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CLINICAL SCIENCE

Bimekizumab treatment in patients with active axial spondyloarthritis: 52-week efficacy and safety from the randomised parallel phase 3 BE MOBILE 1 and BE MOBILE 2 studies

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ABSTRACT

Objectives Bimekizumab (BKZ), a monoclonal IgG1 antibody that selectively inhibits interleukin (IL)-17F in addition to IL-17A, has demonstrated superior efficacy versus placebo in patients with non-radiographic (nr-) and radiographic (r-) axial spondyloarthritis (axSpA) at Week 16. Here, the objective is to report the efficacy and safety of BKZ at Week 52.

Methods BE MOBILE 1 (nr-axSpA; NCT03928704) and BE MOBILE 2 (r-axSpA; NCT03928743) comprised a 16-week, double-blind, placebo-controlled period, then a 36-week maintenance period. From Week 16, all patients received subcutaneous BKZ 160 mg every 4 weeks.

Results Improvements versus placebo in Assessment of SpondyloArthritis International Society ≥40% response (primary endpoint), Ankylosing Spondylitis Disease Activity Score, high-sensitivity C-reactive protein levels and MRI inflammation of the sacroiliac joints/spine at Week 16 were sustained to Week 52 in BKZ-randomised patients. At Week 52, responses of patients switching from placebo to BKZ at Week 16 were comparable to BKZ-randomised patients. At Week 52, ≥1 treatment-emergent adverse events (TEAEs) were reported in 183 (75.0%) and 249 (75.5%) patients with nr-axSpA and r-axSpA, respectively. Serious TEAEs occurred in 9 (3.7%) patients with nr-axSpA and 20 (6.1%) patients with r-axSpA. Oral candidiasis was the most frequent fungal infection (nr-axSpA: 18 (7.4%); r-axSpA: 20 (6.1%)). Uveitis occurred in three (1.2%) and seven (2.1%) patients with nr-axSpA and r-axSpA, and inflammatory bowel disease in two (0.8%) and three (0.9%).

Conclusions At Week 52, dual inhibition of IL-17A and IL-17F with BKZ resulted in sustained efficacy across the axSpA spectrum; the safety profile was consistent with the known safety of BKZ.

Trial registration number NCT03928704; NCT03928743.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic, inflammatory, immune-mediated disease involving the axial skeleton and is characterised by chronic back pain, spinal stiffness, fatigue and extra-musculoskeletal manifestations.[1 2] The disease encompasses patients with definite radiographic

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Axial spondyloarthritis (axSpA) is a chronic, inflammatory, immune-mediated disease involving the axial skeleton that encompasses non-radiographic (nr-) and radiographic (r-) axSpA (ie, ankylosing spondylitis).
⇒ Primary results from the BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (r-axSpA) phase 3 studies of bimekizumab (BKZ), a monoclonal antibody that selectively inhibits interleukin (IL)-17F in addition to IL-17A, demonstrated rapid, clinically relevant improvements in efficacy outcomes versus placebo, and was well tolerated, to Week 24.
⇒ It is essential to evaluate whether the efficacy and safety of potential new treatment options, such as BKZ, are sustained over longer time periods.

WHAT THIS STUDY ADDS

⇒ The 52-week randomised controlled trials BE MOBILE 1 and BE MOBILE 2 assessed the long-term efficacy of BKZ across key clinical response criteria, measures of disease activity, patient-reported outcomes and peripheral manifestations of disease.
⇒ Improvements across a range of outcomes observed at Week 16 were sustained at Week 52 in patients initially randomised to BKZ. Patients switching from placebo to BKZ at Week 16 showed comparable improvements by Week 52 to patients initially randomised to BKZ.
⇒ The safety profile was consistent with the known safety of BKZ.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Results at Week 52 from the BE MOBILE trials suggest that BKZ is an effective treatment option resulting in sustained efficacy across the full disease spectrum of axSpA.
⇒ The long-term efficacy and safety of BKZ up to 3 years of treatment will be assessed in the ongoing open-label extension, BE MOVING.

damage to the sacroiliac joints (SIJ; radiographic (r-) axSpA, ie, ankylosing spondylitis),[3] and patients without such damage (non-radiographic (nr-) axSpA).[1] Regardless of the subtype, axSpA is associated with high disease burden and symptoms can have a profound negative impact on patients' health-related quality of life (HRQoL), impairing activities of daily living, physical function, sleep, mental well-being and ability to work.[2]

Treatment options for patients with axSpA who have active disease despite non-steroidal anti-inflammatory drug (NSAID) treatment or who are intolerant to NSAIDs are limited to biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), namely, tumour necrosis factor inhibitors (TNFi),[4] interleukin 17A inhibitors (IL-17Ai)[5 6] and janus kinase inhibitors (JAKi).[7] Many patients treated with existing DMARDs experience adverse events or treatment failure,[8–10] highlighting an unmet clinical need for treatments with alternative modes of action.

The cytokines interleukin (IL)-17A and IL-17F have been implicated in the pathogenesis of axSpA.[11–13] Although IL-17A is considered to be more biologically active, IL-17F is enriched in the skin and synovial tissue of patients with spondyloarthritis.[11 14–16] Several types of innate-like immune cells, which are thought to be drivers of axSpA pathogenesis, also demonstrate high levels of IL-17F expression.[17 18]

Bimekizumab (BKZ) is a humanised monoclonal IgG1 antibody that selectively inhibits IL-17F in addition to IL-17A. Preclinical studies suggest superior efficacy of BKZ in reducing inflammation and pathological bone formation compared with IL-17Ai alone.[12 13 19] BKZ has also demonstrated superior clinical efficacy, versus an IL-17Ai, in a head-to-head clinical trial in plaque psoriasis.[20] In 2023, the European Commission approved BKZ (160 mg every 4 weeks (Q4W)) for the treatment of nr-axSpA, r-axSpA and psoriatic arthritis, following its approval for plaque psoriasis in 2021.[21]

In the parallel phase 3 studies BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (r-axSpA), patients receiving subcutaneous 160 mg BKZ Q4W achieved the primary and all ranked secondary endpoints at Week 16.[22] At Week 24, no new safety signals were observed with BKZ treatment, compared with the 3-year phase 2b BE AGILE study of BKZ in r-axSpA.[23] Here, we present the clinical efficacy and safety of BKZ in patients with active axSpA up to Week 52 of BE MOBILE 1 and BE MOBILE 2.

METHODS

Study designs and oversight

The study designs, inclusion and exclusion criteria for the BE MOBILE studies have been described previously (online supplemental figure S1).[22] Patients in BE MOBILE 1 had nr-axSpA, determined by clinical diagnosis and fulfilment of Assessment of SpondyloArthritis International Society (ASAS) classification criteria, but without radiographic sacroiliitis.[24] At screening, patients with nr-axSpA were required to have signs of objective inflammation, specifically active sacroiliitis fulfilling ASAS criteria[25] and/or elevated C-reactive protein (CRP) ≥6.0 mg/L. Patients in BE MOBILE 2 had r-axSpA fulfilling modified New York (mNY) criteria.[26] All patients in BE MOBILE 2 also fulfilled ASAS criteria.[24]

Endpoints

The primary efficacy endpoint in both studies was ASAS ≥40% improvement (ASAS40) response at Week 16. The statistical hierarchy of primary and secondary ranked endpoints has been described previously.[22]

Prespecified clinical response criteria, including ASAS40 response, ASAS40 response in TNFi-naïve (ranked secondary endpoint in BE MOBILE 2) and TNFi-inadequate response (IR) patients (exploratory endpoint), ASAS≥20% improvement (ASAS20) and ASAS partial remission (ASAS PR), were assessed at Week 52.

Measures of disease activity assessed at Week 52 included Ankylosing Spondylitis Disease Activity Score CRP (ASDAS), ASDAS states (including inactive disease (ID; ASDAS <1.3) and low disease activity (LDA; ASDAS <2.1)), ASDAS major improvement (ASDAS-MI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and BASDAI ≥50% response (BASDAI50), Bath Ankylosing Spondylitis Metrology Index (BASMI), objective measures of inflammation including high-sensitivity CRP (hs-CRP) levels, Berlin modification of the spine ASspiMRI-a score ('Berlin spine')[27] and Spondyloarthritis Research Consortium of Canada (SPARCC) MRI SIJ inflammation score.[28] MRI scoring information is reported in the online supplemental methods.

Patient-reported outcomes of pain (total and nocturnal spinal pain), morning stiffness (mean of BASDAI questions 5 and 6), fatigue (BASDAI question 1), physical function (Bath Ankylosing Spondylitis Functional Index (BASFI), Short-Form 36-Item Health Survey Physical Component Summary (SF-36 PCS)) and HRQoL (Ankylosing Spondylitis Quality of Life Score (ASQoL)) were assessed at Week 52.

Maastricht Ankylosing Spondylitis Enthesitis (MASES) score and complete resolution of enthesitis (MASES=0 in patients with MASES >0 at baseline), swollen joint count (SJC; patients with SJC >0 at baseline) and tender joint count (TJC; patients with TJC >0 at baseline), assessed in 44 joints, and resolution of peripheral arthritis (SJC=0 in patients with SJC >0 at baseline) were also assessed at Week 52.

Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs) and TEAEs leading to withdrawal from the study drug were prespecified secondary endpoints. TEAEs, SAEs and prespecified safety topics of interest are as described previously.[22] Definitions of TEAEs and SAEs are in the online supplemental methods. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) v.19.0.

