Bimekizumab: Exploring the fast onset, high level, and durability of clinical and molecular responses in patients with psoriatic disease – Design and rationale behind the exploratory, multicentre, open-label phase 3b BE UNIQUE study

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Objective

To describe the design and rationale of the phase 3b BE UNIQUE study, which will explore whether molecular and cellular changes correlate with the rapid, high-level (PASI 100), and durable clinical responses to bimekizumab (BKZ) treatment in patients with psoriasis and psoriatic arthritis (PsA).

Introduction

- BKZ is a monoclonal IgG1 antibody that selectively inhibits interleukin (IL)-17A and IL-17F, both of which are pivotal drivers of psoriasis pathogenesis (**Figure 1**).[1–3]
- BKZ has demonstrated rapid, superior efficacy versus comparators in multiple phase 3/3b studies in patients with moderate to severe plaque psoriasis, with durable clinical responses.[4–8]
- BKZ has also shown rapid normalisation of the psoriatic skin transcriptome to levels consistent with non-lesional skin, and normalisation of tissue-resident memory T (T_{RM}) cell signatures, by Week 8, which may help to explain the molecular mechanisms underlying the high levels and durability of complete skin clearance (100% improvement from baseline in Psoriasis Area and Severity Index; PASI 100) observed over 4 years in patients treated with BKZ every 4 weeks (Q4W) for 16 weeks, then every 8 weeks (Q8W) thereafter (Q4W/Q8W).[9–11]
- Questions remain on the very early and long-term effects of BKZ on key inflammatory pathways and mechanisms behind observed clinical responses in psoriatic disease, including in patients with both psoriasis and concomitant PsA.
- We hypothesise that fast and long-lasting complete normalisation of inflammatory gene expression and cellular biomarkers correlates with rapid, high-level, and durable clinical responses with BKZ in psoriatic disease.

Trial Design

- BE UNIQUE is an ongoing, multicentre phase 3b study enrolling 80 patients with moderate to severe plaque psoriasis, defined as PASI ≥12, body surface area (BSA) ≥10%, and Investigator's Global Assessment (IGA) ≥3.
- Patients in Cohort B (N=40) have concomitant active PsA, whereas patients in Cohort A (N=40) do not have concomitant PsA. A matching control cohort of 10 healthy individuals will also be enrolled.
- For patients in Cohort B, active PsA is defined as a diagnosis of PsA meeting Classification Criteria for Psoriatic Arthritis (CASPAR), ≥1/68 tender joint count, and ≥1/66 swollen joint count (SJC).
- In Part 1, patients will receive BKZ 320 mg Q4W to Week 16, then Q8W to Week 48 (**Figure 2**).
- In Part 2 (Weeks 48–96), patients with PASI=0 (and low PsA activity for Cohort B) will be randomised 1:1 to BKZ Q8W or every 12 weeks (Q12W); patients with PASI >0 and/or without low PsA activity will continue on BKZ Q8W (**Figure 2**).
- Lesional skin biopsies will be collected at baseline and Weeks 1, 48, and 96. Non-lesional skin biopsies will be collected at baseline and Week 48. Synovial tissue biopsies will be optional for Cohort B at baseline and Week 48. Biopsies will undergo transcriptomic analyses. Blood samples will also be collected (**Figure 3**).
- Skin biopsies and blood samples will also be taken from the Control Cohort.

Trial Objectives

- The primary objective is to assess change in composite gene expression score to Week 48, using reverse transcription-polymerase chain reaction (RT-PCR) of lesional skin biopsies, in preselected genes based on BKZ's mechanism of action and psoriatic disease pathways.
- The secondary objective is evaluation of BKZ safety/tolerability.
- Exploratory objectives include investigating the effect of BKZ on skin and blood bulk, single-cell, and spatial transcriptomics. Systemic effects of BKZ on gene and protein expression, and BKZ clinical response, will also be assessed (**Figure 3**).

