Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double-blind, placebo-controlled, dose-ranging study

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CLINICAL SCIENCE

Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double-blind, placebo-controlled, dose-ranging study

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ABSTRACT

Objectives Bimekizumab selectively neutralises both interleukin (IL)-17A and IL-17F. We report efficacy and safety in a phase IIb dose-ranging study in patients with active ankylosing spondylitis (AS).

Methods Adults with AS (fulfilling modified New York criteria) were randomised 1:1:1:1:1 to bimekizumab 16 mg, 64 mg, 160 mg, 320 mg or placebo every 4 weeks for 12 weeks (double-blind period). At week 12, patients receiving bimekizumab 16 mg, 64 mg or placebo were re-randomised 1:1 to bimekizumab 160 mg or 320 mg every 4 weeks to week 48; other patients continued on their initial dose (dose-blind period). The primary end point was Assessment of SpondyloArthritis international Society (ASAS) 40 response at week 12 (non-responder imputation (NRI) for missing data).

Results 303 patients were randomised: bimekizumab 16 mg (n=61), 64 mg (n=61), 160 mg (n=60), 320 mg (n=61) or placebo (n=60). At week 12, significantly more bimekizumab-treated patients achieved ASAS40 vs placebo (NRI: 29.5%–46.7% vs 13.3%; p<0.05 all comparisons; OR vs placebo 2.6–5.5 (95% CI 1.0 to 12.9)). A significant dose-response was observed (p<0.001). The primary end point was supported by all secondary efficacy outcomes. At week 48, 58.6% and 62.3% of patients receiving bimekizumab 160 and 320 mg throughout the study achieved ASAS40, respectively (NRI); similar ASAS40 response rates were observed in re-randomised patients. During the double-blind period, treatment-emergent adverse events occurred in 26/60 (43.3%) patients receiving placebo and 92/243 (37.9%) receiving bimekizumab.

Conclusions Bimekizumab provided rapid and sustained improvements in key outcome measures in patients with active AS, with no unexpected safety findings versus previous studies.

Trial registration number NCT02963506.

Key messages

What is already known about this subject?
► There remains a need for treatment options in ankylosing spondylitis (AS) that can provide sustained, long-term disease control and improve patient quality of life.

What does this study add?
► Bimekizumab, a monoclonal antibody that neutralises both interleukin (IL)-17A and IL-17F, has shown clinically relevant improvements in both psoriasis and psoriatic arthritis, leading to its evaluation in other IL-17-mediated diseases.
► This is the first study to assess bimekizumab in patients with active AS.
► A significant dose-response was observed with bimekizumab for ASAS40 at week 12 (p<0.05), with a rapid onset and greater ASAS40 response rates for all doses of bimekizumab versus placebo, which continued to increase to week 48.
► A similar pattern was observed across secondary outcomes, representing improvements in quality of life measures versus placebo and over time.
► Safety was in line with previous bimekizumab studies and comparable with the IL-17A inhibitor class.

How might this impact on clinical practice or future developments?
► Results from this study contribute to the growing body of evidence supporting dual neutralisation of IL-17A and IL-17F with bimekizumab as a novel therapeutic option for the treatment of AS.
► Phase III studies in patients with AS and non-radiographic axial spondyloarthritis are ongoing.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic disease, characterised by inflammation of the axial skeleton.[1] It is also referred to as radiographic axial spondyloarthritis (r-axSpA). AS can often be accompanied by other manifestations such as peripheral enthesitis and arthritis, uveitis, inflammatory bowel disease (IBD) and psoriasis.[1 2] Expression of human

leucocyte antigen (HLA)-B27 is strongly associated with the disease, and patients often have elevated levels of inflammatory markers such as C reactive protein (CRP).[1] Patients experience chronic pain and functional impairment, impacting on sleep, daily activities and overall quality of life,[3–5] with some patients experiencing physical disability due to structural damage of the spine.[6]

Non-steroidal anti-inflammatory drugs (NSAIDs) are a first-line treatment to provide symptomatic relief to patients with AS.[7] However, response to NSAIDs may be inadequate or they may be contraindicated. Conventional synthetic disease-modifying antirheumatic drugs, such as methotrexate or sulfasalazine, are not efficacious in axial disease, although the latter may be effective for patients with peripheral arthritis.[7] Tumour necrosis factor (TNF) inhibitors are the first-line biologic in patients with high disease activity, but not all patients achieve adequate disease control or tolerate treatment.[8 9] Interleukin (IL)-17A inhibitors are effective second-line therapies[10 11]; however, some patients may still experience unsatisfactory response and require alternative treatments.

The IL-17 axis represents an established target in AS treatment, and inflammation is associated with an increase in IL-17-producing innate immune cells.[12] Two members of the IL-17 cytokine family, IL-17A and IL-17F, share ~50% structural homology and have similar pro-inflammatory function, signalling via the same receptor complex.[13 14] Preclinical evidence from human in vitro assays has shown that IL-17A and IL-17F cooperate with other mediators of inflammation, such as TNF, to amplify inflammatory responses.[15] The contribution of IL-17F, in addition to IL-17A, to pathological bone formation has been shown in a human periosteum-derived stem cell model of osteogenic differentiation, indicating that neutralisation of both cytokines inhibits this process to a greater extent than IL-17A alone.[16 17] In addition, levels of IL-17A and IL-17F have been found to be higher in the serum of patients with AS versus healthy controls, correlating with markers of systemic inflammation.[18 19]

Bimekizumab is a monoclonal antibody developed to selectively neutralise both IL-17A and IL-17F,[20] and has been previously evaluated in a first-in-human study in patients with mild psoriasis, a proof-of-concept study in patients with moderate-to-severe psoriatic arthritis (PsA) and a phase IIb dose-ranging study in patients with moderate-to-severe plaque psoriasis.[15 20 21] The overlap in symptoms between psoriasis, PsA and AS,[2 22] and involvement of the IL-17 pathway, led to the evaluation of bimekizumab as a potential therapeutic option in AS. Here, we report results of the phase IIb BE AGILE study, the first dose-ranging clinical study evaluating the efficacy and safety of bimekizumab in patients with active AS.

METHODS

Study design

This phase IIb, randomised, 48-week, double-blind, placebo-controlled, parallel-group, dose-ranging study (BE AGILE) (online supplementary files 1; 2) was conducted at 74 centres across 10 countries in Europe and the USA.

Patient and public involvement

Patients with AS were consulted to understand treatment needs and recommend ways to facilitate study participation while minimising the burden of study visits. Study participants were recruited by the study sites and provided written consent to participate.

Participants

Eligible patients were ≥18 years of age with AS, as determined by documented radiographic sacroiliitis (X-rays were centrally read by two readers and a third in case of discrepancy), fulfilling the modified New York (mNY) criteria for AS,[23] symptom duration of ≥3 months, age at onset of <45 years, with active disease as defined by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 and spinal pain ≥4 on a 0–10 numerical rating scale (NRS) (from BASDAI question 2). Patients were required to have at least one of the following: inadequate response to NSAIDs (defined as a lack of response for ≥4 weeks of continuous NSAID therapy or the lack of response to ≥2 NSAIDs at the maximum tolerated dose for ≥4 weeks), intolerance to ≥1 NSAID or contraindication(s) to NSAIDs. Prior treatment with up to one TNF inhibitor was permitted, which must have been discontinued because of inadequate response, intolerance or loss of access.

Patients with active/symptomatic Crohn's disease or ulcerative colitis (UC) were excluded; previous history of Crohn's disease or UC was not an exclusion criterion. Other exclusion criteria were total ankylosis of the spine, a concurrent or history of malignancy during the past 5 years, a diagnosis of other inflammatory conditions (eg, rheumatoid arthritis), active infection or infection requiring antibiotics within 2 weeks of baseline, a history of chronic or recurrent infections or a serious/life-threatening infection within 6 months of baseline, presence of significant, uncontrolled neuropsychiatric disorder, active suicidal ideation, or positive suicide behaviour within the past 6 months.

