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Dual inhibition of IL-17A and IL-17F in psoriatic disease

Helena Iznardo and Lluís Puig

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***Abstract*:** Psoriasis and psoriatic arthritis are chronic immune-mediated disorders with involvement of interleukin (IL)-17 cytokines in their pathogenesis. IL-17A has been considered to be the most biologically active, but IL-17F is also over-expressed in skin and synovial tissues of patients with these diseases. Many therapeutic advances have been made in the past years, but some needs remain unmet. Dual inhibitor and bispecific antibodies simultaneously targeting IL-17A and IL-17F could provide better disease control. Herein we review current evidence on bimekizumab and sonelokimab. The antigen-binding site of bimekizumab neutralizes both IL-17A and IL-17F; phase I, II, and III studies have demonstrated its efficacy and safety in psoriasis and psoriatic arthritis. Sonelokimab is a trivalent nanobody targeting IL-17A and IL-17F; phase I and II studies with this molecule have yielded promising results in psoriasis.

Keywords: bimekizumab, dual inhibition, IL-17, IL-17A, IL-17F, psoriasis, psoriatic arthritis, sonelokimab

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Introduction

Psoriasis is a chronic and recurrent immune-mediated, multisystem disorder that affects mainly the skin, but entails other domains of involvement and multiple comorbidities.[1] Epidemiological studies show that approximately 3% of the western population suffer from psoriasis.[2,3] Psoriasis has a great impact on quality of life and can be associated with relevant functional as well as psychosocial impairment.[4] Psoriatic arthritis (PsA) is a complex inflammatory joint disease, included in the spondyloarthropathy spectrum, and affects approximately one third of patients, especially those with moderate to severe psoriasis.[5] PsA produces stiffness, pain and swelling of joints, and can progress to debilitating joint destruction. Enthesitis and dactylitis are observed in 30–50% and 40–50% of patients, respectively.[6] Psoriasis manifestations precede the diagnosis of PsA in 85% of patients, although they can be synchronous or, more rarely, follow.[7] This comprehensive review has been based on a PubMed search with the search strategy '(IL-17A OR IL-17F) AND (psoriasis OR psoriatic arthritis) AND (bimekizumab OR sonelokimab OR dual OR bispecific)', from the start of records.

Interleukin-17 cytokines and their involvement in psoriasis pathogenesis

The interleukin (IL)-17 family of cytokines consists of at least six structurally similar cytokines (IL-17A to F).[8] These proinflammatory cytokines participate in defence against extracellular bacteria and fungi, and are also involved in promoting chronic inflammation and autoimmunity.[8–10] IL-17A can exist as a homodimer of two IL-17A chains or as a heterodimer with IL-17F.[11,12] IL-17F has the highest structural homology with IL-17A (close to 50%) and is expressed by the same immune cell types as IL-17A, mainly T helper (Th)17 cells but also CD8 T cells, natural killer (NK) cells, lymphoid tissue inducer (LTi) cells, type 3 innate lymphoid cells and γδ T cells.[8] IL-17 receptors are composed of five subunits (IL-17RA–RE) in different heterodimeric combinations. IL-17A and IL-17F bind to the same complex of IL-17RA and IL-17RC.[13] IL-17RA is widely expressed, while the cell type expression of other IL-17R family receptors is more restricted. On ligand binding, these receptors engage with cytoplasmic protein ACT1 to enact downstream signaling pathways.[14] IL-17F is considered to act

Correspondence to:
Lluís Puig
Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Sant Antoni Maria Claret, 167, Barcelona 08025, Spain
lpuig@santpau.cat

Helena Iznardo
Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma, Barcelona, Spain

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similarly to IL-17A but with less potent effects, as it has less affinity for the IL-17RA/RC complex. However, IL-17F levels are consistently more elevated (30-fold higher on average) in psoriatic lesional tissues and serum than those of IL-17A,[15] with similar findings in spondylarthritis patients.[16] Several studies have demonstrated the central role of IL-17A and IL-17F in the pathogenesis of psoriasis, PsA and spondyloarthritis.[17–19] Targeted biological therapies directed against IL-17A include secukinumab and ixekizumab – approved for the treatment of psoriasis, PsA and ankylosing spondylitis (AS)[20,21] – with later addition of the IL-17RA blocker brodalumab, approved for the treatment of psoriasis in USA and Europe[22] and psoriasis and PsA in Japan.[23] Dual and bispecific IL-17A and IL-17F inhibitors have been developed following the rationale that neutralization of IL-17A and IL-17F could be more efficacious than IL-17A neutralization alone,[24,25] and the clinical data are very promising so far, especially for bimekizumab (Table 1).

Bimekizumab for treatment of psoriasis and PsA

Bimekizumab (formerly UCB4940; UCB) is an immunoglobulin G1 (IgG1) humanized antibody with strong affinity for IL-17A and IL-17F. Strictly speaking, bimekizumab is not bispecific, but divalent (two binding sites) with dual specificity (each one of them binds both IL-17A and IL-17F monomers) (Figure 1).[26] Preclinical studies comparing bimekizumab with other IL-17A inhibitors showed the affinity of ixekizumab and bimekizumab for IL-17A to be equivalent and higher than that of secukinumab, whereas the ability of bimekizumab to neutralize IL-17F was unique.[24] Bimekizumab has now completed phase I, phase II and phase III clinical trials in patients with psoriasis, PsA, AS, and rheumatoid arthritis (RA)[27eum] and has provided clinically meaningful improvements in hidradenitis suppurativa.[35]

