Bimekizumab Improves Signs and Symptoms Including Inflammation in Patients with Active Ankylosing Spondylitis: 24-Week Efficacy & Safety from a Phase 3, Multicenter, Randomized, Placebo-Controlled Study

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Objective

To report efficacy and safety of bimekizumab (BKZ) vs placebo (PBO) in patients with active ankylosing spondylitis (AS; i.e. radiographic axial spondyloarthritis) up to Week 24 in the pivotal phase 3 study, BE MOBILE 2.

Background

- BKZ, a monoclonal IgG1 antibody that selectively inhibits interleukin (IL)-17F in addition to IL-17A, has demonstrated sustained efficacy and was well tolerated up to 156 weeks in a phase 2b study in patients with AS.[1]

Methods

- BE MOBILE 2 (NCT03928743) comprised a 16-week double-blind, PBO-controlled period followed by a 36-week maintenance period (**Figure 1**).
- Primary and secondary efficacy endpoints were assessed at Week 16, selected endpoints are also presented in this analysis to Week 24 (randomized set).
- Treatment-emergent adverse events (TEAEs; MedDRA v19.0) are reported to Week 16 by treatment group, and to Week 24 for exposure to BKZ (safety set).

Results

Patients

- Of 332 randomized patients (BKZ: 221; PBO: 111), 322 (97.0%) completed Week 16 and 313 (94.3%) completed treatment up to Week 24.
- Baseline characteristics were comparable between groups (**Table 1**).

Efficacy

- At Week 16, the primary (ASAS40) and all ranked secondary endpoints were met, with rapid separation of BKZ from PBO as early as Week 2 for ASAS40 (**Figures 2–3**).
  - Week 24 ASAS40 responses among patients switching from PBO to BKZ at Week 16 reached similar levels to those seen in BKZ-randomized patients (**Figure 3A**).
  - ASAS40 responses at Week 16 were consistent across both TNFi-naïve and TNFi-inadequate responders (IR; **Figure 3B**).
- At Week 24, around half of patients across both treatment arms achieved ASDAS <2.1 (low disease activity; **Figure 4**).
- Substantial reductions of hs-CRP by Week 2, and sacroiliac joints (SIJ) and spine MRI inflammation scores by Week 16, were achieved with BKZ vs PBO (**Figure 5**).
  - Among CRP+ patients (hs-CRP >5.0 mg/L) a greater proportion of BKZ vs PBO-treated patients achieved normalization of CRP (hs-CRP ≤5.0 mg/L, NRI: 52.6% vs 19.4%) at Week 16.
  - A greater proportion of BKZ vs PBO-treated patients with baseline SIJ or spine inflammation on MRI (scores >2) achieved MRI remission (score ≤2, NRI: 38.6% vs 0% [SPARCC MRI SIJ]; 54.3% vs 22.2% [Berlin MRI spine]) at Week 16.
- Complete resolution of enthesitis (MASES=0 in patients with baseline MASES >0, NRI) at Week 16 was achieved by 51.5% of BKZ vs 32.8% PBO-treated patients (53.0% vs 49.3% at Week 24)

Safety

- Up to Week 24, 183/330 (55.5%) patients had ≥1 TEAE on BKZ, including those who switched from PBO to BKZ at Week 16 (**Table 2**).
- The most frequent were nasopharyngitis (6.4%) and diarrhea (3.9%). All fungal infections were mild to moderate, non-severe, non-systemic and mucocutaneous; 2 (0.6%) led to treatment discontinuation.
- No systemic candidiasis, tuberculosis, adjudicated major adverse cardiovascular events, or deaths were reported. Incidence of inflammatory bowel disease and uveitis were low (**Table 2**).