Interventions

Initially, patients were randomised 1:1:1:1:1 to receive subcutaneous bimekizumab 16 mg, 64 mg, 160 mg, 320 mg or placebo every 4 weeks. At the end of the double-blind period at week 12, following all assessments, patients were re-allocated treatment for the dose-blind period as follows: patients initially receiving placebo, bimekizumab 16 mg or 64 mg were randomised 1:1 to receive bimekizumab 160 or 320 mg every 4 weeks through to week 48. Patients in the bimekizumab 160 and 320 mg groups continued on the same schedule through to week 48 (figure 1; see online supplementary methods for additional information on interventions and randomisation and masking).

Outcomes

The primary efficacy end point was the percentage of patients with an Assessment of SpondyloArthritis international Society (ASAS) 40 response at week 12, defined according to the ASAS Handbook.[24]

Secondary efficacy end points were ASAS20 response, ASAS5/6 response, change from baseline in BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI) and Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS), all at week 12. Additional efficacy end points included ASAS40, ASAS20, ASDAS inactive disease (ID; <1.3), ASDAS low disease activity (ASDAS-LDA; 1.3–<2.1),[25] ASDAS major improvement (ASDAS-MI; reduction ≥2.0 from baseline), ASAS partial remission (PR), change from baseline in the linear version of the Bath Ankylosing Spondylitis Metrology Index (BASMI)[26] and change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) index. Additional outcomes included measurement of high-sensitivity CRP (hs-CRP) levels in blood samples and MRI performed in a subset of patients (20 planned per treatment group) to evaluate the effect of bimekizumab on objective
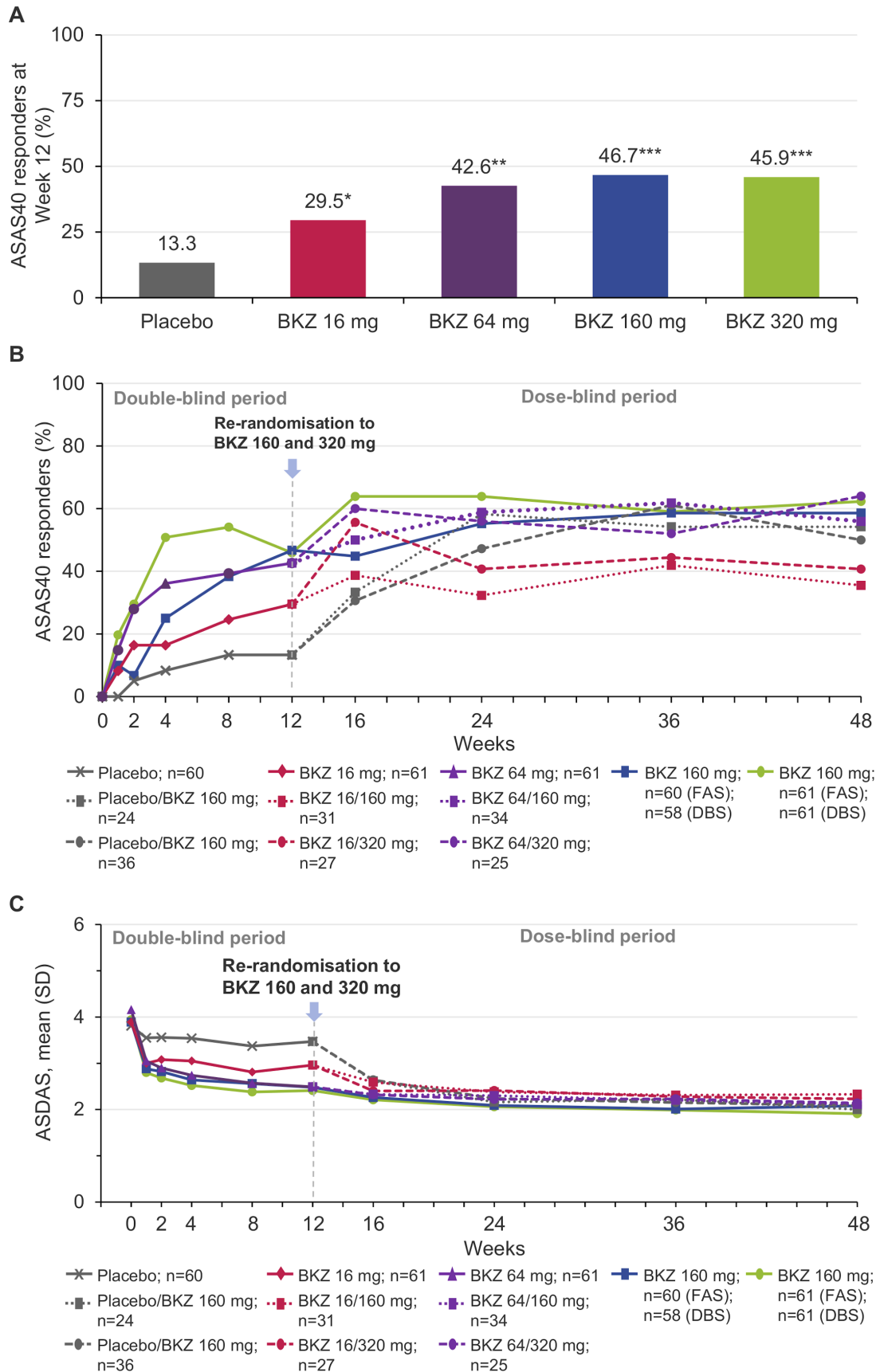
Figure 1 (A) ASAS40 response at week 12 (primary efficacy end point; FAS, NRI). *P value vs placebo calculated from a logistic regression model including fixed effects for treatment, geographic region and prior TNF inhibitor exposure; *p<0.05, **p<0.01, ***p<0.001. (B) ASAS40 responses over 48 weeks; FAS, NRI (weeks 0–12); DBS, NRI (weeks 12–48). (C) ASDAS over time; FAS, MI (weeks 0–12); DBS, MI (weeks 12–48). ASAS40, Assessment of SpondyloArthritis international Society improvement of ≥40%; ASDAS, Ankylosing Spondylitis Disease Activity Score; BKZ, bimekizumab; DBS, dose-blind set; FAS, full analysis set; MI, multiple imputation; NRI, non-responder imputation.

signs of inflammation (see online supplementary methods for additional information).

Patient-reported outcomes (PROs) included change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL), 36-Item Short Form Survey (SF-36) and sleep quality (Medical Outcomes Study (MOS)-12 item scale). Post hoc analyses included patients achieving a ≥50% improvement in BASDAI response (BASDAI 50) and change from baseline in fatigue (BASDAI question 1).

Safety monitoring included incidence of adverse events (AEs), serious AEs (SAEs), withdrawal due to AEs and AEs of special interest. AEs identified for additional safety monitoring included: serious infections including opportunistic and tuberculosis, cytopenia, severe hypersensitivity reactions, IBD, suicide ideation or behaviour, depression and anxiety, major cardiovascular events (MACE), malignancies and liver function test changes.

Statistical analysis

The sample size was calculated using a two-sided test for detecting a linear trend across proportions at a significance level of 0.05.[27] Assuming 57 patients in each treatment group, the test for detecting the overall dose response based on ASAS40 treatment response was powered at >99%. Sample size calculations were based on ASAS40 response data from phase III studies of TNF inhibitors and secukinumab in patients with AS,[11 28 29] performed using nQuery Advisor 7.0.

The full analysis set (FAS) consisted of all randomised patients who received ≥1 dose of study drug and had a valid measurement of the ASAS components at baseline. All patients starting the dose-blind period and who received ≥1 dose of study drug were included in the dose-blind set. The per-protocol set (PPS) consisted of all patients in the FAS who had no important protocol deviation affecting the primary efficacy end point. The safety set (SS) consisted of all randomised patients who received at least one dose of study drug.

