All study timepoints are reported relative to baseline (week 0) of the initial randomized controlled study. We report here results up to week 156 (up to 3 years total treatment duration).

Randomization and blinding. At baseline of the double-blind period, patients were randomized 1:1:1:1:1 to receive subcutaneous injection of bimekizumab at a dose of 16 mg, 64 mg, 160 mg, or 320 mg, or placebo every 4 weeks. At week 12 of the BE AGILE study, patients initially randomized to receive 16 mg or 64 mg of bimekizumab or placebo were rerandomized 1:1 to receive 160 mg or 320 mg of bimekizumab every 4 weeks through week 48, while patients initially randomized to receive 160 mg or 320 mg of bimekizumab continued their dosing to week 48. All patients in the OLE study received 160 mg of open-label bimekizumab every 4 weeks, regardless of prior dosing regimen (Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.42282).

The BE AGILE study and the affiliated OLE study were conducted in accordance with the Declaration of Helsinki and the International Conference for Harmonisation Guidelines for

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Data may be requested by qualified researchers 6 months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized IPD and redacted study documents which may include raw datasets, analysis-ready datasets, study protocol, blank case report form, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password protected portal.

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Good Clinical Practice. Ethical approval was obtained from the relevant institutional review boards at participating sites. The results presented in this article are in aggregate form, and no personally identifiable information was used for this study. All patients provided written informed consent in accordance with local requirements, with additional written informed consent required for enrollment in the OLE study.

Study procedures and outcomes. During the OLE study, safety was assessed on study entry (week 48), then every 4 weeks up to week 60, then every 12 weeks up to week 156. Most efficacy outcomes were assessed at OLE study entry, then every 12 weeks up to week 156. The Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire (30) and the Short Form 36 (SF-36) health survey (31) were assessed at the same timepoints but were not assessed at week 156. The Bath Ankylosing Spondylitis Metrology Index (BASMI) (32) was assessed on OLE study entry and then every 48 weeks. The Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) (33) was assessed every 12 weeks from entry to the OLE study, then every 24 weeks after week 96.

Safety outcomes (Medical Dictionary for Regulatory Activities [MedDRA] version 19.0) of the OLE study (primary objective) included incidence of treatment-emergent adverse events (TEAEs), serious TEAEs (primary safety variables), study withdrawals due to TEAEs (secondary safety variable), and prespecified adverse events of interest. Adverse events of interest included infections (serious, opportunistic, or fungal infections [including *Candida*] and tuberculosis), neutropenia, hypersensitivity, suicidal ideation and behavior, depression, major cardiovascular events, liver function test changes/enzyme elevations, and malignancies. TEAEs of inflammatory bowel disease (IBD) including ulcerative colitis, Crohn's disease, and IBD not otherwise specified as well as anterior uveitis were also reported as extramusculoskeletal manifestations and are presented by the patient's history of the event.

The efficacy of treatment with bimekizumab in AS patients in the OLE study (secondary objective) was evaluated using the Assessment of SpondyloArthritis international Society (ASAS) criteria for 20% improvement (ASAS20) (34) and ASAS criteria for 40% improvement (ASAS40) (35), the ASAS5/6 criteria (35), the ASAS criteria for partial remission (35), the Ankylosing Spondylitis Disease Activity Score using CRP (ASDAS-CRP) (36), the ASDAS showing major improvement (36), the ASDAS showing clinically important improvement (ASDAS-CII) (36), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (37), the BASDAI criteria for 50% improvement (BASDAI50) (37), the Bath Ankylosing Spondylitis Functional Index (BASFI) (38), the BASMI, the MASES, and the total resolution of the MASES. Efficacy of treatment with bimekizumab was also evaluated by assessment of high-sensitivity CRP, elevated high-sensitivity CRP (>5 mg/liter), BASDAI questions 1 (fatigue) and 2 (total spine, neck, back, or hip pain), the ASQoL, the SF-36 physical component summary (PCS) and mental component summary (MCS) scores, morning stiffness (mean of BASDAI question 5 + question 6), and the Patient Global Assessment of Disease Activity (PGADA).

Statistical analysis. Safety analyses are presented for exposure to bimekizumab across the total treatment period (weeks 0–156), as well as separately (weeks 0–48 and weeks 48–156) for the respective BE AGILE and OLE safety sets (patients who had ≥1 dose of bimekizumab in the relevant study period). To account for long-term, cumulative patient exposure to bimekizumab, exposure-adjusted incidence rates (EAIRs) per 100 patient-years are presented for TEAEs. EAIRs were calculated by dividing the number of patients with the specified TEAE by (i) the sum of each of those patients' time at risk (in years) at the onset of the (first, if they had >1) specified TEAE, plus (ii) the sum of time at risk for patients who did not experience that TEAE; the result was scaled to 100 patient-years.

Unless stated otherwise, efficacy variables are reported for the dose-blind set, comprising all patients who started the dose-blind period at week 12 of the BE AGILE study and who received at least 1 dose of bimekizumab during the dose-blind period, including the dose at week 12. This was to ensure that a full treatment sequence was available for each patient. For efficacy data reported by initial randomization group (baseline to week 12), outcomes are reported for the full analysis set, comprising all randomized patients who received at least 1 dose of the study drug and had a valid measurement of the ASAS components at baseline. Outcomes are summarized descriptively by visit and treatment group. Responses and change from baseline were derived relative to efficacy measurements at the double-blind period at baseline (week 0).

For binary outcomes, missing data were imputed in the most conservative manner, using the nonresponder imputation (NRI) method relative to week 0. For a given outcome and timepoint, a patient was classed as a nonresponder if data (or baseline values) were missing or if they had discontinued from the study; patients who did not enter the OLE study were considered nonresponders from week 48 onward. For continuous outcomes, missing data were imputed using multiple imputation (MI) based on the assumption that data were missing at random. Observed case data are also reported. All statistical analyses were conducted in SAS version 9.3 or later.

Ethics approval. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidance for Good Clinical Practice. Independent institutional review board approvals were obtained, and all patients provided written informed consent in accordance with local requirements.

RESULTS

Patient disposition and baseline characteristics. Of the 303 patients randomized to receive treatment with bimekizumab or placebo at baseline (full analysis set and BE AGILE safety set), 297 patients (98.0%) completed the double-blind period, and 296 patients (97.7%) started the dose-blind period at week 12 (dose-blind set). The dose-blind period was completed at week 48 by 265 of 303 patients (87.5%), at which point 256 of 303 patients (84.5%) entered the OLE study; the remaining 9 patients did not enroll in the OLE study. Of those 256 patients, 255 were included in the OLE safety set, since 1 patient was enrolled in the OLE study but did not subsequently receive bimekizumab (Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.42282). Patient retention was high during the OLE study, with 224 of 256 patients (87.5%; 224 of 303 patients [73.9%]) remaining in the study up to week 156 (Supplementary Figures 2–3, http://onlinelibrary.wiley.com/doi/10.1002/art.42282). There were 32 discontinuations during the OLE study: 15 due to adverse events, 12 due to withdrawn consent, 2 due to lack of efficacy, 1 lost to follow-up, and 2 due to other reasons.

At baseline of the double-blind period, there were no notable differences in patient demographics and disease characteristics between the randomized population and the subset of patients who received bimekizumab in the OLE study (Table 1). In the latter group (n = 255), 217 patients (85.1%) were male, 232 patients (91.0%) were positive for HLA–B27, and 29 patients (11.4%) had received prior tumor necrosis factor inhibitor (TNFi) therapy. At baseline of the double-blind period in the OLE study safety set, the median duration of AS from diagnosis was 4.6 years (range 0.0–37.3 years), and the median duration of symptoms was 12.1 years (range 0.2–47.2 years). The mean ± SD ASDAS and BASDAI scores were 3.9 ± 0.8 and 6.4 ± 1.4, respectively, and the median high-sensitivity CRP level was 12.1 mg/liter (range 0.3–130.1 mg/liter).

