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REVIEW

IL-23 Inhibitors in Psoriasis: What Have We Learnt so Far?

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Abstract: Interleukin-23 (IL-23) inhibitors represent a major advance in the management of moderate-to-severe plaque psoriasis, grounded in the central pathogenic role of the IL-23/Th17 axis. By selectively targeting the p19 subunit, guselkumab, risankizumab, and tildrakizumab effectively suppress disease-driving inflammation while preserving IL-12-mediated host defence. Pivotal randomized trials have demonstrated high levels of skin clearance, durable efficacy, and favourable safety profiles. Nevertheless, such trials only partially reflect the heterogeneous and medically complex populations treated in everyday practice. Against this background, this narrative review focuses on the expanding body of real-world evidence, which has provided novel insights into the long-term durability, drug survival, performance in difficult-to-treat anatomical sites, and safety of IL-23 inhibitors in special and comorbid populations. Real-world studies consistently confirm high effectiveness in elderly patients, individuals with multiple comorbidities, and those with extensive prior biologic exposure, as well as in challenging disease localisations such as scalp, nails, palmoplantar, genital, and pretibial psoriasis. Across large observational cohorts, IL-23 inhibitors show excellent treatment persistence, largely driven by sustained efficacy and low rates of discontinuation for adverse events. Reassuring safety profiles have also been documented in patients with a history of malignancy, latent infections, or cardiometabolic disease, together with improvements in quality of life and systemic inflammatory burden. By integrating evidence from randomized trials with large real-world cohorts, this narrative review provides a clinically oriented synthesis of the efficacy, safety, and therapeutic positioning of IL-23 inhibitors in psoriasis. Although all three agents demonstrate high and durable effectiveness, real-world data suggest subtle intraclass differences, with guselkumab and risankizumab often achieving faster or deeper early responses, and tildrakizumab offering greater dosing flexibility with comparable long-term persistence in selected patient profiles. Overall, IL-23 blockade has evolved from a highly effective trial-based strategy into a versatile and reliable long-term therapeutic approach capable of addressing unmet needs in routine clinical practice.

Keywords: psoriasis, IL-23 inhibitors, guselkumab, risankizumab, tildrakizumab, real-world evidence

Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease affecting up to 3% of worldwide population.[1] Over the last decade, significant advances in the understanding of psoriatic disease have highlighted the pivotal role of the interleukin (IL)-23/Th17 axis, which is now considered the central pathogenic driver of psoriasis.[2–5] IL-23 is a heterodimeric cytokine composed of a unique p19 subunit and the p40 subunit shared with IL-12.[2–5] While IL-12 primarily promotes Th1 differentiation and contributes to host defence, IL-23 is essential for the expansion, maintenance and pathogenic activity of Th17 cells.[2–5] Through activation of the JAK2–TYK2–STAT3 pathway, IL-23 supports the maturation and survival of Th17 lymphocytes, driving sustained production of key effector cytokines, including IL-17A, IL-17F, IL-22 and Tumor Necrosis Factor (TNF)-α.[2–5] These cytokines are involved in keratinocyte hyperproliferation and atypical differentiation, recruitment of neutrophils and other inflammatory leukocytes, aberrant epidermal signalling, and amplification of innate-adaptive immune crosstalk.[2–5] Furthermore, IL-23 not only initiates but maintains chronic inflammation

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by stabilizing tissue-resident Th17 cells and generating a durable inflammatory memory, contributing to disease persistence and recurrence.[2–5] Beyond IL-23 and IL-17, multiple cytokines contribute to the psoriatic inflammatory network. IL-17A and IL-17F are the main downstream effectors responsible for keratinocyte activation, neutrophil recruitment, and epidermal hyperproliferation, while IL-22 promotes epidermal thickening and barrier dysfunction. Tumour necrosis factor (TNF) acts as a central amplifier of inflammation by enhancing cytokine production and immune cell recruitment. Together, these mediators form a self-sustaining inflammatory loop that drives both the acute and chronic components of psoriatic disease.[2–5] In addition, increasing evidence highlights the pivotal role of tissue-resident memory T (TRM) cells in psoriasis. These long-lived lymphocytes persist in clinically resolved skin and retain the capacity to rapidly produce IL-17 and IL-22 upon re-exposure to inflammatory stimuli, thereby contributing to disease recurrence at previously affected sites. By stabilising pathogenic TRM populations, the IL-23/Th17 axis supports the formation of an "inflammatory memory" in the skin, providing a biological explanation for the chronicity and relapsing nature of psoriasis. Targeting this pathway may therefore not only clear active lesions but also reduce relapse risk and promote more durable remission, making TRM cells an emerging therapeutic focus.[2–5] Because the IL-23/Th17 axis is predominantly responsible for sustaining chronic pathogenic inflammation, the selective blockade of the IL-23p19 subunit allows targeted suppression of disease-driving pathways without compromising essential host defences.[2–5]

Currently, among selective IL-23p19 inhibitors, guselkumab, risankizumab, and tildrakizumab are the only agents approved by both the FDA and EMA for the treatment of moderate-to-severe plaque psoriasis.[6–10] Phase III clinical trials have consistently shown rapid and robust skin improvements, durable responses over time, and a high proportion of patients reaching near complete or complete clearance.[6–10]

In line with these data, real-world evidence has confirmed the performance of IL-23 inhibitors outside the controlled environment of randomized studies.[6–10] Specifically, several real-life studies, including large multicenter cohorts, national registries, and long-term observational series, have reinforced and expanded trial findings.[6–10] These data have clarified drug persistence rates, safety profiles in special populations, and determinants of treatment success or failure.[6–10] Moreover, they have highlighted the effectiveness of IL-23 inhibitors in challenging locations such as the scalp, nails, palmoplantar surfaces, genital area, and pretibial region.[6–10] This review aims to address these gaps by providing an in-depth and up-to-date synthesis of real-world evidence, with a specific focus on long-term outcomes, drug survival, and safety in special populations that are under-represented in randomized controlled trials. In this context, several clinically relevant questions arise: how do IL-23 inhibitors perform in routine practice in terms of long-term efficacy, safety, and treatment persistence? To what extent do real-world data confirm or refine results from pivotal trials? And how do these agents behave in special and clinically complex populations, such as elderly patients, individuals with multiple comorbidities, prior biologic exposure, or psoriasis affecting difficult-to-treat anatomical sites? Addressing these questions is essential to better define the clinical positioning of IL-23 inhibitors within the current biologic treatment landscape.

Methods

For this narrative review, comprehensive literature research was conducted on MEDLINE/PubMed, Google Scholar and Embase databases until November 2025. The following keywords were used to research data: "interleukin (IL)-23", "IL-23p19", "IL-23 receptor" "psoriasis", "treatment", "guselkumab", "risankizumab", "tildrakizumab". For each of the drugs, both data from published clinical trials and evidence from the real-world were evaluated. Data from clinical cases and case series were also considered. The bibliographic references of the selected manuscripts were evaluated to include articles that could have been missed. This article does not contain any studies with human participants or animals performed by any of the authors and all data discussed are from previously published research. Only studies in English were considered.

Results

Guselkumab

Guselkumab is a fully human IgG1λ monoclonal antibody that binds to the p19 subunit of IL-23 and is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. Furthermore, it is

approved for the treatment of psoriatic arthritis (PsA) in adult patients, either alone or in combination with methotrexate, and inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis.[11–13] The recommended dose for plaque psoriasis, as well as for PsA, is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks.[11–13] However, for patients at high risk of joint damage based on clinical assessment, a dosage of 100 mg every 4 weeks may be considered.[13]

Clinical Trial

Phase III clinical studies have consistently shown that guselkumab offers a strong balance between efficacy and safety in psoriasis management.[14] In the VOYAGE 1 trial (NCT02207231), the drug was well tolerated over the first treatment year and demonstrated clear superiority over the anti-TNF agent adalimumab.[15] By week 16, guselkumab significantly outperformed placebo (P <0.001), with 85.1% versus 6.9% of patients achieving an Investigator Global Assessment (IGA) score of 0/1, and 73.3% versus 2.9% reaching PASI 90. Guselkumab also surpassed adalimumab at week 16 (IGA 0/1: 85.1% vs 65.9%; PASI 90: 73.3% vs 49.7%), and these advantages persisted through week 48 (IGA 0/1: 80.5% vs 55.4%; PASI 90: 76.3% vs 47.9%). The VOYAGE 2 trial (NCT02207244) corroborated these findings and highlighted the benefits of continuous treatment versus withdrawal, as well as the efficacy of guselkumab in patients who did not respond adequately to adalimumab.[16] Long-term follow-up data indicate that guselkumab maintains high and durable clinical responses, along with sustained improvements in patient-reported outcomes for up to five years.[17] In the NAVIGATE study (NCT02203032), guselkumab demonstrated superior performance compared with ustekinumab in individuals who failed to achieve IGA 0/1 on ustekinumab. Higher proportions of patients receiving guselkumab reached PASI 90, PASI 100, and DLQI 0/1 at week 52 compared with ustekinumab, while the adverse-event profile remained comparable between the two agents, with infections being the most frequently observed events.[18,19] The ECLIPSE trial (NCT03090100) further reinforced the long-term advantages of guselkumab, showing significantly higher PASI 90 response rates at week 48 compared with the IL-17A inhibitor secukinumab (84% vs 70%; p<0.0001).[19] Additional evidence from the phase IIIb GUIDE study (NCT03818035) showed that patients with a short disease duration (SDD ≤2 years) had a greater probability of achieving super-responder (SRe) status when treated early with guselkumab.[20] SDD patients more frequently reached absolute PASI 0 at week 28 (51.8% vs 39.4%) and were more often classified as SRe (43.7% vs 28.1%; overall 34.4%). They also attained complete skin clearance more rapidly (median 141 vs 200 days).[20] Paediatric data from the PROTOSTAR trial (NCT03451851) demonstrated robust and clinically meaningful improvements in children and adolescents (≥6 to <18 years) with moderate-to-severe plaque psoriasis, with safety outcomes similar to placebo and in line with adult data.[21] Findings from cohort A of the VISIBLE study (NCT05272150) indicated that guselkumab is highly effective across diverse skin tones in individuals with skin of colour, with improvements continuing and stabilizing through week 48.[22] The SPECTREM trial (NCT06039189), a phase IIIb placebo-controlled study in patients with low body surface area involvement (2–15%) but psoriasis affecting high-impact locations (such as scalp, face, genitals, or intertriginous regions), confirmed the drug's efficacy and tolerability up to week 16.[23] Finally, data from the GAP study, a multicentre Phase II trial in 50 patients with moderate-to-severe palmoplantar pustulosis (PPP), suggested that guselkumab may offer meaningful benefit even in Caucasian populations, complementing its existing approval for PPP in Japan.[24] Pivotal and supportive clinical trials of guselkumab in psoriasis have been summarized in Table 1.