The primary analysis was based on a Mantel-Haenszel test[30] and modified ridit scores with the corresponding p value. Non-responder imputation (NRI) was used to account for missing data. Pairwise comparisons of each bimekizumab dose versus placebo for ASAS40 at week 12 were based on a logistic regression model with fixed effects for treatment, region and prior TNF inhibitor exposure. Multiplicity was accounted for using a fixed sequence testing procedure with each bimekizumab dose tested sequentially versus placebo from the highest to lowest dose; each test was only conducted if the previous test reached significance at a two-sided significance level of α=0.05, to control the overall type 1 error rate. Further information is provided in the online supplementary files 1 and supplementary file 2. Other categorical end points (ASAS20 response and ASAS5/6) were analysed as for the primary efficacy end point, using NRI to account for missing patient data. For continuous end points (ASDAS, BASDAI and BASFI), multiple imputation (MI) was used to account for missing patient data. Data for the secondary and additional efficacy end points are descriptive only. Post hoc analyses and safety data were summarised using descriptive statistics by each visit.

RESULTS

In total, 601 patients were screened, with 303 randomised and included in the FAS and SS, and 282 in the PPS. The majority of screening failures were patients not fulfilling radiographic sacroiliitis according to mNY criteria (online supplementary figure 2).

The majority of patients (98.0%; 297/303) completed the double-blind period (online supplementary figure 2); 89.5% (265/296) completed the dose-blind period.

Patient demographics and baseline disease characteristics were similar across dose groups (table 1). The study population was typical of a cohort of patients with highly active, established AS;

Table 1 Patient demographics and baseline disease characteristics (FAS)

	Placebo Q4W (n=60)	BKZ 16 mg Q4W (n=61)	BKZ 64 mg Q4W (n=61)	BKZ 160 mg Q4W (n=60)	BKZ 320 mg Q4W (n=61)	All patients (n=303)
Age, years, mean (SD)	39.7 (10.3)	43.3 (12.6)	40.4 (10.9)	42.4 (13.1)	45.0 (11.4)	42.2 (11.8)
Sex (male), n (%)	49 (81.7)	53 (86.9)	52 (85.2)	52 (86.7)	50 (82.0)	256 (84.5)
Caucasian, n (%)	60 (100)	58 (95.1)	60 (98.4)	59 (98.3)	61 (100)	298 (98.3)
HLA-B27 positive, n (%)	57 (95.0)	51 (83.6)	56 (91.8)	52 (86.7)	54 (88.5)	270 (89.1)
Time since onset of first symptoms, years, mean (SD)	14.1 (8.4)	16.2 (10.6)	12.4 (8.3)	14.8 (10.3)	15.3 (10.6)	14.6 (9.7)
Time since diagnosis, years, mean (SD)	6.6 (7.2)	8.0 (9.4)	7.3 (7.8)	8.8 (9.2)	8.8 (8.8)	7.9 (8.5)
ASDAS, mean (SD)	3.8 (0.9)	3.9 (0.7)	4.2 (0.8)	3.9 (0.8)	3.9 (0.7)	3.9 (0.8)
hs-CRP, mg/L, mean (SD)	17.6 (24.6)	15.2 (17.7)	23.5 (21.6)	20.5 (19.3)	18.4 (20.6)	19.0 (20.9)
BASDAI, mean (SD)	6.5 (1.4)	6.7 (1.4)	6.7 (1.3)	6.3 (1.3)	6.5 (1.6)	6.5 (1.4)
BASFI, mean (SD)	5.6 (2.0)	5.9 (1.7)	6.0 (1.8)	5.6 (2.2)	5.9 (2.0)	5.8 (2.0)
BASMI, mean (SD)	4.4 (1.6)	4.8 (1.7)	4.7 (1.7)	4.6 (1.8)	4.8 (1.8)	4.7 (1.7)
Spinal pain score, mean (SD)	7.0 (1.7)	7.2 (1.9)	7.4 (1.6)	6.6 (2.0)	7.3 (1.5)	7.1 (1.7)
PGADA, mean (SD)	7.0 (1.7)	7.1 (1.5)	7.3 (1.6)	6.5 (1.8)	7.1 (1.9)	7.0 (1.7)
Previous TNF inhibitor therapy, n (%)	7 (11.7)	8 (13.1)	7 (11.5)	7 (11.7)	5 (8.2)	34 (11.2)
Current NSAID therapy, n (%)						
1	51 (85.0)	53 (86.9)	50 (82.0)	54 (90.0)	56 (91.8)	264 (87.1)
2	2 (3.3)	3 (4.9)	1 (1.6)	1 (1.7)	1 (1.6)	8 (2.6)
Receiving csDMARDs, n (%)	13 (21.7)	9 (14.8)	18 (29.5)	18 (30.0)	21 (34.4)	79 (26.1)

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BKZ, bimekizumab; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HLA-B27, human leucocyte antigen-B27; NSAID, non-steroidal anti-inflammatory drug; PGADA, patient global assessment of disease activity; Q4W, every 4 weeks; TNF, tumour necrosis factor.

Table 2 Primary and secondary efficacy end points (week 12; FAS, NRI/MI)

	Placebo Q4W (n=60)	BKZ 16 mg Q4W (n=61)	BKZ 64 mg Q4W (n=61)	BKZ 160 mg Q4W (n=60)	BKZ 320 mg Q4W (n=61)
ASAS40*, n (%)					
Week 12	8 (13.3)	18 (29.5)	26 (42.6)	28 (46.7)	28 (45.9)
ASAS20*, n (%)					
Week 12	17 (28.3)	25 (41.0)	38 (62.3)	35 (58.3)	44 (72.1)
ASAS5/6*, n (%)					
Week 12	4 (6.7)	18 (29.5)	30 (49.2)	32 (53.3)	33 (54.1)
BASDAI†, mean (SD)					
Baseline	6.5 (1.4)	6.7 (1.4)	6.7 (1.3)	6.3 (1.3)	6.5 (1.6)
Week 12	5.5 (2.2)	5.0 (2.1)	3.9 (2.1)	3.8 (2.0)	3.7 (2.1)
Change from baseline	−1.0 (1.7)	−1.7 (2.3)	−2.7 (2.2)	−2.5 (1.8)	−2.9 (2.2)
BASFI, mean (SD),					
Baseline	5.6 (2.0)	5.9 (1.7)	6.0 (1.8)	5.6 (2.2)	5.9 (2.0)
Week 12	5.0 (2.4)	4.6 (2.4)	4.1 (2.3)	3.9 (2.2)	3.7 (2.5)
Change from baseline	−0.6 (1.9)	−1.4 (2.2)	−1.9 (2.4)	−1.7 (1.8)	−2.2 (2.0)
ASDAS†, mean (SD),					
Baseline	3.8 (0.9)	3.9 (0.7)	4.2 (0.8)	3.9 (0.8)	3.9 (0.7)
Week 12	3.5 (1.1)	3.0 (0.9)	2.5 (0.9)	2.5 (1.0)	2.4 (0.9)
Change from baseline	−0.4 (0.7)	−0.9 (1.0)	−1.7 (1.1)	−1.4 (0.9)	−1.5 (0.9)

*NRI.
†MI.
ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BKZ, bimekizumab; FAS, full analysis set; MI, multiple imputation; NRI, non-responder imputation; Q4W, every 4 weeks.

mean ASDAS was >3.5 (3.8–4.2) in all treatment groups and mean time since diagnosis was 7.9 (6.6–8.8) years.

Efficacy
Double-blind period (to week 12)
The primary efficacy end point was reached with significantly more patients achieving ASAS40 at week 12 in all bimekizumab-treated groups (16 mg: 29.5%, OR vs placebo 2.6 (95% CI: 1.0 to 6.5); 64 mg: 42.6%, OR 4.5 (95% CI: 1.8 to 10.9); 160 mg: 46.7%, OR 5.5 (95% CI: 2.3 to 13.5); 320 mg: 45.9%, OR 5.3 (95% CI: 2.2 to 12.9)) compared with placebo (13.3%; all comparisons p<0.05) (figure 1A, table 2 and online supplementary table 1). A statistically significant dose response was observed for ASAS40 at week 12 (p<0.001), with a dose-response effect observed across bimekizumab 16–160 mg doses and similar ASAS40 response between the 160 and 320 mg groups. Rapid responses with bimekizumab were observed, with 8.2%–19.7% and 16.4%–50.8% of patients achieving ASAS40 at week 1 and at week 4 vs 0% and 8.3% receiving placebo, respectively (figure 1B and online supplementary figure 3).