Summary

Patients with active ankylosing spondylitis bimekizumab achieved the primary and all ranked secondary endpoints, resulting in clinically meaningful improvements in:

Disease activity
ASAS40, ASAS40 in TNFi-naïve patients, ASAS20, ASAS partial remission, ASAS 5/6, ASDAS, ASDAS-MI, ASDAS <2.1

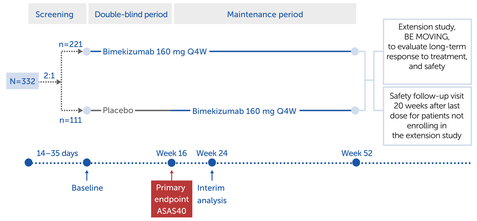
Signs and symptoms
BASDAI, nocturnal spinal pain, MASES (enthesitis)

Mobility, physical function and HRQoL
BASMI, BASFI, SF-36 PCS, ASQoL

Objective signs of inflammation
hs-CRP, SPARCC MRI SIJ score, Berlin MRI spine score

Safety
No new safety signals were observed

Figure 1 Study design



Enrolled patients were eligible to receive non-biologic rescue therapy from Week 20, at the discretion of the investigator, while continuing to receive BKZ. Patients were aged ≥18 years, met modified New York criteria, had active AS (BASDAI ≥4, spinal pain ≥4) at baseline. Patients with active, symptomatic IBD at baseline or screening, or active anterior uveitis within 6 weeks of baseline visit were excluded.

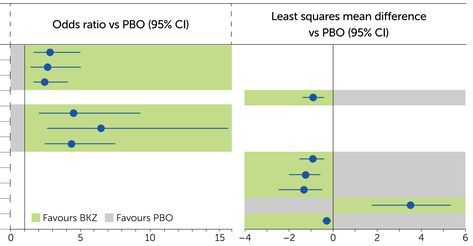
Table 1 Baseline characteristics

	PBO n=111	BKZ 160 mg Q4W n=221
Age, years, mean (SD)	39.2 (12.6)	41.0 (12.1)
Sex, male, n (%)	80 (72.1)	160 (72.4)
HLA-B27 positive, n (%)	93 (83.8)	191 (86.4)
Symptom duration, years, mean (SD)	11.9 (8.6)	14.2 (11.0)
ASDAS-CRP, mean (SD)	3.7 (0.8)	3.7 (0.8)
BASDAI, mean (SD)	6.5 (1.3)	6.5 (1.3)
hs-CRP, mg/L, median (min, max)	6.3 (0.3, 104.3)	8.2 (0.1, 105.4)
hs-CRP >ULN,[a] n (%)	67 (60.4)	137 (62.0)
Total spinal pain, mean (SD)	7.2 (1.2)	7.1 (1.6)
Patients with MASES >0, n (%)	67 (60.4)	132 (59.7)
Berlin MRI spine score, mean (SD) [Nsub][b]	3.3 (4.9) [45]	3.8 (5.3) [82]
SPARCC MRI SIJ score, mean (SD) [Nsub][b]	5.8 (7.7) [45]	7.4 (10.7) [83]
Prior TNFi exposure, n (%)	17 (15.3)	37 (16.7)
Medical history of IBD, n (%)	1 (0.9)	3 (1.4)
Medical history of uveitis, n (%)	24 (21.6)	33 (14.9)

Randomized set. [a]ULN value for hs-CRP is 5 mg/L. [b]Only patients enrolled in the SIJ and spine MRI sub-study are included in this analysis.

Figure 2 Primary and all ranked secondary endpoints at Week 16

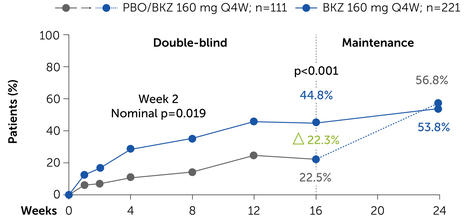
Efficacy endpoint	PBO n=111	BKZ 160 mg Q4W n=221	p value[a]
1. ASAS40,* n (%)	25 (22.5)	99 (44.8)	<0.001
2. ASAS40 (TNFi-naïve patients),† n (%)	22 (23.4)[b]	84 (45.7)[c]	<0.001
3. ASAS20,† n (%)	48 (43.2)	146 (66.1)	<0.001
4. BASDAI CfB,† mean (SE)	−1.9 (0.2)	−2.9 (0.1)	<0.001
5. ASAS partial remission,† n (%)	8 (7.2)	53 (24.0)	<0.001
6. ASDAS-MI,† n (%)	6 (5.4)	57 (25.8)	<0.001
7. ASAS 5/6,† n (%)	21 (18.9)	109 (49.3)	<0.001
8. BASFI CfB,† mean (SE)	−1.1 (0.2)	−2.2 (0.1)	<0.001
9. Nocturnal spinal pain CfB,† mean (SE)	−1.9 (0.2)	−3.3 (0.2)	<0.001
10. ASQoL CfB,† mean (SE)	−3.2 (0.3)	−4.9 (0.3)	<0.001
11. SF-36 PCS CfB,† mean (SE)	5.9 (0.8)	9.3 (0.6)	<0.001
12. BASMI CfB,† mean (SE)	−0.2 (0.1)	−0.5 (0.1)	0.006



