Efficacy and Safety of Bimekizumab in Axial Spondyloarthritis: Results of Two Parallel Phase 3 Randomized Controlled Trials

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SUPPLEMENTARY METHODS

Trial design and oversight

The stratification categories for randomization in BE MOBILE 1 were MRI/CRP classification (MRI+/CRP+, MRI+/CRP−, MRI−/CRP+) and region (Asia, Eastern Europe, Western Europe, and North America). MRIs of the sacroiliac joints (SIJ) were assessed as ASAS positive (MRI+) or negative (MRI−) through central reading by two independent expert readers with an adjudicator.[1] Elevated CRP was defined as ≥6.0 mg/L according to the central laboratory. The stratification categories for randomization in BE MOBILE 2 were previous tumor factor inhibitor (TNFi) exposure (Yes, No) and region (Asia, Eastern Europe, Western Europe, and North America). The maximum proportion of patients with prior TNFi exposure permitted to enroll in each trial was restricted to approximately 30%.

From Week 20 onwards, all patients were eligible for non-biologic rescue therapy at the investigator's discretion. All patients, investigator site personnel, and operational staff employed by the sponsor remained blinded to the initial treatment group assignment until completion of the maintenance period at Week 52. Study sponsor personnel who were not involved in conducting the trial remained blinded until the database lock for the Week 24 analysis.

In response to the COVID-19 pandemic, a protocol amendment was made to include supportive analyses of an additional COVID-19 free data set, enabling the impact of the pandemic on the BE MOBILE trials to be evaluated. The COVID-19 free set consists of all patients in the randomized set who had no COVID-19 impact up to the primary efficacy endpoint at Week 16. The impact of the COVID-19 pandemic on trial procedures/conduct (including a listing of trial visits affected by COVID-19) and the primary efficacy endpoint and safety endpoints (treatment-emergent adverse events

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[TEAEs], treatment-emergent serious adverse events [SAEs], and discontinuation from the trial due to TEAEs) were also investigated and additional analysis outputs provided as appropriate. These additional analyses were not planned as part of the protocol as the pandemic was not ongoing at the time of protocol finalization.

The sponsor, UCB Pharma, funded and designed the trials with participation of authors who advised the sponsor. UCB Pharma provided the trial drug and conducted the statistical analyses. All authors had full access to the trial data and vouch for its accuracy and completeness and for the fidelity of the trial to the protocol. Confidentiality agreements were in place between UCB Pharma and the authors. All patients provided written informed consent documented in accordance with local regulations, the International Council for Harmonisation Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. Ethical approvals were obtained from the relevant institutional review boards at participating sites.

Patient exclusion criteria

Assessments of eligibility were initiated during the screening period with a minimum duration of approximately 14 days (unless a screen-failed subject from BE MOBILE 2 was screened in BE MOBILE 1) and a maximum duration of up to 35 days. The screening period enabled washout of medications not permitted for use during the trial, initiation of latent tuberculosis (TB) treatment where necessary, and completion of imaging assessments, including central reading, required to determine eligibility. Full inclusion criteria are provided in the main text.

Patients were excluded if they had received >1 tumor necrosis factor inhibitor (TNFi), >2 additional biologic response modifiers (other than TNFis; including investigational biologics received in prior clinical trials), or any interleukin (IL)-17 response modifier. Patients who had previously received a TNFi must have been intolerant or

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experienced an inadequate response (IR) to previous treatment given at an approved dose for at least 12 weeks. Patients with inflammatory conditions other than nr-axSpA/r-axSpA were excluded. Previous history of inflammatory bowel disease (IBD) was permitted provided the patient had no active symptoms at screening or baseline; history of anterior uveitis was also permitted provided there was no flare within 6 weeks of baseline. Other exclusion criteria included active infection (except common cold), diagnosis of active TB or high risk of acquiring TB, fibromyalgia or osteoarthritis symptoms with potential to interfere with efficacy assessments, and moderately severe or severe major depression indicated by a score ≥15 on the Patient Health Questionnaire (PHQ)-9 at screening. Latent TB was permitted provided the patient had received ≥4 weeks of appropriate infection therapy and had no evidence of therapy related hepatotoxicity (alanine transaminase [ALT]/aspartate transaminase [AST] remaining ≤3 times upper limit of normal [ULN]) prior to administration of the first treatment dose.

Efficacy endpoints

The components comprising ASAS40,[4] ASAS ≥20% improvement (ASAS20) and ASAS partial remission were Patient's Global Assessment of Disease Activity (PtGADA), pain assessment measured by total spinal pain score (derived from question 1 of the total and nocturnal spinal pain questionnaire), physical function measured by Bath Ankylosing Spondylitis Functional Index (BASFI), and morning stiffness measured using the mean of BASDAI questions 5 and 6. Each of the ASAS components are scored using a numeric rating scale (NRS) from 0–10, with higher numbers reflecting higher severity. ASAS40 was defined as ≥40% reduction (improvement) and absolute reduction (improvement) of ≥2 units on the NRS in ≥3 of the 4 ASAS components scores, as well as no worsening in the remaining component score. ASAS20 was defined as ≥20% reduction (improvement) and

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absolute reduction (improvement) of ≥1 unit on the NRS in ≥3 of the 4 ASAS components, as well as no deterioration (relative worsening of at least 20% and an absolute worsening of at least 1 unit) in the remaining component score. ASAS partial remission was defined as a score of ≤2 units on each of the 4 components. ASAS 5/6 response was defined as ≥20% improvement in 5 out of 6 components: the 4 ASAS components in addition of the lateral spinal flexion component of Bath Ankylosing Spondylitis Metrology Index (BASMI) and high sensitivity (hs)-CRP as objective measures.