The primary end point was supported by all secondary efficacy end points (online table 2). At week 12, a higher proportion of patients achieved ASAS20 and ASAS5/6 in the bimekizumab-treated groups compared with placebo. In addition, reductions from baseline in BASDAI, BASFI and ASDAS were greater in the bimekizumab-treated groups compared with placebo (table 2 and figure 1C). Other efficacy end points also indicated improvements from baseline at week 12. ASDAS-MI was achieved by 18.0%–34.4% of bimekizumab-treated patients vs 0% receiving placebo; ASDAS-ID was achieved by 3.3%–10.0% vs 0%, ASDAS-LDA was achieved by 14.8%–32.8% vs 13.3%, while ASAS-PR was achieved by 8.2%–23.0% vs 3.3%, respectively. Reductions from baseline in the MASES index were observed in patients with baseline enthesitis across bimekizumab dose groups (table 3). In post hoc analyses, BASDAI 50 was achieved

by 37.9% and 47.5% of patients receiving bimekizumab 160 and 320 mg, respectively (table 3).

Rapid reductions from baseline in hs-CRP were observed with bimekizumab treatment compared with placebo (table 3). In the 31 patients with MRI follow-up, reductions from baseline in Spondyloarthritis Research Consortium of Canada Sacro-iliac (SPARCC SI) joint score were observed at week 12 in all bimekizumab treatment groups, and in spine Berlin score were observed in the three highest bimekizumab dose groups at week 12 (online supplementary figure 4).

Improvements in patient global assessment of disease activity (PGADA), spinal pain, morning stiffness and BASFI were observed compared with baseline scores, and greater reductions from baseline in BASMI were seen in all bimekizumab-treated patients compared with placebo at week 12 (table 3). From post hoc analyses, reductions from baseline to week 12 in fatigue were observed in all patients, with the greatest reductions in the bimekizumab 160 and 320 mg groups (table 3). Change from baseline to week 12 in MOS Sleep Disturbance and Sleep Problems Index II were greater with bimekizumab in all dose groups versus placebo (table 4). Improvements in patient QoL were observed in all bimekizumab dose groups compared with placebo (table 4). Consistent with this, patient perception of physical health improved, with increases in SF-36 physical component summary (PCS) scores observed in all bimekizumab dose groups and higher scores with bimekizumab compared with placebo (table 4). SF-36 mental component summary (MCS) scores were similar to baseline, with all patients within the normal range.

Dose-blind period (weeks 12–48)
The ASAS40 response rates with bimekizumab treatment continued to increase after the first 12 weeks and were maintained to week 48 in patients continuing on the same bimekizumab dose (160 mg: 58.6%, 320 mg: 62.3%; table 3 and figure 1B). Of patients initially randomised to placebo, ≥50% achieved ASAS40 response at week 48 following re-randomisation to

Table 3   Other efficacy end points up to 48 weeks of bimekizumab treatment (DBS, NRI and MI)

