Bimekizumab 3-year safety and tolerability in moderate to severe plaque psoriasis: Long-term pooled analysis from five phase 3/3b trials

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Synopsis

- Since psoriasis is a chronic disease, assessment of long-term safety of treatments is essential to inform decision-making for clinicians while managing risks for patients.[1]
- Data pooled over 2 years have previously shown that bimekizumab (BKZ), a monoclonal IgG1 antibody that selectively inhibits interleukin (IL)-17F in addition to IL-17A,[2] is well tolerated in the treatment of moderate to severe plaque psoriasis.[3]

Objective

To evaluate 3-year safety data for BKZ in patients with moderate to severe plaque psoriasis from five phase 3/3b clinical trials.

Methods

- Data were pooled from the BE SURE, BE VIVID, and BE READY phase 3 trials, their open-label extension (OLE) BE BRIGHT, and the BE RADIANT phase 3b trial (**Figure 1**).[3–7]
- Included patients received BKZ 320 mg every 4 weeks (Q4W) or every 8 weeks (Q8W).
- Treatment-emergent adverse events (TEAEs) were coded using MedDRA v19.0 and are reported over 3 years using exposure-adjusted incidence rates (EAIRs) per 100 patient-years (PY) for all patients who received ≥1 BKZ dose (BKZ Total); data are also reported separately for Years 1 (Week 0–52), 2 (Week 52–104), and 3 (Week 104–156) of BKZ exposure.

Results

- Total BKZ exposure was 5,461.4 PY (N=2,186; **Table 1**). Overall rates of TEAEs decreased or did not increase with longer exposure to BKZ (**Figures 2–4**) and were numerically lower in patients receiving BKZ Q8W vs Q4W (**Table 1**).
- Over the 3-year period, 21 deaths occurred; none were reported as treatment-related.
- The most common TEAEs were nasopharyngitis (14.1/100 PY), oral candidiasis (10.0/100 PY), and upper respiratory tract infection (6.2/100 PY), consistent with previous reports.[3]
- The EAIR of oral candidiasis decreased with longer BKZ exposure (**Figure 4**). No oral candidiasis events were serious and the vast majority were mild or moderate (99.1%); among patients who experienced oral candidiasis, few discontinued treatment as a result (1.7%).
  - Increasing proportions of patients switching to the approved maintenance dose of BKZ Q8W may have contributed to the decrease in oral candidiasis incidence over time.
- Rates of serious infections were low (1.3/100 PY); the most frequently reported was coronavirus infection (0.3/100 PY).
  - The global COVID-19 pandemic was concurrent with the BE RADIANT and BE BRIGHT OLEs. Serious coronavirus infections occurred at rates of 0.1, 0.2, and 0.5/100 PY in Year 1, 2, and 3 of BKZ exposure, respectively, likely contributing to numerically increased incidence rates of serious infections in Year 3 vs Year 2.
- EAIRs of laboratory elevations in alanine aminotransferase or aspartate aminotransferase >3x and 5x the upper limit of normal remained generally similar across Years 1–3 (**Table 1**; **Figure 3**).
- EAIRs of adjudicated inflammatory bowel disease, adjudicated major adverse cardiac events, malignancies, adjudicated suicidal ideation and behavior, and neutropenia were low (**Table 1**; **Figure 3**). No cases of active tuberculosis were reported.

Conclusions

Over 3 years of treatment, BKZ demonstrated a favorable safety profile, with no new safety signals observed. EAIRs of TEAEs did not increase with longer exposure to BKZ.

Summary

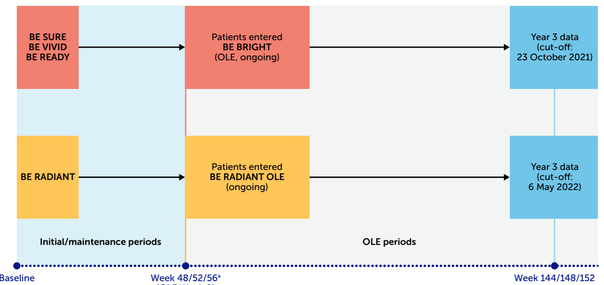
Dosing

	By time period			Over 3 years		
	BKZ Total			BKZ 320 mg Q4W	BKZ 320 mg Q8W	BKZ Total
	Year 1	Year 2	Year 3			
Weeks	0–52	52–104	104–156	0–data cut-off	0–data cut-off	0–data cut-off
Number of patients, N	2,186	1,962	1,547	2,025	1,935	2,186
Total exposure, PY	2,104.6	1,905.2	1,316.9	2,431.4	3,035.3	5,461.4
Median exposure (range), days	364 (23–364)	364 (1–364)	311 (7–364)	364 (23–1,093)	491 (1–1,214)	1,006 (23–1,326)

Total BKZ exposure over 3 years is greater than the sum of BKZ exposure in individual years, as data beyond Week 156 of BKZ exposure are included in the BKZ Total group due to the use of cut-off dates (some patients had proceeded past Week 156 by the cut-off date).