The Short-Form 36-item Health Survey (SF-36) Physical Component Summary T-score was calculated using scores from the 8 SF-36 domains (Physical Functioning [10 items], Role Physical [4 items], Bodily Pain [2 items], General Health [5 items], Vitality [4 items], Social Functioning [2 items], Role Emotional [3 items], Mental Health [5 items]) and standardized with a mean (standard deviation [SD]) of 50 (10) in the general US population, where higher scores reflects higher physical ability and wellbeing.[5]

The Ankylosing Spondylitis Quality of Life (ASQoL), an established, r-axSpA-specific, 18-item health-related quality of life (HRQoL) measure, was scored either 1 ('Yes') or 0 ('No') per item; total scores therefore ranged from 0–18, with a higher score indicating worse HRQoL.[6]

The components comprising ASDAS (Ankylosing Spondylitis Disease Activity Score) were: total back pain (based on BASDAI Q2); duration of morning stiffness (based on BASDAI question 6); PtGADA; peripheral pain/swelling (based on BASDAI question 3), each assessed on a NRS (0–10 units) and natural logarithm of hs-CRP (mg/L) +1, all multiplied by their weighting according to an established formula.[7] If the hs-CRP value is <2 mg/L, 2 mg/L was used as the constant value in the

calculation. ASDAS major improvement (ASDAS-MI) was defined as reduction (i.e., improvement) in ASDAS of ≥2.0 from baseline.

Change from baseline (CfB) in Maastricht Ankylosing Spondylitis Enthesitis index (MASES)[8] and complete resolution of enthesitis for the subset of patients with enthesitis (MASES >0) at baseline were non-ranked secondary endpoints and CfB in swollen joint count (SJC) and tender joint count (TJC) were pre-specified endpoints of clinical importance in both trials (see supplementary results). To assess SJC and TJC, 44 joints were examined for tenderness and swelling across the upper body (4 joints), upper extremity (26 joints) and lower extremity (14 joints), and graded as 0 (SJC: no swelling present; TJC: no tenderness present) or 1 (SJC: detectable synovial thickening; TJC: tenderness present).

Efficacy outcomes were assessed by completion of questionnaires by the patient, or by the investigator, another delegated physician, or an appropriately qualified medical professional, all of whom were unaware of the patients' treatment assignments. For endpoints in the statistical hierarchy, ASAS40, BASDAI, ASAS20, ASAS PR, BASFI and nocturnal spinal pain data were collected at Weeks 1, 2, 4, 8, 12, 16, 24, 36 and 52, ASDAS-MI data at Weeks 2, 4, 8, 12, 16, 24, 36 and 52, ASAS5/6 and BASMI data (BE MOBILE 2) at Weeks 8, 16, 24, 52, ASQoL data at Weeks 4, 8, 12, 16, 24, 36 and 52, and SF-36 PCS data at Weeks 8, 16, 24, 36 and 52. For pre-specified endpoints of key clinical importance, ASDAS and hs-CRP data were collected at Weeks 2, 4, 8, 12, 16, 24, 36 and 52, MASES data at Weeks 4, 8, 16, 24 and 52, and SJC and TJC data at Weeks 8, 16, 24 and 52. Details on MRI assessments are provided below. Supportive analyses were performed to assess the impact of the COVID-19 pandemic on the primary efficacy endpoint (see supplementary results).

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MRI assessments

During the screening period, patients who did not meet the modified New York criteria for r-axSpA and were assessed for eligibility for BE MOBILE 1 had an MRI of the SIJ to identify patients as MRI+/MRI–.[1] MRI assessments were aimed to be conducted in the period from 3 weeks prior to baseline visit and up to the baseline visit when the first dose of trial medication was administered.

MRI assessments of efficacy were conducted for patients who consented to the MRI sub-study of each trial. In BE MOBILE 1, the MRI of the SIJ collected during screening was treated as the baseline assessment, with an additional MRI of the SIJ performed at Week 16 (±5 days of the Week 16 visit), and of the spine at baseline (after confirmation of eligibility based on screening assessments and before administration of the first treatment dose) and Week 16 (±5 days of the Week 16 visit). In BE MOBILE 2, MRI of the SIJ and spine was performed at baseline (after confirmation of eligibility based on screening assessments and before administration of the first treatment dose) and Week 16 (±5 days of the Week 16 visit) for patients in the MRI sub-study.

All MRIs were read independently by two central expert readers; the analysis used the average of the scores from the two readers. Where discrepancies between readers were too large (MRI Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ inflammation: ≥13 difference in change score; MRI Berlin spine: ≥9 difference in change score), a third adjudication reviewer was used. The average of the two closest change scores was recorded.

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Safety endpoints

TEAEs were defined as adverse events with an onset date on or after the first dose of the trial drug and within 20 weeks of the last dose. Treatment-emergent SAEs were defined as any TEAEs meeting one or more of the following criteria: death, life-threatening illness, medically significant or persistent disability or incapacity, congenital anomaly or birth defect (including that occurring in a fetus), important medical event, and initial inpatient hospitalization or prolongation of hospitalization. Pre-specified safety topics of interest for the trials were: infections (serious, fungal, opportunistic, and TB), neutropenia, hypersensitivity (identified using a narrow search hypersensitivity Standardized MedDRA Query), suicidal ideation and behavior (SIB), major adverse cardiovascular events (MACE), liver function test changes or enzyme elevations, malignancies, and IBD. Opportunistic infections were defined by search criteria pre-specified by UCB.[9] These criteria identified preferred terms from MedDRA to be considered when identifying opportunistic infections. Some preferred terms required evaluation on a case-by-case basis by the study physician.

Patients could report adverse events spontaneously, following prompts from investigators at each trial visit, or through self-assessment materials including continuous measurement of mental health for depression and/or suicidality. An independent Data Monitoring Committee and Independent Cardiovascular, Gastrointestinal, Hepatic, and Neuropsychiatric Adjudication Committees regularly reviewed safety data. All potential IBD events were evaluated and classified by the independent Gastrointestinal Adjudication Committee. Exposure-adjusted incidence rates (EAIRs) per 100 patient-years (PY) of exposure to bimekizumab are presented.

Statistical analyses

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Sample size calculations were based on testing of bimekizumab versus placebo with respect to ASAS40 response at Week 16. On the basis of a previous phase 2b trial of bimekizumab and placebo involving patients with active AS (BE AGILE),[10] the assumed ASAS40 response was 40% with bimekizumab and 20% (BE MOBILE 1) or 15% (BE MOBILE 2) with placebo at Week 16. A sample size of 120 patients in each treatment group in BE MOBILE 1, with a two-sided significance level of 0.05, will detect a significant difference between bimekizumab and placebo with 90% power. In BE MOBILE 2, a sample size of 200 patients in the bimekizumab group and 100 patients in the placebo group, with a two-sided significance level of 0.05, will detect a significant difference between bimekizumab and placebo with >99% power. These calculations are based on a two-sample continuity-corrected chi-square test of equal proportions.