Psoriasis key efficacy and safety data

In the phase I first-in-human, double-blind, placebo-controlled, single-dose, dose-escalating psoriasis study (NCT02529956), 26 patients with 'mild to moderate psoriasis', defined in the study as ⩽5% of body surface area (BSA), received escalating intravenous doses of bimekizumab (8 mg, 40 mg, 160 mg, 480 mg and 640 mg) and 13 received placebo.[36] Bimekizumab pharmacokinetics showed linear correlation with dose and its half-life ranged from 17 days (40 mg) to 22 days (160 mg).[36] Five subjects (19.2%) developed anti-bimekizumab antibodies during the follow-up period, but pharmacokinetic parameters were not affected.[36] Rapid and marked skin improvement was seen from week 2 in patients treated with higher doses (160 mg, 480 mg, and 640 mg).[36] Maximal improvement was reached between weeks 4 and 6 and was maintained throughout the 20-week study in patients receiving bimekizumab ⩾160 mg.[36] Maximal psoriasis area and severity (PASI) score reduction was >85% in those treated with higher doses (⩾160 mg). Maximal improvement of baseline physician's global assessment (PGA) score, consisting of 75%, 100%, and 94% reduction, was measured in the 160 mg, 480 mg, and 640 mg bimekizumab groups, respectively.[36] Treatment-emergent adverse events (TEAEs) were observed in 84.6% and 76.9% of subjects treated with bimekizumab and placebo, respectively. The majority were mild, with ⩾10% of all subjects receiving bimekizumab presenting with headache, oropharyngeal pain, nasopharyngitis and not clinically meaningful ECG alterations. Only one serious adverse effect (AE) occurred, but it was not classified as treatment related.[36]

BE ABLE 1 (NCT02905006), a 12-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase IIb study in patients with moderate to severe psoriasis, demonstrated superior efficacy of bimekizumab *versus* placebo in all primary (achievement of PASI90 response at week 12) and secondary [reduction of at least two categories or the achievement of clear or almost clear skin condition as defined by investigator's global assessment (IGA) at week 8 and 12, PASI90 response at week 8, PASI75 response at week 12, and PASI100 response at week 12] endpoints.[28] Two hundred and fifty patients were randomly assigned 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; PASI75 and PASI90 responses were more frequently observed in the 320 mg group (93% and 79.1%, respectively) compared to placebo (4.8% and 0%, respectively), and the highest PASI100 response rate (60%) was detected in the group receiving 160 mg with 320 mg loading dose

Table 1. Summary of the most relevant currently available efficacy and safety data on bimekizumab and sonelokimab.

Drug	Disease	Trial	Active comparator	Objective	Dose regimen	Efficacy		Most common AEs
BIMEKIZUMAB	Psoriasis	BE ABLE 1 (NCT02905006) ($n = 250$)		Efficacy and safety		PASI90 at 12 weeks (%)		Nasopharyngitis, respiratory tract infection and oral candidiasis
					Placebo	0%		
					64 mg Q4W	46		
					160 mg Q4W	67		
					160 mg Q4W (320 mg LD at baseline)	75		
					320 mg Q4W	79		
					480 mg Q4W	72		
		BE ABLE 2 (NCT03010527) ($n = 217$)		Long-term efficacy and safety (extension study from BE ABLE 1)	(*)	PASI90 at 60 weeks (%)		Nasopharyngitis, respiratory tract infection and oral candidiasis
					Placebo → 160 Q4W	90		
					64 mg Q4W	100		
					160 mg Q4W	80		
					320 mg Q4W	85		
					480 mg → 320 Q4W	85		
		BE READY (NCT03410992) ($n = 435$)		Efficacy and safety		PASI90 at 16 weeks (%)	IGA0/1 at 16 weeks (%)	Nasopharyngitis, oral candidiasis, respiratory tract infection
					Placebo	1	1	
					320 mg Q4W	91	93	

(Continued)

Table 1. (Continued)

Drug	Disease	Trial	Active comparator	Objective	Dose regimen	Efficacy		Most common AEs
		Be VIVID (NCT03370133) (*n* = 567)	Ustekinumab	Efficacy and safety	Placebo	5	5	Nasopharyngitis, oral candidiasis, respiratory tract infection
					BKZ 320 mg Q4W	85	84	
					UST 45/90 mg Q12W	50	53	
		BE SURE (NCT03412747) (*n* = 478)	Adalimumab	Efficacy and safety	BKZ 320 mg Q4W until week 16 Q8W	86	85	Upper respiratory tract infections, oral candidiasis, hypertension and diarrhea
					ADA 40 mg Q2W until week 24 BKZ	47	57	
		BE RADIANT (NCT03536884) (*n* = 743)	Secukinumab	Efficacy and safety		PASI100 at 16 weeks (%)	PASI100 at 48 weeks (%)	Upper respiratory tract infections, oral candidiasis, urinary tract infection
					BKZ 320 mg Q4W	62	67	
					SEC 300 mg weekly until week 8 Q4W	49	46	
	PsA	BE ACTIVE (NCT02969525) (*n* = 206)		Efficacy and safety		ACR50 at 12 weeks (%)	ACR20 at 12 weeks (%)	Nasopharyngitis and oral candidiasis
					Placebo	7	19	
					16 mg Q4W	27	54	
					160 mg Q4W	41	73	
					160 mg Q4W 320 mg LD at baseline)	46	61	
					320 mg Q4W	24	51	
		BE COMPLETE (NCT03896581) (*n* = 390)		Efficacy and safety in anti-TNF inadequate-responders	Ongoing			

(Continued)

Table 1. (Continued)

