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ORIGINAL RESEARCH

Real-World Efficacy of IL-23 Inhibitors in Psoriasis Affecting High-Impact Areas: Indirect Comparison of Tildrakizumab 200 mg, Risankizumab, and Guselkumab—IL PSO (Italian Landscape Psoriasis)

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ABSTRACT

Introduction: Psoriasis involving special or high-impact areas (scalp, nails, palms/soles, genitalia) is associated with a disproportionate functional and psychological burden that is often underestimated by conventional severity scores and remains challenging to treat effectively. This study compared the real-world efficacy and safety of three interleukin (IL)-23p19 inhibitors—risankizumab, guselkumab, and tildrakizumab 200 mg—in patients with moderate-to-severe plaque psoriasis with involvement of high-impact sites.

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Methods: This multicenter retrospective study included 670 patients treated for at least 52 weeks across 37 Italian dermatology centers. Patients received risankizumab ($n = 254$), guselkumab ($n = 177$), or tildrakizumab 200 mg ($n = 239$) according to approved regimens. Effectiveness was assessed using Psoriasis Area Severity Index (PASI) and site-specific Physician's Global Assessment (PGA) scores (scalp, nails, palms/soles, genitalia) at weeks 4, 16, 36, and 52. Safety was evaluated through reported adverse events.

Results: Risankizumab demonstrated the fastest and most pronounced reduction in PASI, achieving PASI90 and PASI100 responses in 89.6% and 82.1% of patients at week 52, respectively. Tildrakizumab 200 mg showed a slower onset but comparable long-term efficacy, particularly in nail and palmoplantar psoriasis. At week 52, complete nail clearance (fn-PGA = 0) was achieved in 90.0% of patients treated with risankizumab, 76.7% with tildrakizumab, and 66.7% with guselkumab. Palmoplantar and genital psoriasis showed near-complete resolution across all treatment groups by week 52. Scalp involvement improved markedly with all agents, with lower residual disease observed with risankizumab. All treatments were well tolerated, with infrequent and predominantly mild adverse events and no major safety concerns.

Conclusion: In real-world clinical practice, IL-23p19 inhibitors provide high and sustained efficacy in psoriasis affecting high-impact sites. Risankizumab offers faster and deeper responses, while tildrakizumab 200 mg represents an effective long-term option, particularly in patients with higher BMI or more treatment-resistant disease. These findings support a personalized approach to biologic selection based on disease localization, patient characteristics, and therapeutic goals.

Keywords: Psoriasis; Scalp; Genital; Nail; Palms; IL-23 inhibitors

Key Summary Points

Why carry out this study?

Difficult to treat area remains a therapeutic challenge for dermatologists.

The study aimed to evaluate the real-world efficacy and safety of high-performing IL-23p19 inhibitors—risankizumab, guselkumab, and tildrakizumab 200 mg—in moderate-to-severe plaque psoriasis with high-impact site involvement after 52 weeks of treatment.

What was learned from this study?

Risankizumab produced the most rapid and profound Psoriasis Area Severity Index (PASI) improvements in nail psoriasis.

Tildrakizumab showed a slower initial response but delivered similar long-term benefits, followed by guselkumab.

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Palmoplantar lesions resolved in almost all patients across all treatment arms.

Scalp psoriasis improved substantially, with risankizumab demonstrating the lowest residual disease followed by guselkumab and tildrakizumab.

Genital involvement also approached complete clearance in every group, all three agents were well tolerated, with no significant safety issues observed.

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by keratinocyte hyperproliferation, epidermal thickening, and inflammatory cell infiltration, resulting from complex interactions between genetic predisposition, environmental triggers, and dysregulated immune responses [1]. Over recent decades, progress in understanding the immunopathogenesis of psoriasis has led to the identification of key cytokine pathways involved in its development and maintenance, notably the interleukin (IL)-23/IL-17 axis [2]. This paradigm shift has transformed therapeutic strategies, allowing the development of highly targeted biologic molecules capable of selectively modulating the pathogenic immune response with unprecedented efficacy and safety [3]. Among these, monoclonal antibodies directed against the p19 subunit of IL-23 represent a major therapeutic advance, offering durable disease control, favorable safety, and simplified dosing schedules [4]. While most clinical trials in psoriasis have historically focused on generalized plaque-type disease, the clinical manifestations of psoriasis are heterogeneous and extend beyond the mere extent of body surface involvement [5]. In practice, a substantial subset of patients presents with lesions located in anatomically and functionally "special" or "high-impact" areas, such as the scalp, genitals, nails, palms, and soles. These localizations are associated with disproportionately high functional and psychosocial burden relative to their absolute surface area [6]. The unique features of skin structure and mechanical stress in these regions, as well as challenges in topical drug delivery, often render standard treatments less effective and result in a higher risk of treatment resistance or incomplete control [6]. These manifestations may present in patients with low overall Psoriasis Area and Severity Index (PASI) scores, creating a clinical paradox whereby disease is formally categorized as "mild" yet exerts a physical, psychosocial, and functional burden comparable to moderate-to-severe psoriasis [7]. Conventional severity metrics—such as PASI, body surface area (BSA), and Physician's Global Assessment (PGA)—often fail to reflect the disproportionate burden of psoriasis affecting high-impact areas [8]. An emerging consensus now supports classifying special-site involvement as at least moderate in severity, regardless of PASI or BSA scores, to better align therapeutic eligibility with patient-centered outcomes [9]. This conceptual shift underscores the need for robust evidence on the efficacy of targeted biologics in these challenging localizations [8]. For example, patients with extensive scalp involvement may present with PASI scores below 10 and thus remain ineligible for systemic therapy under certain guidelines, despite experiencing significant quality of life (QoL) impairment [9]. Scalp psoriasis is particularly distressing due to visible scaling, itching, and hair shedding, which can lead to embarrassment, social withdrawal, and reduced self-confidence [10]. Even when affecting a limited surface area, the visibility of lesions makes concealment difficult and contributes to psychological distress [11]. Genital psoriasis, often underreported due to embarrassment, is associated with pain, burning, pruritus, and dyspareunia, affecting sexual function and intimacy, straining relationships and reducing overall life satisfaction [12]. Palmoplantar psoriasis may cause painful fissures, reduced grip strength, and difficulty walking, interfering with occupational activities and mobility [13]. Nail psoriasis, which can manifest as pitting, onycholysis, subungual hyperkeratosis, and nail plate crumbling, poses functional limitations and cosmetic concerns, often hindering manual tasks and exacerbating stigma [14]. These localizations demand tailored therapeutic approaches. Topical