Real-World Evidence

A growing body of real-world evidence has consistently supported both the efficacy and safety of guselkumab across short- and long-term follow-up periods.[25–38] Early (16-week) real-life experiences from Fougerousse et al and Benhadou et al reported rates of PASI 100 comparable to those of Phase III trials (38.3% and 32.1% vs 37.4% in VOYAGE 1 and 34.1% in VOYAGE 2), whereas PASI 90 responses were numerically lower than in registrational studies (50.6% and 55.4% vs 73.3% in VOYAGE 1 and 70% in VOYAGE 2).[26,27] According to Fougerousse et al, these differences may reflect a lower baseline disease severity and a higher proportion of patients with previous biologic exposure.[26] Benhadou et al found no significant differences between biologic-naïve and biologic-experienced patients in achieving PASI 100, PASI 90 or PASI 75.[27] Long-term real-world data have also yielded favourable outcomes.[29–37] An Italian retrospective

Table 1 Pivotal and Supportive Clinical Trials of Guselkumab in Psoriasis

Trial	Phase	Population	Number of Patients (Arms)	Study Period	Primary Endpoint	Main Outcome
VOYAGE-1	Phase III	Adults, moderate-to-severe plaque psoriasis	GUS n=329; PBO→GUS n=174; ADA n=334	W0–48	IGA 0/1 and PASI90 at W16	GUS superior to placebo and adalimumab; PASI90 73.3% vs 49.7% (ADA) at W16; maintained through W48
VOYAGE-2	Phase III	Adults, moderate-to-severe plaque psoriasis	GUS n=496; PBO→GUS n=248; ADA n=248 (ADA-NR switched to GUS; GUS responders randomized to maintenance vs withdrawal)	W0–48 (with withdrawal/ retreatment from W28)	IGA 0/1 and PASI90 at W16	GUS superior to placebo and ADA; better maintenance vs withdrawal; 66.1% of ADA-nonresponders achieved PASI90 after switch
NAVIGATE	Phase III	Adults with inadequate response to ustekinumab	OL UST n=871; randomized: UST→GUS n=135; UST-cont n=133	W0–52	IGA 0/1 with ≥2-grade improvement (W28–40)	Switching to GUS superior to continuing UST; higher PASI90/100 and DLQI0/1 at W52
ECLIPSE	Phase III	Adults, moderate-to-severe plaque psoriasis	GUS n=534; SEC n=514	W0–56 (primary at W48)	PASI90 at W48	GUS superior to secukinumab (84% vs 70% PASI90 at W48)
PROTOSTAR	Phase III	Paediatric (6–17 y) moderate-to-severe plaque psoriasis	Part 1: GUS vs PBO vs ETN (n=92); Part 2 OL-GUS (n=28)	W0–52	IGA0/1 and PASI75 (± PASI90) at W16	GUS superior to placebo; PASI90 56% at W16; sustained responses to W52 with favourable safety
SPECTREM	Phase IIIb	Low-BSA (2–15%) moderate plaque psoriasis with high-impact sites	GUS n=225; PBO n=113	W0–16	IGA 0/1 at W16	GUS superior; IGA0/1 74.2% vs 12.4%; strong clearance in scalp, face, genitals, intertriginous
GAP	Phase II	Palmoplantar pustulosis (PPP)	GUS (single-arm) n=50	W0–24	Δ PPPASI at W24	Median PPPASI −59.6%; PPPASI50 66%, DLQI improved

Notes: PBO→GUS, ADA→GUS, UST→GUS indicate switch to guselkumab after inadequate response. Withdrawal in VOYAGE-2 indicates temporary discontinuation of guselkumab followed by retreatment after loss of response.

Abbreviations: GUS, guselkumab; PBO, placebo; ADA, adalimumab; UST, ustekinumab; SEC, secukinumab; ETN, etanercept; NR, non-responders; OL, open-label; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PPPASI, Palmoplantar Pustulosis Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index.

multicentre study with 60-week follow-up showed PASI 75, PASI 90, and PASI 100 rates of 100%, 96.8%, and 83.9%, respectively, and confirmed guselkumab effectiveness even in individuals with ≥2 prior biologic failures, BMI >30, multiple comorbidities, or involvement of difficult anatomical sites.[32] In a 104-week monocentric cohort of 102 patients, PASI 90 and PASI 100 were reached by 79.63% and 61.11% of patients, with overweight and obese individuals showing response rates comparable to those of normal-weight subjects. No differences emerged between bio-naïve and bio-experienced subgroups, and no major safety concerns were detected.[33] Similar findings were reported by Snast et al, who studied patients previously exposed to multiple biologics: 62% achieved PASI 90 without adverse events.[34] Conversely, Del Alcázar et al observed that obesity (BMI ≥30) and extensive prior biologic exposure reduced the probability of achieving PASI ≤2 at week 24.[36] Valenti et al further documented sustained long-term efficacy and good tolerability of

guselkumab irrespective of concomitant psoriatic arthritis (PsA).[39] Multiple real-world studies have confirmed the utility of guselkumab in PsA, including patients with axial involvement.[40,41] Five large non-interventional European studies, PERSIST,[42] G-EPOSS,[43] GULLIVER,[44] SPRING,[45] and the Nordic cohort by Tskhvarashvili et al,[46] collectively involving more than 1400 treated patients, expanded evidence on both traditional and non-traditional outcomes.[25] These studies encompassed heterogeneous populations: long-term follow-up of moderate-to-severe plaque psoriasis with subgroup analyses for biologic-naïve versus biologic-experienced patients (PERSIST); individuals with nail or anogenital disease with specific assessments of QoL, sexual function and stigma (G-EPOSS); facial and genital psoriasis (GULLIVER); persistence-focused analyses (SPRING); and a large Scandinavian bio-naïve cohort used to compare drug survival across systemic therapies (Tskhvarashvili). Guselkumab also showed improvements in sexual dysfunction and perceived stigmatization,[43] as well as favourable outcomes in sensitive sites under-represented in RCTs.[44] Medina-Catalán et al evaluated 35 patients with biologic-refractory psoriasis, most of whom had prior anti-TNF exposure (77.1%), especially adalimumab (42.9%).[38] Median PASI decreased from 11 (7.3–15.9) at baseline to 0 (0–1.4) at first follow-up; 94.1% achieved PASI ≤5, 82.4% PASI ≤2, and 55.9% PASI 0, with significant improvements in PASI, BSA and DLQI ($p<0.001$). Real-life experiences have also confirmed effectiveness in individuals who previously failed anti-IL-12/23 and/or anti-IL-17 agents.[47–51] In a 52-week single-centre study enrolling 13 patients, 46.1% had prior ustekinumab exposure and 69.2% had failed anti-IL-17 therapy (secukinumab 38.5%, ixekizumab 30.8%, both 38.5%). Mean baseline PASI dropped from 13.2 ± 6.8 to 0.5 ± 0.7 at week 52 ($p <0.001$), while BSA improved from 22.3 ± 10.5 to 0.8 ± 1.1 ($p <0.001$). Responses were similar regardless of prior anti-IL-12/23 or anti-IL-17 use.[47] Additional long-term data from a monocentric cohort of 61 patients with prior anti-IL-17 failure (secukinumab n=30, ixekizumab n=21, brodalumab n=7, dual failure n=3) confirmed sustained improvement over 104 weeks: PASI decreased from 12.8 ± 8.4 (baseline) to 3.3 ± 2.9 (week 16), 1.4 ± 1.8 (week 52), and 1.0 ± 1.4 (week 108; all $p<0.0001$). PASI 90/PASI 100 rates were 60.7%/37.7% at week 16, 72.1%/52.5% at week 52, and 73.8%/59.0% at week 104. Marked improvements were noted in difficult anatomical sites by week 104: scalp (−98.5%), palms/soles (−93.2%), genitals (−98.2%), and nail NAPSI (−91.6%).[51] Treatment was well tolerated, with no severe adverse events and only six discontinuations (1.6% primary failure; 8.2% secondary).[51] Supporting evidence from Berenguer-Ruiz et al also confirmed guselkumab effectiveness after ustekinumab failure,[50] whereas Ryoo et al observed that ustekinumab may offer greater itch relief despite guselkumab's superior cutaneous efficacy.[52] A multicentre study of 233 ustekinumab-inadequate responders followed for 104 weeks after switching to guselkumab reported high response rates: at week 52, PASI 75/90/100 were achieved by 89.88%, 71.43% and 58.83%, and 90.48% reached absolute PASI ≤2, with comparable outcomes maintained through week 104. Early responses were lower in obese individuals and those with difficult-to-treat areas, but these differences disappeared at later timepoints.[53] An Italian retrospective analysis of 28-week follow-up comparing guselkumab, risankizumab and tildrakizumab found all three anti-IL-23 agents similarly effective and safe in real-world practice, with guselkumab and risankizumab showing slightly faster improvements, particularly in palmoplantar disease, than tildrakizumab.[54] Finally, a large Italian longitudinal study across ten centres evaluated 1008 patients treated with guselkumab for ≥20 weeks.[55] Complete clearance at week 20 was achieved by 581 (57.6%) patients classified as super-responders (SRe). Multivariate analysis identified obesity (OR 0.74), prior biologic exposure (OR 0.57), and higher baseline PASI (OR 0.97) as independent negative predictors of SRe status. Long-term outcomes favoured SRe patients, with PASI 100 rates of 93.3% at week 52, 85% at year 4, and 83.4% at year 5, compared to 30.5%, 54% and 59.2% in non-super-responders (nSRe). Discontinuation rates were low (9.6%) and significantly lower in SRe versus nSRe (7.0% vs 13.1%, $p=0.001$); adverse events were infrequent (0.6%).[55]