Drug	Disease	Trial	Active comparator	Objective	Dose regimen	Efficacy	Most common AEs
		BE OPTIMAL (NCT03895203) ($n=840$)	Adalimumab	Efficacy and safety	Ongoing		
		BE VITAL (NCT04009499) ($n=1045$)		Safety (incident AE)	Ongoing		
SONELOKIMAB	Psoriasis	NCT02156466 ($n=44$)		Safety/tolerability, immunogenicity, pharmacokinetics/ pharmacodynamic and efficacy	Days 1, 15, 29	PASI90 at 85 days (%)	Pruritus, headache, hypertension, nasopharyngitis, somnolence and bronchitis
					Placebo	0	
					30 mg	50	
					60 mg	88	
					120 mg	88	
					250 mg	100	
		NCT03384745 ($n=313$)	Secukinumab	Efficacy, safety and tolerability	(**)	IGA 0/1 at 12 weeks (%)	Nasopharyngitis, pruritus, upper respiratory tract infections
					Placebo	0	
					30 mg 0, 2, 4, 8 w	48	
					60 mg 0, 2, 4, 8 w	85	
					120 mg 0, 2, 4, 8 w	77	
					120 mg+ 0, 2, 4, 6, 8, 10 w	88	
					SEC 300 mg 0, 1, 2, 3, 4, 8 w	77	

*Patients who achieved PASI90 at week 12 received bimekizumab 64, 160, or 320 mg for an additional 48 weeks (60 weeks in total). Patients receiving placebo in BE ABLE 1 were switched to bimekizumab 160 mg and patients receiving bimekizumab 480 mg were switched to 320 mg. The other dose regimes were maintained.
**This clinical trial consisted of a 12-week induction period, a 12-week dose escalation period and a 12-week evaluation of response period. Detailed explanation of administration regimes is included in the main text.
ADA, adalimumab; AE, adverse effects; BKZ, bimekizumab; LD, loading dose; PsA, psoriatic arthritis; Q4W, every 4 weeks; SEC, secukinumab; UST, ustekinumab.

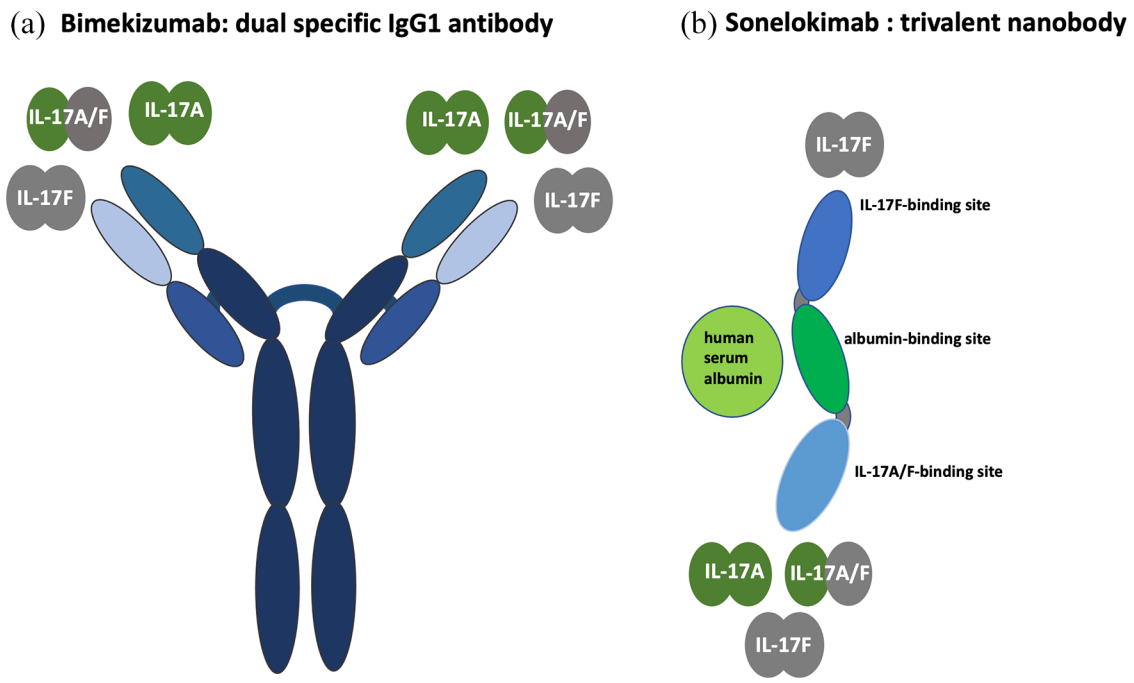

Figure 1. Schematic representation of bimekizumab and sonelokimab's molecular structures. (a) Bimekizumab has an antigen-binding site that neutralizes interleukin (IL)-17A, IL-17F and their heterodimers (dual specificity). (b) Sonelokimab is a trivalent camelid nanobody comprised of an *N*-terminal moiety that binds specifically to IL-17F, a central moiety binding to serum albumin for stabilization and a C-terminal moiety binding IL-17A and IL-17F (bispecific inhibitor).

(*versus* 0% placebo).[28] TEAEs were observed in 126/208 (61%) of bimekizumab-treated patients *versus* 15/42 (36%) of placebo-treated patients, leading to treatment discontinuation in 4.8% and 2.4% of patients in the bimekizumab and placebo groups, respectively. The most common (>5% patients in any group) TEAEs were nasopharyngitis, upper respiratory tract infections, arthralgia, γ-glutamyltransferase increase, neutropenia, rhinitis, tonsillitis, hypertension, oral candidiasis, headache, leukopenia, and vomiting. Fungal infections were reported in nine (4.3%) of bimekizumab-treated patients (four out of nine being oral candidiasis). All were localized, superficial infections of mild or moderate intensity and none of them resulted in treatment discontinuation.[28] There was no apparent dose relationship between TEAEs in patients who discontinued therapy. Two patients reported three serious AEs, none of which were considered related to the study treatment. BE ABLE 2 (NCT03010527) is a phase IIb extension study in which 217 patients from the BE ABLE 1 who achieved PASI90 at week 12 received bimekizumab 64, 160, or 320 mg for an additional 48 weeks (60 weeks in total).[30] Initial PASI90 responders maintained high levels of efficacy through week 60 with 80% to 100% achieving PASI90 and 69% to 83% achieving PASI100 and IGA 0.[30] Incidence of TEAEs was similar between patients in the bimekizumab 160 mg group (88.3%) and 320 mg group (83.5%), and lower in the bimekizumab 64 mg group (66.7%). The majority were mild to moderate and the most frequent were oral candidiasis (13.4%) and nasopharyngitis (12.9%). Overall incidence of serious AEs was 6.9% and only one of them was considered to be related to bimekizumab (serum liver enzyme levels increased in a patient receiving 160 mg).[30] No cases of inflammatory bowel disease, major adverse cardiovascular events, or suicidal ideation or behavior were reported.[30] Limitations of the study include a relatively short duration of observation, a small number of patients in the bimekizumab 64 mg group ($n = 15$) and selection bias due to withdrawal of patients who had not reached PASI75 in the BE ABLE 1 study.[30]