The estimand used for the analysis of binary and continuous endpoints evaluates the treatment effect for all randomized participants under the assumption that withdrawal and switch from randomized treatment does not occur. For binary ranked endpoints, the statistical null hypothesis at Week 16 was that the conditional odds ratio of the bimekizumab group to placebo group is equal to one. Analyses were based on a logistic regression model with treatment included as a fixed effect; MRI/CRP classification and region in BE MOBILE 1, and prior TNFi exposure and region in BE MOBILE 2, included as stratification variables. Comparisons used a 2-sided Wald test. For continuous ranked endpoints, the statistical hypothesis at Week 16 was that the treatment difference between the bimekizumab and placebo groups is equal to zero. Analyses were based on an analysis of covariance (ANCOVA) model with fixed effects for treatment, MRI/CRP classification and region in BE MOBILE 1, and treatment, prior TNFi exposure and region in BE MOBILE 2; baseline values were included as covariates. Due to low numbers of patients in the

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North America region in both trials, Western Europe and North America regions were combined for statistical analyses to avoid convergence issues.

A summary of the imputation methodologies used is provided in the main text. In instances where MI is used, the missing value was replaced by a set of plausible values, where each value was a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data was imputed using the Markov-Chain Monte Carlo method, followed by regression for monotone missing data. The planned multiple imputation procedures were based on an assumption of data missing at random.

All statistical analyses were performed using Statistical Analysis System® (SAS®) Version 9.3 or higher.

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SUPPLEMENTARY RESULTS

Enthesitis (MASES)

In patients with enthesitis, defined by MASES >0 at baseline, a marked reduction from baseline in MASES score was achieved with bimekizumab versus placebo at Week 16 (nr-axSpA: −2.4 [standard error: 0.3] versus −1.3 [0.2]; r-axSpA: −2.4 [0.3] versus −1.5 [0.3]), with associated differences in the proportion of patients achieving complete resolution of enthesitis (MASES=0) (nr-axSpA: 51.1% [48/94] versus 23.9% [22/92]; r-axSpA: 51.5% [68/132] versus 32.8% [22/67]).

Peripheral Arthritis (SJC/TJC)

Across the full trial populations (randomized set), CfB in mean SJC was greater (reduced [i.e., improved] more) in bimekizumab- versus placebo-treated patients at Week 16 (nr-axSpA: −1.0 [standard error: 0.3] versus −0.3 [0.2]; r-axSpA: −0.6 [0.2] versus −0.4 [0.1]); a similar pattern was seen for TJC in patients with nr-axSpA, but not in patients with r-axSpA (nr-axSpA: −1.6 [0.5] versus −0.6 [0.4]; r-axSpA: −1.2 [0.2] versus −1.7 [0.3]). Among patients with SJC >0 at baseline, higher proportions of bimekizumab- versus placebo-treated patients achieved SJC=0 at Week 16 (nr-axSpA: 57.8% [26/45] versus 41.9% [18/43]; r-axSpA: 63.6% [28/44] versus 36.4% [8/22]). Similar results were observed in patients with TJC >0 at baseline achieving TJC=0 at Week 16 (nr-axSpA: 42.3% [33/78] versus 24.7% [21/85]; r-axSpA: 41.4% [48/116] versus 32.8% [20/61]).

COVID-19 Impact

COVID-19 had minimal impact on trial conduct despite the trials being conducted during the COVID-19 pandemic. To Week 12, all trial visits were completed in BE MOBILE 1, and all but 4 (2 bimekizumab, 2 placebo) were completed in BE MOBILE 2. To Week 12, 1 dose of treatment (placebo) was missed in BE MOBILE 1, and 13

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doses (6 bimekizumab, 7 placebo) were missed in BE MOBILE 2. Supportive analyses demonstrated that the pandemic had a negligible impact on the results of the BE MOBILE trials: the treatment effect for ASAS40 in the COVID-19 free set aligned with that for the overall population (data not reported). This observation is consistent with analyses of the pandemic's impacts on the BE AGILE phase 2b trial open-label extension in patients with r-axSpA.[11]

There were similar numbers of confirmed COVID-19 infections between bimekizumab- and placebo-treated patients in both trials during the DBTP (nr axSpA: 1 patient [2.6/100 PY] versus 1 patient [2.5/100 PY]; r-axSpA: 1 patient [1.5/100 PY] versus 3 patients [8.8/100 PY]). In each trial there was one confirmed COVID-19 infection during bimekizumab treatment in Weeks 0–24. All COVID-19 cases were mild to moderate, and none were serious and or led to hospitalization.

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SUPPLEMENTARY TABLES AND FIGURES

Table S1. Individual ASAS components of the primary endpoint at Week 16 and Week 24