Safety. Exposure to bimekizumab over 156 weeks among all patients randomized at baseline was 815.6 patient-years, including 554.7 patient-years during the OLE study (weeks 48–156). For the total treatment period, ≥1 TEAE was observed in 280 of 303 patients (92.4%; EAIR 141.0 per 100 patient-years); ≥1 serious TEAE was observed in 43 of 303 patients (14.2%; EAIR

Table 1. Demographics and disease characteristics of patients with ankylosing spondylitis at baseline*

	BE AGILE safety set (N = 303)	OLE safety set (N = 255)
Age, mean ± SD years	42.2 ± 11.8	41.8 ± 11.4
Male	256 (84.5)	217 (85.1)
HLA–B27, positive†	270 (89.1)	232 (91.0)
Age at first diagnosis, mean ± SD years	34.8 ± 10.4	34.5 ± 10.2
Symptom duration, median (min–max) years	12.3 (0.2–47.2)	12.1 (0.2–47.2)
Disease duration, median (min–max) years	4.6 (0.0–37.3)	4.6 (0.0–37.3)
ASDAS-CRP, mean ± SD	3.9 ± 0.8	3.9 ± 0.8
BASDAI, mean ± SD (0–10)	6.5 ± 1.4	6.4 ± 1.4
BASFI, mean ± SD (0–10)	5.8 ± 2.0	5.7 ± 1.9
Total spinal pain score, mean ± SD (0–10)	7.1 ± 1.7	7.0 ± 1.8
PGADA, mean ± SD (0–10)	7.0 ± 1.7	6.9 ± 1.7
hsCRP, mg/liter‡		
Mean ± SD	19.0 ± 20.9	19.5 ± 21.5
Median (min–max)	12.1 (0.3–130.1)	12.1 (0.3–130.1)
History of IBD		
Crohn's disease	2 (0.7)	1 (0.4)
Ulcerative colitis	5 (1.7)	4 (1.6)
History of anterior uveitis	46 (15.2)	39 (15.3)
History of psoriasis	9 (3.0)	7 (2.7)
Prior TNFi therapy	34 (11.2)	29 (11.4)
Concomitant treatment		
NSAIDs	272 (89.8)	232 (91.0)
csDMARDs	79 (26.1)	67 (26.3)
Corticosteroids	26 (8.6)	23 (9.0)

* Except where indicated otherwise, values are the number (%) of patients. All data are reported for baseline of the double-blind period (week 0), not the start of the open-label extension (OLE) study (week 48). ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using C-reactive protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Function Index; PGADA = Patient Global Assessment of Disease Activity; hsCRP = high-sensitivity CRP; IBD = inflammatory bowel disease; TNFi = tumor necrosis factor inhibitor; NSAIDs = nonsteroidal antiinflammatory drugs; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs.
† Including 6 patients with missing results in the BE AGILE safety set and 5 patients with missing results in the OLE safety set.
‡ For hsCRP level in the BE AGILE safety set n = 300 patients, and n = 254 patients in the OLE safety set.

5.6 per 100 patient-years) (Table 2). TEAEs that occurred during weeks 0–48 and weeks 48–156 are shown in Table 2. For TEAEs that presented in >1 patient, EAIRs did not increase from weeks 0–48 to weeks 48–156 for the vast majority of reported TEAEs. EAIRs for serious TEAEs were 5.1 per 100 patient-years during weeks 0–48 and 5.9 during weeks 48–156; EAIRs for psoriasis were 0 during weeks 0–48 and 1.5 during weeks 48–156 (Table 2). Study discontinuations due to TEAEs were infrequent: 37 patients (12.2%) discontinued during the 156-week study period due to a TEAE, including 14 patients who discontinued during the OLE study. Study discontinuation due to TEAEs during the OLE study were most commonly due to infections and elevated liver enzymes. However, elevated liver enzymes were generally mild to moderate, and none met Hy's Law criteria. The most frequently reported TEAEs by MedDRA preferred term (≥5% of patients) are shown in Table 2.

One death was reported during weeks 0–48 (cardiac arrest in a patient with cardiovascular risk factors) and 1 death was reported during the OLE study (road traffic accident); neither was considered treatment-related by the study investigators. EAIRs during weeks 0–156 were 1.3 per 100 patient-years for serious infections and 0.3 per 100 patient-years for opportunistic infections. There were no cases of active tuberculosis during the study.

A total of 67 of 303 patients (EAIR 9.8 per 100 patient-years) had a fungal infection during weeks 0–156 (Table 2). All fungal infections were assessed as mild to moderate in intensity by the study investigator and the vast majority did not lead to discontinuation (1 patient discontinued due to oral candidiasis during weeks 0–48). There were no patients with serious or systemic fungal infections. Of patients with ≥1 infection, 28 had *Candida* infections (EAIR 3.7 per 100 patient-years), with the majority of these (23 of 28; EAIR 3.0 per 100 patient-years) being oral candidiasis. Thirty-seven patients (12.2%) had fungal infections not elsewhere classified (EAIR 5.0 per 100 patient-years), with 16 of 37 patients experiencing oral infections (EAIR 2.1 per 100 patient-years). Infections at other sites were low, including oropharyngeal candidiasis in 1 patient (0.3%) and vulvovaginal infections in 3 patients (2 *Candida* infections [0.7%] and 1 fungal infection [0.3%]). In total, 8 patients (2.6%) had a *Tinea* infection (EAIR 1.0 per 100 patient-years). Sex, smoking status, and presence of diabetes mellitus were not clear risk factors for susceptibility to *Candida* infections. A total of 10 of 303 patients (3.3%) had more than 1 *Candid*a infection over 156 weeks. All fungal infections, including *Candida* infections, were localized, none were systemic, and the vast majority resolved without sequelae and were easily treated with systemic or topical antifungal treatments such as clotrimazole, fluconazole, itraconazole, and nystatin (Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.42282).

Across weeks 0–156, 1 patient had adjudicated suicidal ideation and behavior, 2 had depression, 2 had adjudicated major adverse cardiovascular events (including the aforementioned cardiac arrest leading to death), and 1 patient had a malignancy (testicular seminoma) (Table 2); all of these events were considered unrelated to treatment by the study investigators. Two patients had neutropenia (both treatment-related), and 4 patients had injection site reactions, with treatment-related events in 3 patients. The most commonly reported skin disorders were dermatitis and eczema (high-level term), which occurred in 30 patients (9.9%; EAIR 3.9 per 100 patient-years); in 22 of these patients, cases of skin disorders were considered unrelated to treatment. Urticaria occurred in 1 patient and led to the patient discontinuing the study. No cases of serious hypersensitivity reactions were reported (Table 2).

Extramusculoskeletal manifestations. Of the 303 patients included in the BE AGILE safety set (none of whom had active/symptomatic IBD at screening and baseline), 2 (0.7%) had a history of Crohn's disease and 5 (1.7%) had a history of ulcerative colitis prior to entry in the BE AGILE study. Across weeks 0–156, 9 patients (3.0%) presented with active IBD (EAIR 1.1 per 100 patient-years), including 4 patients (1.3%) with ulcerative colitis, 4 patients (1.3%) with Crohn's disease, and 1 patient (0.3%) with unspecified IBD. Two of those 9 patients, both with ulcerative colitis, had a history of ulcerative colitis prior to entry in the BE AGILE study (Table 2). No patients presenting with active IBD had diabetes mellitus. Among the 9 patients with IBD, 3 patients experienced temporary interruption of bimekizumab treatment, and 1 patient discontinued participation in the study (due to ulcerative colitis). One patient was diagnosed as having Crohn's disease after discontinuing from the study due to a perirectal abscess; another patient was diagnosed as having Crohn's disease after withdrawing consent and discontinuing from the study to father a child.

Of the 303 patients, 46 (15.2%) had a history of anterior uveitis (which was not an exclusion criterion). Across weeks 0–156, 6 patients (2.0%) had an anterior uveitis flare (EAIR 0.7 per 100 patient-years). All cases were mild to moderate, and none were serious or led to study discontinuation. Of the 6 patients who experienced flares of anterior uveitis, 3 patients had a history of anterior uveitis, but the other 3 patients did not (Table 2 and Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.42282). Across weeks 0–156, psoriasis occurred in 8 patients (2.6%; EAIR 1.0 per 100 patient-years); most cases were mild to moderate, and none led to study discontinuation.