Phase III studies BE READY, BE VIVID, BE SURE and BE RADIANT have also been completed, with efficacy and safety data supporting the therapeutic value of bimekizumab.[33,34]

Furthermore, the BE SURE and BE RADIANT trials have proved superiority and non-inferiority of bimekizumab against adalimumab and secukinumab, respectively.[37,38]

BE READY (NCT03410992) was a 56-week, randomized, double-blinded, placebo-controlled study that consisted of an initial treatment period followed by a randomized withdrawal period and enrolled 435 adults with moderate to severe plaque psoriasis.[33] Patients were randomly assigned (4:1) to receive bimekizumab 320 mg ($n=349$) every 4 weeks or placebo ($n=86$) every 4 weeks. Co-primary endpoints were PASI90 and IGA 0/1 responses at week 16. Bimekizumab-treated patients achieving PASI90 at week 16 were randomly re-allocated (1:1:1) to receive bimekizumab 320 mg every 4 weeks, every 8 weeks, or placebo for weeks 16–56. The study met its co-primary endpoints of PASI90 (91% of patients receiving bimekizumab *versus* 1% receiving placebo) and IGA 0/1 (93% of patients receiving bimekizumab *versus* 1% receiving placebo) at week 16.[33] PASI100 was achieved by 68% of patients in the bimekizumab 320 mg every 4 weeks group *versus* 1% in the placebo group ($p<0.0001$). Differences in response were observed by week 4, after only one dose of bimekizumab. Responses were maintained through week 56 with bimekizumab 320 mg every 8 weeks and every 4 weeks. The median time to relapse (loss of PASI75 response) since randomized allocation to placebo (at week 16) was 28 weeks (95% confidence interval (CI) 24–32, $p<0.0001$); TEAEs up to week 16 were reported in 61% (213/349) and 41% (35/86) of patients receiving bimekizumab 320 mg and placebo every 4 weeks, respectively. From week 16 to week 56, TEAEs were reported in 74% (78/106), 77% (77/100) and 69% (72/105) of patients receiving bimekizumab 320 mg every 4 weeks, every 8 weeks or placebo, respectively, and the safety profile was consistent with that reported in previous bimekizumab studies.[33]

BE VIVID (NCT03370133) is a 52-week, multicenter, double-blind, active comparator and placebo-controlled phase III trial in which 567 patients were randomly assigned (4:2:1) to bimekizumab 320 mg every 4 weeks ($n=321$), ustekinumab 45 mg or 90 mg every 12 weeks ($n=163$) or placebo every 4 weeks ($n=83$).[34] At week 16, patients receiving placebo switched to bimekizumab 320 mg every 4 weeks. Co-primary endpoints were PASI90 and IGA 0/1 at week 16 (non-responder imputation).[34] At week 16, 85% (270/321), 50% (81/163) and 5% (4/83) of patients in the bimekizumab, ustekinumab [risk difference 35 (95% CI 27–43); $p<0.0001$] and placebo groups [risk difference 80 (74–86); $p<0.0001$], had PASI90, respectively; and 84%, 53% and 5% of patients in the bimekizumab, ustekinumab [risk difference 30 (95% CI 22–39); $p<0.0001$] and placebo groups [risk difference 79 (73–85); $p<0.0001$) had an IGA response.[34] PASI100 was achieved by 59% of patients in the bimekizumab group by week 16, and the response was maintained to study completion, with 65% of patients having complete skin clearance by week 52. Serious TEAEs were reported in 6% (24/395) and 8% (13/163) of the patients in the bimekizumab group (including those who switched from placebo at week 16) and the ustekinumab group, respectively. The proportion of TEAEs was similar between bimekizumab and ustekinumab-treated patients, except for oral candidiasis.

In BE SURE (NCT03412747), moderate to severe psoriasis patients were randomly assigned (1:1:1) to receive bimekizumab 320 mg every 4 weeks ($n=158$), bimekizumab 320 mg every 4 weeks until week 16 followed by bimekizumab 320 mg every 8 weeks ($n=161$) or adalimumab (80 mg at week 0, 40 mg at week 1 and 40 mg every 2 weeks until week 23) followed by bimekizumab 320 mg every 4 weeks between weeks 24 and 56 ($n=159$).[37] Co-primary endpoints were met (PASI90 and IGA 0/1 responses compared to adalimumab by week 16), with 86.2% (275/319) and 85.3% (272/319) of bimekizumab-treated patients and 47.2% (75/159) and 57.2% (91/159) of those treated with adalimumab showing PASI90 and IGA 0/1 response, respectively.[37] By week 24, PASI90 and PASI100 response rates remained higher for bimekizumab-treated patients as compared to those treated with adalimumab ($p<0.001$).[37] A fast increase in response rate was observed after switching from adalimumab to bimekizumab. By week 56, response rates in adalimumab-switched patients were similar to those in patients who received only bimekizumab.[37] TEAEs were comparable between the three treatment groups; the most frequent were oral candidiasis, superior respiratory tract infections, hypertension and diarrhea.[37] From weeks 0 to 24, oral candidiasis and diarrhea occurred more frequently in the bimekizumab-treated groups. Serious AEs were reported in 2.5% (4/158), 0.6% (1/161) and 3.1% (5/159) of patients treated with bimekizumab every 4 weeks,

