Bimekizumab Safety in Patients with Axial Spondyloarthritis or Psoriatic Arthritis: Rates of Hepatic Events and Transaminase Elevations in Phase 3 Trials

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Objective

To report rates of hepatic treatment-emergent adverse events (TEAEs) and laboratory elevations in liver transaminases in the phase 3 studies of bimekizumab (BKZ) in patients with axial spondyloarthritis (axSpA) and active psoriatic arthritis (PsA).

Introduction

- BKZ is a monoclonal IgG1 antibody that selectively inhibits interleukin (IL)-17F in addition to IL-17A.
- BKZ was well-tolerated to 1 year in phase 2b/3 studies of patients with axSpA and PsA, with a safety profile consistent with prior studies.[1–3]
- Patients with axSpA or PsA may suffer from hepatic comorbidities, and some systemic treatments are associated with potential hepatotoxicity.[4–6]
- In phase 3/3b trials of BKZ in patients with psoriasis, rates of hepatic TEAEs were low over two years and did not increase with longer exposure to BKZ.[7]

Materials and Methods

- Here, we report data up to the July 2022 data-cut (after Week 52 completion) of the four phase 3 studies in patients with axSpA (BE MOBILE 1 and 2) and PsA (BE OPTIMAL and BE COMPLETE), and their open-label extensions (BE MOVING and BE VITAL; **Figure 1**).
- Patients with hepatitis B or C, or chronic alcohol use were excluded from these studies.
- Hepatic treatment-emergent adverse events (TEAEs), identified via a Standardized MedDRA (v19.0) Query, are reported for patients who received ≥1 BKZ dose.
- We also report elevations in alanine transaminase (ALT) or aspartate aminotransferase (AST) >3x and >5x upper limit of normal (ULN) to Week 16 for patients who received BKZ or placebo, and to Week 52 for patients with PsA who received BKZ or adalimumab (ADA) during controlled double-blind and active treatment periods.
- Data are reported as exposure-adjusted incidence rates (EAIRs) per 100 patient-years (PY).

Results

- Patient baseline characteristics were generally comparable across treatment groups within each study and representative of moderate/severe axSpA and PsA.[1–3]
- 28 (4.9%) patients with axSpA and 70 (5.8%) patients with PsA had a history of hepatocellular damage and hepatitis (non-viral), mostly hepatic steatosis (axSpA: 26 [4.5%]; PsA: 55 [4.5%]). 1 (0.2%) patient with axSpA and 3 (0.2%) patients with PsA had a medical history of non-alcoholic fatty liver.
- To the data cut, EAIRs of hepatic TEAEs were low for patients who received BKZ; most were non-serious transient elevations of liver enzymes (**Table 1**).
  - EAIRs of severe hepatic TEAEs were low. No hepatic TEAEs led to discontinuation in patients with axSpA, and 4 hepatic TEAEs led to discontinuation in patients with PsA; 3 of these TEAEs were resolved or were resolving and 1 remained unresolved at the data cut following treatment withdrawal.
  - EAIRs of hepatic TEAEs were slightly higher in patients with PsA receiving vs not receiving methotrexate (MTX) at baseline.
- EAIRs of laboratory elevations in ALT or AST >3x ULN were 2.6/100 PY and 2.4/100 PY for patients with axSpA and PsA respectively. EAIRs for elevations >5x ULN were 0.9/100 PY and 0.7/100 PY (**Table 1**). No confirmed Hy's law cases (i.e., drug-induced jaundice caused by hepatocellular injury without an obstructive component) were observed.
- To Week 16, EAIRs of laboratory elevations in ALT or AST >3x ULN and >5x ULN were similar with BKZ vs placebo in patients with axSpA, and slightly higher with BKZ vs placebo in patients with PsA (**Figure 2**).
  - During the BE OPTIMAL study active treatment period, EAIRs for ALT or AST elevations >3x ULN and >5x ULN were slightly lower with BKZ vs ADA (**Figure 2**).
  - EAIRs of ALT or AST elevations were also slightly higher in patients with PsA receiving vs not receiving MTX at baseline in BE OPTIMAL and BE COMPLETE (**Table 2**).