		Baseline[a]		Change from baseline				
				Week 16[b]			Week 24[a]	
		PBO	BKZ 160 mg Q4W	PBO	BKZ 160 mg Q4W	BKZ vs PBO difference, mean (95% CI)	PBO→BKZ 160 mg Q4W	BKZ 160 mg Q4W
nr-axSpA (BE MOBILE 1) r-axSpA (BE MOBILE 2)		**n=126 n=111**	**n=128 n=221**	**n=126 n=111**	**n=128 n=221**		**n=126 n=111**	**n=128 n=221**
PtGADA [RBMI/MI] Mean (SE)	nr-axSpA	6.9 (0.2)	7.1 (0.2)	−1.4 (0.2)	−3.2 (0.2)	−1.8 (−2.4, −1.2)	−3.4 (0.2)	−3.4 (0.2)
	r-axSpA	6.7 (0.2)	6.6 (0.1)	−1.6 (0.2)	−2.7 (0.2)	−1.3 (−1.8, −0.8)	−3.3 (0.2)	−3.2 (0.2)
Total spinal pain [RBMI/MI] Mean (SE)	nr-axSpA	7.1 (0.1)	7.3 (0.1)	−1.7 (0.2)	−3.4 (0.2)	−1.6 (−2.2, −1.0)	−3.5 (0.2)	−3.8 (0.2)
	r-axSpA	7.2 (0.1)	7.1 (0.1)	−1.9 (0.2)	−3.3 (0.2)	−1.4 (−1.9, −0.9)	−3.5 (0.2)	−3.8 (0.2)
BASFI [RBMI/MI] Mean (SE)	nr-axSpA	5.3 (0.2)	5.5 (0.2)	−1.0 (0.2)	−2.5 (0.2)	−1.5 (−2.0, −1.0)	−2.3 (0.2)	−2.8 (0.2)
	r-axSpA	5.2 (0.2)	5.3 (0.2)	−1.1 (0.2)	−2.2 (0.1)	−1.1 (−1.5, −0.6)	−2.2 (0.2)	−2.4 (0.2)
BASDAI Q5&6 mean score (morning stiffness) [RBMI/MI] Mean (SE)	nr-axSpA	6.9 (0.1)	7.0 (0.2)	−1.9 (0.2)	−3.6 (0.3)	−1.7 (−2.3, −1.1)	−3.5 (0.2)	−4.0 (0.2)
	r-axSpA	6.8 (0.2)	6.7 (0.1)	−2.1 (0.2)	−3.2 (0.2)	−1.1 (−1.6, −0.7)	−3.7 (0.2)	−3.7 (0.2)

Randomized set. [a]Missing data were imputed using MI; [b]Missing data were imputed using RBMI. Least squares mean differences between BKZ and PBO are reported from the ANCOVA model in which treatment, MRI/CRP classification and region (BE MOBILE 1) or treatment, prior TNFi exposure and region (BE MOBILE 2) were included as fixed effects, and baseline values as covariates. ANCOVA: analysis of covariance; ASAS: Assessment of SpondyloArthritis international Society; BKZ: bimekizumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CI: confidence interval; CRP: C-reactive protein; MI: multiple imputation; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; PBO: placebo; PtGADA: Patient's Global Assessment of Disease Activity; Q: question; Q4W: every 4 weeks; r-axSpA: radiographic axial spondyloarthritis; RBMI: reference-based multiple imputation; SE: standard error; TNFi: tumor necrosis factor inhibitor.

Table S2. Change from baseline in BASDAI Q1 (fatigue) scores at Week 16 and Week 24

		Baseline		Change from baseline				
				Week 16			Week 24	
		PBO	BKZ 160 mg Q4W	PBO	BKZ 160 mg Q4W	BKZ vs PBO difference, mean (95% CI)	PBO→BKZ 160 mg Q4W	BKZ 160 mg Q4W
nr-axSpA (BE MOBILE 1) **r-axSpA (BE MOBILE 2)**		**n=126** **n=111**	**n=128** **n=221**	**n=126** **n=111**	**n=128** **n=221**		**n=126** **n=111**	**n=128** **n=221**
BASDAI Q1, mean (SE)	nr-axSpA	6.4 (0.2)	6.7 (0.1)	−1.1 (0.2)	−2.6 (0.2)	−1.5 (−2.1, −0.9)	−2.6 (0.2)	−2.8 (0.2)
	r-axSpA	6.4 (0.1)	6.4 (0.1)	−1.7 (0.2)	−2.5 (0.2)	−0.9 (−1.3, −0.4)	−2.7 (0.2)	−2.9 (0.2)

Randomized set. Data reported are MI. Least squares mean differences and CI between BKZ and PBO at Week 16 are reported from the ANCOVA model in which treatment, MRI/CRP classification, region, subgroup and treatment subgroup (BE MOBILE 1) or treatment, prior TNFi exposure, region, subgroup and treatment subgroup (BE MOBILE 2) were included as fixed effects, and baseline values as covariates. ANCOVA: analysis of covariance; BKZ: bimekizumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval; CRP: C reactive protein; MI: multiple imputation; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; PBO: placebo; Q: question; r-axSpA: radiographic axial spondyloarthritis; Q4W: every 4 weeks; SE: standard error; TNFi: tumor necrosis factor inhibitor.

1 **Table S3. TEAEs leading to discontinuation of trial drug by preferred term**

n (%) [EAIR/100 PY]		Double-blind treatment period Weeks 0–16		Overall Weeks 0–24
		PBO	BKZ 160 mg Q4W	BKZ 160 mg Q4W Total[a]
	nr-axSpA (BE MOBILE 1) r-axSpA (BE MOBILE 2)	**n=126 (38.1 PY) n=111 (34.6 PY)**	**n=128 (40.4 PY) n=221 (68.3 PY)**	**n=244 (77.1 PY) n=330 (119.1 PY)**
Any TEAE leading to discontinuation of trial drug	nr-axSpA	5 (4.0) [13.2]	2 (1.6) [5.0]	3 (1.2) [3.9]
	r-axSpA	0	7 (3.2) [10.3]	12 (3.6) [10.3]
Uveitis	nr-axSpA	2 (1.6) [5.3]	0	0
	r-axSpA	0	0	0
Colitis ulcerative	nr-axSpA	1 (0.8) [2.6]	0	0
	r-axSpA	0	1 (0.5) [1.5]	1 (0.3) [0.8]
Crohn's disease	nr-axSpA	0	0	0
	r-axSpA	0	1 (0.5) [1.5]	1 (0.3) [0.8]
Psychiatric evaluation abnormal	nr-axSpA	2 (1.6) [5.3]	1 (0.8) [2.5]	1 (0.4) [1.3]
	r-axSpA	0	2 (0.9) [2.9]	3 (0.9) [2.5]
Dizziness	nr-axSpA	0	1 (0.8) [2.5]	1 (0.4) [1.3]
	r-axSpA	0	0	0
Hypoaesthesia	nr-axSpA	0	0	0
	r-axSpA	0	0	1 (0.3) [0.8]
Clear cell renal cell carcinoma	nr-axSpA	0	0	1 (0.4) [1.3]
	r-axSpA	0	0	0
Lymphoid tissue hyperplasia[b]	nr-axSpA	0	0	0
	r-axSpA	0	1 (0.5) [1.5]	1 (0.3) [0.8]
Oesophageal candidiasis	nr-axSpA	0	0	0
	r-axSpA	0	0	1 (0.3) [0.8]
Oral candidiasis	nr-axSpA	0	0	0
	r-axSpA	0	1 (0.5) [1.5]	1 (0.3) [0.8]
Rash	nr-axSpA	0	0	0
	r-axSpA	0	1 (0.5) [1.5]	1 (0.3) [0.8]
Suicidal ideation	nr-axSpA	0	0	0
	r-axSpA	0	0	1 (0.3) [0.8]
Pleural effusion	nr-axSpA	0	0	0
	r-axSpA	0	0	1 (0.3) [0.8]