treatments are frequently limited by poor penetration, irritation, or practical challenges, and phototherapy is less feasible for certain sites, particularly genitals and nails [15]. Conventional systemic agents, while effective in some cases, may offer slower onset and are associated with a less favorable long-term safety profile [16]. Biologics, particularly IL-23p19 inhibitors, offer an attractive option due to their targeted mechanism, sustained efficacy, and ability to improve both cutaneous and QoL outcomes, even in difficult-to-treat sites [17]. Among IL-23p19 inhibitors, three molecules—risankizumab, guselkumab, and tildrakizumab—have been approved for moderate-to-severe plaque psoriasis. Although all share the same target, differences in molecular structure, binding affinity, pharmacokinetics, and dosing may translate into subtle variations in efficacy, onset, and durability, particularly in challenging manifestations. Risankizumab is a humanized IgG1 monoclonal antibody that binds with high specificity to the p19 subunit of IL-23, administered subcutaneously at 150 mg at weeks 0 and 4, followed by maintenance every 12 weeks [18]. Clinical trials have demonstrated high rates of PASI90 and PASI100 responses, sustained over long-term follow-up, with significant QoL improvements [19]. Importantly, post hoc analyses and real-world evidence indicate risankizumab achieves high clearance rates in scalp, nail, and palmoplantar psoriasis, as well as meaningful improvements in genital involvement [20]. The drug's rapid onset, often visible within weeks, and durable control with quarterly maintenance make it a compelling option for patients with special-site disease, requiring both early relief and long-term stability [21]. Guselkumab is a fully human IgG1λ monoclonal antibody, with a dosing schedule of 100 mg subcutaneously at weeks 0 and 4, and every 8 weeks thereafter. Its efficacy has been validated in large phase III trials and long-term extension studies, demonstrating sustained clearance and QoL benefits over years of continuous therapy [22]. Studies have documented its effectiveness in difficult-to-treat areas, including significant improvements in scalp and genital psoriasis scores, nail clearance, and palmoplantar lesion resolution [23, 24]. Tildrakizumab is a humanized IgG1κ monoclonal antibody approved at 100 mg at weeks 0 and 4, and every 12 weeks thereafter [25]. However, a higher 200 mg dose has also been studied and approved, offering an alternative for certain patients or disease phenotypes [26]. Tildrakizumab has a favorable safety profile and steady, durable responses, though generally slower onset compared to some IL-23 inhibitors. Emerging data suggest 200 mg may enhance efficacy, particularly in patients with higher body weight or more resistant disease, including special-site involvement [26, 27]. Reports indicate improvement in nail, scalp, and palmoplantar psoriasis, though direct comparative data with other IL-23 inhibitors remain limited. This creates a gap in the literature for clinicians seeking to optimize therapy for special-site psoriasis in patients who might benefit from higher dosing. Understanding whether differences exist between risankizumab, guselkumab, and tildrakizumab—particularly at higher doses—may allow clinicians to individualize therapy more precisely. An indirect comparison between IL-23 inhibitors has been published for tildrakizumab at 100 mg [28]. However, that analysis did not address the 200 mg dose, which may offer enhanced efficacy and alter the comparative landscape. The present work aims to fill this gap by conducting an indirect treatment comparison including tildrakizumab at 200 mg alongside risankizumab and guselkumab, with emphasis on outcomes in high-impact-site psoriasis.

METHODS

We conducted this multicentric retrospective study by collecting data from the databases of 37 Italian dermatology units. We enrolled 670 patients who were treated with guselkumab, risankizumab, or tildrakizumab 200 mg for at least 1 year. Of these, 177 were treated with guselkumab, 254 with risankizumab, and 239 with tildrakizumab 200 mg. Patients' eligibility for therapy was assessed according to the Italian Adaptation of EuroGuiDerm guideline on the systemic treatment of chronic plaque psoriasis. All patients received guselkumab, risankizumab, or tildrakizumab in accordance with the

Summary of Product Characteristics, and it was administered at the approved dosage for the treatment of moderate–severe psoriasis. Patients' clinical and demographic characteristics, including age, gender, weight, height, body mass index (BMI), concomitant psoriatic arthritis (PsA), other comorbidities, previous exposure to other biological agents, involvement of high-impact areas, and PASI score were obtained from the electronic medical records. Owing to the retrospective nature of the study, missing data could not be recovered or retrieved. The effectiveness of guselkumab, risankizumab, and tildrakizumab 200 mg was evaluated at weeks 4, 16, 36, and 52 in terms of reduction of mean site-specific PGA (fingernail (fn)-PGA, scalp (sc)-PGA, palmoplantar (pp)-PGA, and genitals (g)-PGA) and percentage of patients reaching PGA 0 at each time point. The safety analysis was performed by assessing the occurrence of adverse events (AEs) reported in the medical records at each follow-up visit. The study was conducted in accordance with the Declaration of Helsinki (1964 and subsequent amendments).

Statistical Analysis

Categorical variables were summarized as absolute numbers and percentages, while continuous variables were reported as mean and standard deviation (SD). Statistical differences between patients according to each therapy were analyzed for baseline characteristics and effectiveness outcomes at each time point. Statistical analysis was conducted with R version 4.3.1.

Ethical Approval

Institutional review board approval was exempted, as the study protocol did not deviate from standard clinical practice. All patients received guselkumab, risankizumab, and tildrakizumab 200 mg, as per good clinical practice. All included patients provided written consent for retrospective study of data collected during routine clinical practice (demographics and clinical scores). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Data collection and handling complied with applicable laws, regulations, and guidance regarding patient protection, including patient privacy.