bimekizumab every 4 weeks and then every 8 weeks and adalimumab, respectively. From weeks 24 to 56 serious AEs were reported in 1.3% (2/152), 5.4% (8/149) and 6.0% (9/149) of patients treated with bimekizumab every 4 weeks, bimekizumab every 4 weeks and then every 8 weeks and adalimumab, respectively. No cases of adjudicated major adverse cardiovascular events, adjudicated suicidal ideation or behavior, inflammatory bowel disease (IBD), serious hypersensitivity reactions, or active tuberculosis among patients treated with bimekizumab were observed. No unexpected safety concerns appeared in patients switching from adalimumab to bimekizumab as compared to patients treated only with bimekizumab. The incidence of serious infection was similar across treatment groups.[37]

In BE RADIANT (NCT03536884) 743 patients with moderate to severe plaque psoriasis were randomly assigned (1:1) to receive bimekizumab 320 mg every 4 weeks ($n = 373$), or secukinumab 300 mg weekly until week 4, followed by every 4 weeks to week 48 ($n = 370$).[38] At week 16, patients receiving bimekizumab were re-randomized (1:2) to receive 320 mg every 4 weeks or every 8 weeks to week 48. The primary end point was met, with 61.7% (230/373) and 48.9% (181/370) of bimekizumab-treated and secukinumab-treated patients showing PASI100 response at week 16, respectively. By week 4, 71% (265/373) of the bimekizumab-treated patients had a PASI75 response [*versus* 47.3% (175/373) from the secukinumab group].[38] Response rates continued to increase and were maintained until week 48, with 67% (250/373) and 46.2% (171/370) of bimekizumab and secukinumab-treated patients having PASI100.[38] The most frequent AEs were upper respiratory tract infection, oral candidiasis and urinary tract infection, occurring in more than 5% of patients in any group. Oral candidiasis was more common in bimekizumab than in secukinumab-treated patients (19.3% and 3%, respectively).[38] Most were mild (36/72) or moderate (34/72) and none led to treatment discontinuation. The rate of serious infections was similar in the two treatment groups. There was one case of new-onset ulcerative colitis in the bimekizumab group and one in the secukinumab group. There were two cases of adjudicated major adverse cardiac events in the secukinumab group and none in the bimekizumab group.

PsA safety and efficacy data

In the phase Ib proof-of-concept study (NCT02141763) in patients with moderate to severe adult-onset PsA, 39 patients received different dose regimens of bimekizumab (loading dose ranging from 80 to 560 mg and maintenance doses ranging from 40 to 320 mg) and 14 placebo.[27] Bimekizumab-treated patients experienced rapid improvements for both cutaneous and articular symptoms, detected as soon as week 2 and maintained up to week 20.[27] At week 8, 87% (13/15) of patients achieved PASI100 and 80% (24/30), and 40% (12/30) achieved at least 20% and 50% improvement in the American College of Rheumatology response criteria (ACR20 and 50, respectively).[27] Bimekizumab treatment was not associated with any unexpected safety signals, with two patients in the treatment arm reporting fungal infections.[27] This study also included preclinical *in vitro* experiments showing that IL-17F induced similar inflammatory responses to IL-17A in human skin and joint cells. Furthermore, cytokine responses and neutrophil chemotaxis were suppressed more effectively with dual neutralization of IL-17A and IL-17F with bimekizumab than with inhibition of IL-17A or IL-17F alone.[27]

BE ACTIVE was a 48-week, phase IIb, randomized, double-blind, placebo-controlled, dose-ranging trial to assess the efficacy and safety of bimekizumab in 206 adult patients with active ($\geqslant 3$ tender and swollen joints) PsA.[32] Patients were randomly assigned (1:1:1:1:1) to receive 16 mg, 160 mg with single 320 mg loading dose, 160 mg, 320 mg bimekizumab or placebo *via* subcutaneous injection every 4 weeks for 12 weeks.[32] After week 12, patients on placebo and 16 mg bimekizumab arm were reassigned 1:1 to receive 160 mg or 320 mg bimekizumab. All groups continued to receive treatment every 4 weeks until week 48.[32] Primary endpoint was ACR50 response at 12 weeks, whereas the usual endpoint in PsA trials is ACR20 at 24 weeks.[39] Patients with previous use of one tumor necrosis factor (TNF) inhibitor were enrolled (19%), as well as those with a history of IBD (but no active disease).[32] Statistical analysis of primary response included pairwise comparisons of each bimekizumab dose *versus* placebo for ACR50 at week 12, starting with the highest dose. The primary endpoint was not met, as the response in the 320 mg group did not differ significantly from that in the placebo group [odds ratio (OR) 3.7 (95% CI 1.0–13.7); $p = 0.051$].[32] Exploratory