Efficacy. The efficacy of bimekizumab treatment at weeks 12 and 48 of the BE AGILE study has been reported previously (29). At week 48, over half of the bimekizumab-treated patients achieved an ASAS40 response (51.7% of patients by NRI and 59.8% of observed cases); this response rate was sustained to week 156 (53.7% of patients by NRI and 72.6% of observed cases) (Figure 1A). ASAS20 and ASAS partial remission

Table 2. Safety outcomes for exposure to bimekizumab (BKZ) in patients with ankylosing spondylitis over 156 weeks*

	Weeks 0–48†			Weeks 48–156	Weeks 0–156†
	160 mg BKZ every 4 weeks (n = 149; 114.2 patient-years)‡	320 mg BKZ every 4 weeks (n = 150; 119.6 patient-years)‡	Total BKZ (N = 303; 261.3 patient-years)§	Total BKZ (N = 255; 554.7 patient-years)	Total BKZ (N = 303; 815.6 patient-years)§
Any TEAE	103 (69.1) (168.7)	122 (81.3) (221.1)	235 (77.6) (186.2)	215 (84.3) (110.8)	280 (92.4) (141.0)
Most frequently reported TEAEs (≥5%) by preferred term					
Nasopharyngitis	13 (8.7) (12.0)	19 (12.7) (16.6)	34 (11.2) (13.7)	34 (13.3) (6.7)	57 (18.8) (8.1)
Upper respiratory tract infection	5 (3.4) (4.5)	11 (7.3) (9.5)	17 (5.6) (6.7)	24 (9.4) (4.6)	37 (12.2) (5.0)
Bronchitis	4 (2.7) (3.6)	12 (8.0) (10.4)	18 (5.9) (7.1)	15 (5.9) (2.8)	33 (10.9) (4.4)
Pharyngitis	11 (7.4) (10.0)	7 (4.7) (6.1)	18 (5.9) (7.1)	15 (5.9) (2.8)	29 (9.6) (3.8)
ALT increased	5 (3.4) (4.5)	6 (4.0) (5.1)	13 (4.3) (5.1)	15 (5.9) (2.8)	23 (7.6) (3.0)
Oral candidiasis	8 (5.4) (7.2)	8 (5.3) (7.0)	16 (5.3) (6.3)	13 (5.1) (2.4)	23 (7.6) (3.0)
Hypercholesterolemia	6 (4.0) (5.4)	6 (4.0) (5.2)	12 (4.0) (4.7)	11 (4.3) (2.0)	20 (6.6) (2.6)
Hypertension	4 (2.7) (3.6)	5 (3.3) (4.3)	10 (3.3) (3.9)	11 (4.3) (2.0)	20 (6.6) (2.6)
Rhinitis	7 (4.7) (6.3)	6 (4.0) (5.1)	14 (4.6) (5.5)	6 (2.4) (1.1)	20 (6.6) (2.6)
Tonsillitis	4 (2.7) (3.6)	3 (2.0) (2.5)	8 (2.6) (3.1)	13 (5.1) (2.4)	19 (6.3) (2.4)
Arthralgia	2 (1.3) (1.8)	5 (3.3) (4.3)	8 (2.6) (3.1)	11 (4.3) (2.0)	18 (5.9) (2.3)
Conjunctivitis	3 (2.0) (2.7)	7 (4.7) (6.0)	10 (3.3) (3.9)	10 (3.9) (1.8)	18 (5.9) (2.3)
Headache	6 (4.0) (5.4)	4 (2.7) (3.4)	13 (4.3) (5.1)	6 (2.4) (1.1)	18 (5.9) (2.3)
Respiratory tract infection	4 (2.7) (3.6)	6 (4.0) (5.1)	11 (3.6) (4.3)	8 (3.1) (1.5)	18 (5.9) (2.3)
GGT increased	6 (4.0) (5.4)	4 (2.7) (3.4)	13 (4.3) (5.1)	5 (2.0) (0.9)	17 (5.6) (2.2)
Oral fungal infection	8 (5.4) (7.2)	6 (4.0) (5.1)	14 (4.6) (5.5)	8 (3.1) (1.5)	16 (5.3) (2.1)
AST increased	3 (2.0) (2.7)	5 (3.3) (4.3)	9 (3.0) (3.5)	9 (3.5) (1.6)	16 (5.3) (2.0)
Serious TEAEs	5 (3.4) (4.4)	6 (4.0) (5.1)	13 (4.3) (5.1)	31 (12.2) (5.9)	43 (14.2) (5.6)
Study discontinuations due to TEAEs	7 (4.7)	10 (6.7)	20 (6.6)	14 (5.5)	37 (12.2)
Drug-related TEAEs	48 (32.2)	54 (36.0)	110 (36.3)	90 (35.3)	149 (49.2)
Deaths	1 (0.7)	0	1 (0.3)	1 (0.4)	2 (0.7)
Adverse events of interest					
Serious infections	3 (2.0) (2.7)	1 (0.7) (0.8)	4 (1.3) (1.5)	6 (2.4) (1.1)	10 (3.3) (1.3)
Opportunistic infections	0	0	1 (0.3) (0.4)	1 (0.4) (0.2)	2 (0.7) (0.3)
Active tuberculosis	0	0	0	0	0
Fungal infections	19 (12.8) (17.8)	23 (15.3) (20.9)	44 (14.5) (18.1)	39 (15.3) (8.0)	67 (22.1) (9.8)
Candida infections	10 (6.7) (9.1)	9 (6.0) (7.9)	19 (6.3) (7.5)	15 (5.9) (2.8)	28 (9.2) (3.7)
Oral candidiasis	8 (5.4) (7.2)	8 (5.3) (7.0)	16 (5.3) (6.3)	13 (5.1) (2.4)	23 (7.6) (3.0)
Skin candidiasis	0	1 (0.7) (0.8)	1 (0.3) (0.4)	3 (1.2) (0.5)	4 (1.3) (0.5)
Vulvovaginal candidiasis	2 (1.3) (1.8)	0	2 (0.7) (0.8)	0	2 (0.7) (0.3)
Oropharyngeal candidiasis	0	0	0	1 (0.4) (0.2)	1 (0.3) (0.1)
Candida infection (unspecified)	0	0	0	1 (0.4) (0.2)	1 (0.3) (0.1)
Fungal infections NEC	9 (6.0) (8.1)	13 (8.7) (11.3)	24 (7.9) (9.5)	22 (8.6) (4.3)	37 (12.2) (5.0)
Oral fungal infection	8 (5.4) (7.2)	6 (4.0) (5.1)	14 (4.6) (5.5)	8 (3.1) (1.5)	16 (5.3) (2.1)
Fungal skin infection	0	5 (3.3) (4.2)	7 (2.3) (2.7)	6 (2.4) (1.1)	13 (4.3) (1.6)
Tongue fungal infection	0	3 (2.0) (2.5)	3 (1.0) (1.2)	5 (2.0) (0.9)	7 (2.3) (0.9)
Onychomycosis	0	0	0	4 (1.6) (0.7)	4 (1.3) (0.5)
Ear infection fungal	1 (0.7) (0.9)	0	1 (0.3) (0.4)	0	1 (0.3) (0.1)
Vulvovaginal mycotic infection	0	1 (0.7) (0.8)	1 (0.3) (0.4)	0	1 (0.3) (0.1)
Otitis externa fungal	0	0	0	1 (0.4) (0.2)	1 (0.3) (0.1)

(Continued)

Table 2. (*Cont'd*)