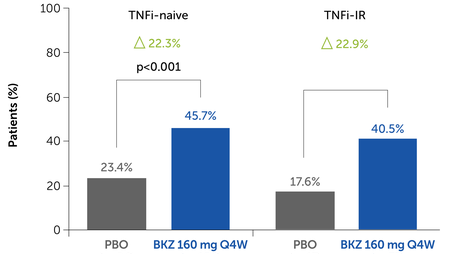
Randomized set. *Primary endpoint; †Secondary endpoint. [a]All tests performed at a 2-sided alpha level of 0.05. For binary variables, p values, odds ratios, and their 95% CIs were calculated by logistic regression with treatment, prior TNFi exposure and region as factors. For continuous variables, p values, least squares mean differences, and their 95% CIs were obtained by ANCOVA with treatment, prior TNFi exposure and region as fixed effects, and baseline values as covariates. [b]n=94; [c]n=184. Missing data were imputed using NRI for binary endpoints and reference based MI for continuous endpoints (based on data from the PBO group).

Figure 3 ASAS40 Response (NRI)

A) ASAS40 to Week 24

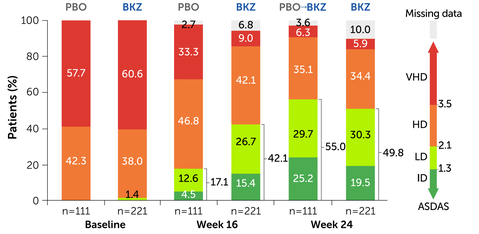


B) ASAS40 at Week 16 in TNFi-naive and TNFi-IR patients



Randomized set. Missing data were imputed using NRI. P values without any multiplicity adjustment are indicated as nominal p values, and should not be used as an indication of statistical significance.

Figure 4 ASDAS states over time (as observed)



Randomized set. Data reported as observed. At Week 16, patients on PBO switched to BKZ. VHD: ASDAS >3.5; HD: ASDAS ≥2.1–≤3.5; LD: ASDAS ≥1.3–<2.1; ID: ASDAS <1.3.

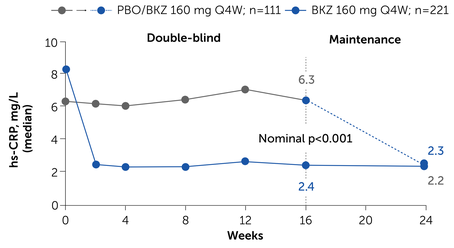
Table 2 Safety table

n (%)	Double-blind period (Weeks 0–16) PBO n=111	Double-blind period (Weeks 0–16) BKZ 160 mg Q4W n=221	Overall (Weeks 0–24) BKZ 160 mg Q4W Total[a] N=330
Any TEAE	48 (43.2)	120 (54.3)	183 (55.5)
Most frequently reported TEAEs[b]			
Nasopharyngitis	4 (3.6)	17 (7.7)	21 (6.4)
Diarrhea	1 (0.9)	7 (3.2)	13 (3.9)
Headache	5 (4.5)	9 (4.1)	12 (3.6)
Oral candidiasis[c]	0	9 (4.1)	10 (3.0)
Serious TEAEs	1 (0.9)	4 (1.8)	12 (3.6)
Study discontinuation due to TEAEs	0	6 (2.7)	11 (3.3)
Drug-related TEAEs	19 (17.1)	65 (29.4)	96 (29.1)
Severe TEAEs	0	3 (1.4)	9 (2.7)
Fungal infections	0	13 (5.9)	21 (6.4)
Systemic fungal infections	0	0	0
Adjudicated IBD[d]	0	2 (0.9)	2 (0.6)
Definite Crohn's disease	0	1 (0.5)	1 (0.3)
Probable ulcerative colitis	0	1 (0.5)	1 (0.3)
Uveitis[e,f]	5 (4.5)	0	2 (0.6)

