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Zasocitinib for the Treatment of Moderate-to-Severe Plaque Psoriasis

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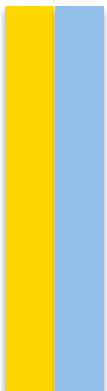

Zasocitinib for the Treatment of Moderate-to-Severe Plaque Psoriasis

Artigo de Revisão Bibliográfica

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Resumo

A introdução dos inibidores da tirosina cinase 2 representou uma mudança estrutural no tratamento da psoríase, ao procurar conciliar a conveniência da via oral com uma seletividade que mimetiza o perfil de segurança dos fármacos biológicos. O Zasocitinib (também conhecido por TAK-279) surge como um expoente desta nova classe, distinguindo-se pelo seu mecanismo de inibição alostérica altamente seletivo, que teoricamente contorna as limitações de segurança historicamente associadas aos inibidores JAK não seletivos.

Este trabalho de revisão analisa a evidência clínica atual do Zasocitinib, desde a caracterização farmacológica inicial até aos resultados mais recentes dos ensaios de Fase IIb e Fase III. Os dados disponíveis demonstram uma eficácia robusta e dose-dependente, com taxas de resposta PASI 75 e PASI 90 que desafiam os padrões atuais das terapêuticas orais. Notavelmente, os resultados preliminares do programa LATITUDE-PsO corroboram a manutenção desta eficácia a médio prazo, apresentando um perfil de tolerabilidade favorável, dominado por eventos adversos ligeiros como acne e cefaleias.

Contudo, apesar do entusiasmo clínico, subsistem questões críticas. A ausência de dados comparativos diretos (*head-to-head*) com biológicos de referência e a necessidade de monitorização de segurança a longo prazo em populações com múltiplas comorbilidades são limitações que não devem ser ignoradas. Em conclusão, o Zasocitinib posiciona-se como uma opção terapêutica promissora e diferenciadora, com potencial para redefinir o algoritmo de tratamento da psoríase moderada a grave, embora a sua integração definitiva na prática clínica dependa da confirmação da sua segurança sustentada e valor real em cenários de mundo real.

Palavras-chave: Psoríase; Zasocitinib; TAK-279; TYK2; Seletividade Alostérica.

Abstract

The introduction of tyrosine kinase 2 inhibitors has represented a structural shift in the treatment of psoriasis, aiming to combine the convenience of oral administration with a selectivity that mimics the safety profile of biological agents. Zasocitinib (also known as TAK-279) stands out as a prominent exponent of this new class, distinguished by its highly selective allosteric inhibition mechanism. This approach theoretically bypasses the safety limitations, namely Major Adverse Cardiovascular Events (MACE) and thromboembolism, historically associated with non-selective JAK inhibitors.

This narrative review analyzes the current clinical evidence for Zasocitinib, ranging from initial pharmacological characterization to the most recent results from Phase 2b and Phase 3 trials. Available data demonstrate robust, dose-dependent efficacy, with PASI 75 and PASI 90 response rates that challenge current standards for oral therapies. Notably, preliminary results from the LATITUDE-PsO program corroborate the maintenance of this efficacy in the medium term, presenting a favorable tolerability profile dominated by mild adverse events such as acne and headaches.

However, despite clinical enthusiasm, critical questions remain. The absence of head-to-head comparative data with reference biologics and the need for long-term safety monitoring in populations with multiple comorbidities are limitations that should not be overlooked. In conclusion, Zasocitinib positions itself as a promising and differentiating therapeutic option with the potential to redefine the treatment algorithm for moderate-to-severe psoriasis, although its definitive integration into clinical practice depends on confirming sustained safety and real-world value.

Keywords: Psoriasis; Zasocitinib; TAK-279; TYK2; Allosteric Selectivity.