	Weeks 0–48†			Weeks 48–156	Weeks 0–156†
	160 mg BKZ every 4 weeks (n = 149; 114.2 patient-years)‡	320 mg BKZ every 4 weeks (n = 150; 119.6 patient-years)‡	Total BKZ (N = 303; 261.3 patient-years)§	Total BKZ (N = 255; 554.7 patient-years)	Total BKZ (N = 303; 815.6 patient-years)§
Tinea infections	1 (0.7) (0.9)	2 (1.3) (1.7)	3 (1.0) (1.2)	4 (1.6) (0.7)	8 (2.6) (1.0)
Tinea pedis	1 (0.7) (0.9)	2 (1.3) (1.7)	3 (1.0) (1.2)	3 (1.2) (0.5)	6 (2.0) (0.8)
Body tinea	0	0	0	1 (0.4) (0.2)	1 (0.3) (0.1)
Tinea capitis	0	0	0	0	1 (0.3) (0.1)
Serious hypersensitivity reactions	0	0	0	0	0
Adjudicated SIB	0	0	0	1 (0.4) (0.2)	1 (0.3) (0.1)
Depression	0	0	1 (0.3) (0.4)	1 (0.4) (0.2)	2 (0.7) (0.3)
Adjudicated MACE	2 (1.3) (1.8)	0	2 (0.7) (0.8)	0	2 (0.7) (0.3)
Liver enzyme elevation					
ALT increased	5 (3.4) (4.5)	6 (4.0) (5.1)	13 (4.3) (5.1)	15 (5.9) (2.8)	23 (7.6) (3.0)
AST increased	3 (2.0) (2.7)	5 (3.3) (4.3)	9 (3.0) (3.5)	9 (3.5) (1.6)	16 (5.3) (2.0)
GGT increased	6 (4.0) (5.4)	4 (2.7) (3.4)	13 (4.3) (5.1)	5 (2.0) (0.9)	17 (5.6) (2.2)
Hepatic enzyme increased	0	3 (2.0) (2.5)	6 (2.0) (2.3)	7 (2.7) (1.3)	12 (4.0) (1.5)
Malignancies	0	0	0	1 (0.4) (0.2)	1 (0.3) (0.1)
IBD	1 (0.7) (0.9)	2 (1.3) (1.7)	4 (1.3) (1.5)	6 (2.4) (1.1)	9 (3.0) (1.1)
Ulcerative colitis	0	1 (0.7) (0.8)	2 (0.7) (0.8)	3 (1.2) (0.5)	4 (1.3) (0.5)
With prior history	0	1 (0.7)	1 (0.3)	1 (0.4)	2 (0.7)
No prior history	0	0	1 (0.3)	2 (0.8)	2 (0.7)
Crohn's disease	1 (0.7) (0.9)	1 (0.7) (0.8)	2 (0.7) (0.8)	2 (0.8) (0.4)	4 (1.3) (0.5)
With prior history	0	0	0	0	0
No prior history	1 (0.7)	1 (0.7)	2 (0.7)	2 (0.8)	4 (1.3)
IBD not otherwise specified	0	0	0	1 (0.4) (0.2)	1 (0.3) (0.1)
Anterior uveitis	1 (0.7) (0.9)	1 (0.7) (0.8)	2 (0.7) (0.8)	4 (1.6) (0.7)	6 (2.0) (0.7)
With prior history	1 (0.7)	1 (0.7)	2 (0.7)	1 (0.4)	3 (1.0)
No prior history	0	0	0	3 (1.2)	3 (1.0)
Psoriasis	0	0	0	8 (3.1) (1.5)	8 (2.6) (1.0)
Injection site reactions	0	3 (2.0) (2.6)	3 (1.0) (1.2)	1 (0.4) (0.2)	4 (1.3) (0.5)

* Values are the number (%) of patients (exposure-adjusted incidence rate). 8 patients discontinued due to infections across weeks 0–156 (1 for each of the following: perirectal abscess, oral bacterial infection, oral candidiasis, conjunctivitis, herpes zoster, impetigo, *Tinea* capitis, and nasopharyngitis). 3 patients discontinued during weeks 48–156 due to a treatment-emergent adverse event (TEAE) that initiated in weeks 0–48 are not counted within weeks 48–156. 1 death occurred in weeks 0–48 (cardiac arrest in a patient with cardiovascular risk factors) and 1 occurred during the open-label extension study (road traffic accident), but neither was considered treatment-related. 1 case of recurrent herpes zoster occurred in weeks 0–48 and 1 case of oropharyngeal candidiasis occurred in weeks 48–156. All fungal infections were mild to moderate, and none were systemic. All oral candidiasis events were mild to moderate (none were serious). Liver enzyme elevations were not associated with clinical symptoms and no cases of Hy's Law were reported. 1 case of testicular seminoma was reported. Inflammatory bowel disease (IBD), anterior uveitis, and psoriasis are extramusculoskeletal manifestations of ankylosing spondylitis. IBD not otherwise specified occurred in 1 patient with no medical history of IBD. Psoriasis occurred in 8 patients with no prior history of psoriasis. ALT = alanine aminotransferase; GGT = gamma-glutamyltransferase; AST = aspartate aminotransferase; NEC = not elsewhere classified; SIB = suicidal ideation and behavior; MACE = major adverse cardiovascular events.
† TEAEs that occurred before week 12 are reported only for patients receiving the indicated dose.
‡ TEAEs reported from the time the patient started the indicated dose.
§ TEAEs while receiving BKZ at any dose.

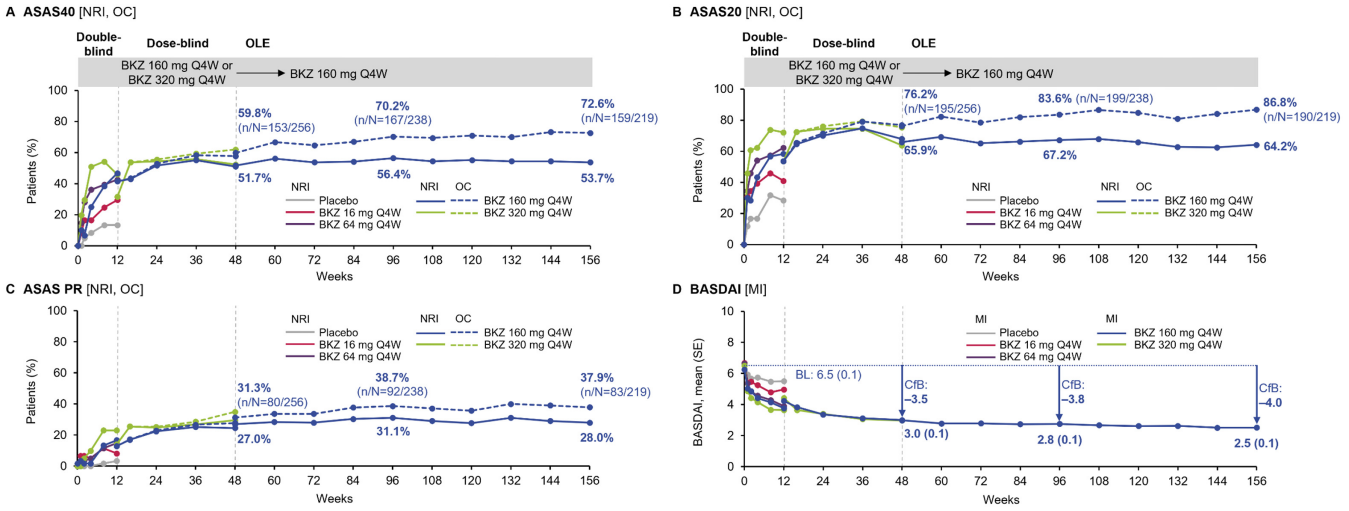

Figure 1. Assessment of SpondyloArthritis international Society (ASAS) criteria and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) outcomes in ankylosing spondylitis (AS) patients receiving bimekizumab (BKZ) or placebo during weeks 0–12 (full analysis set; n = 303) and patients receiving BKZ during weeks 12–156 (dose-blind set; n = 296). Data are shown for 299 patients (297 patients for the BASDAI) at week 12 for the double-blind groups, and data are shown for 296 patients (295 patients for the BASDAI) at week 12 for the dose-blind groups. In **A–C**, proportions of patients achieving a response on the ASAS criteria for 40% improvement (**A**), the ASAS criteria for 20% improvement (**B**), and the ASAS criteria for partial remission (PR) (**C**) were determined using nonresponder imputation (NRI) analysis and observed case (OC) analysis. In the NRI analyses, patients who did not enter the open-label extension (OLE) study were considered nonresponders from week 48 onwards. In **D**, proportions of patients achieving improvement in BASDAI score were determined using multiple imputation (MI) analysis. For BASDAI, baseline (BL) mean (blue dotted line) is shown for the total dose-blind set. Q4W = every 4 weeks; CfB = change from baseline.

responses were similarly sustained from week 48 to week 156 in the NRI analysis, with 65.9% of patients (76.2% of observed cases) achieving ASAS20 and 27.0% of patients (31.3% of observed cases) achieving ASAS partial remission responses at week 48, compared to 64.2% (86.8% of observed cases) and 28.0% (37.9% of observed cases) at week 156 (Figures 1B and C). Sustained ASAS responses through week 156 were comparable across patients who received 160 mg and patients who received 320 mg of bimekizumab every 4 weeks during the dose-blind period (Table 3).