RESULTS

A total of 670 patients with psoriasis were enrolled. Mean patient age was 52.1 ± 24.1 years. The mean body weight was 82.1 ± 17.9 kg with mean BMI of 27.7 ± 5.4. Notably, 26.9% of the cohort had a BMI equal to or greater than 30. Male patients represented 62.7% of the population. In terms of treatment history, 16.7% of patients were naïve to systemic therapies, and 46.0% were biologic-naïve, with 50.4% having experienced prior treatment failure (Table 1). No significant differences were observed among the three groups, except for BMI, which was significantly higher in the tildrakizumab group. This finding was consistent with the greater mean body weight and higher prevalence of obesity (BMI ≥ 30) in the same cohort. Moreover, nail involvement and prior PUVA (psoralen-UVA) therapy were significantly more frequent among patients treated with tildrakizumab, suggesting a potentially distinct clinical profile. A slight but statistically significant difference was also observed in the proportion of biologic-naïve patients, with a lower percentage in the guselkumab group compared to risankizumab and tildrakizumab (Table 1). At baseline, 177 patients were treated with guselkumab, 254 with risankizumab, and 239 with tildrakizumab 200 mg. One-hundred fifty-nine patients in the guselkumab group reached week 16, 102 week 36, and 98 week 52, while in the risankizumab group, 222 patients reached week 16, 113 week 36, and 106 week 52. Finally, in the tildrakizumab group, 217 patients reached week 16, 109 week 36, and 94 week 52.

PASI

At baseline, PASI scores were similar ($p = 0.906$) across the three groups, with mean values of 14.06 for guselkumab, 13.91 for risankizumab, and 14.15 for tildrakizumab (Table 2). By

Table 1 Demographic characteristics of patients enrolled

Variables	Overall	Guselkumab	Risankizumab	Tildrakizumab 200 mg	*p*
Number of patients	670	177	254	239	
Age, years, mean (SD)	52.1 (24.1)	42.5 (28.9)	43 (19.7)	60 (22.6)	< 0.001
Weight, kg, mean (SD)	82.11 (17.96)	79.78 (15.90)	79.97 (17.90)	85.92 (18.69)	< 0.001
Gender					0.359
Male, *n* (%)	414 (61.8)	104 (59.4)	154 (61.8)	156 (66.1)	
Female, *n* (%)	256 (37.3)	73 (40.6)	100 (38.2)	83 (33.9)	
Height, cm, mean (SD)	171.80 (9.60)	171.15 (10.07)	171.59 (9.66)	172.43 (9.23)	0.418
BMI, m/kg^2, mean (SD)	27.75 (5.44)	27.12 (4.74)	27.13 (5.29)	28.81 (5.85)	0.001
BMI ≥ 30 , *n* (%)	180 (26.9)	36 (20.3)	58 (22.8)	86 (36.0)	< 0.001
Age onset psoriasis, years, mean (SD)	34.67 (17.42)	35.10 (16.70)	35.15 (17.67)	33.89 (17.73)	0.701
Arthritis = Yes, *n* (%)	51 (7.6)	12 (6.8)	23 (9.1)	16 (6.7)	0.545
Nails = Yes, *n* (%)	164 (24.5)	48 (27.1)	47 (18.5)	69 (28.9)	0.018
Scalp = Yes, *n* (%)	359 (53.6)	90 (50.8)	130 (51.2)	139 (58.2)	0.209
Genital = Yes, *n* (%)	241 (36.0)	70 (39.5)	85 (33.5)	86 (36.0)	0.433
Palms/soles = Yes, *n* (%)	169 (25.2)	48 (27.1)	59 (23.2)	62 (25.9)	0.625
Naïve cDMARDs = Yes, *n* (%)	112 (16.7)	32 (18.1)	38 (15.0)	42 (17.6)	0.630
CyA = Yes, *n* (%)	326 (48.7)	84 (47.5)	122 (48.0)	120 (50.2)	0.830
MTX = Yes, *n* (%)	196 (29.3)	53 (29.9)	81 (31.9)	62 (25.9)	0.340
PUVA = Yes, *n* (%)	176 (26.3)	43 (24.3)	55 (21.7)	78 (32.6)	0.017
Acitretin = Yes, *n* (%)	98 (14.6)	23 (13.0)	30 (11.8)	45 (18.8)	0.068
Naïve bDMARDs, *n* (%)					
No	362 (54.0)	105 (59.3)	133 (52.4)	124 (51.9)	< 0.001
Yes	308 (46.0)	72 (40.7)	121 (47.6)	115 (48.1)	< 0.001

SD standard deviation, *BMI* body mass index, *cDMARDs* conventional disease-modifying anti-rheumatic disease, *CyA* cyclosporin A, *MTX* methotrexate, *PUVA* psoralen-UVA, *bDMARDs* biological disease-modifying anti-rheumatic disease

week 4, risankizumab showed the most pronounced early improvement, with a mean PASI of 6.46, compared to 7.86 for guselkumab and 8.29 for tildrakizumab ($p < 0.001$). This trend continued at week 16, where risankizumab achieved a mean PASI of 1.86, while guselkumab and tildrakizumab recorded 2.84 and 2.82 respectively ($p < 0.001$). At week 36, risankizumab maintained its lead with a mean PASI of 0.57, followed by guselkumab at 1.04 and tildrakizumab at 1.10 ($p = 0.001$). By week 52, all three treatments demonstrated substantial efficacy, with risankizumab reaching a mean PASI of 0.26, guselkumab 0.57, and tildrakizumab 0.53 ($p = 0.008$) (Fig. 1). These results suggest that risankizumab consistently induced faster and deeper reductions in PASI scores, although the differences narrowed over time, particularly between risankizumab and tildrakizumab. In terms of PASI90

Table 2 Mean Psoriasis Area Severity Index (PASI) values and percentage of patients reaching PASI90 and PASI100 at each time point

Variables	Guselkumab	Risankizumab	Tildrakizumab 200 mg	*p*
Number of patients	177	254	239	
PASI baseline, mean (SD)	14.06 (5.64)	13.91 (6.28)	14.15 (6.22)	0.906
PASI 4w, mean (SD)	7.86 (3.83)	6.46 (3.42)	8.29 (4.09)	< 0.001
PASI 16w, mean (SD)	2.84 (2.09)	1.86 (2.31)	2.82 (2.58)	< 0.001
PASI 36w, mean (SD)	1.04 (1.29)	0.57 (0.95)	1.10 (1.31)	0.001
PASI 52w, mean (SD)	0.57 (0.86)	0.26 (0.62)	0.53 (0.78)	0.008
PASI90 4w, *n* (%)	2 (1.1)	9 (3.5)	3 (1.3)	0.120
PASI90 16w, *n* (%)	43 (27.0)	109 (49.1)	64 (29.5)	< 0.001
PASI90 36w, *n* (%)	66 (64.7)	88 (77.9)	63 (57.8)	0.005
PASI90 52w, *n* %)	78 (77.2)	95 (89.6)	75 (78.9)	0.042
PASI100 4w, *n* (%)	2 (1.1)	6 (2.4)	3 (1.3)	0.516
PASI100 16w, *n* (%)	32 (20.1)	96 (43.2)	48 (22.1)	< 0.001
PASI100 36w, *n* (%)	52 (51.0)	79 (69.9)	48 (44.0)	< 0.001
PASI100 52w, *n* (%)	65 (64.4)	87 (82.1)	59 (62.1)	0.003