BKZ demonstrated a favorable safety profile over 3 years of treatment, with no new safety signals identified; rates of TEAEs did not increase with longer duration of BKZ exposure.

Figure 1 Included trials



Data were pooled for all patients who received ≥1 BKZ dose in the included trials (BKZ Total). [a]Patients entered the BE RADIANT OLE at Week 48; patients entered the BE BRIGHT OLE at Week 52 if they were enrolled in BE VIVID and Week 56 if they were enrolled in BE SURE or BE READY. Patients who received BKZ 320 mg in BE SURE, BE READY, and BE RADIANT could receive Q4W or Q8W dosing; in BE VIVID, patients could only receive BKZ Q4W. All patients received BKZ Q8W from Week 64 in BE RADIANT, Week 100/104 (OLE Week 48) in BE BRIGHT, or the next scheduled clinic visit. Data cut-offs were the dates on which the last enrolled patient completed Week 144 in BE RADIANT and Week 148/152 (OLE Week 96) in BE BRIGHT.

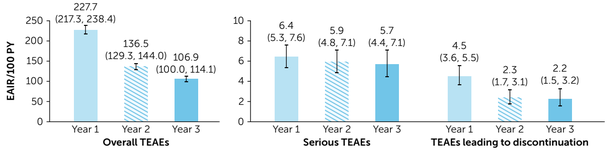
ALT: alanine aminotransferase; **AST:** aspartate aminotransferase; **BKZ:** bimekizumab; **CI:** confidence interval; **EAIR:** exposure-adjusted incidence rate; **IBD:** inflammatory bowel disease; **IL:** interleukin; **MACE:** major adverse cardiac event; **MedDRA:** Medical Dictionary for Regulatory Activities; **NMSC:** non-melanoma skin cancer; **OLE:** open-label extension; **PSOLAR:** Psoriasis Longitudinal Assessment and Registry; **PY:** patient-years; **Q4W:** every 4 weeks; **Q8W:** every 8 weeks; **SIB:** suicidal ideation and behavior; **TEAE:** treatment-emergent adverse event; **ULN:** upper limit of normal.

Table 1 Summary of TEAEs and TEAEs of interest in BKZ-treated patients over 3 years