n (%)		Placebo →		BKZ 16 mg →		BKZ 64 mg →		BKZ 160 mg (n=58)	BKZ 320 mg (n=61)
		BKZ 160 mg (n=24)	BKZ 320 mg (n=36)	BKZ 160 mg (n=31)	BKZ 320 mg (n=27)	BKZ 160 mg (n=34)	BKZ 320 mg (n=25)		
ASAS40*	Baseline	–	–	–	–	–	–	–	–
	Week 12	5 (20.8)	3 (8.3)	12 (38.7)	6 (22.2)	16 (47.1)	10 (40.0)	28 (48.3)	28 (45.9)
	Week 48	13 (54.2)	18 (50.0)	11 (35.5)	11 (40.7)	19 (55.9)	16 (64.0)	34 (58.6)	38 (62.3)
ASAS20*	Baseline	–	–	–	–	–	–	–	–
	Week 12	9 (37.5)	8 (22.2)	14 (45.2)	11 (40.7)	21 (61.8)	17 (68.0)	35 (60.3)	44 (72.1)
	Week 48	17 (70.8)	22 (61.1)	17 (54.8)	14 (51.9)	25 (73.5)	20 (80.0)	45 (77.6)	46 (75.4)
ASAS5/6*	Baseline	–	–	–	–	–	–	–	–
	Week 12	2 (8.3)	2 (5.6)	10 (32.3)	8 (29.6)	19 (55.9)	11 (44.0)	32 (55.2)	33 (54.1)
	Week 48	15 (62.5)	16 (44.4)	13 (41.9)	13 (48.1)	21 (61.8)	20 (80.0)	37 (63.8)	40 (65.6)
ASAS-PR*	Baseline	0	0	0	0	0	0	1.7	0
	Week 12	1 (4.2)	1 (2.8)	3 (9.7)	2 (7.4)	5 (14.7)	4 (16.0)	10 (17.2)	14 (23.0)
	Week 48	8 (33.3)	8 (22.2)	4 (12.9)	8 (29.6)	7 (20.6)	7 (28.0)	17 (29.3)	21 (34.4)
ASDAS-MI†	Baseline	–	–	–	–	–	–	–	–
	Week 12	0	0	7 (22.6)	4 (14.8)	13 (38.2)	8 (32.0)	15 (25.9)	19 (31.1)
	Week 48	8 (33.3)	11 (30.6)	11 (35.5)	9 (33.3)	20 (58.8)	10 (40.0)	24 (41.4)	34 (55.7)
ASDAS-ID†	Baseline	0	0	0	0	0	0	0	0
	Week 12	0	0	1 (3.2)	1 (3.7)	3 (8.8)	3 (12.0)	6 (10.3)	6 (9.8)
	Week 48	4 (16.7)	5 (13.9)	3 (9.7)	6 (22.2)	6 (17.6)	4 (16.0)	15 (25.9)	15 (24.6)
ASDAS-LDA†	Baseline	0	0	0	0	0	0	1.7	0
	Week 12	3 (12.5)	5 (13.9)	6 (19.4)	3 (11.1)	10 (29.4)	9 (36.0)	16 (27.6)	20 (32.8)
	Week 48	9 (37.5)	16 (44.4)	10 (32.3)	7 (25.9)	13 (38.2)	8 (32.0)	17 (29.3)	23 (37.7)
Mean (SD)									
ASDAS†	Baseline	3.71 (0.83)	3.88 (0.93)	3.96 (0.72)	3.84 (0.65)	4.12 (0.80)	4.18 (0.74)	3.86 (0.76)	3.94 (0.74)
Change from baseline	Week 12	−0.31 (0.73)	−0.37 (0.62)	−1.11 (1.07)	−0.85 (1.01)	−1.72 (0.99)	−1.64 (1.21)	−1.40 (0.94)	−1.52 (0.94)
	Week 48	−1.70 (0.89)	−1.80 (0.89)	−1.63 (1.05)	−1.61 (0.93)	−2.01 (1.12)	−2.04 (0.95)	−1.78 (0.95)	−2.03 (0.92)
BASDAI 50*	Baseline	–	–	–	–	–	–	–	–
	Week 12	3 (12.5)	4 (11.1)	9 (29.0)	5 (18.5)	14 (41.2)	12 (48.0)	22 (37.9)	29 (47.5)
	Week 48	11 (45.8)	20 (55.6)	12 (38.7)	10 (37.0)	20 (58.8)	14 (56.0)	30 (51.7)	35 (57.4)
Geometric mean (median)	Baseline	6.2 (6.1)	9.3 (10.9)	11.4 (10.7)	8.1 (9.9)	14.2 (16.7)	14.7 (17.6)	12.0 (16.0)	10.4 (11.3)
hs-CRP†	Week 12	9.1 (9.4)	8.0 (9.4)	5.6 (5.5)	3.8 (4.3)	2.9 (3.0)	5.3 (6.1)	3.7 (4.3)	3.8 (3.5)
	Week 48	2.9 (2.2)	2.9 (3.0)	4.0 (5.0)	3.0 (3.8)	3.4 (3.5)	4.1 (3.9)	3.9 (4.7)	3.0 (3.6)
BASFI†	Baseline	5.8 (1.8)	5.5 (2.2)	5.8 (1.7)	5.9 (1.9)	5.6 (1.8)	6.2 (1.8)	5.5 (2.2)	5.9 (2.0)
Change from baseline	Week 12	−1.0 (2.1)	−0.3 (1.7)	−1.7 (2.0)	−1.1 (2.5)	−1.6 (2.5)	−2.1 (2.3)	−1.7 (1.8)	−2.2 (2.0)
	Week 48	−2.9 (2.2)	−2.4 (2.2)	−2.3 (1.5)	−2.5 (2.0)	−2.8 (2.4)	−2.9 (2.4)	−2.5 (2.0)	−2.9 (2.2)
Spinal pain†	Baseline	6.9 (1.4)	7.0 (1.9)	6.8 (2.1)	7.7 (1.4)	7.4 (1.5)	7.4 (1.8)	6.6 (2.0)	7.3 (1.5)
Change from baseline	Week 12	−1.5 (1.6)	−0.7 (1.7)	−2.2 (2.4)	−2.2 (2.4)	−3.3 (2.2)	−3.2 (2.7)	−2.6 (2.2)	−3.6 (2.4)
	Week 48	−3.7 (2.0)	−3.7 (2.6)	−3.0 (2.9)	−3.8 (2.7)	−4.2 (2.4)	−4.1 (2.2)	−3.8 (2.4)	−4.7 (2.1)
Morning stiffness†	Baseline	6.9 (1.7)	6.7 (2.0)	6.7 (2.0)	6.4 (1.9)	6.5 (2.2)	7.2 (1.7)	6.5 (1.8)	6.6 (2.1)
Change from baseline	Week 12	−1.5 (1.7)	−1.1 (1.5)	−2.6 (3.0)	−1.7 (2.8)	−2.9 (2.9)	−3.5 (2.5)	−2.8 (2.0)	−3.4 (2.7)
	Week 48	−3.9 (2.2)	−3.6 (2.4)	−3.7 (3.0)	−3.2 (2.3)	−3.9 (2.8)	−4.4 (2.0)	−3.9 (2.2)	−4.4 (2.4)
BASMI†	Baseline	4.3 (1.6)	4.5 (1.6)	4.7 (1.7)	4.9 (1.8)	4.5 (1.8)	4.9 (1.5)	4.6 (1.8)	4.8 (1.8)
Change from baseline	Week 12	−0.3 (0.6)	−0.1 (0.8)	−0.5 (1.0)	−0.4 (0.6)	−0.5 (0.8)	−0.4 (0.7)	−0.3 (0.7)	−0.7 (0.7)
	Week 48	−0.9 (1.0)	−0.7 (1.0)	−0.7 (1.1)	−0.9 (0.7)	−0.6 (0.7)	−0.9 (0.7)	−0.5 (1.0)	−1.0 (0.9)
Fatigue†	Baseline	6.4 (1.7)	6.8 (1.6)	7.1 (1.6)	7.1 (1.6)	6.8 (1.2)	6.7 (1.5)	6.4 (1.7)	6.4 (1.9)
Change from baseline	Week 12	−0.7 (2.5)	−1.0 (1.7)	−1.6 (2.2)	−1.6 (2.3)	−2.4 (2.1)	−2.6 (2.4)	−2.1 (2.2)	−2.1 (2.5)
	Week 48	−2.7 (2.2)	−2.8 (2.4)	−2.7 (2.0)	−3.2 (2.7)	−3.5 (2.3)	−3.1 (2.0)	−3.1 (2.1)	−3.3 (2.4)
PGADA†	Baseline	7.0 (1.5)	6.9 (1.9)	7.0 (1.7)	7.4 (1.3)	7.4 (1.5)	7.1 (1.8)	6.5 (1.8)	7.1 (1.9)
Change from baseline	Week 12	−1.5 (1.8)	−0.7 (1.6)	−1.9 (2.9)	−2.0 (2.4)	−3.3 (2.3)	−3.2 (2.7)	−2.2 (2.6)	−3.2 (2.2)
	Week 48	−3.8 (2.3)	−3.5 (2.7)	−3.3 (3.1)	−3.4 (2.6)	−4.0 (2.4)	−4.0 (2.4)	−3.5 (2.3)	−4.5 (2.3)

MASES‡		Placebo →		BKZ 16 mg →		BKZ 64 mg →		BKZ 160 mg (n=40)	BKZ 320 mg (n=42)
		BKZ 160 mg (n=17)	BKZ 320 mg (n=23)	BKZ 160 mg (n=21)	BKZ 320 mg (n=18)	BKZ 160 mg (n=22)	BKZ 320 mg (n=11)		
Change from baseline	Baseline	4.1 (3.0)	5.0 (3.5)	3.5 (2.4)	5.9 (3.4)	4.6 (3.4)	3.9 (2.5)	3.8 (2.2)	4.6 (3.2)
	Week 12	−2.5 (2.1)	−2.1 (3.7)	−1.2 (4.1)	−2.0 (3.1)	−2.4 (1.9)	−3.6 (2.2)	−2.5 (2.3)	−2.7 (2.4)
	Week 48	−3.8 (3.1)	−4.4 (3.6)	−2.5 (3.0)	−4.6 (2.8)	−3.1 (2,7)	−3.2 (2.6)	−3.3 (2.2)	−3.4 (3.2)

*NRI.
†MI.
‡In patients with enthesitis at baseline.
ASAS, Assessment of SpondyloArthritis international Society; ASAS-PR, ASAS partial remission; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASDAS-ID, ASDAS inactive disease; ASDAS-LDA, ASDAS low disease activity; ASDAS-MI, ASDAS major improvement; BASDAI 50, Bath Ankylosing Spondylitis Disease Activity Index ≥50% improvement; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BKZ, bimekizumab; DBS, dose-blind set; hs-CRP, high-sensitivity C reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MI, multiple imputation; NRI, non-responder imputation; NRS, numerical rating scale; PGADA, patient global assessment of disease activity.

Table 4 Patient-reported outcomes (week 12 (FAS) and week 48 (DBS); MI)