PASI Psoriasis Area Severity Index, *SD* standard deviation, *w* weeks

response rates (Fig. 2), at week 16, 49.1% of patients treated with risankizumab achieved PASI90, compared to 27.0% with guselkumab and 29.5% with tildrakizumab ($p < 0.001$). By week 36, the rates increased to 77.9% for risankizumab, 64.7% for guselkumab, and 57.8% for tildrakizumab ($p = 0.005$). At week 52, risankizumab reached 89.6%, while guselkumab and tildrakizumab achieved 77.2% and 78.9% respectively ($p = 0.042$). Although risankizumab maintained the highest response rates throughout, tildrakizumab 200 mg showed a notable catch-up effect, with its PASI90 rate at week 52 nearly matching that of guselkumab and approaching risankizumab performance. PASI100 responses followed a similar trajectory (Fig. 2). At week 16, risankizumab led with 43.2% of patients achieving complete clearance, compared to 20.1% with guselkumab and 22.1% with tildrakizumab ($p < 0.001$). By week 36, risankizumab reached 69.9%, while guselkumab and tildrakizumab recorded 51.0% and 44.0% respectively ($p < 0.001$). At week 52, risankizumab maintained its advantage with 82.1% of patients achieving PASI100, followed by guselkumab at 64.4% and tildrakizumab at 62.1% ($p = 0.003$).

Nails

Nail psoriasis was reported in 48 patients treated with guselkumab, 47 patients with risankizumab, and 69 with tildrakizumab; palmoplantar psoriasis in 48 patients with guselkumab, 59 with risankizumab, and 62 with tildrakizumab; scalp psoriasis in 90 patients with guselkumab, 130 with risankizumab, and 139 with tildrakizumab and genital psoriasis was reported in 70 patients treated with guselkumab, 85 patients with risankizumab and 86 with tildrakizumab (Table 1). In nail psoriasis, the three molecules showed distinct trajectories in terms of clinical

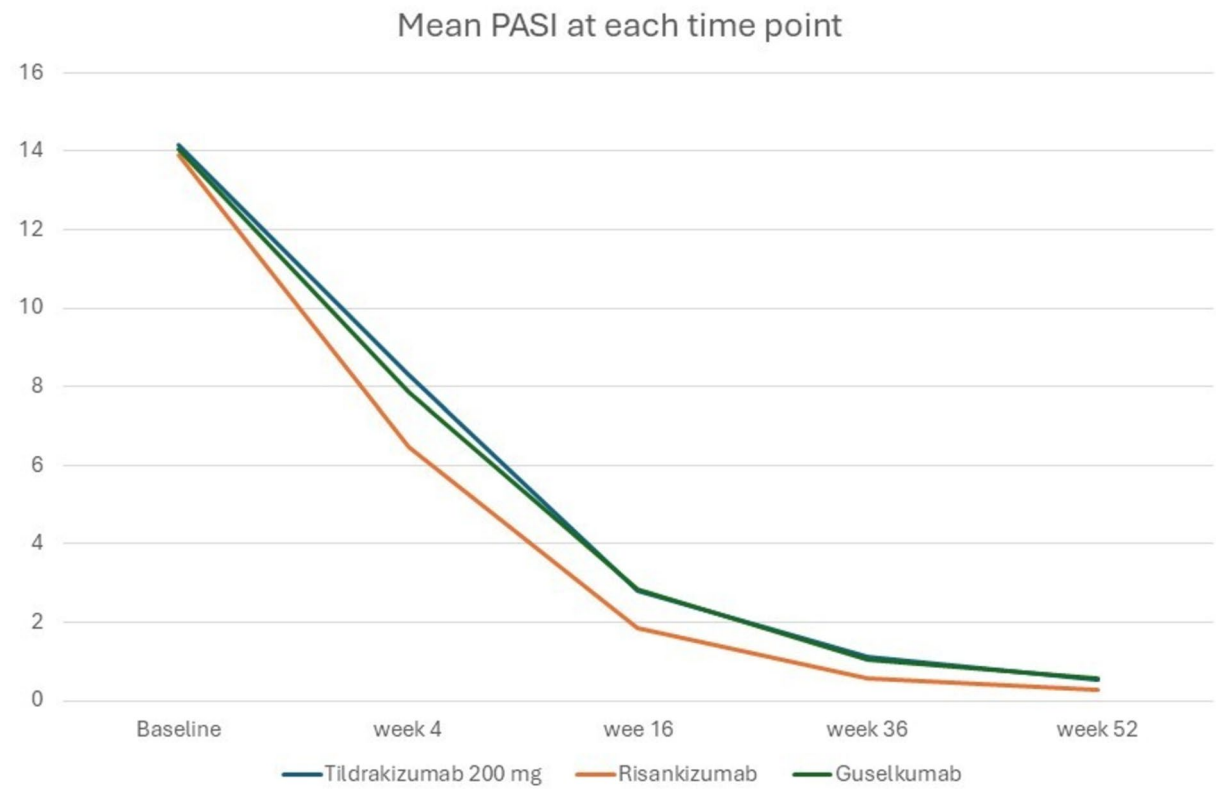

Fig. 1 Evolution of mean PASI scores over time for three psoriasis treatments: tildrakizumab 200 mg (blue line), risankizumab (orange line), and guselkumab (green line). All three therapies led to a clear reduction in disease severity from baseline to week 52, with noticeable improvements by week 4. While each treatment follows a slightly different trajectory, the overall trend confirms their effectiveness in lowering PASI scores over the course of 1 year