The mean ± SEM ASDAS at baseline was 3.9 ± 0.1; in the MI analysis, mean ± SEM ASDAS improved to week 48 (2.1 ± 0.1) and to week 156 (1.9 ± 0.1) (Figure 2A). In NRI analysis, major improvement in the ASDAS was achieved by 38.9% of patients at week 48, and major improvement in ASDAS was maintained by 39.9% of patients at week 156. In the observed case analysis, percentages of patients achieving major improvement in ASDAS increased from 44.9% of patients at week 48 to 54.9% of patients at week 156 (Figure 2B). ASDAS <2.1 and ASDAS showing inactive disease were also sustained in weeks 48–156 in the NRI analysis: 49.3% of patients (57.0% of observed cases) had achieved ASDAS <2.1 and 19.6% of patients (22.7% of observed cases) had achieved ASDAS showing inactive disease at week 48, compared to 49.0% (67.4% of observed cases) and 24.0% (33.0% of observed cases) at week 156, respectively (Figures 2D and 3).

Among patients who received bimekizumab 160 mg every 4 weeks through 156 weeks (n = 60), individual patient-level improvements in ASDAS were largely maintained through successive study visits (Supplementary Figure 4, http://onlinelibrary.wiley.com/doi/10.1002/art.42282). Most patients who achieved low disease activity or inactive disease at week 48 remained in these states at week 156. Additionally, patients who had ASDAS high disease activity at baseline tended to achieve ASDAS low disease activity earlier than those who had very high disease activity at baseline.

As with ASDAS, high baseline high-sensitivity CRP levels (mean 10.6 mg/liter [median 12.0 mg/liter]) improved substantially at week 48 (mean 3.0 mg/liter [median 3.6 mg/liter]) in the MI analysis and were sustained at week 156 (mean 2.5 mg/liter [median 2.9 mg/liter]). The mean ± SEM BASDAI score at baseline was 6.5 ± 0.1; in the MI analysis, BASDAI scores improved rapidly by week 48 (mean ± SEM 3.0 ± 0.1) and further improved by week 156 (mean ± SEM 2.5 ± 0.1) (Figure 1D). Following improvement in the mean ± SEM BASMI score from 4.7 ± 0.1 at baseline to 3.9 ± 0.1 at week 48 (MI), spinal mobility was maintained at week 144 (mean ± SEM BASMI score 4.0 ± 0.1). Similar improvements occurred in mean ± SEM MASES scores (MI) from baseline (mean ± SEM 4.4 ± 0.2) to week 48 (mean ± SEM 1.0 ± 0.1); this improvement was maintained at week 144 (mean ± SEM MASES score 0.7 ± 0.1) (Table 3 and Supplementary Figure 5, http://onlinelibrary.wiley.com/doi/10.1002/art.42282).

Improvements in physical function and health-related quality of life (HRQoL) seen at week 48 were similarly sustained with up to 3 years of bimekizumab treatment (Table 3). The mean ± SEM BASFI score improved from 5.7 ± 0.1 at baseline to 3.1 ± 0.1 at

Table 3. Efficacy outcomes of bimekizumab (BKZ) treatment in ankylosing spondylitis patients to week 156*

	BKZ 160 mg Q4W (dose-blind period) (n = 147)†		BKZ 320 mg Q4W (dose-blind period) (n = 149)†		Total (dose-blind period) (N = 296)	
	Imputed	OC	Imputed	OC	Imputed	OC
ASAS20 by NRI, no. (%)						
Week 48	100 (68.0)	100/130 (76.9)	95 (63.8)	95/126 (75.4)	195 (65.9)	195/256 (76.2)
Week 96	100 (68.0)	100/121 (82.6)	99 (66.4)	99/117 (84.6)	199 (67.2)	199/238 (83.6)
Week 156	97 (66.0)	97/114 (85.1)	93 (62.4)	93/105 (88.6)	190 (64.2)	190/219 (86.8)
ASAS40 by NRI, no. (%)						
Week 48	75 (51.0)	75/130 (57.7)	78 (52.3)	78/126 (61.9)	153 (51.7)	153/256 (59.8)
Week 96	84 (57.1)	84/121 (69.4)	83 (55.7)	83/117 (70.9)	167 (56.4)	167/238 (70.2)
Week 156	84 (57.1)	84/114 (73.7)	75 (50.3)	75/105 (71.4)	159 (53.7)	159/219 (72.6)
ASAS 5/6 by NRI, no. (%)						
Week 48	79 (53.7)	79/130 (60.8)	77 (51.7)	77/126 (61.1)	156 (52.7)	156/256 (60.9)
Week 96	75 (51.0)	75/121 (62.0)	79 (53.0)	79/116 (68.1)	154 (52.0)	154/237 (65.0)
Week 144	82 (55.8)	82/114 (71.9)	75 (50.3)	75/106 (70.8)	157 (53.0)	157/220 (71.4)
ASAS PR by NRI, no. (%)						
Week 48	36 (24.5)	36/130 (27.7)	44 (29.5)	44/126 (34.9)	80 (27.0)	80/256 (31.3)
Week 96	47 (32.0)	47/121 (38.8)	45 (30.2)	45/117 (38.5)	92 (31.1)	92/238 (38.7)
Week 156	46 (31.3)	46/114 (40.4)	37 (24.8)	37/105 (35.2)	83 (28.0)	83/219 (37.9)
ASDAS-CRP by MI, mean ± SEM/SD						
Baseline	3.9 ± 0.1	3.9 ± 0.8	4.0 ± 0.1	4.0 ± 0.8	3.9 ± 0.1	3.9 ± 0.8
Week 48	2.1 ± 0.1	2.1 ± 0.9	2.1 ± 0.1	2.0 ± 0.9	2.1 ± 0.1	2.0 ± 0.9
Week 96	2.0 ± 0.1	1.9 ± 0.9	2.0 ± 0.1	1.9 ± 0.8	2.0 ± 0.1	1.9 ± 0.9
Week 156	1.9 ± 0.1	1.8 ± 0.8	1.9 ± 0.1	1.8 ± 0.7	1.9 ± 0.1	1.8 ± 0.8
ASDAS-ID by NRI, no. (%)						
Week 48	28 (19.0)	28/130 (21.5)	30 (20.1)	30/126 (23.8)	58 (19.6)	58/256 (22.7)
Week 96	36 (24.5)	36/121 (29.8)	36 (24.2)	36/116 (31.0)	72 (24.3)	72/237 (30.4)
Week 156	43 (29.3)	43/113 (38.1)	28 (18.8)	28/102 (27.5)	71 (24.0)	71/215 (33.0)
ASDAS <2.1 by NRI, no. (%)						
Week 48	73 (49.7)	73/130 (56.2)	73 (49.0)	73/126 (57.9)	146 (49.3)	146/256 (57.0)
Week 96	80 (54.4)	80/121 (66.1)	73 (49.0)	73/116 (62.9)	153 (51.7)	153/237 (64.6)
Week 156	79 (53.7)	79/113 (69.9)	66 (44.3)	66/102 (64.7)	145 (49.0)	145/215 (67.4)
ASDAS major improvement by NRI, no. (%)						
Week 48	59 (40.1)	59/130 (45.4)	56 (37.6)	56/126 (44.4)	115 (38.9)	115/256 (44.9)
Week 96	65 (44.2)	65/121 (53.7)	60 (40.3)	60/116 (51.7)	125 (42.2)	125/237 (52.7)
Week 156	63 (42.9)	63/113 (55.8)	55 (36.9)	55/102 (53.9)	118 (39.9)	118/215 (54.9)
ASDAS-CII by NRI, no. (%)						
Week 48	99 (67.3)	99/130 (76.2)	101 (67.8)	101/126 (80.2)	200 (67.6)	200/256 (78.1)
Week 96	99 (67.3)	99/121 (81.8)	95 (63.8)	95/116 (81.9)	194 (65.5)	194/237 (81.9)
Week 156	92 (62.6)	92/113 (81.4)	88 (59.1)	88/102 (86.3)	180 (60.8)	180/215 (83.7)
BASDAI by MI, mean ± SEM/SD						
Baseline	6.4 ± 0.1	6.4 ± 1.4	6.6 ± 0.1	6.6 ± 1.5	6.5 ± 0.1	6.5 ± 1.4
Week 48	3.0 ± 0.2	2.8 ± 1.8	3.0 ± 0.2	2.9 ± 2.1	3.0 ± 0.1	2.8 ± 2.0
Week 96	2.7 ± 0.2	2.5 ± 1.8	2.8 ± 0.2	2.6 ± 2.0	2.8 ± 0.1	2.5 ± 1.9
Week 156	2.5 ± 0.2	2.3 ± 1.8	2.5 ± 0.2	2.3 ± 1.6	2.5 ± 0.1	2.3 ± 1.7