Conclusions

Rates of hepatic TEAEs and transaminases elevations were low in the phase 3 studies of bimekizumab in patients with axSpA or PsA, and their open label extensions, suggesting bimekizumab treatment is not associated with an increased risk of these events.

Summary

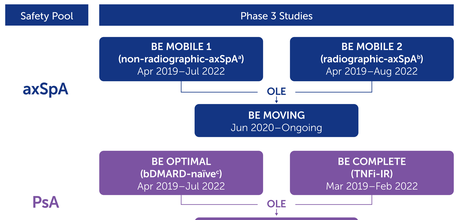
Rates of hepatic TEAEs were **low** in the phase 3 studies of **BKZ** in patients with axSpA or PsA

Over 16 weeks, **liver transaminase laboratory elevations** in patients with axSpA were similar between **BKZ** and **PBO**

In patients with PsA, rates of elevations were **slightly higher** with **BKZ** vs. **PBO** over 16 weeks and **slightly lower** with **BKZ** vs. **ADA** over 52 weeks

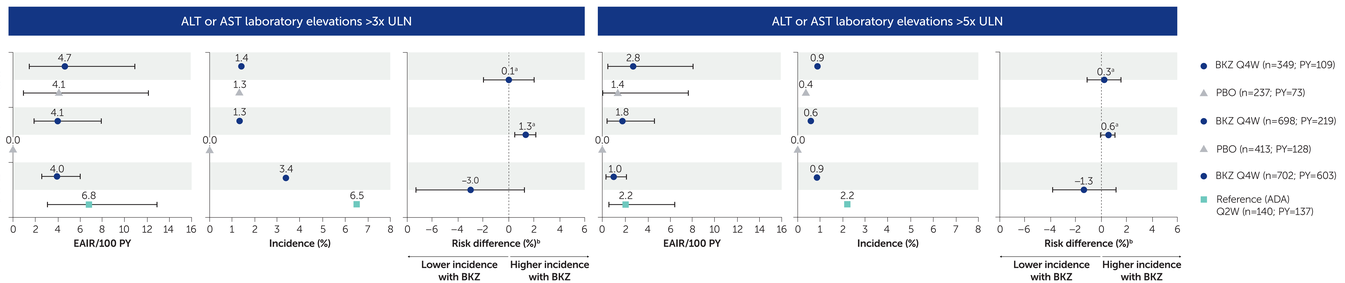
Rates of liver transaminase laboratory elevations were **numerically higher** in patients with PsA who were **receiving** MTX at baseline vs. those who were not

Figure 1 Safety pools (axSpA, PsA) for the phase 3 studies and their open-label extensions



Data from the data-cut (July 2022) shown. Actual study start dates and completion dates provided. [a] Patients with nr-axSpA met Assessment of SpondyloArthritis international Society (ASAS) classification criteria. Patients with radiographic sacroiliitis were excluded. [b] Patients with r-axSpA met modified New York criteria and fulfilled ASAS classification criteria; [c] BE OPTIMAL also included an adalimumab treatment arm. The initial treatment period pools included patients from the phase 3 studies, receiving BKZ 160 mg Q4W or PBO from Week 0 through Week 16. The comprehensive safety pools included patients from the phase 3 studies and their open-label extensions, receiving any dose of BKZ. BE MOBILE 1: NCT03928704; BE MOBILE 2: NCT03928743; BE MOVING: NCT04436640; BE OPTIMAL: NCT03895203; BE COMPLETE: NCT03896581; BE VITAL: NCT04009499.