Safety set. MedDRA (Version 19.0), preferred terms reported. [a]Includes patients who switched from PBO to BKZ (events after switch only); [b]Lymphoid tissue hyperplasia was a TEAE related to gastrointestinal disorders and not related to lymphoid blood cells – the TEAE was diagnosed and reported as 'lymphoid nodular hyperplasia'. BKZ: bimekizumab; EAIR: exposure-adjusted incidence rate; MedDRA: medical dictionary for regulatory activities; nr-axSpA: non-radiographic axial spondyloarthritis; PBO: placebo; PY: patient-years; Q4W: every 4 weeks; r-axSpA: radiographic axial spondyloarthritis; TEAE: treatment-emergent adverse event.

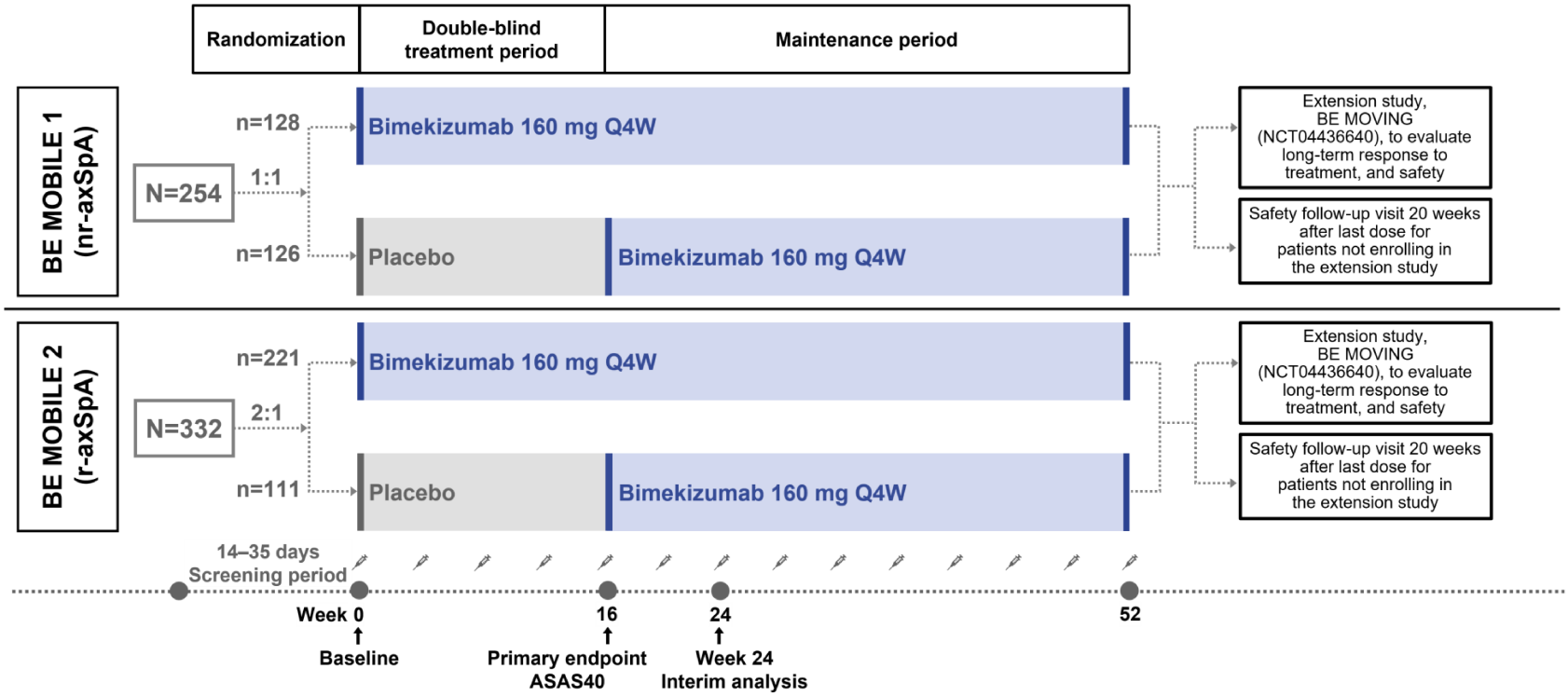
Table S4. Treatment-emergent serious adverse events by preferred term

n (%) [EAIR/100 PY]		**Double-blind treatment period** Weeks 0–16		**Overall** Weeks 0–24
		PBO	**BKZ 160 mg Q4W**	**BKZ 160 mg Q4W Total[a]**
	nr-axSpA (BE MOBILE 1) r-axSpA (BE MOBILE 2)	**n=126 (38.1 PY) n=111 (34.6 PY)**	**n=128 (40.4 PY) n=221 (68.3 PY)**	**n=244 (77.1 PY) n=330 (119.1 PY)**
Any SAE	nr-axSpA	1 (0.8) [2.6]	0	1 (0.4) [1.3]
	r-axSpA	1 (0.9) [2.9]	4 (1.8) [5.9]	12 (3.6) [10.3]
Abdominal adhesions	nr-axSpA	1 (0.8) [2.6]	0	0
	r-axSpA	0	0	0
Colitis ulcerative	nr-axSpA	0	0	0
	r-axSpA	0	1 (0.5) [1.5]	1 (0.3) [0.8]
Crohn's disease	nr-axSpA	0	0	0
	r-axSpA	0	1 (0.5) [1.5]	1 (0.3) [0.8]
Clear cell renal cell carcinoma[b]	nr-axSpA	0	0	1 (0.4) [1.3]
	r-axSpA	0	0	0
Goitre	nr-axSpA	0	0	0
	r-axSpA	0	1 (0.5) [1.5]	1 (0.3) [0.8]
Hepatitis A	nr-axSpA	0	0	0
	r-axSpA	0	1 (0.5) [1.5]	1 (0.3) [0.8]
Otitis media	nr-axSpA	0	0	0
	r-axSpA	0	0	1 (0.3) [0.8]
Viral infection	nr-axSpA	0	0	0
	r-axSpA	1 (0.9) [2.9]	0	0
Infectious pleural effusion	nr-axSpA	0	0	0
	r-axSpA	0	0	1 (0.3) [0.8]
Erysipelas	nr-axSpA	0	0	0