	By time period[a]			Over 3 years		
	BKZ Total			BKZ 320 mg Q4W	BKZ 320 mg Q8W	BKZ Total[b]
	Year 1 (n=2,186)	Year 2 (n=1,962)	Year 3 (n=1,547)	(N=2,025)	(N=1,935)	(N=2,186)
Total exposure, PY	2,104.6	1,905.2	1,316.9	2,431.4	3,035.3	5,461.4
Summary of TEAEs, EAIR/100 PY (95% CI)						
Any TEAE	227.7 (217.3, 238.4)	136.5 (129.3, 144.0)	106.9 (100.0, 114.1)	224.5 (213.8, 235.6)	121.8 (115.6, 128.3)	174.4 (166.9, 182.2)
Serious TEAEs	6.4 (5.3, 7.6)	5.9 (4.8, 7.1)	5.7 (4.4, 7.1)	6.1 (5.1, 7.2)	5.6 (4.7, 6.5)	5.6 (4.9, 6.2)
TEAEs leading to discontinuation	4.5 (3.6, 5.5)	2.3 (1.7, 3.1)	2.2 (1.5, 3.2)	3.9 (3.2, 4.8)	2.5 (1.9, 3.1)	3.1 (2.7, 3.6)
TEAEs leading to death[c]	0.3 (0.1, 0.6)	0.3 (0.1, 0.7)	0.5 (0.2, 1.1)	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)	0.4 (0.2, 0.6)
TEAEs of interest, EAIR/100 PY (95% CI)						
Serious infections	1.6 (1.1, 2.3)	0.8 (0.5, 1.4)	1.4 (0.9, 2.3)	1.4 (1.0, 2.0)	1.3 (0.9, 1.8)	1.3 (1.0, 1.7)
Active tuberculosis	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Fungal infections	29.9 (27.5, 32.6)	18.8 (16.8, 21.0)	12.4 (10.5, 14.6)	26.9 (24.6, 29.3)	14.1 (12.7, 15.6)	17.5 (16.3, 18.9)
Candida infections	21.7 (19.6, 23.9)	12.7 (11.1, 14.4)	8.1 (6.6, 9.8)	19.5 (17.6, 21.5)	8.7 (7.6, 9.9)	11.7 (10.7, 12.7)
Oral candidiasis	18.5 (16.6, 20.5)	10.6 (9.1, 12.2)	7.2 (5.8, 8.8)	16.7 (15.0, 18.5)	7.5 (6.5, 8.6)	10.0 (9.1, 11.0)
Adjudicated IBD[d]	0.3 (0.1, 0.7)	0.2 (0.0, 0.5)	0.1 (0.0, 0.4)	0.3 (0.1, 0.6)	0.1 (0.0, 0.3)	0.2 (0.1, 0.4)
Adjudicated MACE	0.5 (0.3, 0.9)	0.3 (0.1, 0.7)	0.7 (0.3, 1.3)	0.6 (0.3, 1.0)	0.5 (0.3, 0.8)	0.5 (0.3, 0.7)
Malignancies	0.9 (0.5, 1.4)	1.1 (0.7, 1.7)	0.8 (0.4, 1.5)	0.7 (0.4, 1.1)	1.0 (0.7, 1.5)	0.9 (0.6, 1.2)
Excluding NMSC	0.4 (0.2, 0.7)	0.6 (0.3, 1.1)	0.6 (0.3, 1.2)	0.3 (0.1, 0.6)	0.7 (0.4, 1.1)	0.5 (0.3, 0.7)
Adjudicated SIB	0.1 (0.0, 0.4)	0.2 (0.0, 0.5)	0.0 (0.0, 0.0)	0.1 (0.0, 0.4)	0.1 (0.0, 0.3)	0.1 (0.0, 0.2)
Neutropenia events	0.8 (0.5, 1.3)	0.5 (0.3, 1.0)	0.2 (0.0, 0.5)	0.8 (0.5, 1.3)	0.3 (0.1, 0.6)	0.5 (0.3, 0.7)
ALT or AST elevations						
>3x ULN	2.6 (1.9, 3.3)	2.3 (1.7, 3.1)	2.1 (1.4, 3.0)	2.7 (2.1, 3.5)	1.7 (1.3, 2.3)	2.0 (1.6, 2.4)
>5x ULN[e]	0.8 (0.5, 1.3)	0.3 (0.1, 0.7)	0.5 (0.2, 1.0)	0.7 (0.4, 1.1)	0.4 (0.2, 0.7)	0.5 (0.3, 0.7)
Serious hypersensitivity reactions[f]	0.1 (0.0, 0.4)	0.1 (0.0, 0.4)	0.0 (0.0, 0.0)	0.1 (0.0, 0.4)	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)
Injection site reactions	3.2 (2.5, 4.1)	1.1 (0.6, 1.6)	1.1 (0.6, 1.9)	2.9 (2.2, 3.6)	1.2 (0.8, 1.6)	1.9 (1.5, 2.3)