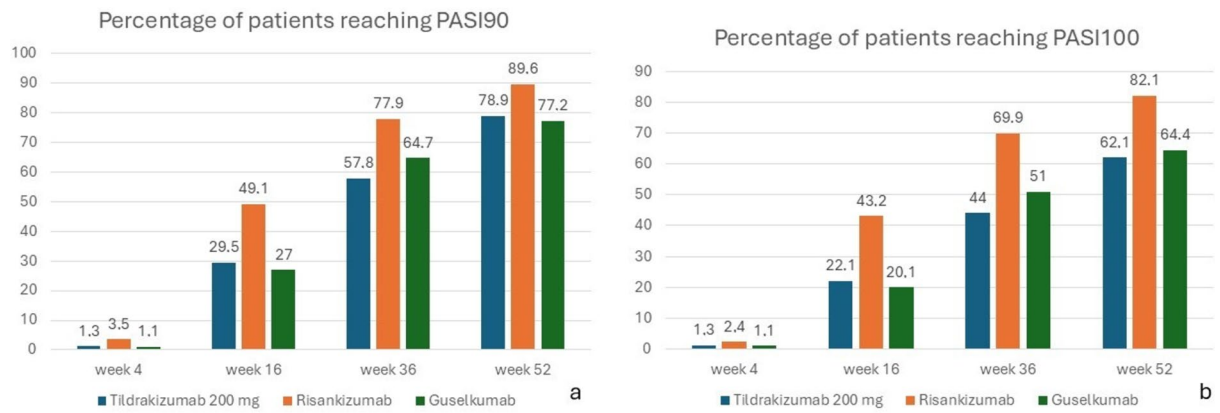

Fig. 2 Percentage of patients achieving PASI90 (**a**) and PASI100 (**b**) at weeks 4, 16, 36, and 52 for three biologic treatments: tildrakizumab 200 mg, risankizumab, and guselkumab. Risankizumab consistently demonstrates the highest rates of response, particularly in complete skin clearance (PASI100), while tildrakizumab and guselkumab show comparable efficacy by week 52

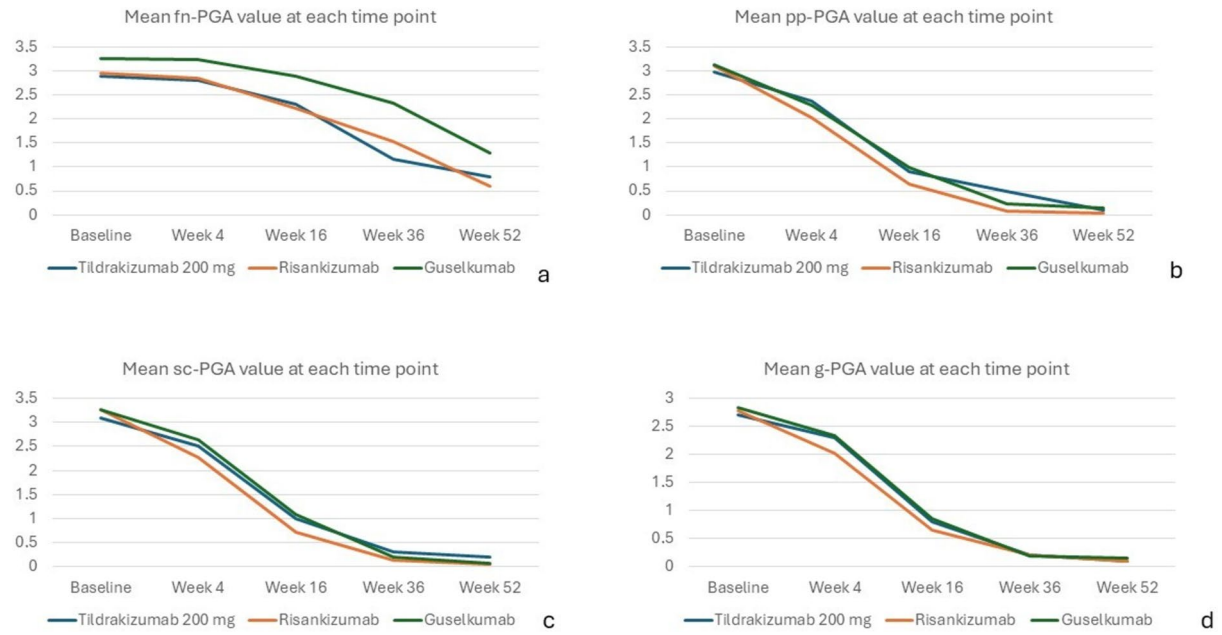

Fig. 3 Mean values of four types of Physician's Global Assessment (PGA)—fn-PGA (**a**), pp-PGA (**b**), sc-PGA (**c**), and g-PGA (**d**)—recorded at baseline and at weeks 4, 16, 36, and 52 for patients treated with tildrakizumab 200 mg, risankizumab, and guselkumab. All graphs display a consistent downward trend over time, indicating clinical improvement across all assessed areas. While the three treatments show similar trajectories, minor differences in the rate and extent of response are visible depending on the PGA subtype

improvement, with risankizumab and tildrakizumab demonstrating superior outcomes compared to guselkumab. At week 52, risankizumab achieved the lowest mean fn-PGA score of 0.60, indicating near-complete resolution of nail lesions (Fig. 3). Tildrakizumab followed closely with a mean fn-PGA of 0.80, while guselkumab lagged behind with a score of 1.28 ($p = 0.003$). The proportion of patients reaching complete clearance at week 52 (fn-PGA = 0) was highest with risankizumab at 90.0% ($p = 0.019$). Still, tildrakizumab also performed well, with 76.7% of patients achieving this endpoint. In comparison, guselkumab reached fn-PGA 0/1 in 60% of patients (Fig. 4). These results highlight a clear advantage for risankizumab. However, the difference between risankizumab and tildrakizumab 200 mg was not as stark as initially suggested, and tildrakizumab maintained a strong performance throughout.

Palms/Soles

In palmoplantar psoriasis, risankizumab again showed the most rapid improvement, with a mean pp-PGA of 0.08 at week 36, compared to 0.33 for guselkumab and 0.25 for tildrakizumab ($p = 0.01$). However, by week 52, all three treatments achieved near-complete clearance ($p = 0.438$). Risankizumab and tildrakizumab both reached a mean pp-PGA 0, while guselkumab recorded a slightly higher score of 0.06 (Fig. 3). Considering pp-PGA 0/1, it was reached at 16 weeks by 73.3%, 83.7% and 77.4% of patients treated with guselkumab, risankizumab, and tildrakizumab 200 mg respectively ($p = 0.47$) and by all patients at week 52 (Fig. 4). These findings suggest that while risankizumab may induce faster resolution, tildrakizumab is equally capable of achieving full clearance over time.