	r-axSpA	0	0	1 (0.3) [0.8]
Depression	nr-axSpA	0	0	0
	r-axSpA	1 (0.9) [2.9]	0	0
Suicidal ideation	nr-axSpA	0	0	0
	r-axSpA	0	0	1 (0.3) [0.8]
Cholelithiasis	nr-axSpA	0	0	0
	r-axSpA	0	0	1 (0.3) [0.8]
Syncope	nr-axSpA	0	0	0
	r-axSpA	0	0	2 (0.6) [1.7]
Rhinoplasty	nr-axSpA	0	0	0
	r-axSpA	0	0	1 (0.3) [0.8]

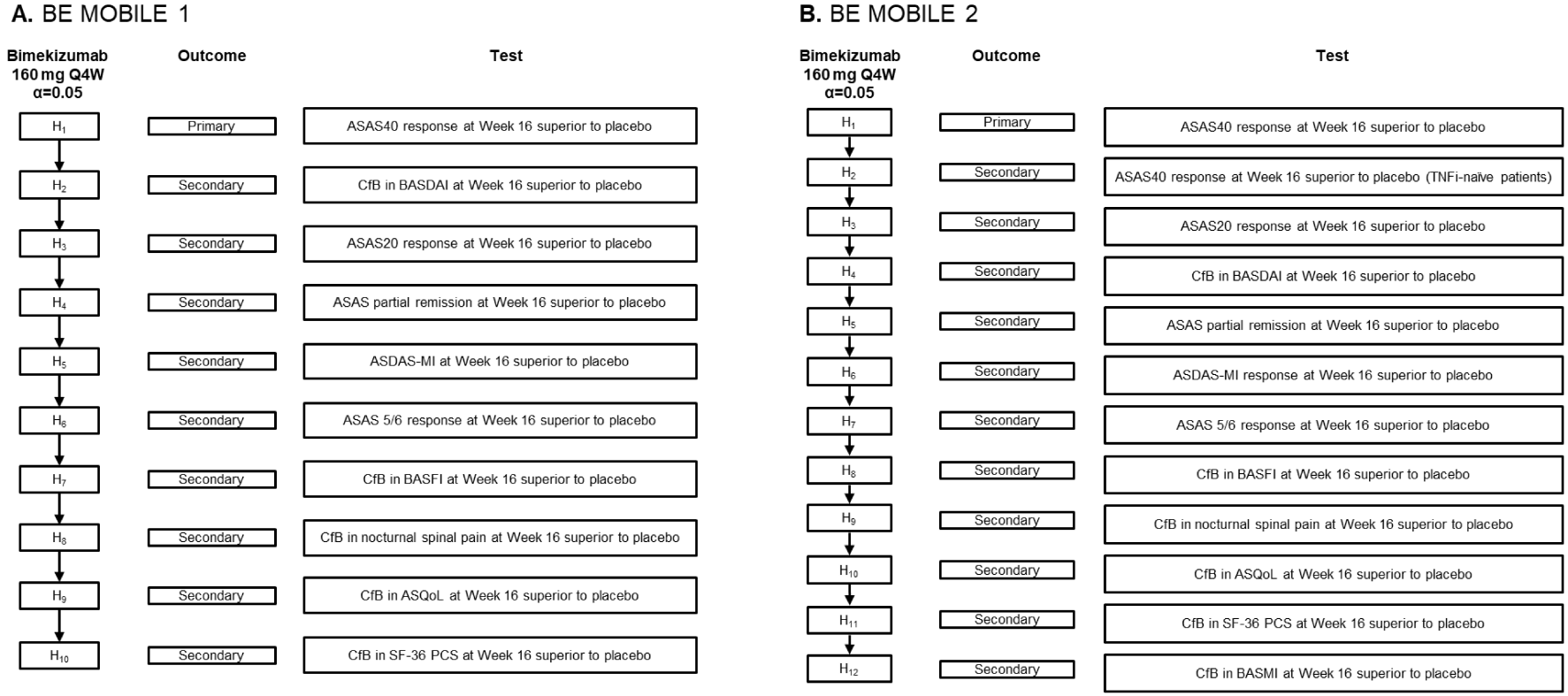
Safety set. MedDRA (Version 19.0), preferred terms reported. [a]Includes patients who switched from PBO to BKZ (events after switch only); [b]SAE occurred 132 days after treatment initiation. AE: adverse event; BKZ: bimekizumab; EAIR: exposure-adjusted incidence rate; MedDRA: medical dictionary for regulatory activities; nr-axSpA: non-radiographic axial spondyloarthritis; PBO: placebo; PY: patient-years; Q4W: every 4 weeks; r-axSpA: radiographic axial spondyloarthritis; SAE: treatment-emergent serious adverse event.

Figure S1. Trial design



Patients were eligible to receive non-biologic rescue therapy from Week 20 at the discretion of the investigator while continuing to receive bimekizumab. ASAS40: Assessment of Spondyloarthritis international Society 40% response; nr-axSpA: non-radiographic axial spondyloarthritis; Q4W: every 4 weeks; r-axSpA: radiographic axial spondyloarthritis.