Safety

Pooled safety analyses from seven phase II/III clinical trials, including 2891 patients with psoriasis and up to five years of treatment (8662 patient-years), showed that the overall incidence of adverse events with guselkumab was comparable to placebo and remained stable throughout long-term follow-up.[56] In the extended monitoring of VOYAGE 1 and VOYAGE 2 up to week 264, Reich et al found that the most frequently reported adverse events (occurring in >10% of participants) were nasopharyngitis, upper respiratory tract infections (URTIs), hypertension, and arthralgia.[17] In the ECLIPSE trial, the spectrum of adverse events was similar between guselkumab and secukinumab; however, Candida

infections (6% vs 2%) and tinea (5% vs 2%) were slightly more common in the secukinumab group.[57] Likewise, in the NAVIGATE study, infections represented the most common category of adverse events, occurring at comparable rates between guselkumab and ustekinumab. Only one serious infection was reported in the guselkumab arm, and injection-site reactions were infrequent.[18] The PROTOSTAR paediatric trial similarly documented nasopharyngitis, URTIs, and COVID-19 as the most common adverse events, with no serious or opportunistic infections observed in children or adolescents.[21] Real-world studies, typically smaller, retrospective, and often involving special patient populations, have consistently shown that guselkumab is well tolerated. The adverse events most often reported mirror those of clinical trials (nasopharyngitis, flu-like symptoms, URTIs), although real-life cohorts generally report lower overall frequencies.[57] Rare events have been described, including a case of transverse myelitis following treatment for severe plaque psoriasis.[58] Safety data in patients with concomitant infections have also been reported. A Chinese multicentre cohort suggested that guselkumab can be used in individuals with latent tuberculosis infection (LTBI) or inactive hepatitis B virus (HBV) infection without major safety issues.[59] Nonetheless, a case of cavitary pulmonary tuberculosis during guselkumab therapy has been described in a 38-year-old man with chronic hepatitis B treated with tenofovir and a family history of tuberculosis.[60] Reactivation of chronic hepatitis C virus (HCV) infection has been reported as well,[61] although multiple real-life studies have shown the drug to be safe in patients with HBV or HCV infection.[28,62] According to Huang et al, antiviral prophylaxis is advisable for HBsAg-positive psoriasis patients receiving guselkumab, accompanied by periodic monitoring of viral load and alanine aminotransferase levels to minimise reactivation risk.[62] A large cohort analysis of 13,699 individuals with psoriasis found that IL-23 inhibitors, particularly guselkumab (the most commonly used agent in this class), were associated with the lowest risk of paradoxical eczema among all biologic categories. Compared with TNF inhibitors, IL-23 inhibitor exposure significantly reduced this risk, supporting a favourable safety profile for this class.[63]

Difficult-to-Treat Areas

Multiple real-world studies have shown that guselkumab provides robust clinical improvement in psoriasis affecting difficult-to-manage anatomical sites, including palmoplantar, facial, scalp, nail, and genital regions.[42,44,64–67] These findings align with signals of efficacy already noted in randomized controlled trials (RCTs).[23,68,69] Among these real-life investigations, the GULLIVER study represents the largest observational cohort specifically evaluating facial and genital psoriasis, with 351 patients included in the effectiveness analysis. At Week 12, 83.3% of patients with facial involvement and 76.5% of those with genital disease achieved the primary endpoint of sPGA 0/1. Data from the PERSIST study further indicated that guselkumab outperformed ustekinumab in improving scalp psoriasis.[42] IL-23 inhibitors are frequently employed for scalp involvement, and although their onset of action may be slower than that observed with anti-IL-17 agents, they generally provide more sustained long-term control of scalp lesions.[70]

Special Populations

Patients with a current or past history of malignancy are generally excluded from randomized controlled trials, making real-world data essential for clinical decision-making in this population.[71,72] A multicentre cohort evaluating guselkumab in individuals with psoriasis and active or prior cancer reported marked and durable improvements in PASI, BSA and DLQI by week 52. Importantly, no cases of tumour progression or recurrence occurred during follow-up, and even patients with active malignancy at baseline did not show signs of oncologic worsening. Guselkumab therapy was also uninterrupted and uncomplicated in the two patients who developed new malignancies during treatment.[72] These findings are in line with other real-life studies, which similarly support both the safety and efficacy of guselkumab in patients with oncological comorbidities.[72–75] Evidence from case series further indicates that guselkumab can be safely used to treat immune checkpoint inhibitor–associated psoriasis, offering effective control without jeopardising cancer immunotherapy outcomes.[76,77] Mortato et al additionally described the favourable safety profile of guselkumab in psoriatic patients with a history of cancer, infectious comorbidities (including HBV, HCV, LTBI and HIV, with no reactivation over a follow-up of 122–188 weeks), and cardiovascular disease.[78] In four Italian centres, guselkumab and risankizumab showed long-lasting clinical effectiveness in HIV-positive patients, with no negative effects on viral load or immune parameters.[79] Since HIV infection can trigger or exacerbate psoriasis, the combination of antiretroviral therapy with guselkumab has

been proposed as a viable option for refractory cases unresponsive to standard treatments.[80] Guselkumab has also demonstrated strong safety and effectiveness in elderly patients with psoriasis.[81,82] This evidence has recently been strengthened by a dedicated real-world study by Fratton et al, which evaluated 66 patients aged ≥65 years treated with guselkumab and followed for up to 104 weeks. In this cohort, mean PASI decreased from 13.3 at baseline to 1.0 by week 24 and remained stable through week 104. High rates of sustained response were observed, with PASI90 and PASI100 achieved by 83.9% and 71.0% at week 36 and maintained in 69.2% and 61.5% of patients at week 104, respectively.[83] Multivariable analyses identified baseline PASI, eosinophil-to-lymphocyte ratio, and early treatment response as predictors of long-term outcomes, while chronic beta-blocker or low-dose aspirin use also influenced PASI90 and PASI100 responses at week 52.[83] Treatment-emergent adverse events occurred in 16.7% of patients, leading to discontinuation in 9.1%, and eczematous or urticarial reactions were associated with higher baseline eosinophils and eosinophil-to-lymphocyte ratio.[83] While patient-specific characteristics such as BMI may influence relative response rates to biologics, Armstrong et al reported that overweight and obese individuals treated with guselkumab achieved absolute improvements comparable to those observed in patients with lower BMI, despite being less likely to reach relative endpoints.[84] Lin et al found that in overweight or obese patients, secukinumab produced superior responses at week 16, whereas guselkumab surpassed secukinumab by week 24.[85] Beyond cutaneous outcomes, IL-23 inhibitors may exert beneficial metabolic effects. Yıldız et al observed reductions in atherogenic dyslipidaemia and insulin resistance with guselkumab and risankizumab, suggesting a potential protective role in cardiovascular and cerebrovascular risk modulation.[86] Successful use of guselkumab has also been described in a patient with concomitant psoriasis and amyotrophic lateral sclerosis.[87] Additional single case reports document its efficacy in erythrodermic psoriasis, generalized pustular psoriasis, and in plaque psoriasis complicated by severe psychiatric comorbidity.[88,89]

Drug Survival

An analysis from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR), covering data from November 2007 to June 2023, showed that guselkumab and risankizumab demonstrated the most favourable drug survival for effectiveness among available biologics, with a safety profile comparable to ustekinumab and superior to other agents included in the registry. These findings reinforce IL-23p19 inhibitors as strong candidates for long-term psoriasis management.[90] In line with this, a two-year real-world evaluation by Strober et al found that treatment persistence was significantly longer for guselkumab than for adalimumab and secukinumab, and showed numerically longer durability compared with ixekizumab in both biologic-naïve and biologic-experienced patients.[91] Long-term outcomes were also supported by a three-year real-world study by Megna et al involving 31 patients with moderate-to-severe psoriasis. Mean PASI decreased from 16.4 ± 6.2 at baseline to 0.6 ± 0.9 at week 144, with 77.4% achieving PASI90 and 58.1% PASI100 by the end of follow-up. Treatment discontinuation occurred in six patients (19.3%), one due to primary failure and five to secondary inefficacy. No serious adverse events were observed, and mild events (pharyngitis 22.6%, headache 16.1%, flu-like symptoms 16.1%) did not necessitate withdrawal of therapy.[92] The most extensive real-world dataset available to date comes from Mortato et al, who analysed 1084 patients treated with guselkumab over five years. The drug produced rapid and sustained PASI improvements, with treatment continuation rates of 95.85%, 91.73%, 89.74%, 87.08%, and 85.76% at 12, 24, 36, 48, and 60 months, respectively.[93] Predictors of discontinuation included female sex, use of ≥3 previous biologics, longer disease duration, and prior anti-IL-17 therapy. Comorbidities did not significantly influence drug survival. Overall, persistence remained high throughout the five-year period, supporting the versatility and long-term reliability of guselkumab in diverse and complex patient populations.[93]

Risankizumab

Risankizumab is a humanised IgG1 monoclonal antibody directed against the p19 subunit of IL-23, thereby inhibiting IL-23–mediated pro-inflammatory cytokine signalling.[94] Its use is authorised in multiple regions worldwide, including the United States, Japan and the European Union, for systemic therapy of moderate-to-severe plaque psoriasis. In Japan, the drug also carries additional indications for generalised pustular psoriasis, erythrodermic psoriasis and palmoplantar pustulosis (PPP).[94] Beyond psoriasis, risankizumab has received approval for psoriatic arthritis (either as monotherapy or in combination with methotrexate) and for inflammatory bowel diseases such as Crohn's disease and ulcerative colitis.[95–

[97] For plaque psoriasis, the recommended regimen consists of 150 mg administered subcutaneously at baseline, at week 4, and subsequently every 12 weeks.[95,97]

Clinical Trials

Risankizumab has shown superior clinical efficacy compared with both placebo and ustekinumab in the phase III trials UltIMMa-1 (NCT02684370) and UltIMMa-2 (NCT02684357) involving patients with moderate-to-severe plaque psoriasis.[98] In UltIMMa-1, by week 16, PASI 90 responses were achieved in 75.3% of individuals receiving risankizumab, compared with 4.9% and 42.0% of those treated with placebo and ustekinumab, respectively. sPGA 0/1 was likewise reached by 87.8%, 7.8%, and 63.0% of patients in the respective treatment arms. Similar trends were reported in UltIMMa-2, where week-16 PASI 90 rates were 74.8%, 2.0%, and 47.5%, and sPGA 0/1 rates were 83.7%, 5.1%, and 61.6%, for risankizumab, placebo, and ustekinumab, respectively. Complete skin clearance (PASI 100 and sPGA 0) also occurred significantly more often with risankizumab. The onset of efficacy was rapid, continued to improve with each 12-week maintenance dose, and remained stable through week 52.[98]