Statistical analysis

For each study, summary efficacy data are presented at Week 52. All analyses were performed on the randomised set. Statistical analyses were performed using Statistical Analysis System v.9.3 or higher. Further details on statistical analyses are in the online supplemental methods.[22]

For the double-blind treatment period (DBTP; Weeks 0–16), safety data are described by treatment arm for patients who received ≥1 dose of BKZ or placebo (PBO; safety set). For the maintenance (Weeks 16–52) and overall (Weeks 0–52) periods, safety data are reported for patients who received ≥1 dose of BKZ (TEAEs while on PBO not included). Exposure-adjusted incidence rates (EAIRs) per 100 patient years (PY) of exposure are presented for Weeks 0–52.

Estimands and statistical analyses for both trials have been reported previously.[22] Missing data or treatment discontinuation for any reason was handled with non-responder imputation (NRI) for binary endpoints (including the primary endpoint). Handling of missing data for other endpoints is described in the online supplemental methods. Supportive observed case (OC) data for

all endpoints are listed in online supplemental table S8. Endpoints that were not part of the statistical hierarchy[22] are summarised with point estimates and are not controlled for multiplicity.

RESULTS

Patient disposition and baseline characteristics

Of the 254 patients randomised in BE MOBILE 1 (BKZ: 128; PBO: 126), 244 (96.1%) completed the DBTP to Week 16, and 220 (86.6%) completed to Week 52 (online supplemental figure S2). For BE MOBILE 2, of the 332 patients randomised (BKZ: 221; PBO: 111), 322 (97.0%) completed the DBTP, and 298 (89.8%) completed Week 52 (online supplemental figure S2). Between Weeks 16 and 52, the main reason for study discontinuation in BE MOBILE 1 was withdrawal of consent in 12 (4.7%) patients, and for BE MOBILE 2, it was due to adverse events in 11 (3.3%) patients; all discontinuation reasons are described in online supplemental figure S2.

Patient demographics and baseline characteristics were similar across treatment groups and reflected the active axSpA population (table 1). COVID-19 had minimal impact on study conduct and results (online supplemental results).

Efficacy

Clinical response criteria

Rapid responses to BKZ were observed for the primary endpoint (ASAS40 at Week 16) across the axSpA spectrum, with separation from PBO observed after the first dose (figure 1A). The primary endpoint was met ($p<0.001$) in both studies. The proportion of patients initially randomised to BKZ achieving ASAS40 response was sustained from Week 16 (nr-axSpA: 47.7%; r-axSpA: 44.8% (NRI)) to Week 52 (nr-axSpA: 60.9%; r-axSpA: 58.4% (NRI)), with improvements seen across all ASAS components (online supplemental table S1). For patients switching from PBO to BKZ at Week 16 (PBO/BKZ), ASAS40 responses approached (nr-axSpA: 50.8% (NRI)) or surpassed (r-axSpA: 68.5% (NRI)) those of patients initially randomised to BKZ at Week 52.

ASAS40 responses at Week 16 in BKZ-randomised patients were largely sustained to Week 52 in both TNFi-naïve (nr-axSpA: 61.9%; r-axSpA: 58.7%) and TNFi-IR patients (nr-axSpA: 50.0%; r-axSpA: 56.8% (NRI); online supplemental table S2). Apart from TNFi-IR patients with nr-axSpA, ASAS40 responses of patients switching from PBO to BKZ at Week 16 approached or exceeded that of BKZ-randomised patients at Week 52 (TNFi-naïve: nr-axSpA: 53.2%, r-axSpA: 71.3%; TNFi-IR: nr-axSpA: 35.3%, r-axSpA: 52.9% (NRI); online supplemental table S2).

All other ranked secondary endpoints, including ASAS20 (figure 1B) and ASAS PR (figure 1C), significantly improved with BKZ, versus PBO, at Week 16, in both studies (table 2). Responses among patients initially randomised to BKZ were sustained at Week 52, while PBO-randomised patients switching to BKZ demonstrated improvements from Week 16, before reaching similar levels to BKZ-randomised patients by the end of the study (table 2).

Disease activity

BKZ treatment led to improvements from baseline in BASDAI score at Week 52 across the axSpA spectrum (mean change from baseline (CfB) in BKZ vs PBO/BKZ: nr-axSpA: −3.9, –3.5; r-axSpA: −3.6, –4.0 (multiple imputation: MI); figure 2A). A substantial proportion of patients achieved BASDAI50 at Week 52, across both treatment arms (nr-axSpA: BKZ: 53.9%, PBO/BKZ: 49.2%; r-axSpA: BKZ: 53.8%, PBO/BKZ: 62.2% (NRI); table 2).

From Week 16 to Week 52, reductions from baseline in ASDAS were observed for patients initially randomised to BKZ and patients switching to BKZ at Week 16 and, by Week 52, mean CfB in ASDAS was comparable between treatment arms (nr-axSpA: BKZ: −1.8, PBO/BKZ: −1.6; r-axSpA: BKZ: −1.7, PBO/BKZ: −1.9 (MI); figure 2B).

Almost all patients (nr-axSpA: 98.4%; r-axSpA: 99.1%) had high/very high disease activity (HDA; ASDAS ≥2.1) at baseline. BKZ treatment resulted in increased proportions of patients achieving ASDAS LDA (ASDAS <2.1) and ASDAS ID (ASDAS <1.3); by Week 52, the majority of patients achieved ASDAS LDA (nr-axSpA: BKZ: 61.6%, PBO/BKZ: 54.5%; r-axSpA: BKZ: 57.1%, PBO/BKZ: 66.4% (MI); figure 2C), and around a quarter achieved ASDAS ID (nr-axSpA: BKZ: 25.2%, PBO/BKZ: 28.0%; r-axSpA: BKZ: 23.4%, PBO/BKZ: 37.1% (MI); figure 2D). BKZ treatment led to substantial proportions of patients achieving ASDAS MI by Week 52, across the axSpA disease spectrum (nr-axSpA: BKZ: 36.7%, PBO/BKZ: 29.4%; r-axSpA: BKZ: 32.1%, PBO/BKZ: 44.1% (NRI); table 2).

Objective signs of inflammation

Rapid reductions in hs-CRP observed at Week 16 were sustained to Week 52 in patients initially randomised to BKZ; patients switching to BKZ at Week 16 achieved comparable hs-CRP levels by Week 52 (geometric mean: nr-axSpA: BKZ: 1.7, PBO/BKZ: 2.0; r-axSpA: BKZ: 2.2, PBO/BKZ: 2.0 (MI); figure 3A).

For the MRI substudies, 59.8% (152/254) of patients with nr-axSpA and 41.6% (138/332) of patients with r-axSpA had SPARCC SIJ assessments; 57.5% (146/254) and 41.3% (137/332) of patients had Berlin spine assessments. Mean SPARCC SIJ score reduced from baseline with BKZ treatment at Week 52 for patients initially randomised to BKZ (nr-axSpA: –7.6; r-axSpA: –4.7 (OC)) and patients who switched from PBO to BKZ at Week 16 (nr-axSpA: –6.4; r-axSpA: –2.8 (OC); figure 3B). At Week 52, mean CfB in Berlin spine score was comparable between patients initially randomised to BKZ and patients switching to BKZ at Week 16 (nr-axSpA: BKZ: –0.7, PBO/BKZ: –0.4; r-axSpA: BKZ: –2.4, PBO/BKZ: –2.1 (OC); figure 3C).

Pain, function and quality of life

Reductions from baseline to Week 52 in total spinal pain (nr-axSpA: BKZ: −4.2, PBO/BKZ: −3.9; r-axSpA: BKZ: −4.1, PBO/BKZ: −4.5 (MI)) and nocturnal spinal pain (nr-axSpA: BKZ: −4.3, PBO/BKZ: −4.1; r-axSpA: BKZ: −4.1, PBO/BKZ: −4.6 (MI)) were observed (table 2). To Week 52, improvements from baseline in morning stiffness (nr-axSpA: BKZ: −4.5, PBO/BKZ: −4.1; r-axSpA: BKZ: −3.9, PBO/BKZ: −4.4 (MI); figure 4) and fatigue (BASDAI question 1) were also observed with BKZ (nr-axSpA: BKZ: −3.2, PBO/BKZ: −2.7; r-axSpA: BKZ: −3.1, PBO/BKZ: −3.4 (MI) (online supplemental table S3). Improvements from baseline in physical function (BASFI: nr-axSpA: BKZ: −3.0, PBO/BKZ: −2.6, r-axSpA: BKZ: −2.8, PBO/BKZ: −2.8 (MI)) and HRQoL (ASQoL: nr-axSpA: BKZ: −5.9, PBO/BKZ: −5.3, r-axSpA: BKZ: −5.7, PBO/BKZ: −5.6 (MI)) were also noted to Week 52 (figure 4).