(Continued)

Table 3. (*Cont'd*)

	BKZ 160 mg Q4W (dose-blind period) (n = 147)†		BKZ 320 mg Q4W (dose-blind period) (n = 149)†		Total (dose-blind period) (N = 296)	
	Imputed	OC	Imputed	OC	Imputed	OC
BASDAI50 by NRI, no. (%)						
Week 48	72 (49.0)	72/130 (55.4)	77 (51.7)	77/126 (61.1)	149 (50.3)	149/256 (58.2)
Week 96	84 (57.1)	84/121 (69.4)	76 (51.0)	76/117 (65.0)	160 (54.1)	160/238 (67.2)
Week 156	79 (53.7)	79/114 (69.3)	77 (51.7)	77/105 (73.3)	156 (52.7)	156/219 (71.2)
BASFI by MI, mean ± SEM/SD						
Baseline	5.6 ± 0.2	5.6 ± 1.9	5.8 ± 0.2	5.8 ± 2.0	5.7 ± 0.1	5.7 ± 2.0
Week 48	3.1 ± 0.2	3.0 ± 2.0	3.2 ± 0.2	3.1 ± 2.4	3.1 ± 0.1	3.0 ± 2.2
Week 96	2.8 ± 0.2	2.7 ± 2.1	2.9 ± 0.2	2.8 ± 2.4	2.8 ± 0.1	2.7 ± 2.2
Week 156	2.7 ± 0.2	2.5 ± 2.0	2.9 ± 0.2	2.8 ± 2.2	2.8 ± 0.1	2.6 ± 2.1
BASMI by MI, mean ± SEM/SD						
Baseline	4.5 ± 0.1	4.5 ± 1.7	4.8 ± 0.1	4.8 ± 1.7	4.7 ± 0.1	4.7 ± 1.7
Week 48	3.9 ± 0.2	4.0 ± 1.8	3.9 ± 0.2	3.9 ± 1.8	3.9 ± 0.1	4.0 ± 1.8
Week 96	3.9 ± 0.1	4.0 ± 1.7	3.9 ± 0.2	4.0 ± 1.9	3.9 ± 0.1	4.0 ± 1.8
Week 144	4.0 ± 0.2	4.0 ± 1.7	4.0 ± 0.2	4.1 ± 2.0	4.0 ± 0.1	4.1 ± 1.8
MASES by MI, mean ± SEM/SD‡						
Baseline	4.0 ± 0.3	4.0 ± 2.7	4.9 ± 0.3	4.9 ± 3.2	4.4 ± 0.2	4.4 ± 3.0
Week 48	0.8 ± 0.2	0.7 ± 1.5	1.1 ± 0.2	1.0 ± 1.9	1.0 ± 0.1	0.8 ± 1.7
Week 96	0.7 ± 0.2	0.5 ± 1.4	1.0 ± 0.2	0.9 ± 2.3	0.8 ± 0.1	0.6 ± 1.9
Week 144	0.5 ± 0.1	0.4 ± 1.0	0.9 ± 0.2	0.7 ± 1.8	0.7 ± 0.1	0.5 ± 1.4
hsCRP by MI, geometric mean (median)						
Baseline	11.1 (13.1)	11.1 (13.1)§	10.2 (11.5)	10.2 (11.4)§	10.6 (12.0)	10.6 (12.0)§
Week 48	3.3 (3.8)	3.3 (3.5)	2.8 (3.4)	3.0 (3.5)	3.0 (3.6)	3.1 (3.5)
Week 96	2.8 (3.0)	2.8 (2.8)	2.3 (2.7)	2.5 (2.6)	2.5 (2.8)	2.7 (2.7)
Week 156	2.5 (2.7)	2.4 (2.3)	2.5 (3.0)	2.7 (2.7)	2.5 (2.9)	2.5 (2.5)
Total spinal pain by MI, mean ± SEM/SD						
Baseline	6.9 ± 0.2	6.9 ± 1.9	7.3 ± 0.1	7.3 ± 1.6	7.1 ± 0.1	7.1 ± 1.8
Week 48	3.2 ± 0.2	3.0 ± 2.1	3.1 ± 0.2	3.1 ± 2.3	3.1 ± 0.1	3.0 ± 2.2
Week 96	2.7 ± 0.2	2.5 ± 2.1	2.6 ± 0.2	2.5 ± 2.1	2.7 ± 0.1	2.5 ± 2.1
Week 156	2.6 ± 0.2	2.5 ± 2.0	2.5 ± 0.2	2.3 ± 1.8	2.5 ± 0.1	2.4 ± 1.9
Neck, back or hip pain (BASDAI question 2) by MI, mean ± SEM/SD						
Baseline	7.4 ± 0.1	7.4 ± 1.4	7.6 ± 0.1	7.6 ± 1.5	7.5 ± 0.1	7.5 ± 1.4
Week 48	3.5 ± 0.2	3.4 ± 2.3	3.4 ± 0.2	3.3 ± 2.4	3.4 ± 0.2	3.3 ± 2.4
Week 96	3.1 ± 0.2	2.9 ± 2.2	3.2 ± 0.2	3.0 ± 2.5	3.1 ± 0.2	3.0 ± 2.3
Week 156	2.8 ± 0.2	2.6 ± 2.1	2.8 ± 0.2	2.5 ± 1.9	2.8 ± 0.1	2.6 ± 2.0
Fatigue (BASDAI question 1) by MI, mean ± SEM/SD						
Baseline	6.6 ± 0.1	6.6 ± 1.6	6.7 ± 0.1	6.7 ± 1.7	6.7 ± 0.1	6.7 ± 1.7
Week 48	3.6 ± 0.2	3.5 ± 2.2	3.6 ± 0.2	3.5 ± 2.4	3.6 ± 0.1	3.5 ± 2.3
Week 96	3.0 ± 0.2	2.8 ± 2.0	3.5 ± 0.2	3.2 ± 2.3	3.3 ± 0.2	3.0 ± 2.1
Week 156	2.9 ± 0.2	2.7 ± 2.0	2.9 ± 0.2	2.7 ± 2.0	2.9 ± 0.1	2.7 ± 2.0
ASQoL by MI, mean ± SEM/SD						
Baseline	8.3 ± 0.4	8.3 ± 4.3	9.1 ± 0.4	9.1 ± 4.3	8.7 ± 0.3	8.7 ± 4.3
Week 48	3.7 ± 0.3	3.5 ± 3.9	3.6 ± 0.3	3.4 ± 4.0	3.7 ± 0.2	3.4 ± 3.9
Week 96	3.4 ± 0.3	3.0 ± 3.7	3.3 ± 0.3	2.7 ± 3.3	3.3 ± 0.2	2.9 ± 3.5
Week 144	3.1 ± 0.3	2.8 ± 3.7	3.1 ± 0.3	2.5 ± 3.0	3.1 ± 0.2	2.7 ± 3.4

(Continued)

Table 3. (*Cont'd*)

	BKZ 160 mg Q4W (dose-blind period) (n = 147)†		BKZ 320 mg Q4W (dose-blind period) (n = 149)†		Total (dose-blind period) (N = 296)	
	Imputed	OC	Imputed	OC	Imputed	OC
SF-36 PCS by MI, mean ± SEM/SD						
Baseline	32.6 ± 0.7	32.6 ± 7.9	31.9 ± 0.6	31.9 ± 7.4	32.3 ± 0.5	32.3 ± 7.7
Week 48	44.3 ± 0.8	44.8 ± 9.1	44.0 ± 0.7	44.5 ± 8.6	44.1 ± 0.5	44.6 ± 8.8
Week 96	45.4 ± 0.8	46.3 ± 9.0	44.6 ± 0.8	45.1 ± 9.0	45.0 ± 0.6	45.8 ± 9.0
Week 144	45.8 ± 0.8	46.6 ± 8.6	44.9 ± 0.8	45.4 ± 8.5	45.3 ± 0.6	46.1 ± 8.6
SF-36 MCS by MI, mean ± SEM/SD						
Baseline	54.5 ± 0.7	54.5 ± 8.4	53.8 ± 0.7	53.8 ± 8.2	54.1 ± 0.5	54.1 ± 8.3
Week 48	56.0 ± 0.6	56.3 ± 7.3	57.1 ± 0.6	57.4 ± 6.7	56.6 ± 0.4	56.8 ± 7.0
Week 96	56.3 ± 0.7	56.6 ± 8.0	57.0 ± 0.6	57.1 ± 6.7	56.6 ± 0.4	56.9 ± 7.4
Week 144	56.5 ± 0.7	57.2 ± 7.6	57.3 ± 0.6	57.5 ± 6.7	56.9 ± 0.4	57.4 ± 7.2

* Data are reported as either imputed (multiple imputation [MI] based on the missing at random assumption or nonresponder imputation [NRI]) or as observed case (OC). For continuous variables, mean ± SEM is reported for MI analyses and mean ± SD is reported for OC analyses. ASAS20 = Assessment of SpondyloArthritis international Society criteria for 20% improvement; ASAS40 = ASAS criteria for 40% improvement; ASAS PR = ASAS partial remission; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASDAS-CII = ASDAS clinically important improvement; ASDAS-CRP = ASDAS using C-reactive protein; ASDAS-ID = ASDAS inactive disease; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASDAI50 = BASDAI 50% response; BASFI = Bath Ankylosing Spondylitis Function Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; SF-36 = Short Form-36; PCS = physical component summary; MCS = mental component summary.

