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Bimekizumab: the first bispecific biologic agent facing phase III trial program in both plaque psoriasis and psoriatic arthritis

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Introduction

Psoriasis is a chronic inflammatory skin disorder that in at least 20% of cases could be associated with arthritis (PsA) [1]. Skin and joint inflammation is driven by a wide array of pathways, though multiple lines of evidence supported the pathogenic model centered on the interleukin (IL)-23/IL-17A axis [2]. Beside IL-23/IL-17 axis playing a pivotal role in psoriasis pathogenesis, other cytokines with pro-inflammatory and/or pro-proliferative activity contribute to the development of the psoriatic phenotype [2]. Among them, IL-17F, showing greater than 50% structural homology and overlapping biological function with IL-17A, results 30-fold less biologically active than IL-17A [3,4]. Both IL-17A and IL-17F are increasingly expressed in psoriatic lesional skin and inflamed synovium from PsA [5-8]. Similarly, to IL-17A, IL-17F can cooperate with TNF in inducing the production of key pro-inflammatory cytokines, and thus, amplifying tissue inflammation [5-7]. The dual blockade of IL-17A and IL-17F induces a more potent suppression of inflammatory signals, compared to the selective IL-17A or IL-17F inhibition, reducing the expression of inflammation-linked genes and cytokines, as well as the disease-relevant immune cell migration, at greater extent [5-7]. These data provided the rationale for developing a bispecific humanized monoclonal IgG1 antibody, named bimekizumab, that can simultaneously neutralize both IL-17A and IL-17F.

Clinical studies testing bimekizumab for the treatment of psoriasis: The first-in-human, placebo-controlled, single-dose-escalating study randomizing 13 subjects to placebo and to escalating doses of bimekizumab (8 mg, 40 mg, 160 mg, 480 mg, and 640 mg), showed promising clinical outcomes [9]. All subjects receiving a single bimekizumab dose at the baseline were followed for 20 weeks. Clinical response was detected with higher bimekizumab doses (160 mg, 480 mg, and 460 mg), by week 2, reaching the maximal improvement between week 4 and 6 that was maintained through 16–20 weeks. In patients treated with 480 mg, and 460 mg bimekizumab injection, the reduction of disease severity estimated as at least 90% improvement of the baseline psoriasis index severity area (PASI) score (PASI 90 response), was achieved by 83% of patients from week 6-12, and in 90% at week 12. Overall, 78 adverse events occurring in all 39 participants (including placebo- and bimekizumab-treated subjects) were classified as mild or moderate, except one. The serious adverse event was not classified as treatment-related: it was observed in one 40 mg bimekizumab-treated patient and it consisted of vomiting that required hospitalization. Subsequently, a multi-center, randomized, double-blinded, placebo-controlled, parallel-group, dose-ranging, phase IIb study (named BE ABLE trial) tested bimekizumab vs. placebo in adult patients with moderate to severe chronic plaque psoriasis [10]. The study included a 12-week treatment period followed an extension phase for eligible patients where as those subjects not enrolling in the extension study, a safety follow-up visit was conducted 20 weeks after the last dose of study medication [10]. The BE ABLE study included 250 patients with chronic plaque psoriasis with an affected body surface area of at least 10% and PASI of at least 12. Patients were randomized 1:1:1:1:1:1 to receive subcutaneous bimekizumab every 4 weeks at doses of 64 mg, 160 mg, 160 mg with 320 mg loading dose, 320 mg, 480 mg, or placebo, subcutaneously [10]. Primary endpoint of this study was the achievement of PASI90 response at week 12. The reduction of at least 2 categories or the achievement of clear or almost clear skin condition as defined by Investigator's Global Assessment (IGA) at week 8 and at week 12, PASI90 response at week 8, PASI75 response at week 12, and PASI100 response at week 12, represented the secondary endpoints [10]. Seventy-nine percent and 60% of patients obtained PASI90 and PASI100 responses at week 12, respectively. Magnitude as well as rapidity of clinical response was impressive as demonstrated by the high number of PASI90 responders at week 8 (up to 86%), PASI75 (up to 93%) and PASI100 (up to 60%) at week 12 [10]. Clinical efficacy was significantly higher compared to placebo in terms of PASI and IGA reduction [10]. Safety data set showed treatment-emergent adverse events (TEAEs) in 61% of bimekizumab-treated patients vs. 36% of placebo-treated patients. The most commonly reported TEAEs (>5% patients in any group) at week 12 were represented by nasopharyngitis, upper respiratory tract infections, arthralgia, γ-glutamyltransferase increase, respiratory tract infection, neutropenia, rhinitis, tonsillitis, hypertension, oral candidiasis, headache, leukopenia, and vomiting [10]. Fungal infections including oral candidiasis, oral fungal infection, vulvovaginal mycotic infection, and tinea pedis were reported in 9 (4.3%) bimekizumab-treated patients and they could be expected because of the protective role of both IL-17 cytokines against fungal infections. AEs led to treatment discontinuation in 4.8% of bimekizumab-treated patients and in 2.4% of the placebo group [10].

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Clinical studies testing bimekizumab for the treatment of psoriatic arthritis: A phase Ib, double-blind, placebo-controlled, proof-of-concept trial randomized PsA patients to bimekizumab (n=39) or placebo (n=14) for 20 weeks [11]. Different bimekizumab dose regimens were tested concomitantly with the use of anti-inflammatory and anti-rheumatic products, folic acid, analgesics, and DMARDs. Disease severity was assessed by the American College of Rheumatology (ACR) score. Patients receiving bimekizumab had greater joint improvement obtaining higher rates of ACR20 (at least 20% improvement of baseline ACR score) response, ACR50, and ACR70, compared with placebo [11]. Primary efficacy endpoint (ACR20 at week 8) was obtained in 80% of patients, ACR50 in 40%, and ACR70 in 23% (ACR70) [11]. ACR50 and ACR70 response rates were more frequently observed at week12 and week 16, in 57% and 37% of patients, respectively [11]. Notably, clinical response was evident as early as week 2.

In patients with skin involvement ≥3% body surface area, week 8 response rates for PASI75 and PASI100 were 100% and 87%, respectively [11]. No unexpected safety signals were detected, with the majority of TEAEs classified as mild or moderate, while serious AEs were not related to the study drug [11]. A more recently performed multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase IIb (BE ACTIVE) study enrolling 206 patients with PsA assigned to bimekizumab or placebo during 12-week double-blind treatment period, followed by re-randomization to the different dose-blind bimekizumab treatment groups for 36 weeks [12]. The overall treatment duration was 48 weeks. ACR50 (primary endpoint) response was obtained in up to 46% of bimekizumab-treated patients, compared to 7% of placebo-treated patients, at week 12 [12]. These results were achieved in a mixed patient population constituted by both biologic naïve and biologic-exposed patients [12].

Bimekizumab-treated patients with skin involvement ≥3% body surface area, in up to 60% of cases experienced a complete skin clearance (PASI100), while up to 65% had PASI90 response (secondary endpoint) vs. 7% of the placebo group, at week 12 [12,13].

Conclusion

Other bispecific biologic agents have been developed for the treatment of psoriasis and they are now being tested in clinical trials [14]. Nevertheless, bimekizumab is the first bispecific biologic agent entering phase III program. These preliminary data remarkably demonstrated an elevated and rapid efficacy of bimekizumab in clearing skin and improving joint inflammation. It would be of interest to have confirmatory data from the 5 trials constituting the current phase III program, in particular from the head-to-head studies comparing bimekizumab with ustekinumab (NCT03370133), adalimumab (NCT03412747), or secukinumab (NCT03536884) [15-17].

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