Enthesitis and peripheral arthritis

At baseline, 73.2% (186/254) of patients with nr-axSpA and 59.9% (199/332) of patients with r-axSpA had enthesitis (MASES >0). At Week 52, the proportion of patients achieving complete resolution of enthesitis (MASES=0; NRI) was 54.3% (BKZ) and 44.6% (PBO/BKZ) for patients with nr-axSpA, and 50.8% (BKZ) and 46.3% (PBO/BKZ) for patients with r-axSpA. At

Table 1 Patient demographics and baseline characteristics

	BE MOBILE 1 (nr-axSpA)		BE MOBILE 2 (r-axSpA)	
	PBO n=126	BKZ 160 mg Q4W n=128	PBO n=111	BKZ 160 mg Q4W n=221
Sex, male, n (%)	65 (51.6)	73 (57.0)	80 (72.1)	160 (72.4)
Age, years, mean (SD)	39.4 (11.8)	39.5 (11.1)	39.2 (12.6)	41.0 (12.1)
HLA-B27 positive, n (%)	94 (74.6)	103 (80.5)	93 (83.8)	191 (86.4)
Geographical region,* n (%)				
Asia†	13 (10.3)	15 (11.7)	21 (18.9)	40 (18.1)
Eastern Europe‡	71 (56.3)	73 (57.0)	55 (49.5)	108 (48.9)
Western Europe§	33 (26.2)	31 (24.2)	32 (28.8)	67 (30.3)
North America¶	9 (7.1)	9 (7.0)	3 (2.7)	6 (2.7)
BMI, kg/m^2, mean (SD)	27.7 (5.5)	27.2 (6.0)	27.1 (5.8)	26.8 (5.7)
Time since first symptoms of axSpA, years, mean (SD)	9.0 (9.0)	9.1 (8.7)	11.9 (8.6)	14.2 (11.0)
Time since first diagnosis of axSpA, years, mean (SD)	3.6 (5.4)	3.7 (6.2)	5.7 (6.9)	6.7 (8.3)
ASDAS, mean (SD)	3.7 (0.7)	3.7 (0.8)	3.7 (0.8)	3.7 (0.8)**
hs-CRP, mg/L, geometric mean (geometric CV, %)	5.0 (230.5)	4.6 (297.7)	6.7 (197.4)	6.5 (275.0)
hs-CRP>ULN,†† n ()	71 (56.3)	70 (54.7)	67 (60.4)	137 (62.0)
BASDAI, mean (SD)	6.7 (1.3)	6.9 (1.2)	6.5 (1.3)	6.5 (1.3)
PtGADA,‡‡ mean (SD)	6.9 (1.9)	7.1 (1.9)	6.7 (1.8)	6.6 (2.0)**
Total spinal pain,‡‡ mean (SD)	7.1 (1.6)	7.3 (1.5)	7.2 (1.2)	7.1 (1.6)
Nocturnal spinal pain, mean (SD)	6.7 (2.1)	6.9 (2.0)	6.8 (1.8)	6.6 (1.9)
Morning stiffness (mean of BASDAI Q5&6),‡‡ mean (SD)	6.9 (1.6)	7.0 (1.8)	6.8 (1.6)	6.7 (1.9)
BASFI,‡‡ mean (SD)	5.3 (2.3)	5.5 (2.2)	5.2 (2.0)	5.3 (2.2)
BASMI, mean (SD)	3.0 (1.2)	2.9 (1.3)	3.8 (1.6)	3.9 (1.6)
ASQoL, mean (SD)	9.4 (4.4)	9.5 (4.6)	8.5 (4.3)	9.0 (4.7)
SF-36 PCS, mean (SD)	33.6 (8.7)	33.3 (8.3)	34.6 (8.7)	34.3 (8.4)**
MRI Berlin spine score,§§ mean (SD)	1.6 (2.9)¶¶	1.6 (2.6)***	3.2 (4.1)†††	3.3 (4.5)‡‡‡
MRI SPARCC SIJ score,§§ mean (SD)	9.8 (12.6)§§§	8.0 (9.9)¶¶¶	3.8 (6.1)†††	5.4 (8.4)****
Current enthesitis (MASES>0), n (%)	92 (73.0)	94 (73.4)	67 (60.4)	132 (59.7)
MASES,†††† mean (SE)	4.9 (0.4)	4.8 (0.3)	4.4 (0.3)	4.2 (0.3)
Current peripheral arthritis (SJC>0), n (%)	43 (34.1)	45 (35.2)	22 (19.8)	44 (19.9)
History of IBD,‡‡‡‡ n (%)	1 (0.8)	3 (2.3)	1 (0.9)	3 (1.4)
History of uveitis,‡‡‡‡ n (%)	21 (16.7)	19 (14.8)	24 (21.6)	33 (14.9)
History of psoriasis,‡‡‡‡ n (%)	7 (5.6)	9 (7.0)	10 (9.0)	16 (7.2)
Prior TNFi exposure (TNFi-IR patients),§§§§ n (%)	17 (13.5)	10 (7.8)	17 (15.3)	37 (16.7)
Concomitant medication use at baseline, n (%)				
NSAIDs	93 (73.8)	96 (75.0)	85 (76.6)	181 (81.9)
Oral glucocorticoids	14 (11.1)	7 (5.5)	8 (7.2)	15 (6.8)
csDMARDs¶¶¶¶	32 (25.4)	29 (22.7)	19 (17.1)	47 (21.3)

Randomised set. Patients in BE MOBILE 1 met ASAS criteria and patients in BE MOBILE 2 met mNY and ASAS criteria.
*Patients categorised by the stratum to which they were randomised.
†Includes Turkey, Japan and China.
‡Includes Bulgaria, Czech Republic, Hungary and Poland.
§Includes Belgium, France, Germany, The Netherlands, Spain and the UK.
¶Includes the USA only.
**n=220.
††ULN value for hs-CRP is 5 mg/L.
‡‡Part of the primary outcome measure.
§§In patients in the MRI substudy.
¶¶n=67.
***n=79.
†††n=48.
‡‡‡n=89.
§§§n=70.
¶¶¶n=82.
****n=90.
††††In patients with MASES >0 at baseline.
‡‡‡‡Based on extra-articular assessments at screening or baseline.
§§§§Defined as patients who were intolerant or experienced an inadequate response to previous TNFi treatment given at an approved dose for at least 12 weeks.
¶¶¶¶Methotrexate in 21 patients with nr-axSpA and 12 patients with r-axSpA, sulfasalazine in 33 patients with nr-axSpA and 52 patients with r-axSpA.
ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BKZ, bimekizumab; BMI, body mass index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, coefficient of variation; HLA-B27, human leukocyte antigen-B27; hs-CRP, high-sensitivity C-reactive protein; IBD, inflammatory bowel disease; IR, inadequate response; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; mNY, modified New York; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, non-steroidal anti-inflammatory drug; PBO, placebo; PtGADA, Patient's Global Assessment of Disease Activity; Q, question; Q4W, every four weeks; r-axSpA, radiographic axial spondyloarthritis; SF-36 PCS, Short-Form 36-Item Health Survey Physical Component Summary; SIJ, sacroiliac joint; SJC, swollen joint count; SPARCC, Spondyloarthritis Research Consortium of Canada; TNFi, tumour necrosis factor inhibitor; ULN, upper limit of normal.

baseline, 34.6% (88/254) of patients with nr-axSpA and 19.9% (66/332) of patients with r-axSpA had SJC >0. While 64.2% (163/254) and 53.3% (177/332) of patients with nr-axSpA and r-axSpA, respectively, had TJC >0. By Week 52, the proportion of patients achieving resolution of peripheral arthritis (SJC=0; NRI) was 62.2% (BKZ) and 65.1% (PBO/BKZ) for patients with