List of Abbreviations

anti-TNF	anti-Tumor Necrosis Factor
BSA	Body Surface Area
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
IFN-I	Type I interferons
IL-12	Interleukin-12
IL-17	Interleukin-17
IL-17A	Interleukin-17A
IL-17F	Interleukin-17F
IL-22	Interleukin-22
IL-23	Interleukin-23
JAK	Janus Kinase
JAK1	Janus Kinase 1
JAK2	Janus Kinase 2
JAK3	Janus Kinase 3
JAK-STAT	Janus Kinase-Signal Transducer and Activator of Transcription
MACE	Major Adverse Cardiovascular Events
PASI	Psoriasis Area and Severity Index
PGA	Physician´s Global Assessment
PsA	Psoriatic Arthritis
sPGA	static Physician´s Global Assessment
STAT	Signal Transducer and Activator of Transcription
Th17	Type 17 helper cells
TYK2	Tyrosine Kinase 2

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Introduction

Psoriasis is a chronic, systemic, immune-mediated inflammatory disease whose global prevalence shows considerable geographic and ethno-racial variation, affecting an estimated 2% to 3% of the world's population.[1] In terms of age distribution, disease incidence follows a bimodal pattern, with an initial increase up to 39 years of age, followed by a decline in the 40–49 age group, and a second peak between 50 and 69 years, subsequently decreasing in older populations.[2]

Contemporary epidemiological studies suggest a latitudinal prevalence gradient, with significantly higher incidence rates in Northern European countries compared to populations in East Asia and Sub-Saharan Africa.[1] In Portugal, a population-based study published in 2023 reported a prevalence of 1.9%, highlighting the substantial burden of this condition within the national context.[3]

Clinically, plaque psoriasis (*psoriasis vulgaris*) represents the most prevalent phenotypic variant, accounting for approximately 80% to 90% of cases.[4] It is characterised by well-demarcated, erythematous, scaly plaques that are often symmetrically distributed. From a histopathological perspective, these lesions reflect accelerated keratinocyte proliferation and abnormal differentiation (parakeratosis), accompanied by a dense dermal inflammatory infiltrate and marked neoangiogenesis.[5]

Disease severity is stratified using metric tools such as the Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA), with moderate-to-severe psoriasis defined when these indices exceed a threshold of 10.[6] This distinction is critical, as it determines the transition from topical therapies to systemic interventions, where Zasocitinib seeks to establish its therapeutic role.

The Impact on Quality of Life and Comorbidities

Psoriasis is now inseparable from a broad spectrum of systemic manifestations that extend beyond cutaneous inflammation. The most prevalent comorbidity is psoriatic arthritis (PsA), which affects approximately one-quarter of patients and may lead to irreversible joint damage and functional disability if not diagnosed and treated early.[7] In this context, the management of these patients often requires a multidisciplinary approach, as recommended by

organisations such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).[8]

Beyond joint involvement, moderate-to-severe psoriasis is associated with an increased risk of MACE. This phenomenon is partly explained by a state of chronic systemic inflammation that contributes to endothelial dysfunction and the formation of atherosclerotic plaques. The relationship between the severity of cutaneous disease and vascular inflammation has been progressively demonstrated, supporting the concept of the "psoriatic march."[9,10] This framework reinforces the importance of therapeutic strategies that go beyond controlling skin lesions and also target the reduction of systemic risk.

In parallel, the impact of psoriasis on mental health is significant and often underestimated. Epidemiological studies show a higher prevalence of depression and anxiety among these patients, which may compromise quality of life and treatment adherence.[11] Furthermore, the chronic and visible nature of the disease demands a continuous psychosocial adaptation, with repercussions across personal, social, and professional domains.[12] Therefore, the evaluation of new therapies, such as Zasocitinib, should not focus solely on improvements in cutaneous clinical indices, but also on their ability to positively impact patients' overall quality of life.[13]

Current Therapeutic Landscape

The therapeutic armamentarium for psoriasis has evolved exponentially in recent decades, in parallel with advances in the understanding of the disease's immunopathogenesis. In mild forms, management is primarily based on topical therapies. However, in clinical practice, adherence to these regimens is often limited, both due to their complexity and the need for repeated applications, which ultimately compromises long-term effectiveness.