outcomes with nominal p values included a significant ACR50 response at week 12 for every bimekizumab group, with the highest efficacy in the 160 mg dose with a 320 mg loading dose group [OR 9.7 (2.7–34.3); $p = 0.0004$].[32] Significant responses in PASI scores were also obtained at week 12 (nominal p values), with 50% of patients in the bimekizumab 160 mg dose with 320 mg loading dose group achieving a PASI90 response [OR 12.9 (1.8–60.5); $p = 0.0011$].[32] Response rates increased up to week 24 and thereafter remained stable, with no loss of efficacy by week 48.[32] Patient-reported outcomes (PROs) such as the health assessment questionnaire disability index (HAQ-DI) and the PsA impact of disease-9 (PsAID-9) also showed rapid and sustained improvement (up to 48 weeks).[40] Recently reported additional data include the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 response rates 43% and 56% at week 12 and 48, respectively, for the 93 patients in the bimekizumab 160–320 mg groups.[41] Regarding safety, by week 12 no differences in the frequency of AEs were found between placebo and the different treatment doses, with 57% (24/42) and 41% (68/164) of patients in the placebo and bimekizumab groups reporting TEAEs, respectively.[32] After reallocation, 74% (151/204) of the patients who received bimekizumab reported AEs between weeks 12 and 48; the most frequent were nasopharyngitis and respiratory tract infections.[32] No direct association with bimekizumab dose was found.[32] *Candida* infections were reported in 7% of patients, not leading to treatment discontinuation in any instance. No cases of IBD were reported. Nine patients (eight receiving bimekizumab) suffered from serious AEs including drug-induced liver injury (one in 320 mg), severe liver enzyme elevation (one in 320 mg), hepatitis E infection (one in 160 mg), cellulitis (one in 160 mg), melanoma *in situ* (one in 160 mg), suicidal ideation (one in 160 mg) and neutropenia (one in 320 mg).[32]

BE ACTIVE2 (NCT03347110) is the open-label extension (OLE) study in which all patients who completed 48 weeks of the BE ACTIVE trial were switched to 160 mg bimekizumab regardless of previous treatments.[42] After 60 more weeks of OLE treatment (making a total of 108 weeks) there were 66.7% ACR50 and 75.4% BSA 0% responses, with complete resolution of dactilytis and enthesitis in 65.9% and 77.9% of patients, respectively.[43] ACR20/50/70 responses were maintained until week 108 in 80%/78%/81% of week 12 responders.[43] Serious AEs occurred in 9.3% of patients, and 8.8% overall withdrew from the study due to AEs by week 108.[43]

Bimekizumab use in AS and RA has also been explored.[29,31] The efficacy and safety of bimekizumab in active AS was proved in BE AGILE (NCT02963506), a phase II randomized, double-blind, placebo-controlled, dose ranging trial[31] with a long-term extension study (NCT03355573), in a currently ongoing phase II trial comparing bimekizumab with certolizumab pegol (NCT03215277),[44] and in a phase III trial for AS (NCT03928743) and non-radiographic axial spondyloarthritis (NCT03928704), which is currently recruiting participants.[45] A proof-of-concept phase IIa study (NCT02430909) tested the addition of bimekizumab to certolizumab pegol in patients with RA and inadequate response to the latter. The rapid decrease in disease activity seen at week 12 without unexpected or new safety signals encourages further study of bimekizumab in RA.[29]

Sonelokimab. Sonelokimab (formerly M1095, MSB0010841, and ALX-0761; Moonlake Immunotherapeutics) is a novel trivalent tandem nanobody that binds specifically to human IL-17F, both human IL-17A and IL-17A/F and human serum albumin (for plasma half-life extension); thus, it is a bispecific IL-17A and IL-17F inhibitor (Figure 1).[25] Compared to common monoclonal antibodies, nanobodies are smaller molecules with a potential for better tissue penetration.[46]

A randomized, double-blind, placebo-controlled phase I study of multiple ascending doses of subcutaneous sonelokimab has been assessed in 44 patients with moderate to severe psoriasis.[25] Patients were randomly assigned (4:1) into four ascending sonelokimab dose cohorts (30, 60, 120 or 240 mg) ($n = 8, 8, 8, 9$, respectively) or placebo ($n = 8$). Treatment was administered *via* subcutaneous injection into the abdominal wall every other week through 6 weeks (days 1, 15 and 29).[25] Marked decreases in psoriasis inflammatory markers (dermal and epidermal CD3+ cells, epidermal thickness and numbers of epidermal Ki67+ cells) and a largely dose-dependent normalization in cutaneous expression of genes coding for IL-17A, IL-17F, CCL20, CXCL1, CXCL8, defensin beta 4A, lipocalin 2, cathelicidin (LL37), and keratin 16 were observed in sonelokimab-treated patients

by day 43; by day 85, 100% and 56% of patients receiving sonelokimab 240 mg achieved PASI90 and PASI100 responses, respectively.[25] All patients (100%) treated with sonelokimab 240 mg achieved a sPGA result of minimal or clear with at least a two-level reduction in static PGA (sPGA) from baseline. All these effects were dose-dependent, and the largest decrease (95%) in BSA scores was observed in the cohort receiving sonelokimab 240 mg. Rapid onset of improvement was observed, as early as the first week of treatment.[25]

Results of the phase IIb randomized, double-blind, placebo-controlled multi-center 12-week study with an additional 40-week follow-up assessing the efficacy, safety and tolerability of sonelokimab in 313 patients with plaque psoriasis have recently been published (NCT03384745).[47] Patients with stable moderate to severe plaque psoriasis (IGA $\geqslant$3, BSA $\geqslant$10% and PASI $\geqslant$12) were randomly assigned 1:1:1:1:1 to receive placebo (n=52), sonelokimab 30 mg (n=52), sonelokimab 60 mg (n=52), sonelokimab 120 mg normal load (induction with administration at weeks 0, 2, 4 and 8) (n=53), sonelokimab 120 mg augmented load (induction with administration at weeks 0, 2, 4, 6, 8 and 10) (n=51) or secukinumab 300 mg (induction period with administration at weeks 0, 1, 2, 3, 4 and 8) (n=53).[47] This first 12-week placebo-controlled induction period was followed by a 12-week dose maintenance or escalation period, in which patients assigned to the placebo group received sonelokimab 120 mg (at weeks 12, 14, 16, and then every 4 weeks); patients receiving sonelokimab 30 mg or 60 mg with IGA score >1 were escalated to 120 mg (every 4 weeks); patients assigned to the sonelokimab 120 mg groups received it at week 12 and then every 8 weeks (normal load group) or every 4 weeks (augmented load); and patients receiving secukinumab 300 mg continued to received it every 4 weeks. Finally, a 24-week response assessment or dose-holding period was studied.[47] At week 24, patients receiving sonelokimab 30 mg and 60 mg without dose escalation, and patients in the two sonelokimab 120 mg groups (including placebo rollover patients) were eligible to stop the study drug. Patients with an IGA score $\geqslant$1 at week 24 continued on the same dosage, and those with an IGA score of 0 were started on placebo. IGA assessment was performed every 4 weeks and treatment was restarted if patients' IGA score became $\geqslant$1.[47]