Mean (SD)		Placebo → BKZ 160 mg (n=24)	Placebo → BKZ 320 mg (n=36)	BKZ 16 mg → BKZ 160 mg (n=31)	BKZ 16 mg → BKZ 320 mg (n=27)	BKZ 64 mg → BKZ 160 mg (n=34)	BKZ 64 mg → BKZ 320 mg (n=25)	BKZ 160 mg (n=58)	BKZ 320 mg (n=61)
MOS Sleep Disturbance	Baseline	45.3 (8.3)	46.2 (6.8)	48.4 (8.3)	44.6 (10.0)	47.6 (9.6)	47.8 (7.5)	47.3 (8.1)	48.0 (8.9)
Change from baseline	Week 12	2.3 (8.4)	1.8 (6.0)	1.9 (8.4)	4.7 (8.7)	5.8 (7.9)	4.7 (5.6)	5.8 (6.2)	6.6 (7.5)
	Week 48	7.3 (7.8)	6.9 (7.0)	3.8 (7.9)	8.8 (8.1)	7.6 (8.9)	6.7 (7.4)	6.6 (6.3)	6.7 (7.7)
MOS Sleep Problems Index II	Baseline	45.5 (8.1)	45.3 (7.9)	48.2 (8.7)	42.4 (10.1)	47.6 (9.4)	47.5 (7.1)	46.9 (7.5)	47.2 (9.4)
Change from baseline	Week 12	2.1 (8.3)	1.8 (6.8)	2.2 (9.4)	5.9 (9.3)	5.9 (8.1)	4.9 (6.1)	5.6 (6.7)	6.8 (7.5)
	Week 48	7.6 (8.7)	8.0 (9.1)	4.1 (7.5)	10.0 (9.0)	8.1 (8.6)	8.0 (7.2)	6.5 (6.1)	8.0 (7.92)
ASQoL	Baseline	8.4 (4.7)	9.2 (4.7)	8.4 (4.4)	9.2 (4.1)	7.9 (4.2)	9.6 (4.0)	8.4 (4.3)	8.7 (4.3)
Change from baseline	Week 12	−1.3 (5.5)	−1.3 (3.7)	−2.8 (5.2)	−1.9 (5.4)	−3.5 (3.6)	−5.0 (4.2)	−3.5 (4.3)	−4.6 (4.8)
	Week 48	−4.2 (5.6)	−5.3 (5.6)	−3.9 (4.6)	−5.0 (4.7)	−5.0 (4.1)	−6.3 (4.4)	−4.9 (4.1)	−5.4 (4.8)
SF-36 PCS	Baseline	32.8 (6.9)	33.0 (8.4)	32.5 (8.7)	30.9 (6.5)	31.9 (7.8)	30.3 (5.6)	33.0 (8.2)	32.4 (7.7)
Change from baseline	Week 12	5.8 (6.9)	2.0 (6.2)	7.8 (7.4)	7.4 (9.3)	8.9 (8.8)	9.5 (8.4)	8.5 (7.6)	8.2 (7.2)
	Week 48	12.8 (9.4)	10.9 (8.1)	10.1 (7.4)	12.6 (9.2)	12.9 (10.2)	13.4 (7.8)	12.0 (9.1)	12.0 (8.5)
SF-36 MCS	Baseline	54.0 (9.1)	53.6 (8.7)	54.6 (9.5)	52.0 (7.8)	55.8 (7.4)	54.4 (7.2)	53.8 (8.1)	54.4 (8.5)
Change from baseline	Week 12	−0.4 (8.5)	0.3 (7.2)	−0.1 (7.9)	3.8 (8.2)	1.7 (6.9)	4.0 (8.1)	1.0 (7.4)	3.4 (6.9)
	Week 48	1.3 (10.2)	1.5 (7.8)	1.8 (7.8)	6.2 (8.4)	2.2 (6.6)	4.0 (7.0)	1.72 (8.2)	3.0 (7.7)

ASQoL, Ankylosing Spondylitis Quality of Life; BKZ, bimekizumab; DBS, dose-blind set; FAS, full analysis set; SF-36 MCS, SF-36 mental component summary; MI, multiple imputation; MOS, Medical Outcomes Study; SF-36 PCS, SF-36 physical component summary; SF-36, 36-Item Short Form Questionnaire.

bimekizumab 160 or 320 mg (54.2% and 50.0%, respectively). ASAS20, ASAS5/6, ASDAS-MI, ASDAS-ID and ASAS-PR responses continued to increase from week 12 to week 48 (table 3). ASDAS levels continued to decrease after week 12 and were maintained to week 48 (figure 1C). In patients with baseline enthesitis, further reductions from baseline in MASES index were observed, with similar reductions seen across all bimekizumab dose groups (table 3). In post hoc analyses, BASDAI 50 response rates increased to week 48, with patients re-randomised from placebo to bimekizumab 160 or 320 mg achieving similar responses to patients receiving 160 and 320 mg throughout the study (table 3).

Following rapid reductions from baseline to week 12, hs-CRP levels were maintained in the bimekizumab 160 and 320 mg groups; in re-randomised patients, hs-CRP levels were similar to those who remained on the same bimekizumab dose throughout the study (table 3). SPARCC SI scores were low but marked reductions from baseline were observed at week 48, with the greatest reductions observed in the group re-randomised from placebo to bimekizumab 160 and 320 mg. MRI data were only available for two patients receiving bimekizumab 160 mg throughout the study and their baseline SPARCC SI scores were low; therefore, reductions in SPARCC SI were not observed in this dose group. Reductions from baseline in spine Berlin score at week 48 were also observed in bimekizumab-treated patients (online supplementary figure 4).

Improvements in PROs continued to week 48, with reductions from baseline in PGADA, spinal pain, morning stiffness, and BASFI observed in all treatment groups (table 3). Continued improvements in mobility were observed, with bimekizumab-treated patients experiencing reductions from baseline in BASMI (table 3). At week 48, similar reductions from baseline in fatigue were observed across bimekizumab dose groups (table 3). Improvements in Sleep Disturbance and Sleep Problems Index II seen at week 12 were maintained to week 48 in bimekizumab-treated patients (table 4). Patients who initially received placebo and were re-randomised to bimekizumab reported similar reductions in ASQoL during the dose-blind period as those receiving bimekizumab 160 and 320 mg from the start of the study (table 4). After initial improvements in SF-36 PCS scores over the first 12 weeks, scores were maintained in bimekizumab-treated patients; scores in SF-36 MCS remained similar to the double-blind period (table 4).

Safety

During the double-blind period, treatment-emergent AEs (TEAEs) were reported by 37.9% (92/243) of bimekizumab-treated patients compared with 43.3% (26/60) of patients receiving placebo. Overall, up to week 48, 77.6% (235/303) of patients reported TEAEs while receiving bimekizumab (table 5); the majority were mild or moderate in severity. The most frequently reported TEAE (≥10% of patients in any treatment group) in bimekizumab-treated patients was nasopharyngitis (11.2%, 34/303; table 5). There was no apparent dose relationship with type or frequency of TEAEs.

During the double-blind period, SAEs were reported by 1.2% (3/243) of bimekizumab-treated patients and 3.3% (2/60) of those receiving placebo. Thirteen of 303 (4.3%) patients receiving bimekizumab experienced SAEs during the 48-week study duration (see online supplementary file). TEAEs leading to discontinuation were reported by 2.5% (6/243) of bimekizumab-treated patients vs 1.7% (1/60) of patients receiving placebo in the double-blind period. Overall, 6.6% (20/303) of patients discontinued due to TEAEs.

Oral candidiasis was reported by 3 (4.9%) patients in the bimekizumab 320 mg group during the double-blind period (table 5) and 16/303 (5.3%) of bimekizumab-treated patients in total. All cases were mild to moderate, resolved with systemic or topical antifungal treatment and no events led to patients withdrawing from the study.

Four cases of IBD were reported (further details in online supplementary file). Two cases were new diagnoses of Crohn's disease and were mild to moderate in intensity. One case (bimekizumab 320 mg group) occurred during the dose-blind period, was identified as related to treatment and resolved, the other (bimekizumab 160 mg group) was considered unrelated to treatment, with diagnosis confirmed after the patient had withdrawn

Table 5 Summary of safety results (SS)