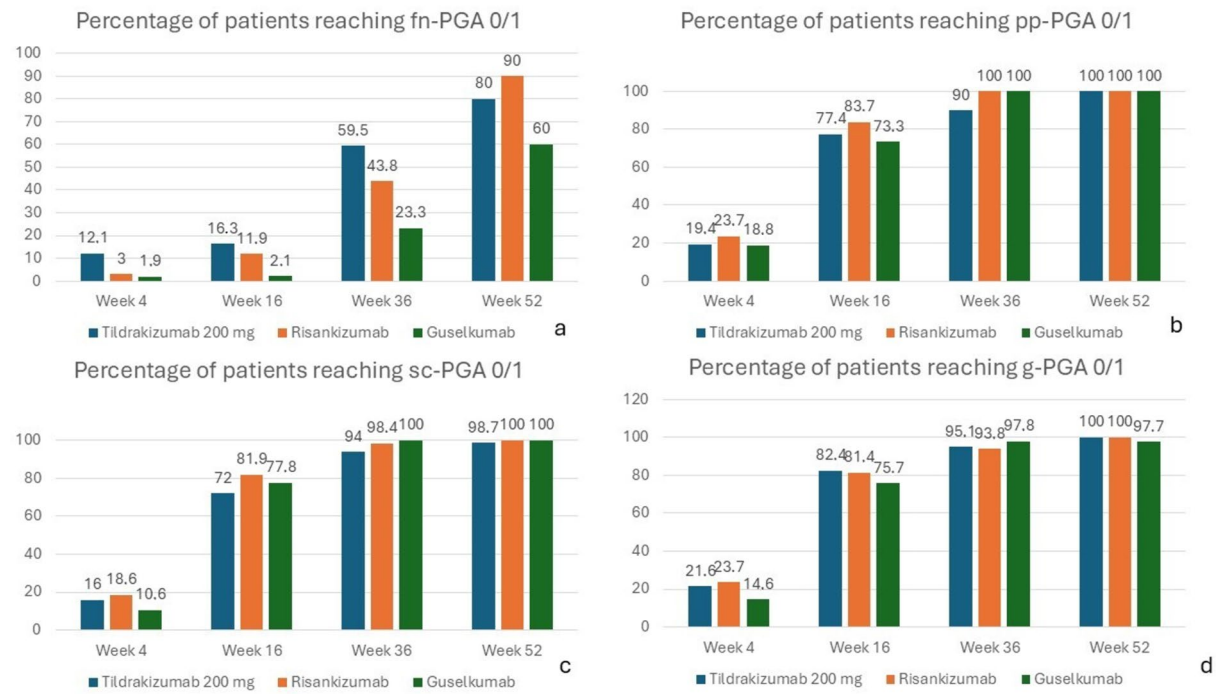

Fig. 4 Percentage of patients achieving a PGA score of 0 or 1—indicating clear or almost clear skin—for four anatomical regions: fingernails (fn-PGA, **a**), palms and soles (pp-PGA, **b**), scalp (sc-PGA, **c**), and genitals (g-PGA, **d**). Data are reported at weeks 4, 16, 36, and 52 for patients treated with tildrakizumab 200 mg, risankizumab, and guselkumab. All treatments show progressive improvement over time, with risankizumab generally reaching the highest response rates, especially in global and facial assessments. Notably, complete clearance of palms and soles is achieved by all three therapies by week 36 and maintained through week 52

Scalp

Scalp psoriasis presented a more complex picture. At baseline, the prevalence of scalp involvement was highest in the tildrakizumab group, which may have influenced subsequent outcomes. At week 16, risankizumab recorded the lowest mean sc-PGA score of 0.72, followed by guselkumab at 1.01 and tildrakizumab at 1.24 ($p = 0.002$). By week 52, risankizumab maintained its lead with a mean PGA of 0.04, while guselkumab and tildrakizumab reached scores of 0.06 and 0.18 respectively ($p = 0.023$) (Fig. 3). About sc-PGA 0/1, 77.8% of patients treated with guselkumab reported it at week 16 versus 81.9% of risankizumab and 72% of tildrakizumab. Although risankizumab showed the most consistent improvement, tildrakizumab 200 mg demonstrated a substantial reduction in sc-PGA over time, particularly considering its higher baseline involvement. These results suggest that risankizumab may offer faster and more complete resolution of scalp lesions, but tildrakizumab is also highly effective, especially in patients with more severe baseline involvement.

Genitals

In genital psoriasis, early differences were observed at week 4, with risankizumab achieving a mean g-PGA of 2.03, compared to 2.34 for guselkumab and 2.27 for tildrakizumab ($p = 0.034$) (Fig. 3). These values indicate a slightly better initial response with risankizumab with g-PGA 0/1 at week 16 in 75.7% guselkumab, 81.4% in risankizumab, and 82.4% in tildrakizumab 200 mg ($p = 0.533$)

and 97.7% in guselkumab at week 52 an 100% in risankizumab and tildrakizumab 200 mg at week 52 ($p = 0.382$). However, by week 52, all three treatments reached near-complete clearance, with risankizumab and tildrakizumab both achieving a mean g-PGA of 0, and guselkumab recording 0.03 ($p = 0.485$). The convergence of scores at the final time point suggests that all three agents are highly effective in treating genital lesions, with no clinically significant differences in long-term outcomes. All the results are reported in Tables 2 and 3.

Safety

Overall, IL-23p19 inhibitors demonstrated a favorable safety profile throughout the 52-week observation period (Table 4). Adverse events were infrequent, occurring in approximately 4.0% of patients overall, and were predominantly mild. The most reported events were upper respiratory tract infections (2.4%), followed by headache (approx. 1.5%) and nausea (approx. 1.0%), with comparable rates across guselkumab, risankizumab, and tildrakizumab 200 mg. Injection site reactions were uncommon (< 1% overall). No serious adverse events were observed, including major cardiovascular events, malignancies, or severe infections, and no treatment discontinuations due to adverse events were recorded. Safety outcomes were consistent across the three IL-23p19 inhibitors, and no unexpected safety signals emerged during follow-up, in line with pivotal trials and real-world evidence.