Additional evidence from the IMMhance trial (NCT02672852) demonstrated risankizumab superiority over placebo through week 16 and maintained benefits even after treatment withdrawal over a two-year period.[99] Long-term outcomes from the LIMMitless open-label extension (NCT03047395) further confirmed sustained, high-level efficacy and favourable tolerability for up to six years of continuous treatment.[100]

Head-to-head trials have similarly highlighted risankizumab's strong performance. IMMvent (NCT02694523), IMMerge (NCT03478787), and IMMpulse (NCT04908475) each showed risankizumab to be superior to adalimumab, secukinumab, and apremilast, respectively, in managing moderate-to-severe plaque psoriasis.[101–103]

The phase IIIb IMMprint trial (NCT04713592) demonstrated its effectiveness in palmoplantar psoriasis: 33.3% of participants achieved the primary endpoint (ppIGA 0/1) at week 16, and the treatment was well tolerated.[104] In the IMMbrace study (NCT03219437), risankizumab outperformed methotrexate at week 28, PASI 90 rates of 84.0% vs 35.4% ($p < 0.001$) and sPGA 0/1 rates of 90.0% vs 64.6% ($p \leq 0.001$), with efficacy maintained and no new safety concerns up to week 112.[105]

Real-world relevance was further explored in the aIMM multicentre Phase 3b study, enrolling 244 adults with moderate-to-severe psoriasis who had exhibited suboptimal response to secukinumab (149/244; 61.1%) or ixekizumab (95/244; 38.9%) and were directly switched to risankizumab 150 mg.[106] The primary endpoint, sPGA 0/1 at week 16, was reached by 57.4% of patients, with complete clearance (sPGA 0) in 20.5%. Responses continued improving through week 52, with absolute PASI outcomes of PASI ≤3 in 66.0%, PASI ≤1 in 37.5%, and PASI 0 in 26.7% of patients. Individuals with ≤2 prior biologics achieved higher sPGA 0/1 rates at week 52 (67.0%) than those with >2 biologics (46.4%).[106] Safety findings aligned with the known profile: 67.2% experienced treatment-emergent adverse events (mostly mild), 18 (7.4%) had severe events, 17 (7.0%) had serious adverse events, and 8 (3.3%) discontinued due to adverse events. The most common TEAEs included COVID-19 (8.6%) and nasopharyngitis (5.7%).[106] Pivotal and supportive clinical trials of risankizumab in psoriasis have been summarized in Table 2.

Real-World Evidence

Short-term real-world data (16 weeks) consistently highlight the strong efficacy and favourable safety profile of risankizumab in routine clinical practice.[107–110] Hansel et al reported PASI 75/90/100 rates comparable to phase III trials; while PASI 90 (63.2%) was slightly lower than values observed in registrational studies (72.0–75.3%), PASI 100 was achieved in 49.1% of patients, similar to UltIMMa-2 (50.7%) and exceeding results from UltIMMa-1 (35.9%) and IMMvent (40.0%).[107] In a smaller cohort of 14 patients, Megna et al found a reduction in mean PASI from 12.3 ± 5.2 at baseline to 2.7 ± 1.7 at week 16 ($p < 0.001$). Over half of the cohort (57.1%) had scalp, nail, or palmoplantar involvement, two patients in all three regions, and marked improvement was observed across these difficult-to-treat areas.[108] A multicentric analysis by Rivera-Díaz et al further revealed that short-term outcomes with risankizumab were not influenced by demographic variables (age, sex, BMI, biologic history) or disease characteristics (duration, baseline PASI).[110]

Table 2 Pivotal and Supportive Clinical Trials of Risankizumab in Psoriasis

Trial	Phase	Population	Arms (Including Switch/ Withdrawal)	Study Period	Primary Endpoint	Main Outcome
UltIMMa-1	Phase III	Adults, moderate-to-severe plaque psoriasis	RZB n=304; UST n=100; PBO→RZB n=102	W0–52	PASI90 & sPGA0/1 (W16)	RZB superior to placebo and ustekinumab (PASI90 75.3% vs 42.0%)
UltIMMa-2	Phase III	Adults, moderate-to-severe plaque psoriasis	RZB n=294; UST n=99; PBO→RZB n=98	W0–52	PASI90 & sPGA0/1 (W16)	RZB superior to placebo and ustekinumab (PASI90 74.8% vs 47.5%)
IMMvent	Phase III	Adults, moderate-to-severe plaque psoriasis	RZB n=301; ADA n=304; ADA→RZB n=53; ADA-cont n=56	W0–44	PASI90 & sPGA0/1 (W16); PASI90 (W44)	RZB superior to ADA; switch ADA→RZB yielded PASI90 66% vs 21%
IMMhance	Phase III	Adults, moderate-to-severe plaque psoriasis	RZB n=407; PBO→RZB n=100; W28 responders rerandomized: RZB-maint n=111; withdrawal n=225	W0–104	PASI90 & sPGA0/1 (W16); sPGA0/1 (W52)	Maintenance superior to withdrawal through 2 years
LIMMitless	Phase III OLE	Adults from UltIMMa-1/2	RZB continuous n=525	W0–256	PASI90/100; site-specific clearance	Durable responses to 5 years; nail, scalp and palmoplantar clearance >81–97%
IMMerge	Phase III	Adults, moderate-to-severe plaque psoriasis	RZB n=164; SEC n=163	W0–52	PASI90 (W16 non-inf; W52 sup)	RZB non-inferior at W16 and superior to secukinumab at W52
IMMpulse	Phase IV	Moderate plaque psoriasis (systemic-eligible)	RZB n=118; APR n=234; APR→RZB n=83; APR-cont n=78	W0–52	PASI90 & sPGA0/1 with ≥2-grade improvement (W16)	RZB superior; switch APR→RZB PASI90 72.3% vs 2.6%
IMMbrace	Phase III	Moderate-to-severe plaque psoriasis	RZB n=50; MTX n=48	W0–112	PASI90 & sPGA0/1 (W28)	RZB superior to methotrexate; sustained efficacy
IMMprint trial	Phase III	Palmoplantar psoriasis	RZB n=87; PBO n=87	W0–52	ppIGA0/1 (W16)	RZB superior; PPASI75/90/100 significantly higher
aIMM	Phase IIIb	SEC/IXE inadequate responders	SEC/IXE→RZB n=244	W0–52	sPGA0/1 (W16)	57.4% at W16, 62.3% at W52; QoL improved

Notes: PBO→RZB, ADA→RZB, APR→RZB, SEC/IXE→RZB indicate switch to risankizumab after inadequate response. Withdrawal in IMMhance indicates temporary discontinuation after response.

Abbreviations: RZB, risankizumab; PBO, placebo; ADA, adalimumab; UST, ustekinumab; SEC, secukinumab; IXE, ixekizumab; APR, apremilast; MTX, methotrexate; OLE, open-label extension; sPGA, static Physician's Global Assessment; PASI, Psoriasis Area and Severity Index; PPASI, Palmoplantar Psoriasis Area and Severity Index; ppIGA, palmoplantar IGA.

Mid-term and long-term real-life studies have reinforced these findings.[111–118] In a multicentre observational study by Ruiz-Villaverde et al, 78 patients completed at least 12 weeks of therapy, and 42 reached week 52. At week 52, 92.5% achieved PASI 90 and 78.5% PASI 100. In terms of absolute PASI, 78.5% reached PASI 0, 85.7% PASI ≤1, and all

patients achieved PASI ≤3, indicating complete disease control.[112] Similarly, a retrospective multicentre study of 73 adults reported PASI 75/90/100 responses of 89.0%, 71.2%, and 56.2% at week 16, rising to 93.2%, 84.9%, and 63.0% at week 52. Drug survival at week 52 was high (89.0%), with only 10.9% discontinuations, mainly due to secondary inefficacy. No serious AEs were observed and mild, infrequent TEAEs predominated.[119]

Large-scale Italian real-world evidence (1047 patients, 156-week follow-up) confirmed a continuous improvement across all clinical endpoints.[115] At week 52, PASI 90/100 rates were comparable or slightly superior to those reported in UltIMMa-1 and UltIMMa-2. PASI 90 was achieved by 81.5% at week 52, 89% at week 104, and 99.1% at week 156. Complete clearance (PASI 100) was reached by 65.7%, 73.7%, and 74.8% at years one, two, and three, respectively. Interestingly, the patient population resembled that of the phase III trials in demographics and BMI, yet had a higher proportion of bio-experienced patients (42.6% vs 34% in UltIMMa-1) and significantly more prior anti-IL-17 exposure, both underrepresented in the RCT setting.[115]

Multiple real-world studies also indicate that prior anti-IL-17 therapy does not diminish response to risankizumab.[113,120,121] Selçuk et al similarly found that both risankizumab and guselkumab were effective regardless of prior biologic class (anti-TNF, anti-IL-17, anti-IL-12/23) and that outcomes were not affected by obesity, sex, or comorbidities.[122] Ruggiero et al confirmed comparable efficacy and safety profiles for risankizumab and guselkumab at week 44, with similar PASI 90/100 rates and discontinuation rates.[123]

Bagit et al provided further insight into intraclass switching by documenting favourable long-term outcomes of risankizumab in patients who had previously failed guselkumab, supporting IL-23 inhibitor switching as a viable therapeutic strategy.[124] Caldarola et al also emphasised the benefit of IL-23 intraclass switching: in their cohort of 116 patients (120 switches), most transitions were from guselkumab (45.0%) or tildrakizumab (44.2%) to risankizumab (70.0%). Switching from risankizumab was associated with lower PASI 90 responses at weeks 16 and 36, whereas switching to risankizumab yielded higher PASI 90 at week 16.[125]

Akdogan et al found that early response at three months strongly predicted long-term outcomes at 12 months, with a 94.9% likelihood of sustained response among early responders, highlighting early clinical improvement as a valuable indicator for personalised treatment decisions.[126] Another 44-week retrospective comparison of guselkumab (n = 23) and risankizumab (n = 21) showed highly similar clinical performance: at week 28, PASI 90 was 69.6% vs 61.9% and PASI 100 was 39.1% vs 33.3%, while week 40–44 PASI 90 rates were 73.9% vs 66.6%, and PASI 100 was 43.5% vs 42.8%. Adverse events were mild, and discontinuation rates remained low (8.7% vs 4.8%).[127]