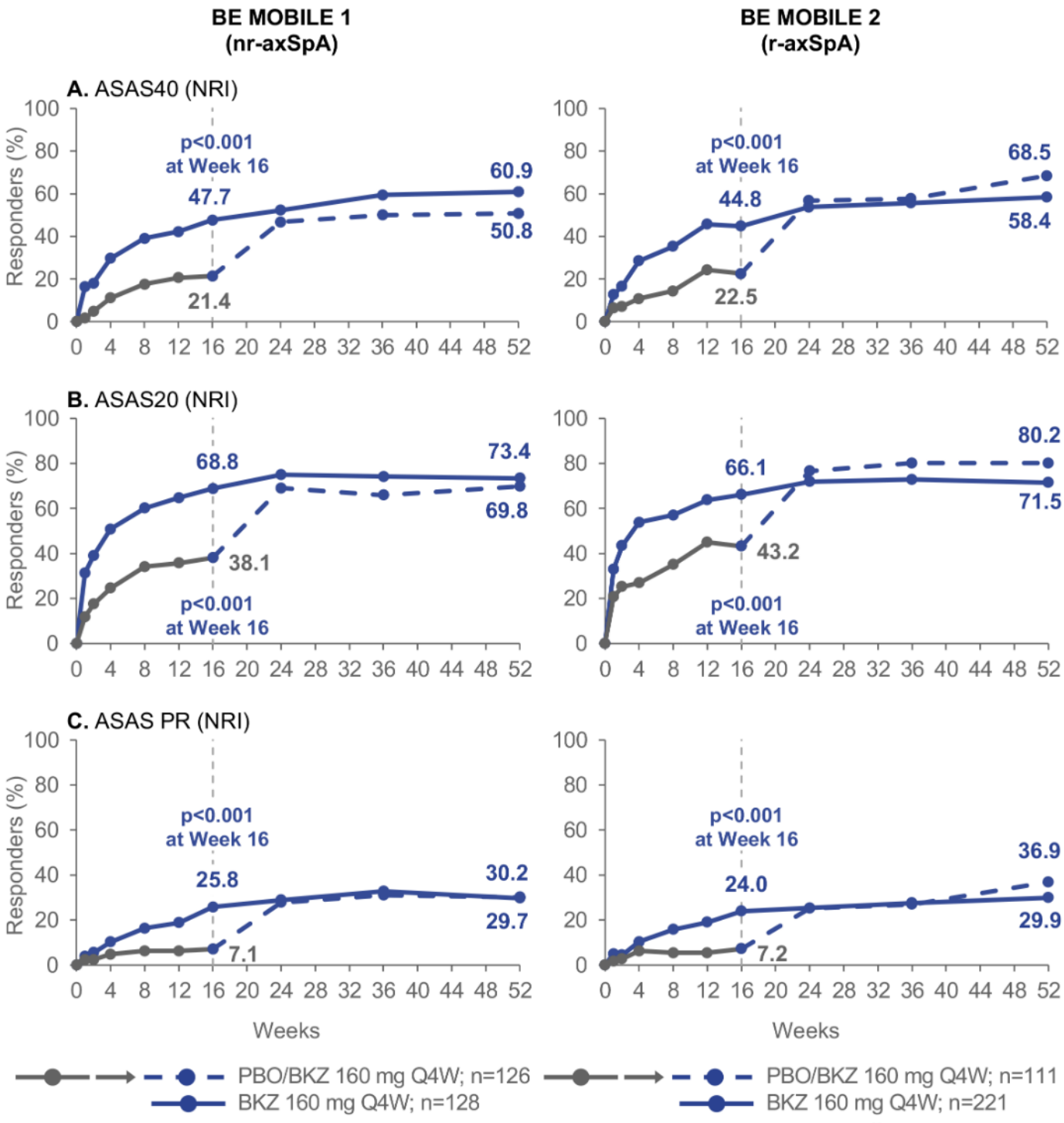

Figure 1 ASAS responses at Week 52 (NRI). Randomised set. Missing data imputed using NRI. ASAS40 was the primary efficacy endpoint in both trials; ASAS20 and ASAS PR were ranked secondary endpoints. p values calculated by logistic regression with treatment, region, MRI/CRP classification (BE MOBILE 1) and prior TNFi exposure (BE MOBILE 2 only) as factors. ASAS20/40/PR, Assessment in SpondyloArthritis International Society 20%/40% response/partial remission; BKZ, bimekizumab; CRP, C-reactive protein; nr-axSpA, non-radiographic axial spondyloarthritis; NRI, non-responder imputation; PBO, placebo; Q4W, every 4 weeks; r-axSpA, radiographic axial spondyloarthritis; TNFi, tumour necrosis factor inhibitor.

nr-axSpA, and 72.7% (BKZ) and 81.8% (PBO/BKZ) for patients with r-axSpA.

At baseline, 34.6% (88/254) of patients with nr-axSpA and 19.9% (66/332) of patients with r-axSpA had SJC >0. While 64.2% (163/254) and 53.3% (177/332) of patients with nr-axSpA and r-axSpA, respectively, had TJC >0. By Week 52, the proportion of patients achieving resolution of peripheral arthritis (SJC=0; NRI) was 62.2% (BKZ) and 65.1% (PBO/BKZ) for patients with nr-axSpA, and 72.7% (BKZ) and 81.8% (PBO/BKZ) for patients with r-axSpA.

Mean CfB in MASES, SJC and TJC at Week 52 is reported in online supplemental table S4.

Safety

Safety data for the DBTP have been reported previously and are summarised in table 3.[22] At Week 52, ≥1 TEAE was reported

Table 2 Efficacy outcomes at Week 16 (primary and ranked secondary endpoints) and Week 52

		Baseline		Week 16			Week 52	
		PBO	BKZ 160 mg Q4W	PBO	BKZ 160 mg Q4W	p value*	PBO→BKZ 160 mg Q4W	BKZ 160 mg Q4W
nr-axSpA (BE MOBILE 1)		**n=126**	**n=128**	**n=126**	**n=128**		**n=126**	**n=128**
r-axSpA (BE MOBILE 2)		**n=111**	**n=221**	**n=111**	**n=221**		**n=111**	**n=221**
Clinical response criteria								
ASAS40 (NRI), n (%)	nr-axSpA	–	–	27 (21.4)	61 (47.7)	<0.001	64 (50.8)	78 (60.9)
	r-axSpA	–	–	25 (22.5)	99 (44.8)	<0.001	76 (68.5)	129 (58.4)
ASAS20 (NRI), n (%)	nr-axSpA	–	–	48 (38.1)	88 (68.8)	<0.001	88 (69.8)	94 (73.4)
	r-axSpA	–	–	48 (43.2)	146 (66.1)	<0.001	89 (80.2)	158 (71.5)
ASAS PR (NRI), n (%)	nr-axSpA	–	–	9 (7.1)	33 (25.8)	<0.001	38 (30.2)	38 (29.7)
	r-axSpA	–	–	8 (7.2)	53 (24.0)	<0.001	41 (36.9)	66 (29.9)
ASAS40 in TNFi-naïve patients† (NRI), n (%)	nr-axSpA	–	–	25 (22.9)‡	55 (46.6)§	<0.001¶	58 (53.2)‡	73 (61.9)§
	r-axSpA	–	–	22 (23.4)**	84 (45.7)††	<0.001	67 (71.3)**	108 (58.7)††
ASDAS-MI (NRI), n (%)	nr-axSpA	–	–	9 (7.1)	35 (27.3)	<0.001	37 (29.4)	47 (36.7)
	r-axSpA	–	–	6 (5.4)	57 (25.8)	<0.001	49 (44.1)	71 (32.1)
Disease activity								
BASDAI CfB (MI), mean (SE)	nr-axSpA	6.7 (0.1)	6.9 (0.1)	–1.5 (0.2)	–3.1 (0.2)	<0.001	–3.5 (0.2)	–3.9 (0.2)
	r-axSpA	6.5 (0.1)	6.5 (0.1)	–1.9 (0.2)	–2.9 (0.1)	<0.001	–4.0 (0.2)	–3.6 (0.1)
BASDAI50 (NRI), n (%)	nr-axSpA	–	–	27 (21.4)	60 (46.9)	<0.001¶	62 (49.2)	69 (53.9)
	r-axSpA	–	–	29 (26.1)	103 (46.6)	<0.001¶	69 (62.2)	119 (53.8)
BASMI CfB† (MI), mean (SE)	nr-axSpA	3.0 (0.1)	2.9 (0.1)	–0.1 (0.1)	–0.4 (0.1)	<0.001¶	–0.4 (0.1)	–0.6 (0.1)
	r-axSpA	3.8 (0.2)	3.9 (0.1)	–0.2 (0.1)	–0.5 (0.1)	0.006	–0.7 (0.1)	–0.7 (0.1)
Pain, physical function and quality of life								
Total spinal pain CfB (MI), mean (SE)	nr-axSpA	7.1 (0.1)	7.3 (0.1)	–1.7 (0.2)	–3.4 (0.2)	<0.001¶	–3.9 (0.2)	–4.2 (0.2)
	r-axSpA	7.2 (0.1)	7.1 (0.1)	–1.9 (0.2)	–3.3 (0.2)	<0.001¶	–4.5 (0.2)	–4.1 (0.2)
Nocturnal spinal pain CfB (MI), mean (SE)	nr-axSpA	6.7 (0.2)	6.9 (0.2)	–1.7 (0.2)	–3.6 (0.3)	<0.001	–4.1 (0.2)	–4.3 (0.3)
	r-axSpA	6.8 (0.2)	6.6 (0.1)	–1.9 (0.2)	–3.3 (0.2)	<0.001	–4.6 (0.3)	–4.1 (0.2)
BASFI CfB (MI), mean (SE)	nr-axSpA	5.3 (0.2)	5.5 (0.2)	–1.0 (0.2)	–2.5 (0.2)	<0.001	–2.6 (0.2)	–3.0 (0.2)
	r-axSpA	5.2 (0.2)	5.3 (0.2)	–1.1 (0.2)	–2.2 (0.1)	<0.001	–2.8 (0.2)	–2.8 (0.1)
SF-36 PCS CfB (MI), mean (SE)	nr-axSpA	33.6 (0.8)	33.3 (0.7)	5.5 (0.7)	9.5 (0.7)	<0.001	11.4 (0.9)	12.2 (0.9)
	r-axSpA	34.6 (0.8)	34.4 (0.6)	5.9 (0.8)	9.3 (0.6)	<0.001	12.3 (0.9)	12.0 (0.6)
ASQoL CfB (MI), mean (SE)	nr-axSpA	9.4 (0.4)	9.5 (0.4)	–2.5 (0.4)	–5.2 (0.4)	<0.001	–5.3 (0.4)	–5.9 (0.4)
	r-axSpA	8.5 (0.4)	9.0 (0.3)	–3.2 (0.3)	–5.0 (0.3)	<0.001	–5.6 (0.4)	–5.7 (0.3)

Randomised set. Missing data were imputed using NRI for binary endpoints, RBMI for ranked continuous endpoints at Week 16, and MI for continuous non-ranked and ranked (post Week 16) endpoints at Week 52.
*All tests were performed at a two-sided alpha level of 0.05. For binary endpoints, p values were calculated by logistic regression with treatment, MRI/CRP classification and region (BE MOBILE 1) or treatment, prior TNFi exposure and region (BE MOBILE 2) as factors. For continuous endpoints, 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.
†Ranked secondary endpoint in BE MOBILE 2.
‡n=109.
§n=118.
¶Outcome was not part of the statistical hierarchy, therefore p values are nominal (no multiplicity adjustment) and should not be used as an indicator of statistical significance.
**n=94.
††n=184.
ANCOVA, analysis of covariance; ASAS20/40/PR, Assessment of SpondyloArthritis International Society 20%/40% response/partial remission; ASDAS-MI, Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI(50), Bath Ankylosing Spondylitis Disease Activity Index (50% response); BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BKZ, bimekizumab; CfB, change from baseline; CRP, C-reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MI, multiple imputation; nr-axSpA, non-radiographic axial spondyloarthritis; NRI, non-responder imputation; PBO, placebo; Q4W, every 4 weeks; r-axSpA, radiographic axial spondyloarthritis; RBMI, reference-based multiple imputation; SF-36 PCS, Short-Form 36-Item Health Survey Physical Component Summary; TNFi, tumour necrosis factor inhibitor.

for 183 out of 244 (75.0%; EAIR/100 PY: 202.1) patients with nr-axSpA and 249 out of 330 (75.5%; EAIR/100 PY: 200.8) with r-axSpA who had received ≥1 dose of BKZ (table 3). TEAEs leading to study drug discontinuation during Weeks 0–52 occurred in 8 out of 244 (3.3%; EAIR/100 PY: 3.9) patients with nr-axSpA and 16 out of 330 (4.8%; EAIR/100 PY: 5.6) patients with r-axSpA (online supplemental table S5).