	Double-blind period					Overall treatment period		
	Placebo Q4W (n=60) n* (%) (#)	BKZ 16 mg Q4W (n=61) n* (%) (#)	BKZ 64 mg Q4W (n=58) n* (%) (#)	BKZ 160 mg Q4W (n=63) n* (%) (#)	BKZ 320 mg Q4W (n=61) n* (%) (#)	BKZ 160 mg Q4W (n=149) n (EAIR)	BKZ 320 mg Q4W (n=150) n (EAIR)	All BKZ† (n=303) n (EAIR)
Any TEAE	26 (43.3) (41)	26 (42.6) (50)	17 (29.3) (33)	20 (31.7) (33)	29 (47.5) (61)	103 (168.7)	122 (221.1)	235 (186.2)
Nasopharyngitis	0	2 (3.3) (2)	1 (1.7) (1)	3 (4.8) (3)	0	13 (12.0)	19 (16.6)	34 (13.7)
Pharyngitis	0	0	0	2 (3.2) (2)	1 (1.6) (1)	11 (10.0)	7 (6.1)	18 (7.1)
Bronchitis	1 (1.7) (1)	0	2 (3.4) (2)	0	0	4 (3.6)	12 (10.4)	18 (7.1)
Upper respiratory tract infection	1 (1.7) (1)	0	1 (1.7) (1)	0	1 (1.6) (1)	5 (4.5)	11 (9.5)	17 (6.7)
Oral candidiasis	0	0	0	0	3 (4.9) (3)	8 (7.2)	8 (7.0)	16 (6.3)
Serious TEAEs	2 (3.3) (2)	0	2 (3.4) (5)	1 (1.6) (2)	0	5 (4.4)	6 (5.1)	13 (5.1)
Permanent withdrawal of study medication due to TEAEs	1 (1.7) (1)	2 (3.3) (2)	1 (1.7) (1)	1 (1.6) (2)	2 (3.3) (2)	7 (6.2)	10 (8.7)	20 (7.9)
Drug-related TEAEs	6 (10.0) (8)	9 (14.8) (12)	6 (10.3) (10)	7 (11.1) (8)	12 (19.7) (17)	48 (52.0)	54 (58.7)	110 (54.0)
Death	0	0	0	1 (1.6) (1)	0	1 (0.9)	0	1 (0.4)
TEAEs of special interest	5 (8.3) (5)	9 (14.8) (10)	6 (10.3) (9)	3 (4.8) (3)	5 (8.2) (7)			
Opportunistic infection	0	1 (1.6) (1)	0	0	0	0	0	1 (0.38)
Candida infections	0	0	0	0	3 (4.9) (3)	10 (9.1)	9 (7.9)	19 (7.5)
Neutropenia	0	0	0	0	0	1 (0.9)	0	1 (0.4)
Severe hypersensitivity reactions	0	0	0	0	0	0	0	0
Suicide ideation	0	0	0	0	0	0	0	0
Psychiatric disorder	2 (3.3) (2)	1 (1.6) (1)	0	0	0	0	0	1 (0.3)
Major cardiovascular events	0	0	0	1 (1.6) (1)	0	2 (1.8)	0	2 (0.8)
Hepatic events	2 (3.3) (2)	6 (9.8) (6)	4 (6.9) (7)	1 (1.6) (1)	1 (1.6) (2)	13 (12.1)	12 (10.4)	33 (13.6)
ALT increased	0	1 (1.6) (1)	1 (1.7) (1)	0	1 (1.6) (1)	5 (4.5)	6 (5.1)	13 (5.1)
AST increased	0	0	1 (1.7) (1)	0	1 (1.6) (1)	3 (2.7)	5 (4.3)	9 (3.5)
GGT increased	1 (1.7) (1)	2 (3.3) (2)	2 (3.4) (3)	0	0	6 (5.4)	4 (3.4)	13 (5.1)
Hepatic enzyme increased	1 (1.7) (1)	2 (3.3) (2)	1 (1.7) (1)	0	0	0	3 (2.5)	6 (2.3)
Malignancies	0	0	0	0	0	0	0	0
Inflammatory bowel disease	0	1 (1.6) (1)	0	0	0	1 (0.9)	2 (1.7)	4 (1.5)

In addition, one patient received doses of 160 and 320 mg in error and was therefore included in both the 160 and 320 mg groups, but only once in the all-BKZ group; (#) the number of individual occurrences of the AE.

*Number of patients reporting at least one TEAE.

†The all-BKZ group included 5 patients who received BKZ in the double-blind period but did not receive BKZ 160 or 320 mg: 2 patients in the 16 mg group and 2 patients in the 64 mg group discontinued before re-randomisation; 1 patient in the 16 mg group did not start the dose-blind period.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BKZ, bimekizumab; EAIR, exposure-adjusted incidence rate per 100 patient-years; GGT, gamma-glutamyltransferase; Q4W, every 4 weeks; SS, safety set; TEAE, treatment-emergent adverse event.

from the study. Two cases were UC, one with a history of UC and one new diagnosis; both were considered mild and unrelated to treatment. The new diagnosis of UC occurred during the double-blind period (bimekizumab 16 mg, week 4). The other case was an exacerbation of UC during the dose-blind period in a patient with a history of UC who was receiving concomitant mesalazine (bimekizumab 320 mg, week 24). Overall, the exposure adjusted incidence rate (EAIR) per 100 patient-years for Crohn's disease and UC was 0.77 each.

There were four cases of acute anterior uveitis during the study; two of these occurred in patients receiving bimekizumab, one during treatment and one after discontinuation (see online supplementary file). Overall, 15.2% of patients in the study reported a history of uveitis or iridocyclitis at baseline (patients with a recent history of uveitis were not excluded); the incidence rate of uveitis in patients receiving bimekizumab was 0.53 (EAIR 0.77).

Two cases adjudicated as MACE were reported: one SAE (described in the online supplementary file), and one myocardial infarction (bimekizumab 160 mg), which resolved, was considered unrelated to treatment and did not lead to treatment discontinuation.

No malignancies, severe hypersensitivity reactions or suicidal ideation were reported during the 48-week study (table 5).

No clinically meaningful changes from baseline in vital sign measurements (systolic and diastolic blood pressure, and pulse rate), or ECG results were observed in any treatment group during the overall study.

DISCUSSION

This was the first phase IIb study of bimekizumab in patients with active AS. Bimekizumab-treated patients had rapid and significant ASAS40 responses versus placebo at week 12 and these were supported by all secondary efficacy end points, as well as additional QoL and patient-reported measures of function and disease activity. All outcomes further improved from week 12 and were sustained to week 48. This study offers insights into the potential efficacy of bimekizumab for the treatment of patients with AS and provides further support for the encouraging findings from clinical and preclinical studies of bimekizumab,[15 21 31] that dual neutralisation of IL-17A and IL-17F may be effective in the treatment of IL-17-mediated inflammatory diseases.

TNF and IL-17A inhibitors are currently recommended for the management of patients with AS[7 9]; the novel biological DMARD bimekizumab may provide an alternative therapeutic approach. A significant dose response was observed in ASAS40 at week 12 with increasing bimekizumab dose from 16 to 320 mg; responses were generally similar for the three highest doses and the greatest response was in the 160 mg group. The parallel study of bimekizumab in PsA also demonstrated the greatest ACR50 response in the 160 mg dose group.[31] In patients with moderate-to-severe plaque psoriasis,[21] the greatest responses were observed with bimekizumab 320 mg; this differing dose response may be due to differences between patient populations and efficacy in axial or joint disease compared with skin manifestations. Here, for all measures of disease activity, response rates increased and were sustained from week 12 through week 48 in patients continuing on bimekizumab 160 and 320 mg. Notably, patients re-randomised at week 12 responded rapidly and achieved similar response rates from week 24 to week 48 to patients receiving bimekizumab 160 or 320 mg continuously throughout the study. Although there was a rapid onset of response for the primary and secondary efficacy end points, more stringent outcomes, such as ASDAS-ID, required observation over a longer time period; by week 48, one-quarter of this patient population with highly active disease achieved inactive disease in both the bimekizumab 160 and 320 mg groups.

Levels of inflammation, as measured by hs-CRP, decreased rapidly with bimekizumab treatment, with low levels of inflammation maintained to week 48 in all bimekizumab-treated patients. SPARCC SI and spine Berlin scores generally improved from week 12 through week 48 across bimekizumab groups; however, results should be interpreted with caution due to the small number of patients per treatment group (range, 2–12) who had MRI assessments.

AS has a substantial impact on patients' QoL in many key areas such as completion of daily activities, fatigue and sleep, with pain acknowledged as one of the most burdensome symptoms.[32] Bimekizumab rapidly improved patient-reported spinal pain and improvements continued over the duration of the study. Changes from baseline to week 12 in sleep disturbance and sleep problems suggested that bimekizumab treatment improved sleep outcomes for patients, which were maintained to week 48. In addition, reductions in fatigue from baseline to week 12 and week 48 indicated sustained improvements for patients in another key symptom of their disease. Changes from baseline in SF-36 PCS domain indicated positive improvements in the physical aspects of patients' disease.