The primary outcome of the study (proportion of patients in the sonelokimab groups with an IGA score of 0 or 1 at week 12 compared with the placebo group) was met, with 0/52 in the placebo group *versus* 25/52 [48.1% (34.0–62.4), $p<0.0001$] in the sonelokimab 30 mg group, 44/52 [84.6% (71.9–93.1), $p<0.0001$] in the sonelokimab 60 mg group, 41/53 [77.4% (63.8–87.7), $p<0.0001$] in the sonelokimab 120 mg normal load group, 45/51 [88.2% (76.1–95.6), $p<0.0001$] in the sonelokimab 120 mg augmented load group, and 41/53 [77.4% (63.8–87.7), $p<0.0001$] in the secukinumab 300 mg group.[47] Onset of response was quick, with 31.4% (16/51) of sonelokimab 120 mg-treated patients achieving PASI90 response by week 4. Post-hoc analysis was performed with a combined group of 142 patients in the sonelokimab 120 mg normal and load group. Sixty-nine of the 142 patients in this group had achieved IGA 0 at week 24, so sonelokimab was stopped. Sixty (87%) of them relapsed over the subsequent 4–12 weeks. After restarting sonelokimab, 47 (78.3%) patients re-achieved IGA 0 status. Regarding safety, AEs occurred in 49.5% (155 of 313) of patients, with a slightly greater incidence in the sonelokimab groups (51.4%, 107/208) at weeks 0–12. Common AEs included nasopharyngitis (13.5%), pruritus (6.7%) and upper respiratory tract infections (4.3%). During weeks 12–52, *Candida* infections were significantly higher in sonelokimab-treated patients, with 1/53 (1.9%) in the secukinumab group *versus* 19/257 (7.4%) in the sonelokimab groups. Four instances of neutropenia (<1000 cells per μL) resolved quickly without changes in sonelokimab dosing. One patient with a family history of IBD developed Crohn's disease while receiving sonelokimab 30 mg; another patient in the sonelokimab 60 mg group died of cardiopulmonary failure while asleep at home.[47]

Furthermore, sonelokimab also demonstrated improvement of arthritis and X-ray score in a preclinical model of RA.[48]

Other bispecific antibodies. Bispecific inhibitors neutralize two different cytokines through two distinct binding sites. Those tested for treatment of psoriasis in clinical trials or animal models include TNF-α/IL-17A inhibitors (COVA322 and ABT-122), IL-6/IL-23 inhibitor AZ17, and the IL-17A/IL-17F inhibitor afasevikumab (NI-1401).[26,48]

COVA 322 is a fynomer antibody, resulting from the fusion of a high-affinity IL-17A binding fynomer to the light chain of the fully human anti-TNF-α antibody, adalimumab[49] and has been explored in a single dose escalation, tolerability, safety, pharmacokinetics and efficacy phase Ib/IIa study in patients with stable chronic moderate to severe plaque psoriasis. ABT-122 has been tested in phase II trials for PsA and RA.[50,51] Results suggest that inhibition of IL-17A does not offer any contribution to TNF-α inhibition, as there were no differences in efficacy between ABT-122 and adalimumab in PsA and RA patients.[52] AZ17 was successfully tested in two relevant preclinical *in vivo* mouse models, showing greater efficacy in improving psoriasiform inflammation and epidermal thickness, as compared to individual anti-IL-6 or anti-IL-23 antibodies.[53] Whereas IL-6 acts early in the initiation phases of Th17 cell differentiation, inducing IL-23 receptor expression, IL-23 is thought to promote Th17 cell lineage stabilization, expansion, and maintenance, whereupon stimulating production of Th17 cytokines.[53] None of these drugs (COVA322, ABT-122 or AZ17) is currently being developed for treatment of psoriasis and/or PsA. Finally, phase Ia and Ib trials of afasevikumab (NI-1401), a fully human monoclonal antibody neutralizing both IL-17A and IL-17F, have been completed in healthy volunteers but no results have been released yet.[26,48]

Discussion

The importance of IL-17 cytokines in psoriasis, PsA and other chronic inflammatory diseases has been widely proved. IL-17A is the leading effector cytokine in tissue inflammation, autoimmunity and host defence, but the role of IL-17F is not insignificant. A clear example is chronic mucocutaneous candidiasis caused by a single mutation in the IL-17F gene.[54] Periodontitis, an inflammation of the gingival tissue significantly associated with psoriasis and PsA,[55] is characterized by neutrophil infiltration and increased expression of IL-17A and IL-17F.[56] Furthermore, IL-17A also plays a key role in vascular inflammation, as shown in animal models with monoclonal antibodies against IL-17A or IL-17RA and with IL-17RA or IL-17A knock-out murine models.[57] Moreover, a positive correlation has been found between circulating levels of IL-17 cytokines and severity and progression of carotid artery plaques in patients with atherosclerosis.[58]