Figure 2 EAIR, incidence, and risk difference of ALT or AST elevations >3x and >5x ULN in the phase 3 trials



Error bars represent 95% CI. Week 0–16 data are reported for patients in the initial treatment period pools who received at least one dose of study treatment during the trials. For BE OPTIMAL (Week 0–52; unpooled) data, BKZ group includes patients that switched from PBO to BKZ. Categories for ALT/AST laboratory elevations are cumulative (i.e., a patient with elevations >5x ULN also has an elevation >3x ULN). [a] For data pooled across studies, risk differences are weighted based upon a study-size adjusted method. [b] Percentage differences in risk are based on the difference in percentages between the given comparator and BKZ; a negative difference indicates a lower incidence with BKZ.

Table 1 Summary of hepatic TEAEs and liver transaminase laboratory elevations in bimekizumab-treated patients in the phase 3 trials

	Patients receiving ≥1 dose of BKZ 160 mg Q4W to July 2022 data-cut (~Week 52)			
	axSpA Pooled Phase 3	PsA Pooled Phase 3		
EAIR/100 PY (95% CI)	All (n=574) [PY=1,003]	All (n=1,209) [PY=2,094]	MTX at Baseline (n=651) [PY=1,189]	No MTX at Baseline (n=558) [PY=905]
Any hepatic TEAE[a]	6.6 (5.1, 8.5)	6.2 (5.1, 7.4)	6.4 (5.0, 8.1)	5.9 (4.4, 7.8)
Elevated liver enzymes[b]	4.8 (3.5, 6.4)	4.8 (3.9, 5.9)	4.6 (3.4, 6.0)	5.0 (3.6, 6.8)
ALT or AST laboratory elevations[c]				
>3x ULN	2.6 (1.7, 3.8)	2.4 (1.8, 3.2)	2.6 (1.7, 3.7)	2.1 (1.3, 3.3)
>5x ULN	0.9 (0.4, 1.7)	0.7 (0.4, 1.1)	0.8 (0.3, 1.4)	0.6 (0.2, 1.3)
Confirmed Hy's law cases[d]	0	0	0	0
Severe hepatic TEAEs[e]	0.2 (0.0, 0.7)	0.1 (0.0, 0.4)	0.3 (0.1, 0.7)	0
Serious hepatic TEAEs[f]	0	0.1 (0.0, 0.3)	0.2 (0.0, 0.6)	0
Discontinuation due to hepatic TEAEs	0	0.2 (0.1, 0.5)	0.3 (0.1, 0.7)	0.1 (0.0, 0.6)

Data are reported for patients in the comprehensive safety pools. The reporting of ALT/AST elevations as an adverse event was at the discretion of the investigator. [a] Includes events in the SMQ 'Drug-related hepatic disorders – comprehensive search (SMQ)', excluding the following two sub-SMQs: 'Liver neoplasms, benign (including cysts and polyps) (SMQ)' and 'Liver neoplasms, malignant and unspecified (SMQ)'; [b] Elevated liver enzymes include the following preferred terms reported as adverse events: increased/abnormal levels of ALT, AST, blood bilirubin, gamma-glutamyltransferase, hepatic enzyme, liver function test, transaminases, or blood alkaline phosphatase; [c] Categories for ALT/AST laboratory elevations are cumulative (i.e., a patient with elevations >5x ULN also had elevations >3x ULN); [d] Defined as ALT or AST elevation >3x ULN, with total bilirubin elevation >2x ULN, absence of initial findings of cholestasis and no other reason to explain the combination of increased ALT and total bilirubin; [e] Severity grading as per investigator assessment; [f] Serious TEAEs met one or more of the following criteria: death, life-threatening, significant or persistent disability/incapacity, congenital anomaly/birth defect, important medical event that may jeopardize the patient and may require medical/surgical intervention to prevent one of the previous mentioned outcomes, or initial inpatient hospitalization/prolongation of hospitalization.