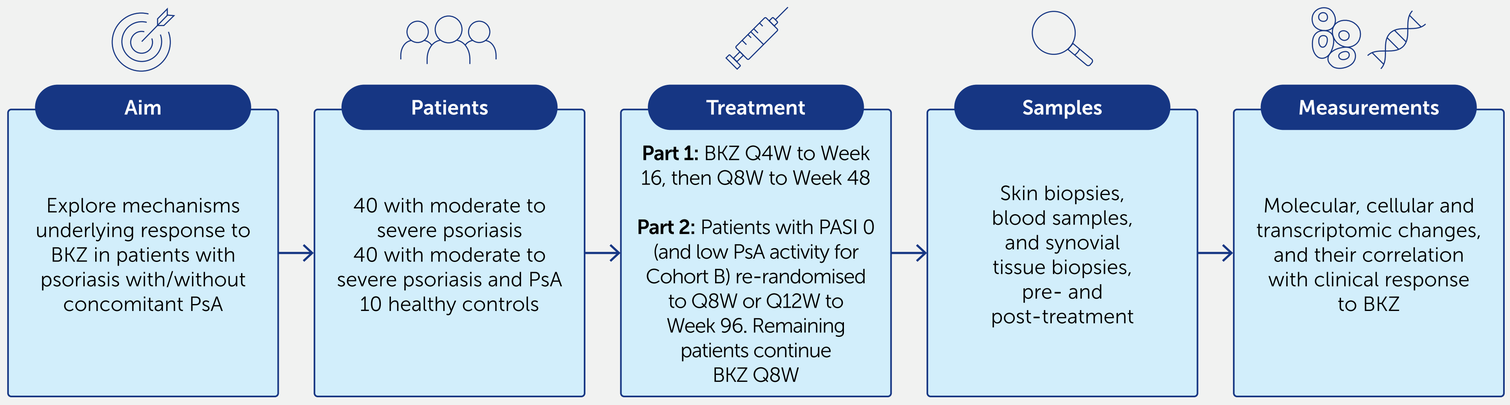
Conclusions

BE UNIQUE will enable exploration of the mechanisms underlying the rapid, high-level, durable clinical responses observed with bimekizumab treatment in patients with psoriasis with and without concomitant psoriatic arthritis.

An extended dosing interval of bimekizumab (Q12W) will be explored, which may improve treatment adherence and patient quality of life, if complete skin clearance is maintained.

Analysis of biopsies and blood samples will help to determine whether durable clinical responses to bimekizumab correlate with molecular, cellular, and transcriptomic changes in the skin, blood, and joints of patients with psoriatic disease.

Summary



BE UNIQUE will explore the molecular and cellular **mechanisms** underlying **rapid, high-level**, **durable** clinical responses to **bimekizumab** treatment over 96 weeks in patients with **psoriasis** with or without concomitant **psoriatic arthritis**, through analysis of **skin** and **synovial tissue** biopsies and **blood** samples.