During the DBTP, one (0.8%) PBO-randomised patient with nr-axSpA reported an SAE, while one (0.9%) PBO-randomised and four (1.8%) BKZ-randomised patients with r-axSpA reported an SAE. For the overall period (Weeks 0–52), 9 (3.7%; EAIR/100 PY: 4.4) patients with nr-axSpA and 20 (6.1%; EAIR/100 PY: 7.1) patients with r-axSpA reported an SAE. SAEs are summarised in online supplemental table S6. No deaths occurred in either study.

To Week 52, the most common TEAEs by preferred term were nasopharyngitis (nr-axSpA: 12.3%; EAIR/100 PY: 15.7; r-axSpA: 9.1%; EAIR/100 PY: 11.0), upper respiratory tract infection

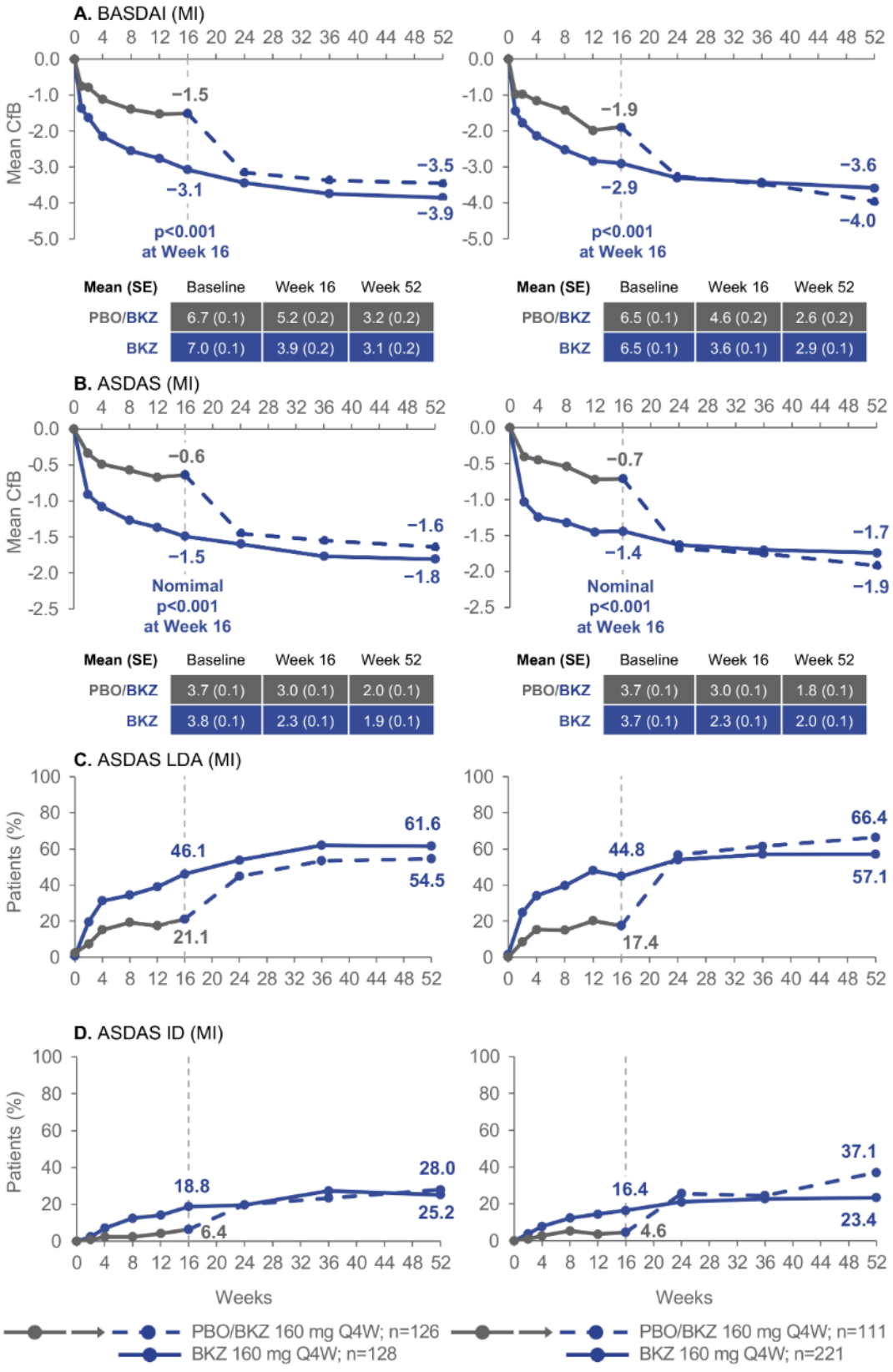

Figure 2 Disease activity (BASDAI, ASDAS) at Week 52. Randomised set. ASDAS LDA when ASDAS <2.1; ASDAS ID when ASDAS <1.3; ASDAS, ASDAS LDA and ID were exploratory endpoints in both trials; CfB in BASDAI was a ranked secondary endpoint in both trials; p value for the comparison of BKZ to PBO was calculated using ANCOVA with treatment, region, MRI/CRP classification (BE MOBILE 1 only), prior TNFi exposure (BE MOBILE 2 only) as fixed effects, and baseline scores as covariate; p values without any multiplicity adjustment are indicated as nominal p values and should not be used as an indicator of statistical significance. ANCOVA, analysis of covariance; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BKZ, bimekizumab; CfB, change from baseline; CRP, C-reactive protein; ID, inactive disease; LDA, low disease activity; MI, multiple imputation; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; Q4W, every 4 weeks; r-axSpA, radiographic axial spondyloarthritis.

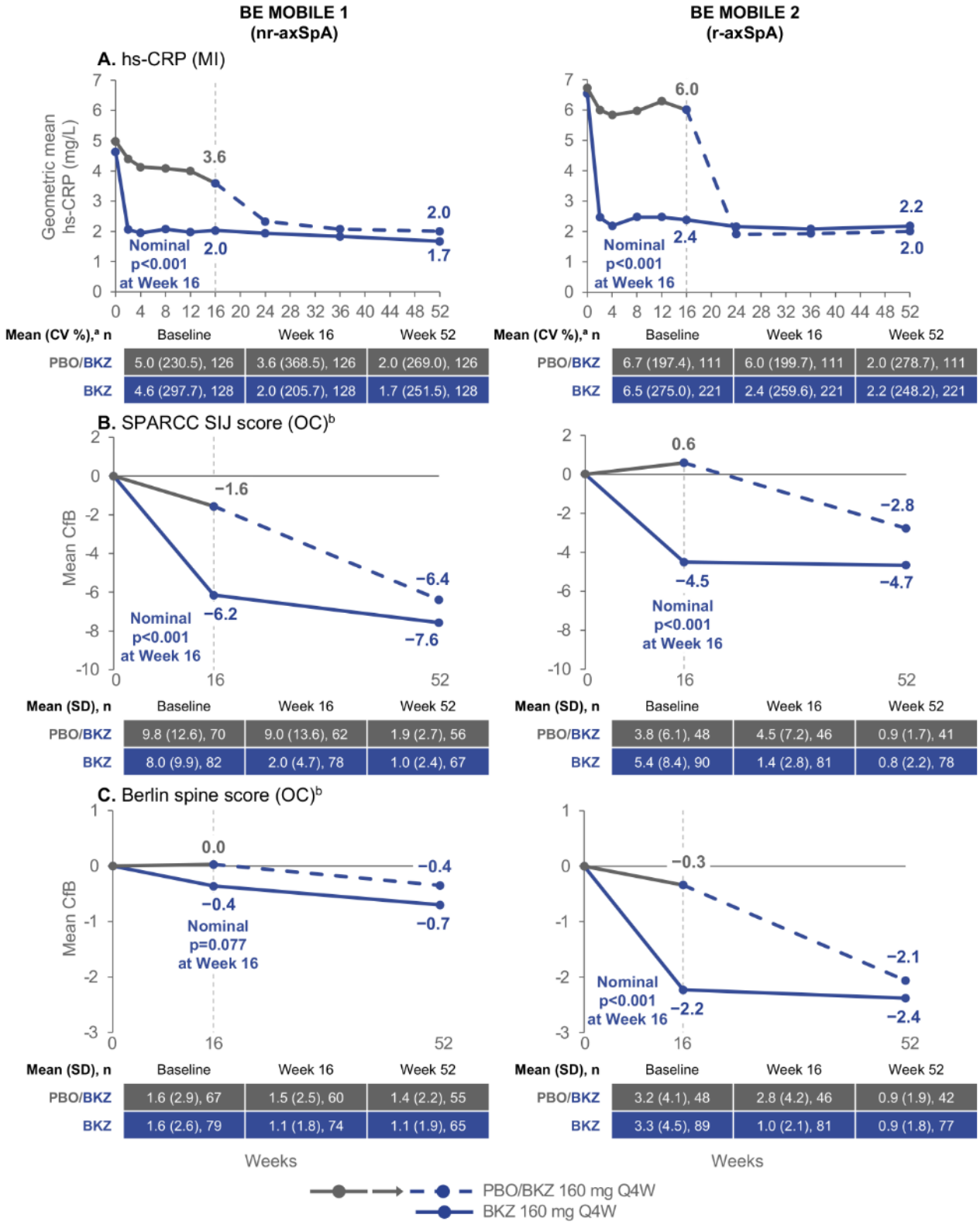

Figure 3 Objective signs of inflammation (hs-CRP, MRI SPARCC SIJ, MRI Berlin spine) at Week 52. Randomised set. Exploratory endpoints. [a]Geometric mean and geometric CV (%). [b]SPARCC SIJ and Berlin spine scores reported for only patients in MRI substudies. MRI SPARCC SIJ inflammation scores range from 0 to 72; lower scores indicate less SIJ inflammation and negative changes represent improvements. MRI Berlin spine score ranges from 0 to 69; lower scores indicate less spinal inflammation and negative changes represent improvements; p value for the comparison of BKZ to PBO was calculated using ANCOVA with treatment, region, MRI/CRP classification (BE MOBILE 1 only), prior TNFi exposure (BE MOBILE 2 only) as fixed effects and baseline scores as covariate; p values without any multiplicity adjustment are indicated as nominal p values and should not be used as an indicator of statistical significance. ANCOVA, analysis of covariance; BKZ, bimekizumab; CfB, change from baseline; CV, coefficient of variation; hs-CRP, high-sensitivity C-reactive protein; MI, multiple imputation; nr-axSpA, non-radiographic axial spondyloarthritis; OC, observed case; PBO, placebo; Q4W: every 4 weeks; r-axSpA, radiographic axial spondyloarthritis; SIJ sacroiliac joint; SPARCC Spondyloarthritis Research Consortium of Canada.