Table 2 EAIR, incidence, and risk difference of ALT or AST elevations >3x and >5x ULN in the PsA phase 3 trials, by MTX at baseline

	PsA Pooled Phase 3 (Weeks 0–16)				BE OPTIMAL (bDMARD-naïve) (Weeks 0–52)			
	MTX at Baseline (n=584)		No MTX at Baseline (n=527)		MTX at Baseline (n=492)		No MTX at Baseline (n=350)	
	BKZ Q4W (n=371) [PY=117]	PBO (n=213) [PY=66]	BKZ Q4W (n=327 [PY=102]	PBO (n=200) [PY=62]	BKZ Q4W (n=410) [PY=356]	ADA Q2W (n=82) [PY=81]	BKZ Q4W (n=292) [PY=248]	ADA Q2W (n=58) [PY=56]
EAIR/100 PY (95% CI)								
>3x ULN	4.3 (1.4, 10.1)	0	3.9 (1.1, 10.1)	0	4.6 (2.6, 7.4)	6.4 (2.1, 15.0)	3.3 (1.4, 6.4)	7.4 (2.0, 18.8)
>5x ULN	2.6 (0.5, 7.6)	0	1.0 (0.0, 5.5)	0	1.1 (0.3, 2.9)	2.5 (0.3, 9.0)	0.8 (0.1, 2.9)	1.8 (0.0, 10.0)
Incidence, n (%)								
>3x ULN	5 (1.3)	0	4 (1.2)	0	16 (3.9)	5 (6.1)	8 (2.7)	4 (7.0)
>5x ULN	3 (0.8)	0	1 (0.3)	0	4 (1.0)	2 (2.4)	2 (0.7)	1 (1.8)
Risk difference (95% CI)[b]								
>3x ULN	1.3 (0.2, 2.5)[b]		1.2 (0.0, 2.4)[b]		−2.2 (−7.7, 3.3)		−4.2 (−10.9, 2.6)	
>5x ULN	0.8 (−0.1, 1.7)[b]		0.3 (−0.3, 0.9)[b]		−1.5 (−4.9, 2.0)		−1.0 (−4.5, 2.4)	

Week 0–16 data are reported for patients in the initial treatment period pools who received at least one dose of study treatment during the trials. For BE OPTIMAL (Week 0–52; unpooled) data, BKZ group includes patients that switched from PBO to BKZ. Categories for ALT/AST laboratory elevations are cumulative (i.e., a patient with elevations >5x ULN also has an elevation >3x ULN). [a] Percentage differences in risk are based on the difference in percentages between the given comparator and BKZ; a negative difference indicates a lower incidence with BKZ. [b] For data pooled across studies, risk differences are weighted based upon a study-size adjusted method.

ADA: adalimumab; **ALT:** alanine transaminase; **AST:** aspartate aminotransferase; **axSpA:** axial spondyloarthritis; **bDMARD:** biologic disease-modifying antirheumatic drug; **BKZ:** bimekizumab; **CI:** confidence interval; **EAIR:** exposure-adjusted incidence rate; **MedDRA:** Medical Dictionary for Regulatory Activities; **MTX:** methotrexate; **OLE:** open-label extension; **PBO:** placebo; **PsA:** psoriatic arthritis; **PY:** patient-years; **Q2W:** every 2 weeks; **Q4W:** every 4 weeks; **SMQ:** Standardized MedDRA Query; **TEAE:** treatment-emergent adverse event; **TNFi:** tumor necrosis factor inhibitor; **ULN:** upper limit of normal.

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References: [1]Baraliakos X. Ann Rheum Dis 2023;0:1–15. [NCT03928704; NCT03928743]; [2]Ritchlin CT. Ann Rheum Dis 2023;0:1–11. [NCT03895203]; [3]Coates LC. RMD Open 2024;10(1):e003855. [NCT03896581]; [4]French JB. Drug Saf 2016;39(3):199–208; [5]Perez-Chada LM. Clin Immunol 2020;214:108397; [6]S Zhao. Rheumatology (Oxford) 2020;59(Suppl 4):iv47–iv57; [7]Lebwohl M. Presented at 42nd Annual Fall Clinical Dermatology Congress (2022).

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