DISCUSSION

Integrated analysis of real-world and clinical trials data confirms the differentiated efficacy profiles of guselkumab, risankizumab, and tildrakizumab 200 mg in the treatment of moderate-to-severe psoriasis. Risankizumab consistently demonstrated the most rapid and sustained reduction in disease severity, with PASI90 and PASI100 response rates exceeding those reported in pivotal trials [19]. In our cohort, risankizumab achieved PASI90 in nearly 90% of patients and PASI100 in over 80% by week 52, surpassing the benchmarks set by UltIMMa-1 and UltIMMa-2. These results align with multicenter real-life studies, which have reported similarly high efficacy, along with favorable drug survival and low discontinuation rates [29–31]. Tildrakizumab, administered at 200 mg, showed a slower initial response but a clear acceleration after week 16, ultimately reaching PASI90 rates close to 80% at week 52. This trajectory is consistent with findings from the reSURFACE trials, where the 200 mg dose outperformed the 100 mg regimen, particularly in patients with elevated BMI [25]. In our cohort, patients treated with tildrakizumab tended to have a higher mean BMI compared with the other treatment groups, which may have influenced both the initial response kinetics and the overall efficacy observed. This characteristic should be considered when interpreting the comparative results. Multicenter studies further support the use of the higher dose, demonstrating improved outcomes in real-world settings [27–32]. Our data confirm that tildrakizumab 200 mg offers robust long-term efficacy, especially in patients with prior systemic exposure or more treatment-resistant disease. Guselkumab, while slightly less effective in early phases, maintained solid long-term performance. PASI90 rates at week 52 approached 77%, in line with VOYAGE 1 and 2 trial outcomes [22]. Though guselkumab showed lower efficacy in nail and scalp psoriasis compared to the other agents, it remained effective in genital and trunk involvement. Observational studies and registries have highlighted guselkumab's durability and safety, making it a reliable option for patients prioritizing long-term disease control over rapid clearance [33]. Site-specific analysis reinforces these trends. A previous 28-weeks study demonstrated a comparable efficacy and safety profile for all anti-IL-23, with guselkumab and risankizumab appearing slightly faster than tildrakizumab 100 mg, particularly on palmoplantar lesions in the short-term [28]. Our study evaluated the double dose of tildrakizumab, which according to expert consensus is specifically recommended in psoriasis involving special sites [26]. Moreover, our patients were observed

Table 3 Mean fingernails (fn)-Physician Global Assessment (PGA), palmoplantar (PP)-PGA, scalp (sc)-PGA, and genitals (g)-PGA values and percentage of patients reaching PASI90 and PASI100 at each time point

Variables	Guselkumab	Risankizumab	Tildrakizumab 200 mg	*p*
Nails, *n* (%)	53 (29.9)	67 (26.4)	91 (38.1)	0.018
fn-PGA Baseline, mean (SD)	3.25 (0.83)	2.96 (0.89)	2.89 (1.13)	0.107
fn-PGA 4w, mean (SD)	3.23 (0.89)	2.85 (0.91)	2.81 (1.18)	0.054
fn-PGA 6w, mean (SD)	2.89 (0.81)	2.22 (0.87)	2.31 (1.01)	< 0.001
fn-PGA 36w, mean (SD)	2.32 (1.02)	1.53 (0.92)	1.17 (0.96)	< 0.001
fn-PGA 52w, mean (SD)	1.28 (0.76)	0.60 (0.77)	0.80 (0.82)	0.003
fn-PGA 0 4w, *n* (%)	1 (1.9)	2 (3.0)	11 (12.1)	0.021
fn-PGA 0 16w, *n* (%)	1 (2.1)	7 (11.9)	14 (16.3)	0.049
fn-PGA 0 36w, *n* (%)	7 (23.3)	14 (43.8)	25 (59.5)	0.010
fn-PGA 0 52w, *n* (%)	18 (60.0)	27 (90.0)	32 (80.0)	0.019
Palms/Soles, *n* (%)	48 (27.1)	59 (23.2)	62 (25.9)	0.625
pp-PGA Baseline, mean (SD)	3.12 (0.87)	3.10 (0.92)	2.97 (0.97)	0.617
pp-PGA 4w, mean (SD)	2.29 (0.99)	2.03 (0.98)	2.37 (1.01)	0.159
pp-PGA 16w, mean (SD)	0.98 (0.81)	0.65 (0.80)	0.89 (0.85)	0.142
pp-PGA 36w, mean (SD)	0.24 (0.44)	0.08 (0.28)	0.50 (0.68)	0.010
pp-PGA 52w, mean (SD)	0.14 (0.36)	0.04 (0.20)	0.08 (0.27)	0.438
pp-PGA 0 4w, *n* (%)	9 (18.8)	14 (23.7)	12 (19.4)	0.775
pp-PGA 0 16w, *n* (%)	33 (73.3)	41 (83.7)	41 (77.4)	0.470
pp-PGA 0 36w, *n* (%)	29 (100.0)	25 (100.0)	27 (90.0)	0.061
pp-PGA 0 52wv (%)	28 (100.0)	24 (100.0)	26 (100.0)	NA
Scalp, *n* (%)	104 (58.8)	161 (63.4)	194 (81.2)	< 0.001
sc-PGA Baseline, mean (SD)	3.27 (0.82)	3.26 (0.82)	3.11 (0.96)	0.196
sc-PGA 4w, mean (SD)	2.63 (1.00)	2.27 (0.96)	2.52 (1.03)	0.008
sc-PGA 16w, mean (SD)	1.09 (0.83)	0.72 (0.85)	1.01 (0.89)	0.002
sc-PGA 36w, mean (SD)	0.19 (0.39)	0.14 (0.40)	0.32 (0.62)	0.081
sc-PGA 52w, mean (SD)	0.06 (0.24)	0.04 (0.19)	0.18 (0.41)	0.023
sc-PGA 0 4w, *n* (%)	11 (10.6)	30 (18.6)	31 (16.0)	0.210
sc-PGA 0 16w, *n* (%)	61 (67.8)	113 (81.9)	126 (72.0)	0.036
sc-PGA 0 36w, *n* (%)	54 (100.0)	62 (98.4)	79 (94.0)	0.098
sc-PGA 0 52w, *n* (%)	51 (100.0)	56 (100.0)	74 (98.7)	0.488

Table 3 continued

Variables	Guselkumab	Risankizumab	Tildrakizumab 200 mg	*p*
Genitals, *n* (%)	82 (46.3)	114 (44.9)	102 (42.7)	0.750
g-PGA Baseline, mean (SD)	2.84 (0.66)	2.78 (0.70)	2.68 (0.98)	0.358
g-PGA 4w, mean (SD)	2.34 (0.88)	2.03 (0.85)	2.27 (1.00)	0.034
g-PGA 16w, mean (SD)	0.86 (0.82)	0.65 (0.83)	0.74 (0.81)	0.259
g-PGA 36w, mean (SD)	0.18 (0.44)	0.21 (0.54)	0.24 (0.62)	0.851
g-PGA 52w, mean (SD)	0.16 (0.43)	0.09 (0.29)	0.08 (0.28)	0.485
g-PGA 0 4w, *n* (%)	12 (14.6)	27 (23.7)	22 (21.6)	0.284
g-PGA 0 16w, *n* (%)	53 (75.7)	83 (81.4)	75 (82.4)	0.533
g-PGA 0 36w, *n* (%)	44 (97.8)	45 (93.8)	39 (95.1)	0.637
g-PGA 0 52w, *n* (%)	42 (97.7)	45 (100.0)	37 (100.0)	0.382