In psoriasis, IL-17A and IL-17F are the main pro-inflammatory mediators. Currently approved therapies targeting IL-17 include IL-17A inhibitors secukinumab and ixekizumab and anti-IL-17RA brodalumab. IL-17 blockers have demonstrated superior and faster efficacy compared to previous therapies, but primary and secondary therapeutic failure are still relatively frequent.[59] Some of these non-responder patients can be successfully switched between IL-17A inhibitors – perhaps as a consequence of reinduction – but others become resistant.[60] The broader blockade of brodalumab may account for its high efficacy and speed of response, but quick relapses have been reported on treatment discontinuation; increased levels of active IL-17 cytokines on blockade of their common receptor subunit IL-17RA might provide a mechanistic explanation.[61] Dual inhibition of IL-17A and IL-17F represents a novel approach that has proved to be effective in multiple models of disease, in both preclinical and clinical studies.[36] Bispecific antibodies might bind preferentially to cells containing both targets instead of those expressing only one (avidity hypothesis),[48] and become an interesting option for patients with IL-17 signaling pathway-refractory disease.[62]

In this review we have provided a comprehensive review of the current available data on bimekizumab and sonelokimab, the first inhibitors of both IL-17A and IL-17F (albeit with different mechanisms of dual and bispecific inhibition, respectively) with significant clinical development in psoriasis. Accumulating data from phase I, II and III clinical trials have shown the superior efficacy of bimekizumab with respect to ustekinumab, adalimumab and secukinumab in psoriasis head-to-head trials. Rapid onset of improvement, with some patients showing near complete resolution of psoriasis plaques in 2 weeks, points to the superiority of dual IL-17A and IL-17F blockade over IL-12/23, TNF-α and IL-17A blockade as regards cutaneous manifestations. Maintenance dose every 8 weeks has been shown to be effective with bimekizumab, which could offer substantial advantages compared with other IL-17 inhibitors. Interestingly, sustained skin clearance beyond pharmacokinetic expectations after randomized withdrawal, heretofore considered a hallmark of specific IL-23 inhibitors, has also been observed for bimekizumab: in the randomized withdrawal phase of the BE READY trial, the median time to

loss of PASI75 response was 32 weeks after the last dose, and the corresponding value was 28 weeks for PASI90.[33,63] In addition, the efficacy of bimekizumab has been tested in patients with BSA ≤5.[36] Furthermore, in its proof-of-concept trial, sonelokimab has shown some of the highest levels of efficacy so far, achieving PASI90 in 100% of patients at day 85.[25] Moreover, results from the phase IIb study of sonelokimab suggest a more rapid effect and higher peak response than with secukinumab, although formal comparisons cannot be established.[47] Further research will provide more information on how their different mechanism of action influences the efficacy and safety of each drug.

The role of IL-17 cytokines in PsA has been demonstrated in preclinical trials, with both IL-17A and IL-17F being able to induce proinflammatory cytokines in synoviocytes, periosteum and the skin. Dual neutralization of these cytokines resulted in synergy suppressing these activator pathways.[27] Despite the encouraging results of the phase Ib proof-of-concept study,[27] BE ACTIVE[32] failed its primary endpoint. The difference between placebo group and bimekizumab 320 mg group in ACR50 response at week 12 was very close to statistical significance ($p = 0.051$); the ACR50 responses at week 12 with all other bimekizumab doses were significantly superior than placebo, albeit with nominal p values: bimekizumab 16 mg OR 4.2, 95% CI 1.1–15.2, $p = 0{\cdot}032$; bimekizumab 160 mg OR 8.1, 95% CI 2.3–28.7, $p = 0.0012$; bimekizumab 160 mg with loading dose OR 9.7, 95% CI 2.7–34.3, $p = 0.0004$).[32] Furthermore, patients included in the 320 mg bimekizumab group had a higher mean tender joint count, mean pain and patient global assessment of diseases activity scores, with a slightly higher mean body mass index than those in the other groups.[32] The primary endpoint chosen (ACR50 at week 12) was more ambitious than in other trials of IL-17 inhibitors, and the number of patients in each dose group was small, accounting perhaps for insufficient statistical power.[39] Upcoming phase III clinical trials will clarify the optimal dosing, loading dose and treatment regimes, and will arguably confirm the superiority of dual inhibition of IL-17A and IL-17F over inhibition of IL-17A alone in PsA.

Regarding safety, common concerns with IL-17 inhibitors include the induction or exacerbation of IBD and fungal infections, mainly mucocutaneous candidiasis in up to 4% of patients[64] and dermatophyte infections (probably underreported).[65] Although most trials excluded patients with a prior history of IBD, there was no increased IBD signal with dual IL-17A and IL-17F inhibition compared to IL-17A inhibition alone. As for mucocutaneous candidiasis, both bimekizumab and sonelokimab have shown numerically higher rates of oral candidiasis than currently approved IL-17 inhibitors, pointing towards the protective role of IL-17F against mucosal *Candida* infections.[64] Anyhow, most instances of candidiasis were mild to moderate and resolved with topical or oral antifungal treatment. Whether the better efficacy and faster action of these new molecules compensates for the increased incidence of candidiasis remains to be clarified, but will have to be assessed and discussed with each patient individually.

Conclusion

Throughout this text we have analyzed extensively the current evidence supporting the use of dual inhibitors of IL-17A and IL-17F in psoriasis. The main limitation of this work is that we have chosen to perform a comprehensive review instead of a systematic review. Blockade of IL-17A and IL-17F with a dual specific agent (bimekizumab) is likely to provide a fast onset and highly efficacious option for treatment of moderate to severe psoriasis and PsA, with a good safety profile and acceptable tolerability. Furthermore, phase II results with sonelokimab, a bispecific nanobody, have generated great expectations.

Author contributions

LP: conceptualization, formal analysis, supervision, validation, visualization, writing – original draft preparation, writing – review and editing.
HI: conceptualization, methodology, investigation, writing – original draft preparation, writing – review and editing.
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ORCID iDs

Helena Iznardo https://orcid.org/0000-0002-0710-5521

Lluís Puig https://orcid.org/0000-0001-6083-0952

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