† Patients received BKZ 16 mg, 64 mg, 160 mg, or 320 mg, or placebo, every 4 weeks (Q4W) up to week 12, at which point patients receiving BKZ 16 mg or 64 mg, or placebo, were re-randomized to receive BKZ 160 mg or 320 mg Q4W from week 12 to week 48 (dose-blind period). Thereafter, during the open-label extension (OLE) period up to week 156, all patients received 160 mg Q4W, regardless of prior dosing regimen before the OLE.

‡ Among patients who had Maastrich Ankylosing Spondylitis Enthesitis Score (MASES) >0 at baseline, data were available as follows: n = 100 in the dose-blind BKZ 160 mg group, n = 94 in the dose-blind BKZ 320 mg group, and n = 194 in the total dose-blind group.

§ Among patients with high-sensitivity C-reactive protein (hsCRP) values in the OC analysis at baseline, data were available as follows: n = 146 in the dose-blind BKZ 160 mg group, n = 148 in the dose-blind BKZ 320 mg group, and n = 294 in the total dose-blind group.

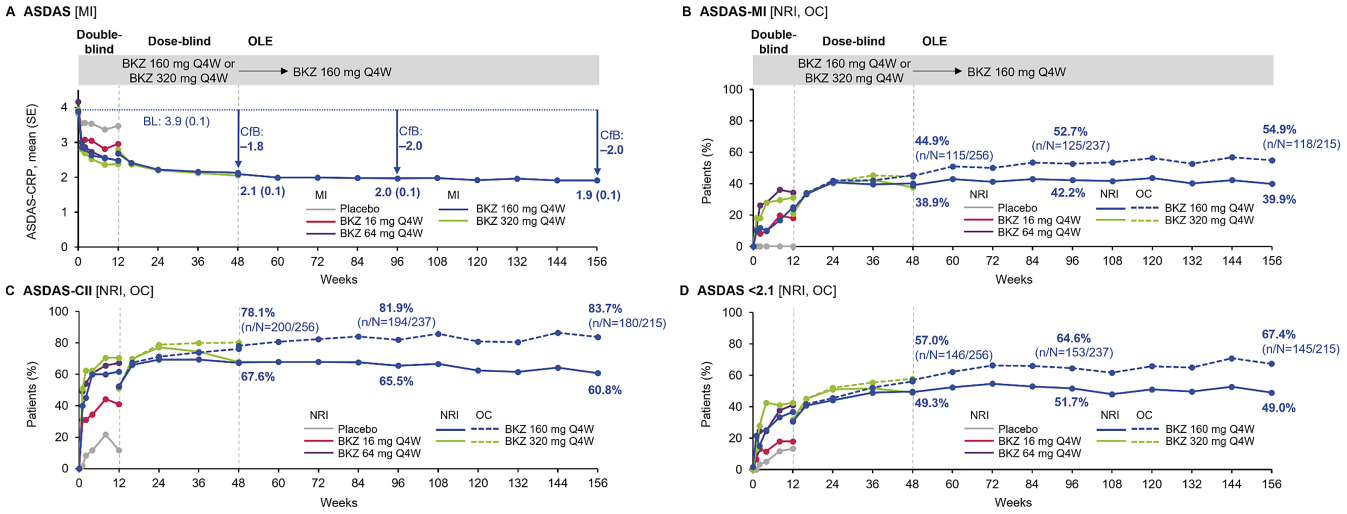

Figure 2. Ankylosing Spondylitis Disease Activity Score (ASDAS) outcomes to week 156. ASDAS outcomes in AS patients receiving BKZ or placebo during weeks 0–12 (full analysis set; n = 303) and patients receiving BKZ during weeks 12–156 (dose-blind set; n = 296). In **A**, improvements in the mean ± SEM ASDAS using C-reactive protein were determined using multiple imputation analysis. Baseline mean score (blue dotted line) is shown for the total dose-blind set. In **B–D**, proportions of patients achieving major improvement in ASDAS (ASDAS-MI) (**B**), proportions of patients achieving clinically important improvement in ASDAS (ASDAS-CII) (**C**), and proportions of patients achieving ASDAS scores <2.1 (**D**) were determined using NRI and OC analyses. In the NRI analyses, patients who did not enter the OLE study were considered nonresponders from week 48 onward. See Figure 1 for other definitions. Q4W = every 4 weeks; CfB = change from baseline. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42282/abstract.

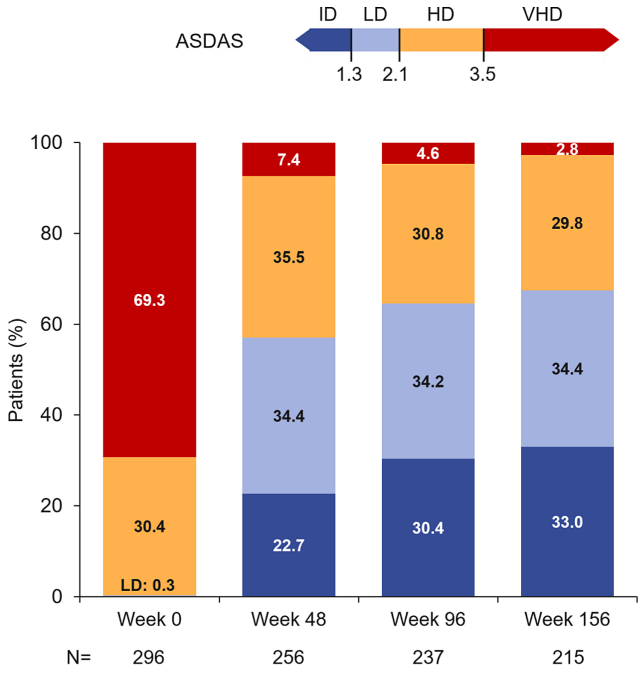

Figure 3. ASDAS disease states over time up to week 156. Proportions of AS patients in the dose-blind set (n = 296) showing inactive disease (ID), low disease (LD) activity, high disease (HD) activity, and very high disease (VHD) activity. Data are reported as observed case (OC). See Figure 1 for other definitions. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42282/abstract.

week 48 and was sustained at 2.8 ± 0.1 at week 156. Mean ± SEM baseline scores for the SF-36 PCS (mean ± SEM 32.3 ± 0.5) and the ASQoL (mean ± SEM 8.7 ± 0.3) were indicative of impaired physical function and reduced HRQoL in this patient population with longstanding disease. At week 48 in the MI analysis, mean ± SEM SF-36 PCS scores had improved to 44.1 ± 0.5 and mean ± SEM ASQoL scores had improved to 3.7 ± 0.2; these improvements were maintained up to week 144, where the mean ± SEM scores were 45.3 ± 0.6 and 3.1 ± 0.2, respectively. In contrast, the mean baseline SF-36 MCS score (mean ± SEM 54.1 ± 0.5) was suggestive of nonimpaired psychological function (as it was greater than the US general population mean value of 50) and was maintained over 144 weeks of bimekizumab treatment (39).

DISCUSSION

In this first report of the BE AGILE OLE study, inhibition of IL-17F in addition to IL-17A with bimekizumab treatment for up to 3 years in patients with active AS was found to be well tolerated, with efficacy sustained in the long term. The safety profile of bimekizumab was found to be in line with previous observations, with no new safety signals or increased risk identified following up to 3 years of cumulative exposure to bimekizumab (29). These long-term results support and extend previous 1-year findings that demonstrated the efficacy and tolerability of bimekizumab in patients with AS (29).