Figure 1 The role of IL-17A and IL-17F in psoriasis pathobiology

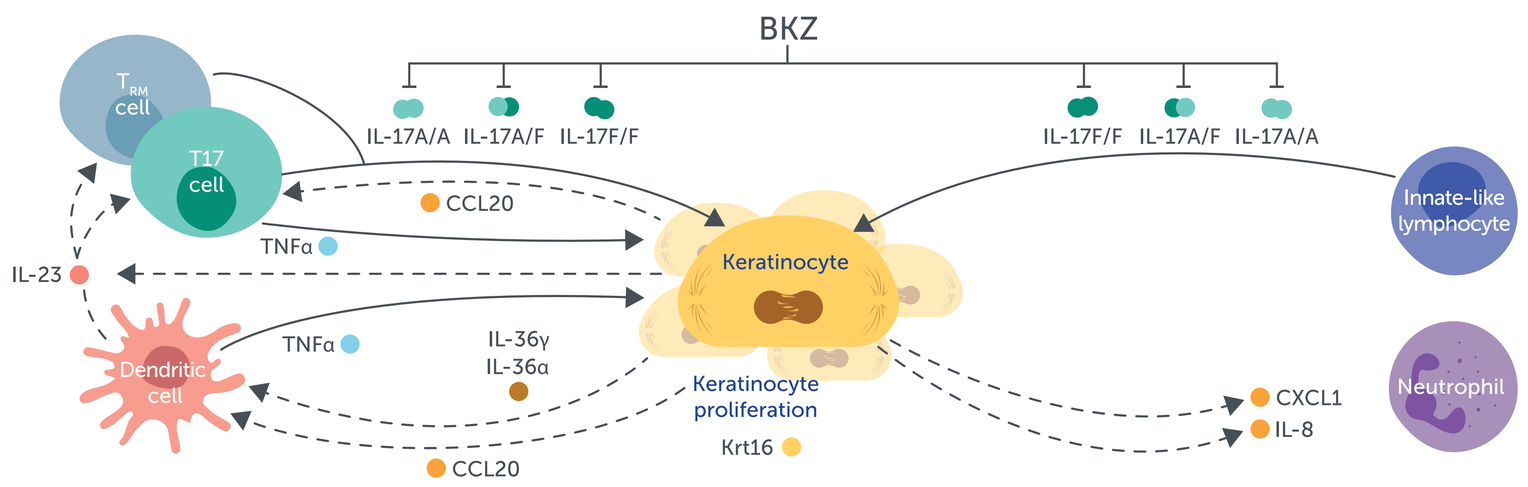
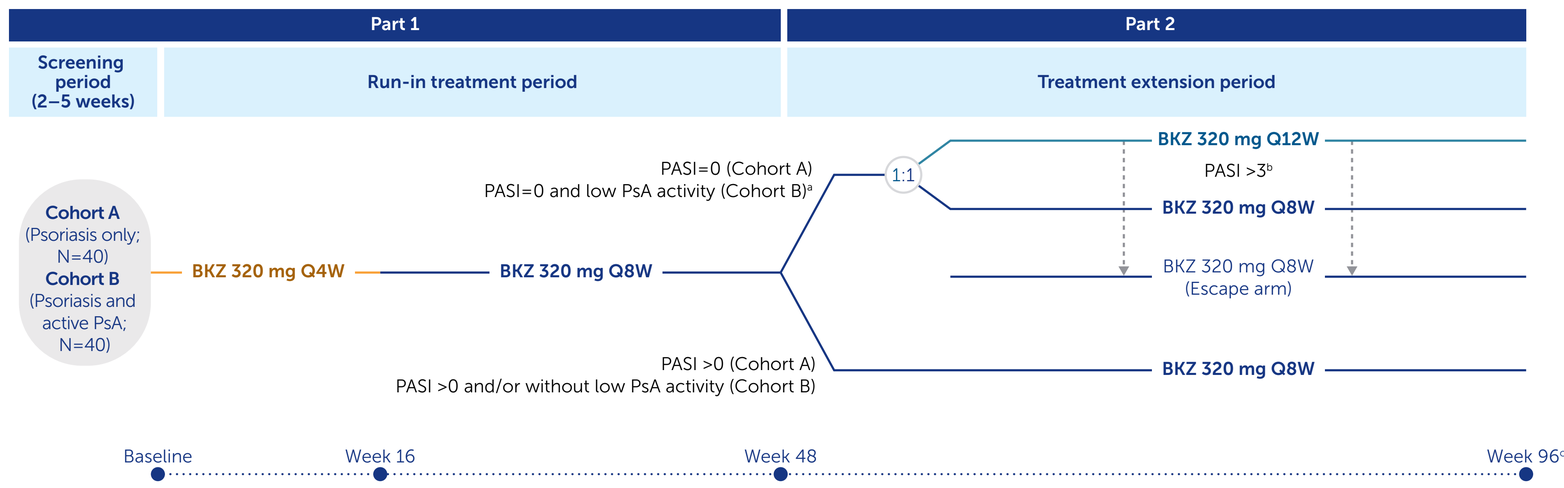
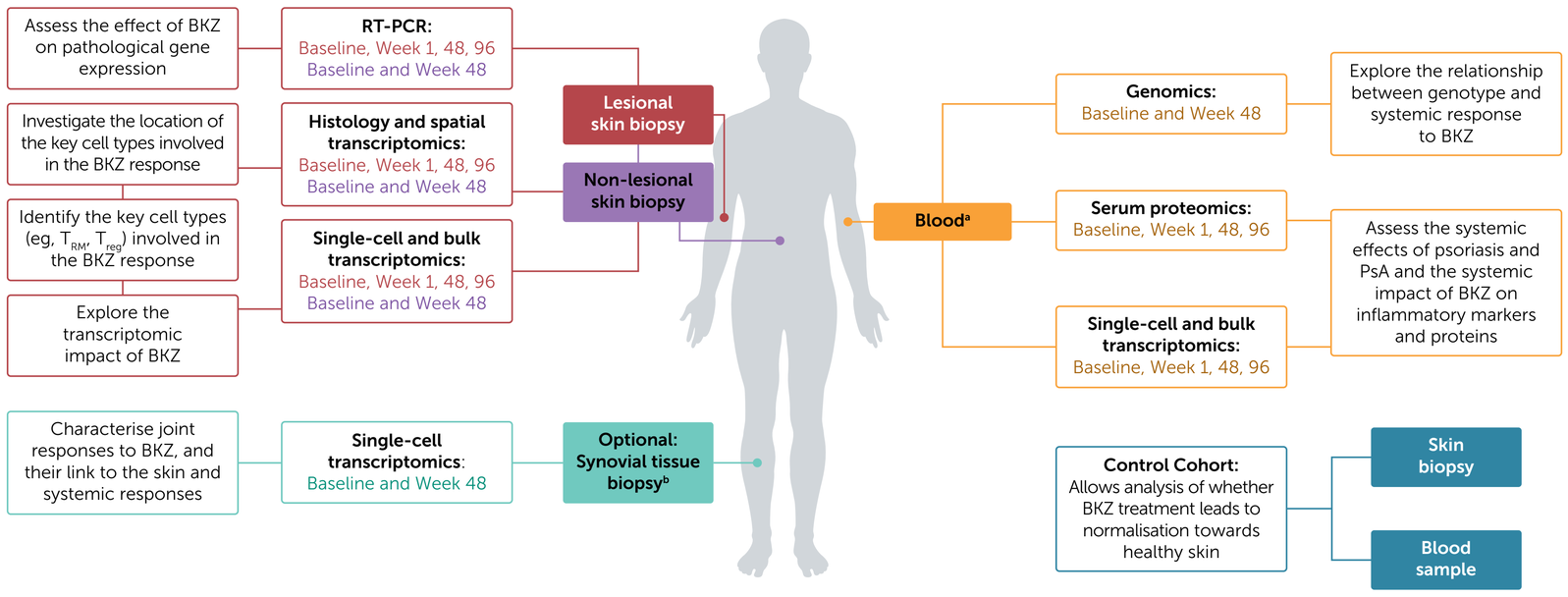