Overall, bimekizumab was generally well tolerated across the treatment groups. The safety profile in patients with active AS was as expected given previous studies of bimekizumab in patients with psoriasis or PsA.[15 21] Consistent with the mechanism of action of therapies targeting the IL-17 pathway, 16 cases (5%) of oral candidiasis were reported in bimekizumab-treated patients across the 48 weeks of treatment.[11 33] However, all cases were mild or moderate and did not lead to discontinuation. Four cases of IBD were reported, including one in a patient with a history of UC; incidence of IBD is a known side effect of IL-17A inhibition but is also a recognised manifestation of axSpA. The incidence of IBD reported in this study of bimekizumab is comparable to that seen with TNF inhibitors,[34] secukinumab[35] and ixekizumab in AS.[36] To date, IBD has not been reported with bimekizumab in studies involving patients with psoriasis or PsA.[21 31]

The ASAS40 responses and secondary outcomes observed with bimekizumab in this phase IIb study compare favourably with those observed with ixekizumab[10] and secukinumab[11] in recent phase III studies in AS, involving similar numbers of patients. The 48-week duration of this study, providing long-term efficacy data for bimekizumab ahead of completion of the phase III studies and demonstrating maintenance of responses over time, represents a strength of the study design. Study limitations include the relatively short placebo control period of 12 weeks, small patient numbers per treatment group due to the nature of the study design, a high number of Caucasian patients and MRI data being available for only a subset of patients.

In summary, bimekizumab may provide a promising therapeutic option for patients with AS. Bimekizumab treatment resulted in rapid and sustained improvements across multiple outcomes of disease activity, QoL and function. These results support phase III evaluation of bimekizumab in axSpA (BE MOBILE 1, NCT03928704; BE MOBILE 2, NCT03928743) to determine the clinical benefits that may be associated with neutralising IL-17F in addition to IL-17A.

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Data availability statement Underlying data from this manuscript may be requested by qualified researchers six 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 pre-specified time, typically 12 months, on a password protected portal.

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Correction: *Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double blind, placebo-controlled, dose-ranging study*

Van der Heijde D, Gensler LS, Deodhar, *et al*. Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double blind, placebo-controlled, dose-ranging study. *Ann of Rheum Dis* 2020;79:595–4.
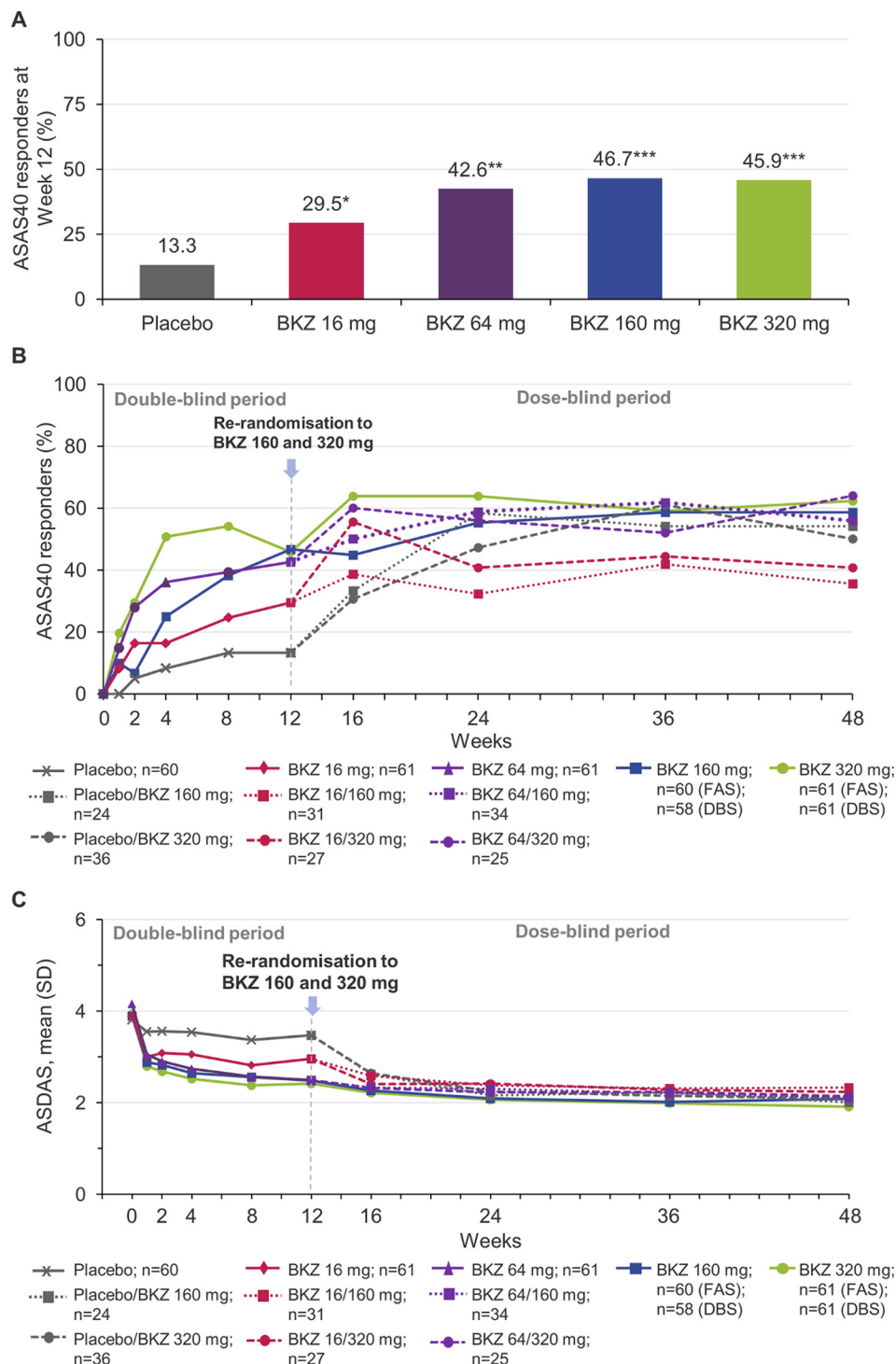
The legend for the Figure 1B,C labels should read 'Placebo/BKZ **320** mg; n=36' instead of 'Placebo/BKZ 160 mg; n=36'; and 'BKZ **320** mg; n=61 (FAS); n=61 (DBS)' instead of 'BKZ 160 mg; n=61 (FAS); n=61 (DBS)'.

A citation to the following paper should be included after first mention of the copyrighted SPARCC instrument: Maksymowych WP, *et al*. Spondyloarthritis Research Consortium of Canada MRI index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. Arthritis Rheum 2005;53(5):703–9. doi: 10.1002/art.21445.

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Van der Heijde D, Gensler LS, Deodhar, *et al*. Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double blind, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2020;79:595–604. doi: 10.1136/annrheumdis-2020-216980

The authors have been made aware that one patient initially randomised to the bimekizumab 320 mg group withdrew from the study during the dose-blind period due to an event of oral candidiasis. Therefore, the current article contains an error in the Safety section of the Results and Discussion section:

In both instances, the statements regarding the lack of study withdrawals/discontinuations due to oral candidiasis are incorrect, as one patient withdrew from the study due to oral candidiasis.

The correct text should state:

Safety section of the Results

Oral candidiasis was reported by 3 (4.9%) patients in the bimekizumab 320 mg group during the double-blind period (table 5) and 16/303 (5.3%) of bimekizumab-treated patients in total. All cases were mild to moderate, none were serious, and resolved with systemic or topical antifungal treatment. One patient withdrew from the study during the dose-blind period due to oral candidiasis.

Discussion

Consistent with the mechanism of action of therapies targeting the IL-17 pathway, 16 cases (5%) of oral candidiasis were reported in bimekizumab-treated patients across the 48 weeks of treatment.[11 33] However, all cases were mild or moderate, and most did not lead to discontinuation.

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