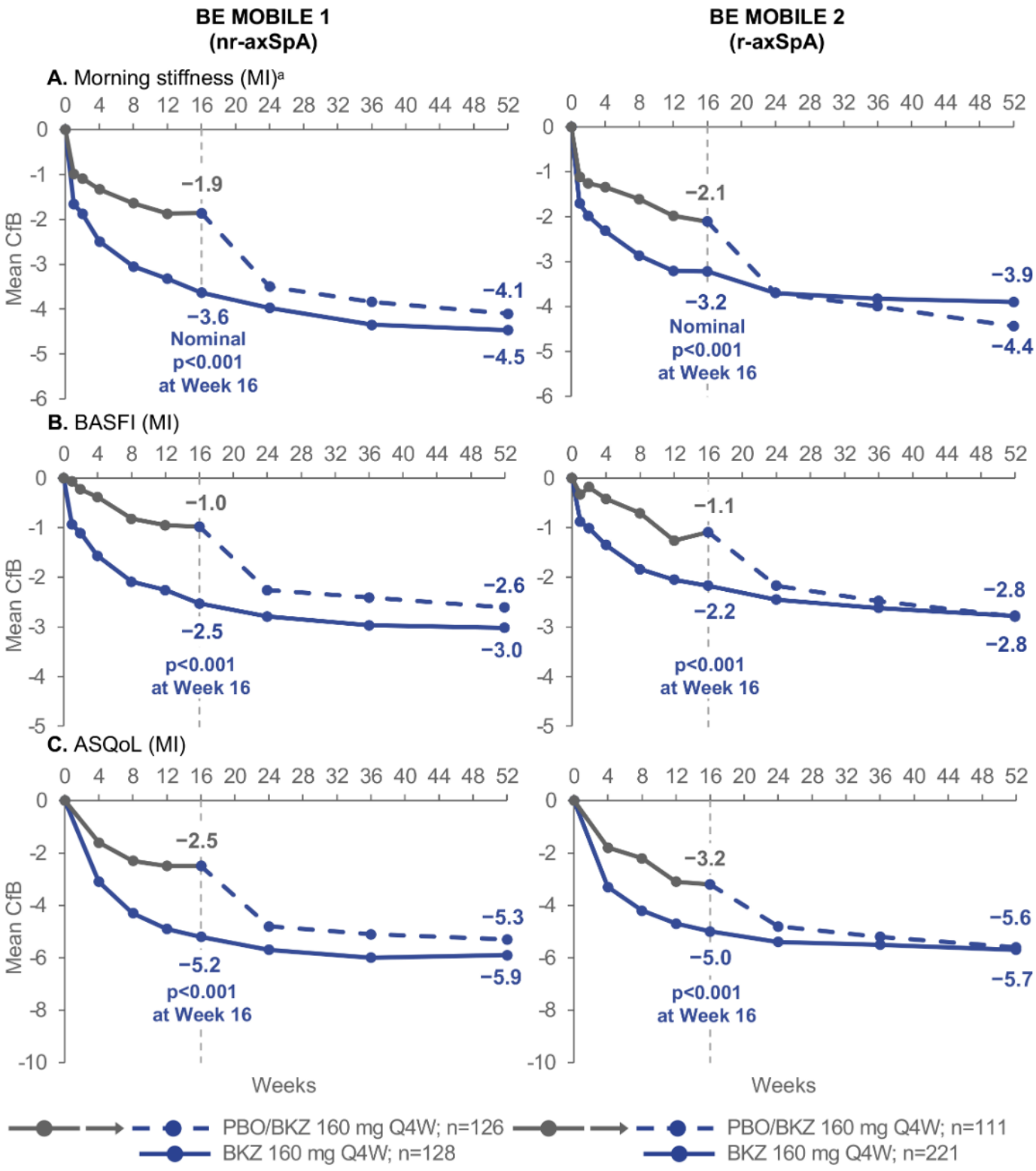

Figure 4 Morning stiffness, physical function and quality of life at Week 52. Randomised set. Morning stiffness was an exploratory endpoint; BASFI and ASQoL were ranked secondary endpoints. [a]Morning stiffness was calculated as the mean of BASDAI questions 5 and 6; p value for the comparison of BKZ to PBO was calculated using ANCOVA with treatment, region, MRI/CRP classification (BE MOBILE one only), prior TNFi exposure (BE MOBILE two only) as fixed effects and baseline scores as covariate; p values without any multiplicity adjustment are indicated as nominal p values and should not be used as an indicator of statistical significance. ANCOVA, analysis of covariance; ASQoL, Ankylosing Spondylitis Quality of Life Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BKZ, bimekizumab; CfB, change from baseline; MI, multiple imputation; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; Q4W, every 4 weeks; r-axSpA, radiographic axial spondyloarthritis.

Table 3 Safety overview for the double-blind treatment (Weeks 0–16) and overall periods (Weeks 0–52)

		Double-blind treatment period Weeks 0–16		Maintenance period Weeks 16–52	Overall Weeks 0–52
n (%), overall period: (EAIR/100 PY)		PBO	BKZ 160 mg Q4W	BKZ 160 mg Q4W	BKZ 160 mg Q4W*
nr-axSpA (BE MOBILE 1)		n=126 (38.1 PYAR)	n=128 (40.4 PYAR)	n=242 (167.8 PYAR)	n=244 (208.2 PYAR)
r-axSpA (BE MOBILE 2)		n=111 (34.6 PYAR)	n=221 (68.3 PYAR)	n=319 (220.0 PYAR)	n=330 (290.9 PYAR)
Overview					
Any TEAE	nr-axSpA	71 (56.3)	80 (62.5)	164 (67.8)	183 (75.0) (202.1)
	r-axSpA	48 (43.2)	120 (54.3)	217 (68.0)	249 (75.5) (200.8)
Severe TEAEs	nr-axSpA	1 (0.8)	0	8 (3.3)	8 (3.3) (3.9)
	r-axSpA	0	4 (1.8)	10 (3.1)	14 (4.2) (4.9)
TEAEs leading to discontinuation from the study	nr-axSpA	5 (4.0)	2 (1.6)	4 (1.7)	6 (2.5) (2.9)
	r-axSpA	0	6 (2.7)	9 (2.8)	15 (4.5) (5.2)
TEAEs leading to discontinuation of study drug	nr-axSpA	5 (4.0)	2 (1.6)	6 (2.5)	8 (3.3) (3.9)
	r-axSpA	0	7 (3.2)	9 (2.8)	16 (4.8) (5.6)
Drug-related TEAEs	nr-axSpA	17 (13.5)	33 (25.8)	67 (27.7)	81 (33.2) (51.3)
	r-axSpA	19 (17.1)	65 (29.4)	133 (35.4)	135 (40.9) (67.1)
SAEs	nr-axSpA	1 (0.8)	0	9 (3.7)	9 (3.7) (4.4)
	r-axSpA	1 (0.9)	5 (2.3)	15 (4.7)	20 (6.1) (7.1)
Death	nr-axSpA	0	0	0	0
	r-axSpA	0	0	0	0
Most frequently reported TEAEs†					
Nasopharyngitis	nr-axSpA	6 (4.8)	13 (10.2)	18 (7.4)	30 (12.3) (15.7)
	r-axSpA	4 (3.6)	17 (7.7)	17 (5.3)	30 (9.1) (11.0)
Upper respiratory tract infection	nr-axSpA	10 (7.9)	9 (7.0)	15 (6.2)	23 (9.4) (11.9)
	r-axSpA	8 (7.2)	6 (2.7)	16 (5.0)	21 (6.4) (7.5)
Oral candidiasis‡	nr-axSpA	0	4 (3.1)	17 (7.0)	18 (7.4) (9.0)
	r-axSpA	0	10 (4.5)	12 (3.8)	20 (6.1) (7.2)
Corona virus infection	nr-axSpA	1 (0.8)	1 (0.8)	17 (7.0)	17 (7.0) (8.3)
	r-axSpA	3 (2.7)	1 (0.5)	6 (1.9)	7 (2.1) (2.4)
Headache	nr-axSpA	2 (1.6)	3 (2.3)	10 (4.1)	13 (5.3) (6.5)
	r-axSpA	5 (4.5)	9 (4.1)	11 (3.4)	18 (5.5) (6.5)
Pharyngitis	nr-axSpA	1 (0.8)	4 (3.1)	7 (2.9)	11 (4.5) (5.4)
	r-axSpA	0	5 (2.3)	7 (2.2)	11 (3.3) (3.9)
Diarrhoea	nr-axSpA	2 (1.6)	3 (2.3)	6 (2.5)	9 (3.7) (4.4)
	r-axSpA	1 (0.9)	7 (3.2)	12 (3.8)	18 (5.5) (6.5)
Prespecified safety topics of interest and other important TEAEs					
Serious infections	nr-axSpA	0	0	4 (1.7)	4 (1.6) (1.9)
	r-axSpA	1 (0.9)	1 (0.5)	5 (1.6)	6 (1.8) (2.1)
Opportunistic infections	nr-axSpA	0	1 (0.8)	4 (1.7)	5 (2.0) (2.4)
	r-axSpA	0	0	3 (0.9)	3 (0.9) (1.0)
Any fungal infections	nr-axSpA	0	9 (7.0)	32 (13.2)	37 (15.2) (19.6)
	r-axSpA	0	14 (6.3)	31 (9.7)	40 (12.1) (14.9)
Candida infections	nr-axSpA	0	5 (3.9)	23 (9.5)	25 (10.2) (12.8)
	r-axSpA	0	11 (5.0)	15 (4.7)	23 (7.0) (8.3)
Fungal infections NEC	nr-axSpA	0	4 (3.1)	9 (3.7)	13 (5.3) (6.4)
	r-axSpA	0	5 (2.3)	11 (3.4)	14 (4.2) (5.0)
Tinea infections	nr-axSpA	0	0	2 (0.8)	2 (0.8) (1.0)
	r-axSpA	0	1 (0.5)	5 (1.6)	6 (1.8) (2.1)
Neutropenia	nr-axSpA	0	1 (0.8)	2 (0.8)	2 (0.8) (1.0)
	r-axSpA	0	1 (0.5)	2 (0.6)	2 (0.6) (0.7)
Hepatic events§	nr-axSpA	3 (2.4)	7 (5.5)	14 (5.8)	20 (8.2) (10.2)
	r-axSpA	4 (3.6)	10 (4.5)	24 (7.5)	33 (10.0) (12.1)
Potential Hy's law	nr-axSpA	0	0	0	0
	r-axSpA	0	1 (0.5)¶	0	1 (0.3) (0.3)
Liver enzyme elevations					
>3 xULN ALT or AST	nr-axSpA	1 (0.8)	2 (1.6)	4 (1.7)	6 (2.5) (2.9)
	r-axSpA	2 (1.8)	3 (1.4)	9 (2.8)	12 (3.6) (4.3)