Finally, the long-term IL-PSO real-life analysis confirmed durable risankizumab effectiveness and identified a distinct super-responder (SR) profile. Among 1047 patients with at least one post-baseline visit (out of 1572 treated), PASI 90 rates reached 81.4% at week 52, 89% at week 104, and 99.1% at week 156; PASI 100 occurred in 65.7%, 73.7%, and 74.7% at the same time points. Key positive predictors included bio-naïve status (week-52 PASI90: OR 2.38; PASI100: OR 1.91) and short disease duration <2 years (week-52 PASI100: OR 2.05), whereas involvement of difficult-to-treat areas and cardiometabolic disease negatively influenced complete clearance.[128]

Safety

Comprehensive pooled analysis of safety data from 17 completed or ongoing clinical trials of risankizumab in moderate-to-severe psoriasis, encompassing 3072 treated patients and 7927 patient-years (PY) of exposure, confirmed that the drug is appropriate for long-term management.[129] Across extended treatment durations, the incidence of serious adverse events was 7.8 per 100 PY; serious infections occurred at a rate of 1.2 per 100 PY; non-melanoma skin cancers (NMSC) at 0.7 per 100 PY; malignant tumours excluding NMSC at 0.5 per 100 PY; and adjudicated major adverse cardiovascular events at 0.3 per 100 PY. No new or unexpected safety signals emerged, and the majority of these frequencies aligned with those observed in the PSOLAR registry.[129] The most common adverse events reported in randomized trials were upper respiratory tract infections, nasopharyngitis, headache, and arthralgia.[130]

Both short-term and long-term safety have been consistently confirmed in real-world settings.[131–133] In their real-life evaluation, Ständer et al noted no clinically meaningful safety concerns associated with risankizumab.[131] Raimondo et al further demonstrated that risankizumab is safe and effective for psoriasis patients with latent tuberculosis infection (LTBI). Among 39 LTBI patients, 24 (61.5%) underwent TB prophylaxis and 15 (38.4%) did not. At week 52, all patients

underwent repeat QuantiFERON testing and chest radiography, and no cases of active tuberculosis were identified in either group. Treatment effectiveness remained high, with PASI 100, PASI 90, and PASI 75 achieved in 63%, 89%, and 100% of LTBI patients, respectively.[134]

Likewise, multiple studies have confirmed that risankizumab is safe in the context of viral hepatitis.[135,136] In a real-world cohort by Ciolfi et al, none of the 26 HBV-infected patients (42.3% with chronic HBV, 26.9% with serological evidence of prior or occult infection, 30.8% with resolved infection) experienced viral reactivation or elevations in liver function tests. Similarly, none of the 23 patients with HCV exhibited increases in liver enzymes or viral load during treatment.[135]

A rare adverse event was described by Vinod et al, who reported a case of severe epistaxis temporally associated with risankizumab initiation and resolving upon discontinuation, suggesting a potential causal association.[137] Additionally, risankizumab has been successfully employed in managing severe psoriasis flare-ups triggered by COVID-19 infection, demonstrating both efficacy and good tolerability in this setting.[138]

Difficult-to-Treat Areas

Multiple real-world studies have demonstrated that risankizumab is effective in psoriasis affecting sensitive or otherwise difficult-to-treat anatomical regions.[139–141] In the VESPA study, patients with very severe plaque psoriasis and involvement of challenging sites, including scalp, palms/soles, genital areas, and nails, were treated with risankizumab. Baseline disease severity was high, with a mean PASI of 35.1 ± 5.1. Marked improvement was already evident by week 16 (PASI 3.0 ± 4.3, $p < 0.001$) and persisted through week 104, when the mean PASI further decreased to 0.3 ± 0.8 ($p < 0.001$). Parallel improvements were observed in both PGA and DLQI scores.[139]

Recent evidence has also identified the lower limbs, particularly the pretibial region, as an emerging difficult-to-treat site, often representing the last area of residual activity even in patients on biologic therapy.[142,143] Bernardini et al reported that risankizumab can induce substantial improvement in recalcitrant pretibial plaques, supporting its utility in this newly recognised problematic location.[143]

Furthermore, Caldarola et al performed a retrospective study involving 16 patients with palmoplantar psoriasis, showing progressively increasing ppPASI90 responses throughout follow-up: 18.7% at week 4, 62.2% at week 16, 75.0% at week 28, and 81.2% at week 52.[140]

Special Populations

Sousa et al analyzed a small sample of 14 patients with a history of malignancy (the median interval between cancer diagnosis and initiation of risankizumab was 6.70 years [range, 0.17–20.25 years] and 43% of the patients initiated risankizumab within 5 years of their cancer diagnosis), demonstrating no cases of malignancy progression in patients who initiated risankizumab, either within or beyond 5 years of their cancer diagnosis.[144] This safety profile is consistent with other findings in the literature. A case of regression of human papillomavirus-associated high-grade vaginal intraepithelial neoplasia was described after switching from ustekinumab to risankizumab in a psoriasis patient.[145] Risankizumab was also effective and safe in a patient with psoriasis and liver transplant patient with recurrent metastatic hepatocellular carcinoma.[146] Several case series also report the efficacy and safety of risankizumab in the treatment of immunotherapy-induced psoriasis in cancer patients.[147–150] Several studies demonstrated that high BMI values can negatively impact on the treatment response to biologics.[151] However, risankizumab seems to be a promising therapeutic approach in obese patients. A monocentric study by Rompoti et al compared 54 overweight (25 kg/m2 ≥ BMI < 30 kg/m2) and 37 normal-weight (BMI < 25 kg/m2) patients under risankizumab treatment, with no statistically significant differences in the drug survival observed between two groups.[151–153] Koumprentziotis reported a sustained efficacy and persistence along with a favorable safety profile in elderly patients (≥65 years) with psoriasis over a three-year period of treatment with risankizumab, as PASI75 response rates increased from 77.4% at week 12 to 90.9% at week 52 and remained stable at 90.5% by week 156.[154] Real-life experiences confirmed efficacy and safety of risankizumab in elderly patients, which are often excluded from RCTs.[154,155] A case series by Orsini et al supported the role of risankizumab as a safe and effective option for psoriasis amongst patients living with HIV.[156] A 3-year retrospective study by Ibba et al including 333 patients treated with risankizumab for at least one year reported that patients with cardiometabolic

comorbidity (CMDs) showed comparable rates of PASI90 and PASI100 to those without CMDs.[157] Several case reports have also confirmed the efficacy and safety of risankizumab in the treatment of erythrodermic psoriasis,[158–160] Lapière's circinate generalized psoriasis,[161] and pustular psoriasis, both generalised and palmoplantar.[162–164]

Drug Survival

In a large Italian real-world cohort, Gargiulo et al analysed 1047 patients from 17 referral centres who had received risankizumab according to national plaque psoriasis guidelines and had attended at least one follow-up visit.[115] At three years, drug persistence remained remarkably high, with 90.73% of patients (CI 88.44–92.58%) still on treatment. Notably, drug survival did not differ according to BMI, sex, age, comorbidities, disease duration, involvement of difficult-to-treat sites, or previous biologic exposure.[115]

Corresponding results were observed in a three-year multicentre retrospective study by Torres et al, which included 459 patients.[118] Treatment discontinuation occurred in 12.2% of cases, most frequently due to insufficient efficacy (6.8% overall), comprising primary failure (2.6%), secondary failure (2.2%), and lack of PsA response (2.0%). Cumulative drug survival rates at one, two, and three years were 0.95 (95% CI 0.93–0.97), 0.89 (95% CI 0.87–0.92), and 0.87 (95% CI 0.84–0.90), respectively.[118]

Further confirmation of risankizumab durability emerged from a multicentre long-term study by Michelucci et al focusing on hard-to-treat areas.[165] Drug-survival analysis revealed 97.6% persistence at one year and 95% at three years. Secondary loss of response was the main cause of discontinuation, especially among patients with palmoplantar involvement. Overall, BMI, sex, age, disease duration, baseline severity, and prior biologic exposure did not significantly influence drug survival, whereas palmoplantar psoriasis represented a negative predictor (HR 4.72).[165]

Additional real-world findings by Luz et al highlighted that risankizumab dose-spacing can maintain clinical control while improving long-term persistence.[166] Eighty-two patients were able to initiate and sustain extended-interval dosing, with a mean treatment duration of 18.4 ± 8.2 months. Interval prolongation varied, with 61.0% extending to 13–16 weeks, 13.4% to 17–20 weeks, 24.4% to 21–24 weeks, and 1.2% to 25–28 weeks. Between weeks 12 and 16, complete clearance (PASI = 0) was significantly more frequent in the dose-spaced cohort than in those on standard intervals (56.1% vs 38.6%; $p = 0.004$). Drug survival was also superior with dose-spacing, as demonstrated by a significantly higher treatment persistence (log-rank $p < 0.001$).[166]

Tildrakizumab

Tildrakizumab is a humanized IgG1/κ monoclonal antibody that selectively targets the p19 subunit of IL-23 and is approved for systemic treatment of adults with moderate-to-severe plaque psoriasis.[167] The standard regimen consists of 100 mg administered subcutaneously at baseline (week 0), at week 4, and subsequently every 12 weeks. In patients with a particularly high disease burden or weighing more than 90 kg, a 200 mg dose may enhance clinical effectiveness, making tildrakizumab the only anti–IL-23 agent with an approved flexible dosing option.[168]

Clinical Trials

The phase III reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754) trials demonstrated that both tildrakizumab 200 mg and 100 mg were effective and well tolerated compared with placebo, and with etanercept in reSURFACE 2, for the treatment of moderate-to-severe chronic plaque psoriasis.[169] These three-part, parallel-group, double-blind, randomized controlled trials allocated adults to tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo in reSURFACE 1 (2:2:1 design), and to tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg in reSURFACE 2 (2:2:1:2 design).[169]

The co-primary endpoints consisted of the proportions of patients achieving PASI 75 and a PGA response (score 0 or 1 with ≥2-grade improvement from baseline) at week 12. In reSURFACE 1, PASI 75 responses at week 12 were achieved by 62% and 64% of patients in the 200 mg and 100 mg groups, respectively, compared with 6% in the placebo arm. PGA 0/1 responses occurred in 59% and 58% of tildrakizumab-treated patients versus 7% with placebo ($p < 0.0001$ for both dose groups vs placebo). In reSURFACE 2, week-12 PASI 75 rates were 66%, 61%, 6%, and 48% for the 200 mg group,

100 mg group, placebo, and etanercept, respectively. Both tildrakizumab doses significantly outperformed placebo ($p < 0.0001$), and the 200 mg and 100 mg doses were also superior to etanercept ($p < 0.0001$ and $p = 0.0010$, respectively).[169]

A significantly higher proportion of patients receiving tildrakizumab 200 mg achieved PASI 75 ($p < 0.0001$) and PGA responses ($p = 0.0031$) at week 12 compared with etanercept. Although the 100 mg dose also yielded superior PASI 75 responses relative to etanercept (nominal unadjusted $p < 0.0001$), differences in PGA responses between these two groups were not statistically significant at week 12. Discontinuations due to adverse events remained rare across the studies.[169]

Additional evidence from a phase IIIb randomized, double-blind, placebo-controlled trial (NCT03897088) in patients with moderate-to-severe scalp psoriasis confirmed efficacy in this difficult-to-treat region. At week 16, 49.4% of participants receiving tildrakizumab 100 mg achieved the primary endpoint of IGA mod 2011 (scalp) response versus 7.3% with placebo, corresponding to a treatment difference of 40% (95% CI: 28.2–51.8; $p < 0.00001$).[170]

Furthermore, a multicentre, double-blind phase III study in Chinese patients with moderate-to-severe plaque psoriasis demonstrated sustained efficacy and good tolerability through week 52. At week 12, PASI 75 was achieved by 66.4% of patients in the tildrakizumab 100 mg group compared with 12.7% in the placebo group (difference 51.4% [95% CI: 40.72–62.13]; $p < 0.001$).[171] Pivotal and supportive clinical trials of tildrakizumab in psoriasis have been summarized in Table 3.