SD standard deviation, *FN* fingernails, *PGA* Physician Global Assessment, *PP* palmoplantar, *SC* scalp, *G* genitals, *w* weeks

Table 4 Data are reported as percentage (number of patients)

Adverse events (AEs)	Guselkumab (*n* = 177)	Risankizumab (*n* = 254)	Tildrakizumab 200 mg (*n* = 239)	Overall (*n* = 670)
Any AE	4% (7)	4.3% (11)	3.8% (9)	4% (27)
Upper respiratory tract infections	2.3% (4)	2.8% (7)	2.1% (5)	2.4% (16)
Headache	1.1% (2)	1.6% (4)	1.3% (3)	1.3% (9)
Nausea	0.6% (1)	1.2% (3)	1.3% (3)	1% (7)
Injection site reactions	1.1% (2)	0.8% (2)	0.8% (2)	0.9% (6)
Serious adverse events	0	0	0	0
Discontinuation due to AEs	0	0	0	0

No major cardiovascular events, malignancies, or severe infections were observed. No unexpected safety signals emerged during the observation period. Adverse events were collected during routine clinical practice; therefore, mild self-limiting events may have been underreported

AEs adverse events

for 52 weeks, a longer follow-up compared to previous real-life studies, better reflecting the physiological timelines of response and maintenance in these areas. In our study, risankizumab achieved the lowest PGA scores in nail and scalp psoriasis, with a mean of 0.60 in nail involvement at week 52, followed closely by tildrakizumab at 0.80. Guselkumab recorded a higher score of 1.28, suggesting less complete resolution in this domain. These findings are consistent

with other studies, which emphasized risankizumab's superior performance in the early weeks of treatment, with the three molecules appearing to converge around 52 weeks [34]. In palmoplantar psoriasis, tildrakizumab showed notable efficacy, with long-term outcomes comparable to risankizumab. Guselkumab, while effective in genital and scalp areas, appeared less potent in nail clearance, a pattern observed in multiple real-world cohorts. The narrowing efficacy gap between risankizumab and tildrakizumab 200 mg by week 52 underscores the importance of tailoring treatment to individual patient profiles. Risankizumab remains the preferred option for patients requiring rapid symptom relief or complete clearance in difficult-to-treat areas. Tildrakizumab at 200 mg offers a compelling alternative for patients with higher BMI, prior biologic exposure, or those who may benefit from a more gradual but sustained response. Guselkumab continues to be a dependable choice, particularly for patients seeking predictable efficacy and long-term safety. Psoriasis is a genetically complex and heterogeneous disease, with more than one hundred susceptibility loci identified through large-scale genome-wide association studies (GWAS) , many of which converge on immune regulation and cytokine signalling pathways, including the IL-23/Th17 axis. Recent GWAS data suggest that interindividual variability in treatment response may, at least in part, reflect underlying genetic architecture, supporting the hypothesis that differential responsiveness to IL-23p19 inhibition could be genetically determined [35, 36]. Beyond static genetic susceptibility, increasing evidence indicates that the transcriptional landscape of psoriatic skin is highly dynamic and clinically informative. Whole-transcriptome RNA sequencing and transcriptomic fingerprinting approaches have been shown to predict therapeutic response, capture early molecular changes preceding clinical improvement, and enable longitudinal monitoring of biologic treatment efficacy [37–39]. In this context, integrating transcriptomic profiling into clinical practice may improve patient stratification and optimize treatment selection for IL-23p19 inhibitors, including guselkumab, risankizumab, and tildrakizumab, which, despite sharing the same molecular target, differ in epitope binding, molecular structure, and pharmacokinetic properties. Furthermore, additional cytokine pathways, such as those involving IL-20, have been implicated in keratinocyte activation and epidermal inflammation and may contribute to residual disease activity or variability in response even under effective IL-23 blockade [40]. A key limitation of the present study is the absence of integrated genetic and transcriptomic analyses, which precluded the identification of molecular predictors of response and the evaluation of treatment-induced biological changes over time. Future prospective studies incorporating genomic stratification and longitudinal transcriptomic profiling are therefore warranted to enhance response prediction, personalize therapeutic strategies, and refine outcome monitoring beyond clinical endpoints alone. Taken together, our findings integrate and extend existing evidence from both clinical trials and real-world studies. The retrospective design of this study inherently limits causal inference and may introduce selection bias. Additionally, a proportion of patients were lost to follow-up at later time points, which could affect the accuracy of long-term efficacy and safety estimates. Future prospective studies with longer and more complete observation periods are warranted to validate these findings.

Limitations

This study has some limitations. The retrospective design may limit causal interpretation, and a proportion of patients were lost to follow-up at later time points, which could influence long-term outcome estimates. In addition, the lack of integrated genetic and transcriptomic analyses did not allow exploration of potential molecular predictors of response. Prospective studies with more complete follow-up and molecular characterization are warranted to further refine these findings.

CONCLUSION

These results support a personalized approach to biologic therapy in psoriasis, where treatment selection is guided by factors such as anatomical involvement, baseline severity, prior treatment history, and individual therapeutic goals. By re-evaluating the potential differences in efficacy among these molecules at clinically relevant dosing, this study seeks to provide actionable insights for optimizing biologic therapy in patients whose disease burden is concentrated in high-impact areas, even when total PASI scores might otherwise be considered mild. Importantly, these findings also allow us to reframe the real-life effectiveness of tildrakizumab 200 mg in special site psoriasis, showing that, over longer follow-up, the differences in efficacy between IL-23p19 inhibitors appear less pronounced than previously suggested. Ultimately, refining our understanding of the relative performance of IL-23p19 inhibitors in these challenging scenarios will help bridge the disconnect between conventional severity metrics and the lived reality of patients, ensuring that treatment decisions align with both clinical efficacy and patient-centered outcomes.

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Declarations

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