Continued

Table 3 Continued

n (%), overall period: (EAIR/100 PY)		Double-blind treatment period Weeks 0–16		Maintenance period Weeks 16–52	Overall Weeks 0–52
		PBO	BKZ 160 mg Q4W	BKZ 160 mg Q4W	BKZ 160 mg Q4W*
nr-axSpA (BE MOBILE 1)		n=126 (38.1 PYAR)	n=128 (40.4 PYAR)	n=242 (167.8 PYAR)	n=244 (208.2 PYAR)
r-axSpA (BE MOBILE 2)		n=111 (34.6 PYAR)	n=221 (68.3 PYAR)	n=319 (220.0 PYAR)	n=330 (290.9 PYAR)
>5 xULN ALT or AST	nr-axSpA	0	0	1 (0.4)	1 (0.4) (0.5)
	r-axSpA	1 (0.9)	3 (1.4)	3 (0.9)	6 (1.8) (2.1)
Hypersensitivity**	nr-axSpA	3 (2.4)	3 (2.3)	17 (7.0)	18 (7.4) (9.1)
	r-axSpA	2 (1.8)	17 (7.7)	28 (8.8)	41 (12.4) (15.3)
Anaphylactic reactions	nr-axSpA	0	0	0	0
	r-axSpA	0	0	0	0
Injection site reactions	nr-axSpA	1 (0.8)	0	1 (0.4)	1 (0.4) (0.5)
	r-axSpA	0	1 (0.5)	0	1 (0.3) (0.3)
Dermatitis and eczema	nr-axSpA	0	1 (0.8)	7 (2.9)	8 (3.3) (3.9)
	r-axSpA	1 (0.9)	6 (2.7)	17 (5.3)	19 (5.8) (6.8)
Adjudicated MACE	nr-axSpA	0	0	0	0
	r-axSpA	0	0	0	0
Malignancies††	nr-axSpA	0	0	1 (0.4)	1 (0.4) (0.5)
	r-axSpA	0	0	1 (0.3)	1 (0.3) (0.3)
Adjudicated SIB‡‡	nr-axSpA	0	0	1 (0.4)	1 (0.4) (0.5)
	r-axSpA	0	0	1 (0.3)	1 (0.3) (0.3)
Adjudicated IBD§§	nr-axSpA	1 (0.8)	0	2 (0.8)	2 (0.8) (1.0)
	r-axSpA	0	2 (0.9)	1 (0.3)	3 (0.9) (1.0)
Ulcerative colitis¶¶***	nr-axSpA	1 (0.8)	0	1 (0.4)	1 (0.4) (0.5)
	r-axSpA	0	1 (0.5)	0	1 (0.3) (0.3)
Crohn's disease¶¶†††	nr-axSpA	0	0	1 (0.4)	1 (0.4) (0.5)
	r-axSpA	0	1 (0.5)	1 (0.3)	2 (0.6) (0.7)
Uveitis‡‡‡§§§	nr-axSpA	6 (4.8)	2 (1.6)	3 (1.2)	3 (1.2) (1.5)
	r-axSpA	5 (4.5)	0	7 (2.2)	7 (2.1) (2.4)

Safety set. MedDRA (v.19.0). Overall period includes all data available up to the last Week 52 visit, including data for patients treated beyond Week 24.
*Includes patients who switched from PBO to BKZ (events after switch only).
†TEAEs >5% in any group are reported by preferred term.
‡Only one case of oral candidiasis (in BE MOBILE 1) was severe, the remainder were mild or moderate.
§Most reported hepatic events were associated with non-serious abnormal liver function elevations; those that were markedly abnormal were associated with factors other than the study treatment.
¶Potential Hy's law case was diagnosed with hepatitis A infection
**Hypersensitivity events were identified using the MedDRA standardised medical query 'Hypersensitivity (SMQ)'.
††One clear cell renal carcinoma event in BE MOBILE 1 and one superficial spreading melanoma stage I event in BE MOBILE 2, both adjudicated as not related to study drug by investigator.
‡‡One intentional self-injury event in BE MOBILE 1 adjudicated as not related to study drug by investigator and one suicidal ideation event in BE MOBILE 2, adjudicated as related to study drug by investigator.
§§Definite or probable IBD reported per external adjudication committee.
¶¶No patients with nr-axSpA and one patient with r-axSpA who had IBD events had a medical history of IBD.
***Moderate ulcerative colitis in a patient with nr-axSpA and severe ulcerative colitis in patients with r-axSpA, both of which led to discontinuation of study drug.
†††One case of mild Crohn's disease in a patient with nr-axSpA that did not lead to discontinuation of study drug and two cases of moderate Crohn's disease that led to discontinuation of study drug.
‡‡‡Of these patients in BE MOBILE 1, one BKZ-treated patient and four PBO-treated patients in Weeks 0–16, and one BKZ-treated patient in Weeks 0–52, had a medical history of uveitis at baseline. Of these patients in BE MOBILE 2, five PBO-treated patients in Weeks 0–16, and five BKZ-treated patients in Weeks 0–52, had a medical history of uveitis at baseline.
§§§Includes the preferred terms autoimmune uveitis, uveitis, iridocyclitis and iritis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BKZ, bimekizumab; DILI, drug-induced liver events; EAIR, exposure-adjusted incidence rate; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; n, number of patients reporting at least one TEAE in that category; NEC, not elsewhere classified; PBO, placebo; PY, patient years; PYAR, patient years at risk; Q4W, every 4 weeks; SAE, serious adverse event; SIB, suicidal ideation and behaviour; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

(nr-axSpA: 9.4%; EAIR/100 PY: 11.9; r-axSpA: 6.4%; EAIR/100 PY: 7.5) and oral candidiasis (nr-axSpA: 7.4%; EAIR/100 PY: 9.0; r-axSpA: 6.1%; EAIR/100 PY: 7.2).

For the overall period, serious infections were reported in four (1.6%; EAIR/100 PY: 1.9) patients with nr-axSpA, one case each of bacterial tonsilitis and erysipelas and two cases of appendicitis (all occurring during the maintenance period). In patients with r-axSpA, six (1.8%; EAIR/100 PY: 2.1) reported serious infections; one case of hepatitis A (BKZ-randomised patient) and one case of viral infection (PBO/BKZ-randomised patient) occurred during the DBTP and one case each of diverticulitis, cellulitis, otitis media, infectious pleural effusion (reported as pleural empyema; patient previously had pneumonia) and erysipelas occurred during the maintenance period (online supplemental

table S6). All cases of serious infections in both studies resolved. There were no cases of active tuberculosis.

Fungal infection TEAEs are summarised in online supplemental table S7. During Weeks 0–52, fungal infections were reported in 37 out of 244 (15.2%; EAIR/100 PY: 19.6) and 40 out of 330 (12.1%; EAIR/100 PY: 14.9) BKZ-treated patients with nr-axSpA and r-axSpA, respectively (table 3). The majority were *Candida* infections (nr-axSpA: n=25; r-axSpA: n=23), with the most frequent preferred term being oral candidiasis (nr-axSpA: n=18; r-axSpA: n=20). The remainder were fungal infections not elsewhere classified (NEC; nr-axSpA: n=13; r-axSpA: n=14) and tinea infections (nr-axSpA: n=2; r-axSpA: n=6). All fungal infections were non-systemic and localised, and only one case (nr-axSpA) was classed as severe. In total, three nr-axSpA cases (all oral candidiasis) and two r-axSpA cases (one oral candidiasis and one oesophageal candidiasis) led to treatment discontinuation (online supplemental table S5).