Safety set. MedDRA (Version 19.0). [a]Includes patients who switched from PBO to BKZ (events after switch only). [b]TEAEs >3% in patients receiving BKZ are reported by preferred term. [c]All oral candidiasis cases were mild to moderate; [d]Neither patient had a medical history of IBD. [e]At baseline, 24/111 (21.6%) patients on PBO and 33/221 (14.9%) patients on BKZ had a medical history of uveitis; [f]Includes the preferred terms autoimmune uveitis, uveitis, iridocyclitis and iritis.

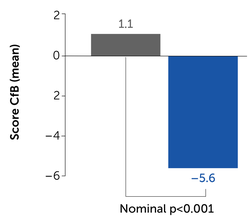
Figure 5 Objective measures of inflammation

A) hs-CRP to Week 24 (MI)



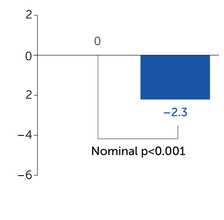
B) SPARCC MRI SIJ score Week 16 CfB (OC)[a]

Mean (n)	PBO	BKZ
Baseline	5.8 (45)	7.4 (83)
Week 16	6.5 (43)	2.0 (79)



C) Berlin MRI spine score Week 16 CfB (OC)[a]

Mean (n)	PBO	BKZ
Baseline	3.3 (45)	3.8 (82)
Week 16	3.4 (43)	1.4 (79)



Randomized set. [a]Includes only patients enrolled in the SIJ and spine MRI sub-study. P values without any multiplicity adjustment are indicated as nominal p values, and should not be used as an indication of statistical significance.

Conclusions

Dual inhibition of IL-17F in addition to IL-17A with BKZ in patients with active AS resulted in rapid, clinically relevant improvements of key signs and symptoms of disease and reduction of disease activity, including around 50% patients achieving ASDAS <2.1 (low disease activity) at Week 24.

Objective signs of inflammation, as measured by CRP and MRI, were also markedly reduced with BKZ.

No new safety signals were observed.[1]

ANCOVA: analysis of covariance; **ASAS20/40:** Assessment of SpondyloArthritis international Society 20/40 response; **ASDAS:** Ankylosing Spondylitis Disease Activity Score; **ASDAS-MI:** ASDAS major improvement; **AS:** ankylosing spondylitis; **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; **CfB:** change from baseline; **CI:** confidence interval; **CRP:** C-reactive protein; **HD:** high disease; **HLA-B27:** human leukocyte antigen-B27; **HRQoL:** health-related quality of life; **hs-CRP:** high sensitivity CRP; **IBD:** inflammatory bowel disease; **IR:** inadequate responder; **ID:** inactive disease; **LD:** low disease; **MASES:** Maastricht Ankylosing Spondylitis Enthesitis Score; **MI:** major improvement; **MRI:** magnetic resonance imaging; **NRI:** non-responder imputation; **NSAID:** non-steroidal anti-inflammatory drug. **Nsub:** number of patients in subgroup; **PBO:** placebo; **PCS:** Physical Component Summary; **Q4W:** every 4 weeks; **SD:** standard deviation; **SE:** standard error; **SIJ:** sacroiliac joint; **SF-36:** Short-Form 36-item Health Survey; **SPARCC:** Spondyloarthritis Research Consortium of Canada; **TNFi:** tumor necrosis factor inhibitor; **TEAE:** treatment-emergent adverse event; **ULN:** upper limit of normal; **VHD:** very high disease.

References: [1]Baraliakos X. Arthritis Rheumatol 2022;10.1002/art.42282.

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