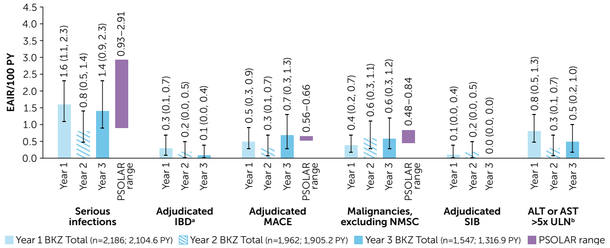
Data and any adjudication are shown as of the data cut-offs (BE BRIGHT: 23 October 2021; BE RADIANT: 6 May 2022). [a]Year 1: Week 0–52 of BKZ exposure; Year 2: Week 52–104 of BKZ exposure; Year 3: Week 104–156 of BKZ exposure. BE RADIANT has a duration of 144 weeks only, while the BE BRIGHT OLE is ongoing beyond Week 144 of BKZ treatment; data beyond Week 144 in BE RADIANT are therefore from the safety follow-up period. [b]Patients are included in the relevant BKZ dose group based on the dose most recently received prior to the date of the adverse event. Patients who received both BKZ 320 mg Q4W and Q8W are included in the population count of both treatment groups, but only once in each BKZ Total group. [c]Causes of death were reported under the following MedDRA preferred terms, each for one patient unless otherwise specified (patients could have multiple preferred terms identified as leading to death): aortic aneurysm rupture, brain neoplasm, cardiac arrest (5 patients), cardiopulmonary failure, chronic intestinal pseudo-obstruction, cytotoxic pulmonary disease, circulatory collapse, completed suicide, coronavirus infection (5 patients), death (2 patients, unknown cause, approximately 3 months after last BKZ dose), hemorrhagic anaemia, hepatic pain, hypovolemic shock, myocardial infarction, and road traffic accident; [d]Includes any TEAE adjudicated as definite or probable IBD; [e]Patients with elevations >5x ULN were a subset of patients with elevations >3x ULN. [f]No anaphylactic reactions associated with BKZ were reported.

Figure 2 Overall TEAEs, serious TEAEs, and TEAEs leading to discontinuation by year



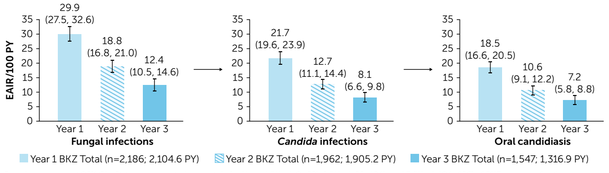
Error bars represent 95% CIs. Data are presented separately for Years 1 (Week 0–52), 2 (Week 52–104), and 3 (Week 104–156) of BKZ exposure for the BKZ Total group.

Figure 3 TEAEs of interest by year



Error bars represent 95% CIs. Psoriasis Longitudinal Assessment and Registry (PSOLAR) ranges are presented where available to provide context.[8,9] Data are presented separately for Years 1 (Week 0–52), 2 (Week 52–104), and 3 (Week 104–156) of BKZ exposure for the BKZ Total group. [a]Includes any TEAE adjudicated as definite or probable IBD; [b]Not all hepatic laboratory parameter elevations were reported as adverse events.

Figure 4 Fungal infections by year



Error bars represent 95% CIs. Data are presented separately for Years 1 (Week 0–52), 2 (Week 52–104), and 3 (Week 104–156) of BKZ exposure for the BKZ Total group.

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J Drugs Dermatol 2015; 14: 706–14; [9]Gottlieb AB & Langhoff W J Drugs Dermatol 2020:19:573–4. **Author Contributions:** Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **ML**, **BS**, **RGL**, **YO**, **PF**, **RBW**, **LP**, **NC**, **SW**, **DD**, **DT**; Drafting of the publication, or reviewing it critically for important intellectual content: **ML**, **BS**, **RGL**, **YO**, **PF**, **RBW**, **LP**, **NC**, **SW**, **DD**, **DT**; Final approval of the publication: **ML**, **BS**, **RGL**, **YO**, **PF**, **RBW**, **LP**, **NC**, **SW**, **DD**, **DT**. **Author Disclosures: ML:** Employee of Mount Sinai and receives research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen Research & Development, LLC, Ortho Dermatologics, Sanofi-Regeneron, and UCB Pharma; consultant for Almirall, AltruBio Inc., AnaptysBio, Arcutis, AstraZeneca, Avotres, Boehringer Ingelheim, Brickell Biotech, Bristol Myers Squibb, Castle Biosciences, Celltrion, CorEvitas, Dermavant Sciences, EPI, Evommune Inc., Facilitatation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, Strata, Trevi, and Verrica. **BS:** Consultant (honoraria) for AbbVie, Alamar, Almirall, Alumis, Amgen, Arcutis, Arena, Aristea, Asana, Boehringer Ingelheim, Bristol Myers Squibb, Capital One, Connect Biopharma, CorEvitas, Dermavant, Eli Lilly, Evelo Biosciences, Immunic Therapeutics, Janssen, Kanggu Pharmaceuticals, LEO Pharma, Maruho, Meiji Seika Pharma, Mindera Health, Monte Carlo, Novartis, Pfizer, Protagonist, Regeneron, Sanofi-Genzyme, Sun Pharma, Takeda/Nimbus, UCB Pharma, Union Therapeutics, Ventyxbio, and vTv Therapeutics; 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