Figure S2. Statistical testing hierarchy

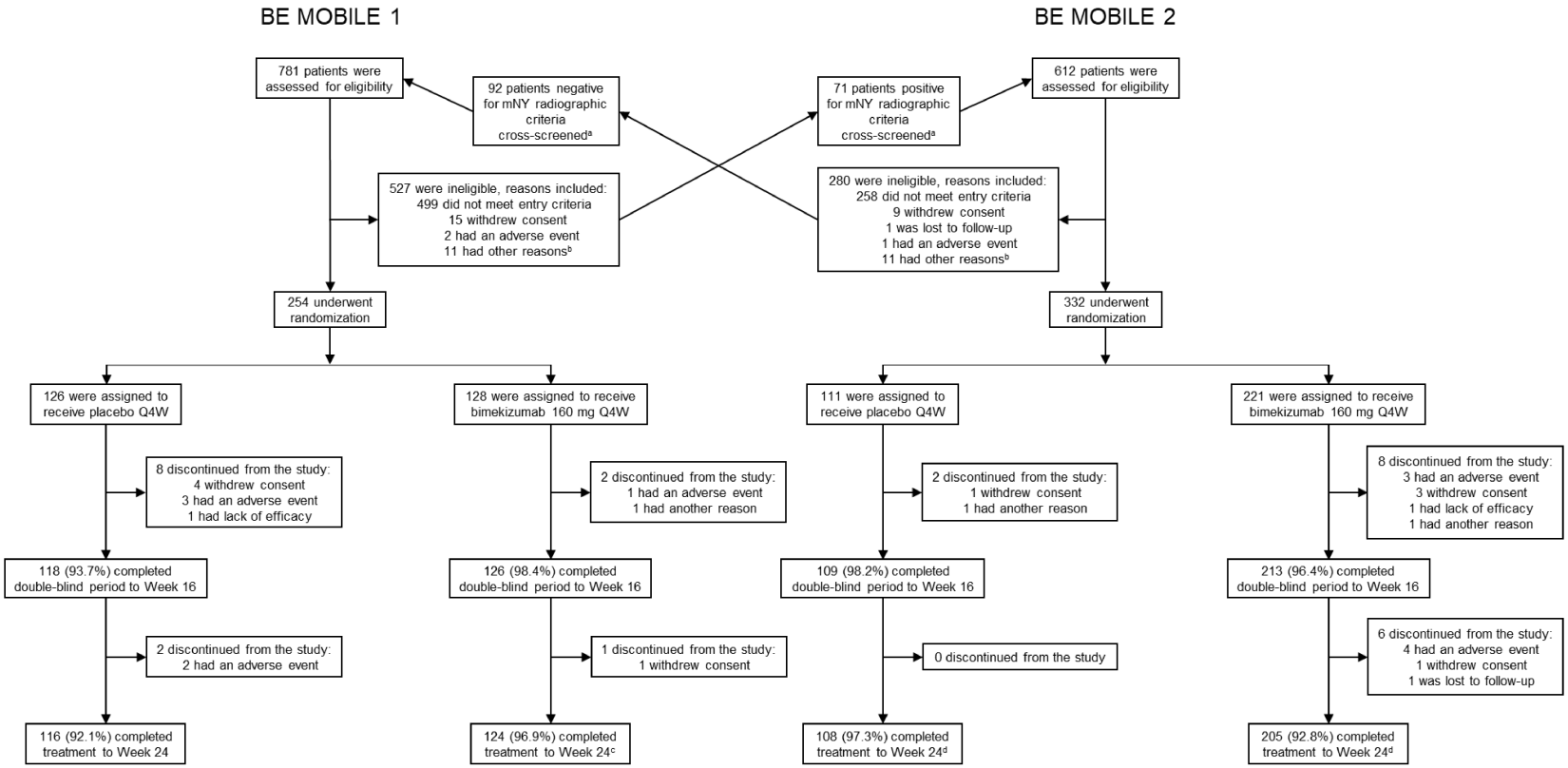


ASAS20/40: Assessment of Spondyloarthritis international Society 20%/40% response; ASAS 5/6: ≥20% improvement in 5 out of 6 components; ASDAS-MI: Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath

1 Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CfB: change from baseline; H: hypothesis; Q4W: every 4 weeks; SF-36 PCS:
2 Short-Form 36-item Health Survey Physical Component Summary; TNFi: tumor necrosis factor inhibitor.

3

Figure S3. Enrollment, randomization, and treatment

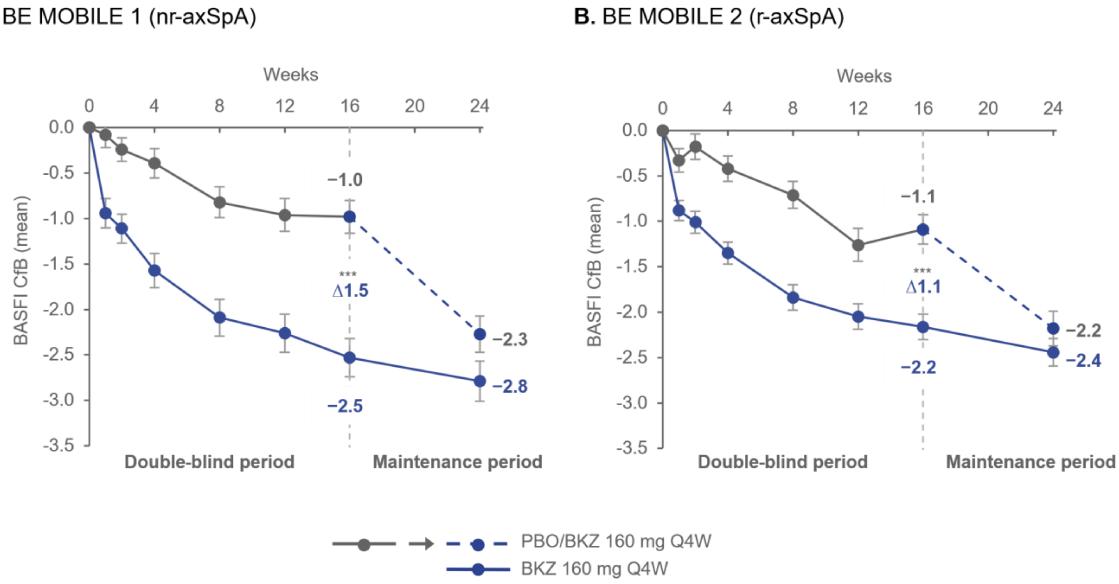


[a]Patients who have failed screening in both trials cannot be re-screened; [b]Screen failure reasons noted as 'other' mainly related to the COVID-19 pandemic (e.g. hospital closures or the halt in enrolment early in the pandemic); [c]One patient in the bimekizumab group missed the Week 24 visit in BE MOBILE 1 and is therefore not included in this

1 total; [d]One patient in the placebo group and two patients in the bimekizumab group missed the Week 24 visit in BE MOBILE 2 and are therefore not included in these totals.