Real-World Evidence

Both short- and long-term real-world studies have assessed the performance of tildrakizumab following its approval, consistently confirming its favourable efficacy and safety profile.[172–182] In an initial Italian single-centre analysis of 34 patients with moderate-to-severe psoriasis, treatment produced a rapid and progressive reduction in disease severity: mean PASI decreased from 12.7 ± 6.1 at baseline to 7.2 ± 5.5 at week 4, 4.1 ± 5.2 at week 12, and 1.8 ± 5.2 at week 28. Mean BSA similarly declined (18.4 ± 13.6 to 11.8 ± 9.6, 9.7 ± 5.3, and 4.7 ± 3.5, respectively).[172] PASI90 and PASI100 responses were obtained by 52.9% and 35.3% of patients at week 12, rising to 76.5% and 61.8% at week 28. Treatment discontinuation occurred in five patients (14.7%) due to primary (n=3) or secondary (n=2) inefficacy. Adverse events were mild, mainly pharyngitis (11.8%), flu-like symptoms (8.8%), headache (8.8%), and diarrhoea (5.9%), and no serious AEs were reported.[172]

In another 28-week real-life cohort of 59 patients, Caldarola et al found an average PASI reduction of 88% from baseline, with 79.7% achieving an absolute PASI < 3; PASI75 and PASI90 rates at week 28 were 81.4% and 64.4%,

Table 3 Pivotal and Supportive Clinical Trials of Tildrakizumab in Psoriasis

Trial	Phase	Population	Arms (Including Switch/ Withdrawal)	Study Period	Primary Endpoint	Main Outcome
reSURFACE-1	Phase III	Adults, moderate-to-severe plaque psoriasis	TIL 200 mg n=308; TIL 100 mg n=309; PBO→TIL n=155	W0–52	PASI75 & PGA0/1 (W12)	Both TIL doses superior to placebo (PASI75 ≈62–64%; PGA0/1 ≈58–59%)
reSURFACE-2	Phase III	Adults, moderate-to-severe plaque psoriasis	TIL 200 mg n=314; TIL 100 mg n=307; PBO→TIL n=156; ETN n=313	W0–52	PASI75 & PGA0/1 (W12)	TIL 200 mg > ETN; TIL 100 mg: PGA response comparable vs ETN (no superiority).
NCT03897088	Phase IIIb	Moderate-to-severe scalp psoriasis	TIL 100 mg n=89; PBO n=82	W0–16	IGA-mod (scalp) 0/1 (W16)	TIL superior: IGA 0/1 49.4% vs 7.3%; PSSI90 60.7% vs 4.9%
NCT05108766	Phase III	Chinese pts with moderate-to-severe plaque psoriasis	TIL 100 mg n=110; PBO→TIL n=110	W0–52	PASI75 (W12)	TIL superior to placebo (66.4% vs 12.7%); durable responses through W52

Notes: PBO→TIL indicates patients initially randomized to placebo who switched to tildrakizumab during the maintenance phase.
Abbreviations: IL, tildrakizumab; PBO, placebo; ETN, etanercept; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; IGA-mod, modified Investigator's Global Assessment; PSSI, Psoriasis Scalp Severity Index.

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respectively. No significant associations emerged between treatment response and gender, BMI, baseline PASI, or prior biologic exposure.[173] Supporting these findings, Burlando et al documented substantial improvement in 26 patients followed for 24 weeks: mean PASI dropped from 12.5 ± 6.5 to 0.6 ± 2.1, and 91% achieved PASI90 at week 24.[175] The small sample size and predominance of bio-naïve patients (80.8%) likely contributed to the high efficacy rates relative to RCTs and other real-world datasets.[173] The study also suggested that clinical response may occur earlier than previously reported in clinical trials, with visible improvements already by week 4.[175]

Mid-term (52-week) data likewise support robust treatment outcomes.[176–179] In a cohort of 91 patients treated with tildrakizumab, Melgosa Ramos et al reported that 96.5% achieved absolute PASI ≤ 3 at week 52, with no significant influence from age (>65 years), weight, metabolic syndrome, psoriatic arthritis, or prior biologic exposure.[177] Similarly, Ruggiero et al observed high PASI90 (73.8%) and PASI100 (59.5%) responses in 42 patients over 52 weeks, with very few adverse events.

In a larger real-world cohort of 237 patients, Narcisi et al reported week-52 PASI75/90/100 rates of 90.9%, 73.5%, and 58.7%, respectively; 85.9% achieved an absolute PASI ≤ 2. Interestingly, patients who had not responded to prior biologics and those with cardiometabolic comorbidities were more likely to achieve PASI100 at week 28 and PASI90 at week 52. Higher BMI did not negatively affect the probability of reaching PASI75/90/100 at any timepoint. No serious safety issues emerged, and no patients discontinued due to AEs.

Long-term durability was further supported by a three-year real-life experience including 136 patients, where Burlando et al reported that PASI100 was achieved in >20% of cases by week 4, >50% by month 4, and stabilised between 70–80% from week 36 through year 3. Early initiation of treatment appeared beneficial, as a shorter disease duration was associated with a higher likelihood of achieving PASI90/100 within 36 weeks.

Megna et al also showed that prior biologic exposure, specifically anti-IL-17 failure, did not substantially reduce treatment effectiveness. In their 28-week cohort of 23 anti-IL-17 non-responders, 82.6% achieved PASI75 and 56.6% achieved PASI90 at week 28, with only one case each of primary and secondary inefficacy (4.3%).[183] Abu-Hilal et al similarly found no significant differences between bio-naïve and bio-experienced patients.[184]

Finally, improvements in health-related quality of life (HRQoL) with tildrakizumab have been repeatedly documented across several real-world studies, further supporting its role as a reliable long-term therapeutic option.[185–187]

Safety

In reSURFACE 1, the most frequent adverse events in both tildrakizumab-treated and placebo groups were nasopharyngitis (4–8%) and upper respiratory tract infections (URTIs; 3–7%). In reSURFACE 2, nasopharyngitis (4–14%) and injection-site erythema (0–9%, occurring more often with etanercept) were the most commonly reported AEs across all treatment arms.[44] A pooled analysis of the two trials confirmed a favourable long-term safety profile for tildrakizumab over a five-year follow-up, with low rates of adverse events of special interest, mirroring those observed in PSOLAR. Incidence rates of AEs leading to discontinuation and drug-related serious AEs were low for both the 100 mg and 200 mg doses, and only a small number of severe infections, malignancies, or MACEs were reported.[188]

Safety has also been demonstrated in special patient groups, including individuals with inflammatory bowel disease, cardiovascular comorbidities, metabolic syndrome, and older adults.[189] Multiple real-world studies have similarly confirmed good tolerability of tildrakizumab in routine clinical practice.[170–180]

Regarding latent tuberculosis infection (LTBI), Li et al showed that IL-17 and IL-23 inhibitors, including tildrakizumab, do not appear to increase the risk of TB reactivation in psoriatic patients. Their review included 581 LTBI patients treated with IL-23 inhibitors without chemoprophylaxis (guselkumab n=22, risankizumab n=539, tildrakizumab n=20), and no TB reactivation was reported among individuals receiving risankizumab or tildrakizumab. Overall, the rate of reactivation among LTBI patients using IL-23 inhibitors without prophylaxis was 0.17%.[190]

Additional real-world evidence also supports the safety of tildrakizumab in patients with chronic HBV infection, with no relevant increases in viral activity or liver function abnormalities reported.[191,192]

Difficult-to-Treat Areas

Consistent with findings from randomized controlled trials, multiple real-world studies have confirmed the effectiveness of tildrakizumab in psoriasis involving difficult-to-treat areas.[193–196] Diotallevi et al reported that tildrakizumab provides a rapid and meaningful clinical response in palmoplantar psoriasis, with improvements visible as early as week 4.[194] Among the patients included, isolated palmar involvement was present in 27 (27.3%), isolated plantar involvement in 18 (18.2%), and combined palmar–plantar involvement in 54 (54.5%); pustular lesions were observed in 39 patients (39.4%). Mean ppPASI was 16.9 ± 13.2 at baseline, improving to 8.9 ± 9.1 at week 4, 2.1 ± 3.1 at week 16, and 0.5 ± 1.0 by week 52.[194]

A retrospective analysis by Brunasso demonstrated similarly rapid benefits in nail psoriasis. In eight patients with a mean baseline mNAPSI of 51.9, scores decreased to 30.8 at week 4 (40.6% improvement) and further to 5.1 at week 20 (90% improvement).[193] Excellent results across several difficult sites, including genital, nail, palmoplantar, and scalp disease, were also highlighted by Galluzzo et al.[196]

Cacciapuoti et al provided additional evidence on scalp, palmoplantar, and nail disease in a real-world cohort. Among 32 patients with scalp involvement, mean PSSI declined from 19.9 ± 10.7 at baseline to 2.7 ± 4.2 at week 16 ($p < 0.0001$). Corresponding improvements were observed in ppPASI (mean 15.4 ± 6.9 to 1.9 ± 2.3 in 13 patients; $p < 0.0001$) and NAPSI (20.3 ± 16.9 to 7.6 ± 10.8 in 14 patients; $p < 0.05$) over the same period.[195]