To Week 52, five (2.0%; EAIR/100 PY: 2.4) patients with nr-axSpA and three (0.9%; EAIR/100 PY: 1.0) patients with r-axSpA had infections defined as opportunistic, all of which were fungal. One (0.8%) nr-axSpA case of opportunistic fungal infection occurred in the DBTP (BKZ-randomised patient), while all three (0.9%) r-axSpA cases occurred in the maintenance period. In both studies, all opportunistic fungal infections were localised and mucocutaneous: four oropharyngeal candidiasis cases and one fungal oropharyngitis case in patients with nr-axSpA, and one case each of oesophageal candidiasis, oropharyngeal candidiasis and fungal oesophagitis in patients with r-axSpA.

No anaphylactic reactions or adjudicated major adverse cardiovascular events occurred during Weeks 0–52 (table 3). For both studies, all cases of hypersensitivity reaction (identified using the MedDRA standardised medical query 'Hypersensitivity (SMQ)') were non-serious and the vast majority were mild/moderate and did not lead to study discontinuation (table 3).

Hepatic events occurred in 20 (8.2%; EAIR/100 PY: 10.2) and 33 (10.0%; EAIR/100 PY: 12.1) patients with nr-axSpA and r-axSpA, respectively. All hepatic events were non-serious, and the majority were liver enzyme elevations (>3 or >5 times upper limit of normal (ULN) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST)), and none led to treatment discontinuation. No confirmed cases of Hy's law were identified (table 3).

Among BKZ-treated patients, there was one (0.4%; EAIR/100 PY: 0.5) case of malignancy (clear cell renal cell carcinoma) in a patient with nr-axSpA, and one (0.3%; EAIR/100 PY: 0.3) case of malignancy (superficial spreading melanoma stage I) in a patient with r-axSpA; both events were assessed as not related to the study drug (online supplemental table S6). There was one (0.4%; EAIR/100 PY: 0.5) case of intentional self-injury in a patient with nr-axSpA reported and one (0.3%; EAIR/100 PY: 0.3) case of suicidal ideation reported in a patient with r-axSpA (both adjudicated as suicidal ideation and behaviour; online supplemental table S6). Both patients had several social and medical confounding factors at the time of the event.

During Weeks 0–52, among patients with nr-axSpA, no patients with a history of IBD (n=4) had TEAEs adjudicated as definite or probable IBD (per adjudication committee), while 2 out of 240 (0.8%; EAIR/100 PY: 1.0) patients with no history of IBD, had IBD events (table 3). Of these patients, one (0.4%; EAIR/100 PY: 0.5) had definite moderate ulcerative colitis leading to discontinuation of the study drug and one (0.4%; EAIR/100 PY: 0.5) had probable mild Crohn's disease that did not lead to study drug discontinuation. For patients with r-axSpA, 1 out of 4 (25.0%; EAIR/100 PY: 30.3) patients with and 2 out of 326 (0.6%; EAIR/100 PY: 0.7) patients without a history of IBD had definite or probable IBD events. Of patients with r-axSpA who had IBD events, two (0.6%; EAIR/100 PY: 0.7) had definite moderate Crohn's disease and one (0.3%; EAIR/100 PY: 0.3) had probable severe ulcerative colitis. All three cases led to discontinuation of the study drug (table 3, online supplemental table S5).

During Weeks 0–52, 1 out of 39 (2.6%; EAIR/100 PY: 3.2) patient with nr-axSpA with a history and 2 out of 205 (1.0%; EAIR/100 PY: 1.2) patients with nr-axSpA without a history of uveitis, had a uveitis event. For patients with r-axSpA, 5 out of 56 (8.9%; EAIR/100 PY: 10.8) patients with and 2 out of 274 (0.7%; EAIR/100 PY: 0.8) patients without a history of uveitis had uveitis events. In both studies, all uveitis events were mild or moderate and only one case (iridocyclitis) in a patient with nr-axSpA led to study discontinuation (table 3).

DISCUSSION

Dual inhibition of IL-17A and IL-17F with subcutaneous BKZ 160 mg Q4W led to clinically meaningful improvements in a range of efficacy outcomes, across the full disease spectrum of axSpA to Week 52. Improvements in ASAS40 and key measures of disease activity such as ASDAS and BASDAI observed at Week 16 were sustained at Week 52 in patients initially randomised to BKZ; for instance, >54% of patients achieved ASDAS <2.1 by Week 52. Responses of patients switching from PBO to BKZ at Week 16 were comparable to those initially randomised to BKZ by Week 52. Marked reductions in objective measures of inflammation (MRI scores and hs-CRP levels) were observed to Week 52, with consistent responses between treatment arms and studies. In line with the sustained reductions in ASDAS, BKZ resulted in improvements in measures of patient symptoms such as pain, morning stiffness, fatigue and physical function to Week 52.[29] Treatment with BKZ also led to sustained efficacy in key peripheral manifestations of axSpA, enthesitis and peripheral arthritis, with large proportions of patients achieving resolution by Week 52. The observed efficacy of BKZ across measures of disease activity, patient-reported outcomes and peripheral manifestations demonstrates the potential of BKZ to elicit sustained responses in clinically relevant therapeutic targets.[1 30 31]

Among patients with r-axSpA initially randomised to BKZ, consistent ASAS40 responses were observed regardless of prior TNFi exposure at Week 52, mirroring observations from phase 3 studies of BKZ in TNFi-naïve and TNFi-IR patients with psoriatic arthritis.[32 33] Differences in the Week 52 ASAS40 response between TNFi subgroups was observed in patients initially randomised to BKZ in the nr-axSpA patient population; however, the number of patients in the TNFi-IR subgroup was small (n=10). Evidence from preclinical studies, a phase 2b BE AGILE study of BKZ in r-axSpA and clinical studies of other rheumatic diseases, suggests an important role of IL-17F in spondyloarthritis pathogenesis.[12 20 23 34] For instance, preclinical data have shown that BKZ more effectively suppresses the proinflammatory cytokine response in skin and synovial cells than IL-17A or IL-17F inhibition alone.[12] Analysis of serum biomarkers in patients with psoriatic arthritis has demonstrated elevated IL-17F serum levels in TNFi-IR patients,[34] implicating a potential role of IL-17F in driving disease. This is further substantiated by the consistent responses to BKZ observed in the BE OPTIMAL and BE COMPLETE phase 3 studies, in TNFi-naïve and TNFi-IR patients, respectively.[33 35] Moreover, in patients with plaque psoriasis, in which both IL-17 isoforms are overexpressed

in psoriatic tissue, BKZ significantly improved outcomes compared with IL-17Ai alone, in a head-to-head phase 3b study.[20] As such, dual inhibition of IL-17A and IL-17F may confer a mechanistic benefit compared with inhibition of only one isoform, potentially contributing to the sustained clinical efficacy of BKZ observed across the spectrum of axSpA. However, head-to-head studies of BKZ and IL-17Ai alone in axSpA are needed to determine whether preclinical data may translate to a clinical benefit.

BKZ was well tolerated in patients across the axSpA disease spectrum and safety findings were similar to previous studies in axSpA, consistent with the known profile of BKZ.[22 23 36] In line with the mechanism of action of BKZ and the contribution of IL-17A and IL-17F to host protection against oral mucosal fungal infection,[37 38] fungal infections were more common with BKZ than PBO. All fungal infections were mucocutaneous, and the majority were *Candida* infections, specifically oral candidiasis. The vast majority were mild or moderate and no cases were serious or systemic. All cases were managed with standard antifungal therapy and the vast majority did not lead to treatment discontinuation.

In the current studies with BKZ, EAIRs of IBD were comparable to those observed in phase 3 studies of IL-17Ai alone.[5 6] Conflicting literature has suggested that inhibition of IL-17A may lead to induction or exacerbation of IBD.[39 40] However, EAIRs in patients treated with BKZ also aligned with expected IBD background rates in the axSpA population.[41] In fact, preclinical evidence suggests that dual inhibition of IL-17A and IL-17F may attenuate the development of colitis.[42 43] Studies in a larger cohort of patients with a longer follow-up period are needed to draw conclusions on the effect of dual IL-17A and IL-17F inhibition on IBD rates in axSpA.

Incidence of uveitis, the most common extra-musculoskeletal manifestation of axSpA,[1] was noticeably lower in BKZ-treated versus PBO-treated patients during the DBTP in both BE MOBILE studies. Rates of uveitis at Week 52 were low and comparable with the uveitis EAIR (0.7/100 PY) from BE AGILE at Week 156, and pooled data from the phase 2b and 3 trials of BKZ (1.2/100 PY; n=848).[23 44]

Strengths of the BE MOBILE studies include the coverage of the full disease spectrum of axSpA, while limitations include the lack of a PBO control after Week 16 and therefore patients' awareness of receiving active treatment from Weeks 16–52. There was also no active comparator arm in either study, limiting any direct comparisons between BKZ and other inhibitors of IL-17A alone. Further limitations of the BE MOBILE study designs are outlined in the Week 24 publication.[22]

To conclude, dual inhibition of IL-17A and IL-17F with subcutaneous BKZ 160 mg Q4W led to sustained and consistent efficacy in patients with nr-axSpA and r-axSpA across the domains of axSpA over the 52-week period. The safety profile over 52 weeks was consistent with previous evidence on BKZ from phase 2b/3 studies in axSpA and phase 3 studies in psoriatic arthritis.[22 23 33] Results from the BE MOBILE studies at Week 52 along with 3-year and upcoming 5-year results, from the BE AGILE study,[23] will continue to provide further insights into the long-term safety and efficacy of BKZ.

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forms, statistical analysis plans, dataset specifications and clinical study reports. 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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