2 mNY: modified New York; Q4W: every 4 weeks.

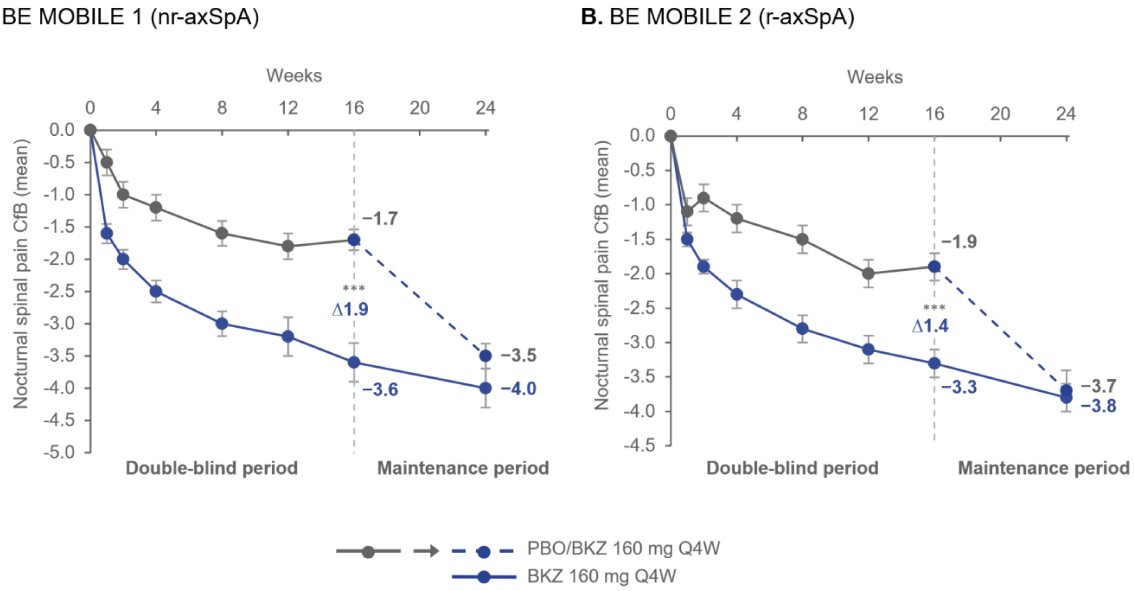
Figure S4. BASFI over time



Randomized set. ***p<0.001. Secondary ranked endpoint, data reported are MI. Error bars show standard error. All statistical tests were performed at a 2-sided alpha level of 0.05. p values were obtained by ANCOVA with treatment, MRI/CRP classification and region (BE MOBILE 1) or treatment, prior TNFi exposure and region (BE MOBILE 2) as fixed effects, and baseline values as covariates.

ANCOVA: analysis of covariance; BASFI: Bath Ankylosing Spondylitis Functional Index; BKZ: bimekizumab; CfB: change from baseline; CRP: C-reactive protein; MI: multiple imputation; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; PBO: placebo; Q4W: every 4 weeks; r-axSpA: radiographic axial spondyloarthritis; TNFi: tumor necrosis factor inhibitor.

Figure S5. Nocturnal spinal pain over time



Randomized set. ***p<0.001. Secondary ranked endpoint, data reported are MI. Error bars show standard error. All statistical tests were performed at a 2-sided alpha level of 0.05. p values were obtained by ANCOVA with treatment, MRI/CRP classification and region (BE MOBILE 1) or treatment, prior TNFi exposure and region (BE MOBILE 2) as fixed effects, and baseline values as covariates.

ANCOVA: analysis of covariance; BKZ: bimekizumab; CfB: change from baseline; CRP: C-reactive protein; MI: multiple imputation; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; PBO: placebo; Q4W: every 4 weeks; r-axSpA: radiographic axial spondyloarthritis; TNFi: tumor necrosis factor inhibitor.

REFERENCES

1. Lambert RG, Bakker PA, van der Heijde D, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis*. 2016;75(11):1958-63. doi:10.1136/annrheumdis-2015-208642.
2. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis*. 2009;68(6):777-83. doi:10.1136/ard.2009.108233.
3. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum*. 1984;27(4):361-8. doi:10.1002/art.1780270401.
4. Brandt J, Listing J, Sieper J, et al. Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. *Ann Rheum Dis*. 2004;63(11):1438-44. doi:10.1136/ard.2003.016717.
5. Maruish ME. User's manual for the SF-36v2 Health Survey: Quality Metric Incorporated; 2011.
6. Doward LC, Spoorenberg A, Cook SA, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. *Ann Rheum Dis*. 2003;62(1):20-6. doi:10.1136/ard.62.1.20.
7. van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2009;68(12):1811-8. doi:10.1136/ard.2008.100826.
8. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, et al. Assessment of enthesitis in ankylosing spondylitis. *Ann Rheum Dis*. 2003;62(2):127. doi:10.1136/ard.62.2.127.

9. Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*. 2015;74(12):2107-16. doi:10.1136/annrheumdis-2015-207841.

10. van der Heijde D, Gensler LS, Deodhar A, 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(5):595. doi:10.1136/annrheumdis-2020-216980.

11. Robinson PC, Machado PM, Haroon N, et al. Minimal Impact of the COVID-19 Pandemic on Disease Activity and Health-Related Quality of Life in Patients With Ankylosing Spondylitis Receiving Bimekizumab: Exploratory Analyses From a Phase 2b Open-Label Extension Study. *ACR Open Rheumatol*. 2022;4(9):819-24. doi:10.1002/acr2.11486.