Finally, a prospective real-life study evaluated 20 adults with severe nail psoriasis of both hands and feet who had failed at least one cDMARD and one anti-TNF agent. All patients had extensive baseline nail involvement (mean NAPSI 77.6; ≥12 affected nails per patient) and were treated with guselkumab (n = 9), risankizumab (n = 7), or tildrakizumab (n = 4), with follow-up to week 52.[196] No meaningful clinical change was observed at week 4, consistent with the slow growth rate of the nail unit. However, by week 24, clear therapeutic benefit emerged: nearly 60% of patients achieved NAPSI75 and around 40% reached NAPSI50, with mean NAPSI falling to approximately 32. Response deepened over time, and at week 52, almost 75% of patients achieved NAPSI90, with a mean NAPSI of 7.6, indicating near-complete nail clearance. Although risankizumab exhibited a slightly faster early response, all three IL-23 inhibitors showed comparable long-term performance, with no significant differences in NAPSI outcomes at week 52.[196]

Special Populations

Baniandrés et al conducted a retrospective, multicentre observational study including patients with moderate-to-severe plaque psoriasis and a prior history of active malignancy at the time of initiating tildrakizumab.[197] By week 24, 82.4% of evaluable patients had achieved a PASI < 3, and at week 48, 80.0% had reached PASI < 1 while 50.0% achieved PASI 0. Twelve individuals (25%) initiated tildrakizumab within one year of their cancer diagnosis, and four patients had already been receiving the drug before their malignancy was detected, yet therapy was not interrupted. Among the remaining 32 patients, treatment began on average 4.95 years after cancer diagnosis. Seven patients presented with active malignancy at baseline. Overall, cancer recurrence or progression did not occur in 95.8% of the cohort.[198] Additional real-world evidence similarly supports the safety of tildrakizumab in patients with oncologic histories. Tildrakizumab also achieved rapid and sustained clearance in a case of ponatinib-induced psoriasis, demonstrating its versatility in complex clinical settings.[199]

A notable advantage of tildrakizumab is its flexible dosing, unique among IL-23 inhibitors, which allows clinicians to individualise therapy. The 200 mg dose has shown enhanced efficacy in patients with higher body weight, more severe disease, psoriatic arthritis, and cardiometabolic comorbidities, as well as in situations of partial secondary loss of response.[200] These observations have been reproduced across multiple real-world experiences.[201–203] Moreover, dose escalation to 200 mg in partial responders with metabolic syndrome not only improved cutaneous disease severity but also favourably modulated metabolic parameters, including reductions in cholesterol, LDL, and glucose, suggesting a biologically plausible dose–response relationship driven by deeper IL-23 inhibition.[204]

A 52-week multicentre retrospective study involving 23 Italian centres assessed 540 adults with moderate-to-severe psoriasis and either a high disease burden or body weight ≥90 kg, comparing tildrakizumab 100 mg (n=363) with 200 mg (n=177).[205] At week 16, the 200 mg group achieved significantly higher PASI90 (43.5% vs 34.3%) and PASI100 (36.4% vs 24.2%) rates, with this advantage persisting at week 52 (PASI90: 68.6% vs 57.3%; p=0.028; PASI100: 52.9% vs 35%;

p<0.001). Absolute PASI ≤2 also favoured the 200 mg dose at week 52 (81.8% vs 77.1%). Subgroup analyses consistently supported the superiority of 200 mg, especially in patients with body weight ≥90 kg, PASI ≥16, difficult-to-treat areas, cardiometabolic disease, or prior biologic exposure. Safety outcomes were excellent, with no severe AEs, no AE-related discontinuations, and comparable adverse event frequencies between groups (URTI 3.4% vs 3%; headache 0.6% in both groups).[205]

The ESTER study further demonstrated tildrakizumab's favourable safety and efficacy in elderly patients (n=49, ≥65 years; mean age 73.1 ± 6.0). By week 28, PASI75, PASI90, and PASI100 were reached by 77.5%, 60%, and 45.2% of patients, respectively, with mean PASI decreasing from 13.6 ± 9.9 to 1.3 ± 1.7. Improvements were also noted across several difficult-to-treat regions, including genitals, nails, palms/soles, and scalp.[206] A larger multicentre retrospective study evaluating up to two years of therapy in 217 elderly patients, 89 of whom were classified as frail, reported ≥80% drug survival at two years, with PASI90 and PASI ≤2 achieved by 75% and 87.5% of patients, respectively. Importantly, effectiveness and safety did not differ between frail and non-frail individuals.[207]

Tildrakizumab has also shown favourable tolerability in patients living with HIV.[208,209] Although approved solely for plaque psoriasis, emerging evidence suggests potential benefit in psoriatic arthritis.[210,211] Case reports have described successful use in Hallopeau's continuous acrodermatitis,[212] erythrodermic psoriasis,[213,214] and in a patient with both psoriatic and eczematous manifestations complicated by epilepsy.[215] While paradoxical eczema is rare with IL-23(p19) inhibitors, a tildrakizumab-associated case has been reported.[216]

Drug Survival

Torres et al described two-year real-world outcomes of tildrakizumab in adults with plaque psoriasis, reporting cumulative drug-survival probabilities of 0.95 (95% CI 0.92–0.98) at 6 months, 0.88 (95% CI 0.85–0.93) at 1 year, and 0.80 (95% CI 0.74–0.85) at 2 years. Discontinuations occurred in 19.9% of patients, most commonly due to lack of efficacy (12.6%), including both primary (4.9%) and secondary (5.7%) loss of skin response, while PsA non-response accounted for an additional 2.0%.[217] Overall, these findings supported tildrakizumab as an effective, durable, and well-tolerated therapeutic option.[217]

Comparable results were obtained in an international retrospective multicentre study involving 517 adults treated with tildrakizumab, which assessed long-term retention up to three years.[218] Drug survival remained consistently high, with 91.3% at 12 months, 85.3% at 24 months, and 82.4% at 36 months. In total, 17% (88/517) of patients discontinued therapy, mainly because of inadequate response (9.5%). Adverse events accounted for 2.3% of discontinuations (12 patients), including infections (1.2%), malignancies (0.4%), lymphocytosis (0.2%), myalgia (0.2%), alopecia areata (0.2%), and uncontrolled dyslipidaemia (0.2%).[218] Treatment-emergent AEs were reported in 10.8%, with infections being the most frequent (5.6%), though hospitalisation was required in only 0.2% of cases. Multivariate analysis identified biologic-naïve status (HR 0.57; 95% CI 0.37–0.87; p=0.01) and male sex (HR 0.63; 95% CI 0.41–0.96; p=0.03) as independent predictors of lower discontinuation risk, whereas higher baseline PASI increased the likelihood of treatment withdrawal (HR 1.1; p=0.007).[218]

Additional real-world evidence from Santos-Juanes Galache et al indicated that concomitant psoriatic arthritis (p = 0.02), previous biologic therapy (p = 0.02), and arterial hypertension (p = 0.012) were associated with reduced drug survival for tildrakizumab.[219]

The large multicentre Italian IL-PSO study evaluated 5932 treatment courses across 5300 patients treated with various interleukin inhibitors and reported comparable four-year drug-survival probabilities for tildrakizumab (83.5%), ixekizumab (82.6%), guselkumab (82.4%), and brodalumab (81.8%).[220] Risankizumab showed the highest overall drug survival. Notably, the study confirmed that IL-23 inhibitors as a class were associated with superior long-term persistence over a four-year follow-up period, consistent with trends observed across the literature.[221]

Emerging IL-23 Inhibitors

Icotrokinra

Icotrokinra is an oral, receptor-selective IL-23 antagonist peptide designed to inhibit IL-23 signalling by directly binding the IL-23 receptor.[222] After encouraging results in phase II studies for psoriasis,[223] multiple phase III programmes were launched to further evaluate its efficacy and safety.[222,224,225]

In the ICONIC-LEAD trial (NCT06095115), a Phase III, double-blind, randomized, placebo-controlled study including adults and adolescents aged ≥12 years with moderate-to-severe plaque psoriasis, icotrokinra showed clear superiority over placebo at week 16. A total of 684 participants were randomized, with 456 receiving icotrokinra and 228 placebo. By week 16, IGA 0/1 and PASI90 responses were achieved by 65% and 50% of patients in the icotrokinra arm, compared with 8% and 4% in the placebo arm (both $P < 0.001$). Complete skin clearance was also significantly more common in the icotrokinra group: IGA 0 in 33% versus 1%, and PASI100 in 27% versus <1% (both $P < 0.001$).[222]

The ICONIC-TOTAL trial (NCT06095102) examined patients aged ≥12 years with moderate psoriasis involving high-impact areas. At week 16, significantly more subjects treated with icotrokinra achieved overall clearance or minimal disease, including in the scalp and genital regions, whereas outcomes for hands and feet did not differ significantly from placebo.[224]

Further evidence from the phase III ICONIC-ADVANCE 1 (n=774) and ICONIC-ADVANCE 2 (n=731) trials confirmed the strong therapeutic effect of icotrokinra. These studies compared once-daily icotrokinra 200 mg with placebo and with deucravacitinib in adults with moderate-to-severe plaque psoriasis non-responsive to topical therapies. Participants were randomized to icotrokinra (311 and 322 patients), placebo (156 and 82), or deucravacitinib (307 and 327). At week 16, icotrokinra produced markedly superior IGA 0/1 responses compared with placebo: 213/311 (68%) vs 17/156 (11%) in ADVANCE 1 and 227/322 (70%) vs 7/82 (9%) in ADVANCE 2. PASI90 results paralleled this pattern: 171/311 (55%) vs 6/156 (4%) and 184/322 (57%) vs 1/82 (1%), respectively (all $p < 0.0001$).[225]

Up to week 16, adverse-event rates were 303/632 (48%) with icotrokinra and 136/237 (57%) with placebo; nasopharyngitis (6%) and URTI (4%) were the most frequent events. Between weeks 16 and 24, AE rates remained lower for icotrokinra (359/632, 57%) than for the active comparator deucravacitinib (411/634, 65%).[225] Collectively, these trials indicate that oral icotrokinra can deliver biologic-like efficacy with a favourable tolerability profile, outperforming both placebo and deucravacitinib.