Figure 2 BE UNIQUE study design



[a] In addition to PASI=0, Cohort B patients must have low PsA disease activity at Week 48 (SJC ≤1 and no increase in concomitant medications for the treatment of PsA symptoms [such as non-steroidal anti-inflammatory drugs (NSAIDs), weak opioids, intra-articular injections] compared with baseline) to be randomised in the treatment extension period; **[b]** Patients in Cohort A and Cohort B who are randomised at Week 48 and who have a PASI score >3 during the treatment extension period will enter an escape arm and receive BKZ Q8W to study end, undergoing additional assessments; a lesional skin biopsy will be taken at the visit the patient has a PASI score >3, instead of at Week 96; **[c]** The safety follow-up visit will occur at least 12 weeks after the final dose and not before 4 weeks after the last skin biopsy.

Figure 3 Summary of samples and aims of genetic, cellular, and protein analyses



[a] Blood samples for single-cell transcriptomics will be collected from a subset of Cohort A and Cohort B patients and from all Control Cohort participants. Blood samples for bulk transcriptomics will not be collected from participants who provide samples for single-cell transcriptomics; **[b]** Optional biopsy in a subset of patients with active PsA only.

BKZ: bimekizumab; **BSA:** body surface area; **CASPAR:** Classification Criteria for Psoriatic Arthritis; **CCL:** chemokine ligand; **CXCL:** C-X-C motif chemokine ligand; **IGA:** Investigator's Global Assessment; **IgG1:** immunoglobulin G1; **IL:** interleukin; **Krt:** keratin; **NSAID:** non-steroidal anti-inflammatory drug; **PASI:** Psoriasis Area and Severity Index; **PsA:** psoriatic arthritis; **Q4/8/12W:** every 4/8/12 weeks; **RT-PCR:** reverse transcription-polymerase chain reaction; **SJC:** swollen joint count; **T17:** IL-17-producing T-cell; **TNF:** tumour necrosis factor; **T_{RM}:** tissue-resident memory T cell.

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