Across weeks 0–156, study discontinuations due to TEAEs were infrequent, with only 2 patients discontinuing due to lack of efficacy; incidence rates of serious infections and injection site reactions remained low. The most frequently reported TEAEs over 3 years, which included nasopharyngitis, upper respiratory tract infections, and bronchitis, were consistent with previous 1-year studies of bimekizumab in AS and PsA patients (28,29).

A recent meta-analysis of IL-17A inhibitor trials in AS patients found that the risk of serious adverse events and serious infections did not differ significantly between active treatment and placebo (40). However, inhibition of IL-17 is known to increase susceptibility to mucosal infections by *Candida* species, which reflects the role of type 17 immunity at the oral mucosa (41–44). Indeed, increased rates of infections and candidiasis have been associated with IL-17A inhibitor treatment in patients with AS and other chronic inflammatory diseases (45,46). Here, we report data which indicate that *Candida* infections were among the most commonly reported TEAEs. While the EAIR of *Candida* infections (3.7 per 100 patient-years) in this phase IIb study was higher than those in phase III studies of IL-17A inhibitors in AS patients (12–14,47,48), the majority of cases in this study were oral candidiasis and only 1 case led to study discontinuation. Furthermore, all fungal infections were of mild or moderate intensity, localized (none were systemic), and easily managed, and none were serious. Overall, findings on safety suggest that there are no new safety concerns with increased cumulative bimekizumab exposure in patients with AS over a time period of 3 years.

IBD is a known extramusculoskeletal manifestation of axial SpA, and is also thought to be associated with exposure to IL-17A inhibitors (49). The exact mechanism by which IL-17 inhibition may exacerbate IBD has not been elucidated, with contradictory findings regarding the absolute risk reported in some epidemiologic studies (50). Of the 303 patients in the study, 7 had a history of IBD. Active IBD was infrequent with bimekizumab treatment across this 156-week study (occurring in 9 patients, including 2 with a history of IBD), and most patients who experienced IBD continued in the study. EAIRs of 0.5 cases of ulcerative colitis per 100 patient-years and 0.5 cases of Crohn's disease per 100 patient-years with bimekizumab treatment were comparable to those reported in the pooled analysis of the MEASURE 1–4 studies for patients receiving secukinumab for up to 4 years (EAIR 0.2 cases of ulcerative colitis per 100 patient-years and EAIR 0.4 cases of Crohn's disease per 100 patient-years) (51). EAIRs of ulcerative colitis and Crohn's disease with bimekizumab treatment were also comparable to those reported in a pooled analysis of the COAST-V and COAST-W studies for patients receiving ixekizumab for over 1 year (EAIR 0.4 cases of ulcerative colitis per 100 patient-years and EAIR 0.8 cases of Crohn's disease per 100 patient-years) (14). These results suggest that dual inhibition of IL-17F and IL-17A does not impact IBD flares relative to IL-17A inhibition alone; however, results from phase III studies are needed to confirm these findings.

Anterior uveitis is another extramusculoskeletal manifestation of axial SpA. Incidence of anterior uveitis across 156 weeks was low, with only 6 patients presenting with a flare, 3 of whom had histories of anterior uveitis prior to entry in the BE AGILE study. The EAIR of 0.7 cases of anterior uveitis per 100 patient-years for treatment with bimekizumab was lower than the EAIR of 1.4 cases of anterior uveitis per 100 patient-years reported in the pooled analysis of the MEASURE 1, MEASURE 2, and MEASURE 3 studies for up to 4 years of treatment with secukinumab (52), as well as a 1-year EAIR of 3.9 cases of anterior uveitis per 100 patient-years reported in a pooled analysis of the COAST-V and COAST-W studies for treatment with ixekizumab (14). The recent elucidation of a feedback loop through which the inhibition of IL-17A up-regulates IL-17F suggests that the dual inhibition of both cytokines could potentially confer additional benefits in the control of AS and its manifestations, including anterior uveitis (53). However, this prediction would need to be confirmed in subsequent studies of bimekizumab.

Efficacy analyses demonstrated that clinical outcomes were sustained over the 3-year OLE study following the rapid and clinically meaningful improvements occurring within the first year of bimekizumab treatment. Under the strictest method for handling missing data (NRI), the proportion of patients having achieved ASAS40 was >50% at all timepoints through weeks 48–156. At the time of enrolment, all patients enrolled had high or very high disease activity. By week 156, approximately half of the patient population had achieved ASDAS disease activity scores of <2.1, and approximately a quarter of the patient population had achieved ASDAS scores showing inactive disease and ASAS scores showing partial remission, demonstrating the stringent disease control attained with bimekizumab. Rapid and sustained reductions in the severity of inflammation were observed, with substantial reductions in high-sensitivity CRP levels from baseline to week 48, and low levels sustained at week 156. Additionally, BASDAI scores were sustained at very low levels with long-term bimekizumab treatment, reflecting substantial reductions, relative to baseline, across disease symptoms including spinal pain, fatigue, and stiffness. Mobility, physical function, and improvements in HRQoL achieved at week 48 were also sustained during the following 2 years of treatment with bimekizumab in this study.

The demonstrated long-term tolerability and efficacy of treatment with bimekizumab were further supported by the high rate of patient retention, with week 156 completed by nearly three-quarters of the patients randomized at baseline, or ~88% of those who enrolled in the OLE study. Efficacy at week 48 was similar among patients receiving 160 mg or 320 mg of bimekizumab every 4 weeks, and no appreciable decrease in efficacy was observed in patients who reduced their dosage from 320 mg to 160 mg every 4 weeks at the start of the OLE study.

A limitation of this analysis is the lack of an active or placebo comparator for bimekizumab during the OLE study. Placebo was only administered up to week 12, after which all patients received 160 mg or 320 mg of bimekizumab every 4 weeks. Study discontinuations also presented a limitation by potentially biasing observed results. However, patient retention was high through 3 years and imputation methods were implemented to combat potential bias, notably through NRI, the most conservative imputation approach for analyzing binary variables which may even underestimate true efficacy. We note that the underlying assumption of the MI analyses for continuous variables—that data were missing at random—may not have been met, and therefore the possibility of bias in the MI analysis cannot be eliminated. Another limitation was the absence of MRI assessment after week 48 to evaluate the long-term impact of bimekizumab on active inflammation of the spine and sacroiliac joint. In addition, as with most phase II studies of AS, no spinal radiographs were obtained during the study, and hence the impact of bimekizumab on spinal progression could not be evaluated. This will be an important area of focus in future studies.

A key strength of this phase IIb study is its 5-year duration and relatively large sample size of patients, which allows the long-term systematic monitoring of adverse events and significantly contributes to the growing evidence base for the safety and tolerability of bimekizumab in patients with AS (29,54). This study also provides the most comprehensive and long-term evidence to date of the efficacy of bimekizumab in patients with AS. The BE AGILE study and its OLE study demonstrate the sustainability of treatment effect with this first-in-class dual inhibitor of IL-17A and IL-17F. The OLE study is currently ongoing and will allow assessment of 5-year safety and efficacy outcomes upon completion. This will supplement phase III trials that are currently underway to assess bimekizumab dosages of 160 mg every 4 weeks in axial SpA patients with active nonradiographic axial SpA (ClinicalTrials.gov identifier: NCT03928704), and in patients with active AS (ClinicalTrials.gov identifier: NCT03928743). These trials will further evaluate the clinical benefits that may result from dual inhibition of IL-17A and IL-17F.

In conclusion, the safety of bimekizumab over 3 years of treatment was consistent with previous 48-week results (29). Bimekizumab delivered sustained, long-term efficacy in patients with AS, including reduced disease activity and improved patient function and quality of life. Overall, these results support bimekizumab as a promising potential treatment option in AS.

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ROLE OF THE STUDY SPONSOR

UCB Pharma facilitated the study design, funded writing assistance for the manuscript, and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Publication of this article was contingent upon approval by UCB Pharma.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Baraliakos had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Baraliakos, Deodhar, Dougados, Gensler, Molto, Ramiro, Kivitz, Poddubnyy, Oortgiesen, Vaux, Fleurinck, Shepherd-Smith, de la Loge, de Peyrecave, van der Heijde.

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