Mirikizumab

Mirikizumab (LY3074828) is a humanized IgG4 monoclonal antibody directed against the p19 subunit of IL-23.[226] Its efficacy in psoriasis has been investigated across multiple phase II and III clinical trials.[226–228] In the phase III OASIS-1 study (NCT03482011), a double-blind, placebo-controlled, randomized-withdrawal trial, 530 adults with moderate-to-severe plaque psoriasis were randomized 4:1 to receive subcutaneous mirikizumab 250 mg or placebo every four weeks up to week 16. Patients achieving clinical response were then rerandomized (1:1:1) to mirikizumab 250 mg, mirikizumab 125 mg, or placebo every eight weeks through week 52.

Mirikizumab met all primary and major secondary endpoints at weeks 16 and 52, demonstrating clear superiority over placebo. Approximately 33% of patients receiving mirikizumab achieved complete skin clearance, as indicated by sPGA (0) and PASI100, during the initial 16-week treatment period. By week 52, both mirikizumab maintenance doses remained significantly more effective than placebo across all secondary measures, and the two active regimens yielded comparable response rates.[226]

Despite its early success in psoriasis, subsequent clinical development of mirikizumab shifted its focus primarily toward inflammatory bowel disease, including ulcerative colitis and Crohn's disease, where it has shown substantial therapeutic benefit.[229,230]

IBI112

IBI112 is an IL-23p19–targeting monoclonal antibody[231] that showed good tolerability and a favourable safety profile in a Phase I study.[232] A large multicentre, randomized, double-blind, placebo-controlled phase III trial (NCT06049810), which includes randomized withdrawal and retreatment phases, has been initiated to assess the efficacy and safety of

subcutaneous IBI112 in adults with moderate-to-severe plaque psoriasis, although results from this study are not yet available.[233]

QX004N

QX004N is a humanized monoclonal antibody directed against IL-23. In a two-part randomized clinical trial, including a Phase 1a safety evaluation in 55 healthy volunteers and a phase 1b efficacy assessment in 30 patients with moderate-to-severe plaque psoriasis, QX004N demonstrated good tolerability, dose-proportional linear pharmacokinetics, and superior clinical efficacy compared with placebo in psoriasis participants.[234]

Discussion

In recent years, IL-23 inhibitors have reshaped the therapeutic landscape for moderate-to-severe psoriasis. Beyond their dermatologic indications, guselkumab and risankizumab are now also approved for PsA and for inflammatory bowel diseases, including Crohn's disease and ulcerative colitis. Several core concepts emerge from the available evidence. IL-23 acts as a pivotal upstream cytokine that drives Th17 expansion and sustains effector cytokine production; blockade of the p19 subunit allows for highly selective suppression of pathogenic Th17 responses, which likely explains the robust levels of clinical improvement, frequent achievement of PASI 90 or better, and sustained durability observed with this class.[235]

Data from VOYAGE 1, VOYAGE 2, and NAVIGATE clearly illustrate the rapid onset and long-lasting responses seen with guselkumab, even in biologic-experienced patients, with benefits maintained for up to five years.[15] Similarly, findings from the UltIMMa trials, multiple head-to-head studies, and the long-term LIMMitless extension show that risankizumab achieves steep early gains and durable control with 12-weekly dosing.[98] Tildrakizumab has been directly compared only with etanercept, and while indirect comparisons suggest that short-term clearance rates may be slightly slower or somewhat lower than with other IL-23 inhibitors, long-term outcomes remain meaningful, with a favourable tolerability profile. Across biologic classes, IL-23 inhibitors have consistently outperformed anti-TNF agents (adalimumab for guselkumab and risankizumab; etanercept for tildrakizumab), ustekinumab, and even an anti-IL-17A agent (secukinumab for guselkumab and risankizumab).[236]

A major strength of this therapeutic class is the remarkable alignment between RCT efficacy and real-world outcomes. Registry and real-life data show particularly strong persistence and tolerability. In a large 16-year comparative cohort of 19,034 biologic-treated patients, risankizumab and guselkumab produced the highest adjusted drug-survival times for efficacy (both 1.93 years).[90] A meta-analysis of 69 studies including 48,704 patients similarly identified guselkumab and risankizumab as the biologics with the best long-term survival.[237] In keeping with this, the IL-PSO multicentre Italian study reported four-year survival probabilities of 83.5% for tildrakizumab, 82.6% for ixekizumab, 82.4% for guselkumab and 81.8% for brodalumab, with risankizumab reaching 91.6%, the highest overall.[220]

The safety profile of IL-23 inhibitors is highly favourable. Long-term extension studies demonstrate low incidences of serious adverse events, with no unexpected patterns such as increased opportunistic infections, malignancies, or cardiovascular complications. In the cohort mentioned above, risankizumab (1.94 years) and guselkumab (1.92 years) also had the longest AE-free survival times.[91] Their selective mechanism likely preserves broader immune integrity, resulting in less global immunosuppression. Common AEs, URTI, nasopharyngitis, headache, mirror those of IL-17 inhibitors, but without the heightened susceptibility to Candida seen with IL-17 blockade.[55] This distinction reflects key immunological principles: IL-17 plays an essential role in mucosal defence, coordinating neutrophil recruitment and antimicrobial peptide production.[238] IL-23 inhibition dampens Th17-mediated responses but does not fully abolish IL-17 production, as innate lymphocytes such as γδ T cells and NKT cells continue to produce IL-17 independently of IL-23 signalling.[239] Consequently, mucocutaneous Candida defence is preserved. The same reasoning helps explain why IL-23 inhibitors have not been associated with new-onset or exacerbation of IBD, an uncommon but recognised AE of IL-17 inhibitors, where IL-17 is essential for maintaining epithelial integrity and mucosal barrier function.[240]

An especially impactful area is oncology. Historically, psoriasis treatments in patients with prior or active malignancy required caution. Yet real-world evidence increasingly supports the safe use of IL-23 inhibitors in this population. In a retrospective cohort by Satolli et al, among 198 patients with a history of malignancy, only 3% experienced progression

or recurrence.[75] Psoriasis is also a known immune-related adverse event in patients receiving immune checkpoint inhibitors (ICIs), and IL-23 blockade is emerging as a promising therapeutic option in this setting. Anti-IL-23 agents appear to carry a low risk of impairing ICI antitumour efficacy,[241] and several case series describe successful management of ICI-induced psoriasis using this class.[242] A recent international consensus even identifies IL-23 inhibitors as the preferred biologic therapy for patients undergoing ICI treatment.[242]

Another emerging concept relates to immunological "reprogramming." IL-23 may be essential for maintaining pathogenic tissue-resident memory (TRM) T cells within psoriatic skin, which are believed to drive relapse after treatment interruption. Early evidence suggests that IL-23 blockade may reduce TRM persistence, potentially prolonging remission or slowing relapse once therapy is stopped.[243] If confirmed, this could redefine long-term disease management.

Despite the robust and increasingly consistent evidence supporting IL-23 inhibitors, several residual uncertainties remain. Very long-term safety data beyond five to six years are still limited, particularly in specific subgroups such as patients with active malignancy, complex immunologic conditions, or multiple concomitant immunosuppressive therapies. Indeed, rare AEs may only become evident with longer follow-up, requiring continued pharmacovigilance and robust registry participation. Moreover, although real-world studies provide invaluable insights into routine practice, their observational nature, heterogeneous designs, and potential selection biases must be carefully considered when interpreting outcomes. Direct comparative trials between IL-23 and IL-17 inhibitors remain limited; although IL-17 agents may induce faster early clearance, IL-23 inhibitors often demonstrate more durable long-term control. Optimal switching strategies are also not fully defined, especially for patients who fail IL-17 therapy, where questions regarding washout duration and potential biomarkers of response remain open. Finally, economic factors, healthcare system constraints, and access to biologic therapies represent important real-world determinants that were not uniformly captured across studies. These considerations may influence treatment sequencing and persistence and should be integrated into personalised therapeutic decision-making alongside clinical and biological factors.

Lastly, precision medicine represents a promising frontier. As our understanding of psoriasis biology deepens, biomarkers, ranging from cytokine profiles to genetic signatures and T-cell phenotypes, may help identify patients most likely to respond optimally to IL-23 inhibitors, those who may sustain remission during treatment holidays, and those who require continuous therapy. Moreover, emerging oral or small-molecule inhibitors of the IL-23/IL-23R pathway may further expand therapeutic possibilities and improve accessibility.

In summary, IL-23 inhibitors have validated IL-23 as a central therapeutic target in psoriasis, delivering deep and durable responses while maintaining a highly reassuring safety profile. They represent one of the most significant advances in modern psoriasis management. Future priorities will include refining long-term treatment strategies, expanding comparative evidence, integrating pharmacoeconomic considerations, and harnessing biomarker-driven approaches to maximize the transformative potential of IL-23 blockade.

Notably, the conclusions of this review are based on the synthesis of data derived from individual randomized controlled trials and real-world observational studies, rather than from a formal meta-analysis or indirect treatment comparison across all available biologic classes. Although the consistency of the evidence strongly supports the central role of IL-23 inhibitors in contemporary psoriasis management, several important limitations should be acknowledged. Continued long-term pharmacovigilance is required to detect rare or very late-onset adverse events, particularly in selected and medically complex populations. Moreover, the number of true head-to-head trials comparing IL-23 inhibitors with other biologic classes, and among agents within the IL-23 class itself, remains limited. Finally, economic considerations, healthcare system constraints, and access to biologic therapies may substantially influence real-world treatment choices and may limit the generalizability of idealised therapeutic positioning.

Data Sharing Statement

Data that support the findings of this study are available from the corresponding author, upon reasonable request.

Author Contributions

Matteo Megna: Conceptualization; Methodology; Validation; Formal analysis; Investigation; Resources; Data Curation; Writing - Original Draft; Writing - Review & Editing; Visualization; Supervision; Project administration;

Funding acquisition. Michela D'Agostino: Conceptualization; Methodology; Validation; Formal analysis; Investigation; Resources; Data Curation; Writing - Original Draft; Writing - Review & Editing. Federica Feo: Conceptualization; Methodology; Validation; Formal analysis; Investigation; Resources; Data Curation; Writing - Original Draft; Writing - Review & Editing. Valentina Ventura: Conceptualization; Methodology; Validation; Formal analysis; Investigation; Resources; Data Curation; Writing - Original Draft; Writing - Review & Editing. Nello Tommasino: Conceptualization; Methodology; Validation; Formal analysis; Investigation; Resources; Data Curation; Writing - Original Draft; Writing - Review & Editing. Luca Potestio: Conceptualization; Methodology; Validation; Formal analysis; Investigation; Resources; Data Curation; Writing - Original Draft; Writing - Review & Editing; Visualization; Supervision; Project administration. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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