In moderate-to-severe psoriasis, the introduction of biologic agents has represented a paradigm shift. Initially with anti-Tumor Necrosis Factor (anti-TNF) therapies and, more recently, with interleukin-17 (IL-17) and interleukin-23 (IL-23) inhibitors, it has become possible to achieve high levels of clinical response, including PASI 90 and PASI 100 rates that were previously unattainable.[14,15]

This progress has been driven by the development of therapies targeting specific molecular pathways, with particular emphasis on the IL-23 axis, now recognised as central to

the inflammatory cascade in psoriasis. Its inhibition not only enables greater efficacy in resolving cutaneous lesions, but also contributes to a more sustained therapeutic response over time.[16]

However, current clinical management continues to face significant challenges. Despite the demonstrated efficacy of next-generation biologics, factors such as the reliance on parenteral administration, high costs, and the potential for loss of response over time, often associated with immunogenicity, perpetuate a substantial therapeutic gap in dermatological practice.[17]

Accordingly, there remains an unmet clinical need for therapeutic options that combine the convenience of oral administration with efficacy and safety profiles comparable to those of biologic agents, which has driven the development of novel small molecules targeting specific pathways.

The Unmet Need for Oral Therapies

Despite the paradigm-shifting advances introduced by biologic agents, a substantial unmet clinical need remains in the treatment of moderate-to-severe psoriasis. Studies assessing patient preferences indicate that a significant proportion favour the oral route of administration, associating it with greater convenience and autonomy in disease management, with aversion to injectable therapies being a commonly reported factor.[18]

However, the currently available oral options present important limitations, particularly in terms of efficacy. While biologic agents consistently achieve high levels of clinical response, such as PASI 90 or PASI 100, traditional oral therapies, including phosphodiesterase-4 inhibitors such as Apremilast, tend to yield more modest responses, rarely exceeding PASI 75 in most clinical trials.[14,19]

Beyond suboptimal efficacy, the safety and tolerability of current oral options represent critical barriers to long-term treatment persistence. The chronic use of methotrexate or ciclosporin is limited by cumulative organ toxicity, necessitating rigorous laboratory monitoring that places a burden on both patients and healthcare systems, as outlined in current European guidelines.[20,21]

Conversely, newer oral therapies, particularly phosphodiesterase-4 inhibitors such as Apremilast, are often associated with gastrointestinal adverse effects that negatively impact daily quality of life.[19] There is, therefore, an urgent clinical need for novel oral molecules capable

of mimicking the selectivity and molecular potency of biologic agents while maintaining the convenience of once-daily administration.

In this context, the approval of Deucravacitinib marked a turning point. As the first allosteric Tyrosine Kinase 2 (TYK2) inhibitor to demonstrate superiority over Apremilast, this molecule validated selective TYK2 inhibition as a viable and safe long-term strategy to elevate the therapeutic ceiling of oral agents.[22,23] However, the pharmacological profile of Deucravacitinib suggests that greater selectivity and more potent inhibition of the TYK2 JH2 domain may translate into more robust and sustained clinical responses.[24]

Zasocitinib thus emerges as a next-generation TYK2 inhibitor. Designed to optimise allosteric selectivity, Zasocitinib aims to address this gap by offering efficacy approaching that observed with biologic agents, without compromising systemic safety.

Objectives

The primary objective of this narrative review is to analyse the available scientific evidence on Zasocitinib in the treatment of moderate-to-severe plaque psoriasis. To this end, it aims to describe the role of the TYK2 pathway in the pathophysiology of psoriasis, with particular emphasis on the IL-23/IL-17 axis, as well as to characterise the mechanism of action of Zasocitinib and its selectivity in relation to conventional Janus Kinase (JAK) inhibitors.

In addition, this work seeks to evaluate efficacy and safety data derived from preclinical studies and phase I, II, and III clinical trials, to compare Zasocitinib with other therapeutic options, namely Deucravacitinib and biologic agents, and to discuss its potential positioning within the therapeutic algorithm for psoriasis.

Methods

A narrative literature review was conducted to analyse the role of the TYK2 pathway in the pathophysiology of psoriasis and to evaluate the available clinical evidence on Zasocitinib in the treatment of moderate-to-severe plaque psoriasis.

The literature search was performed using the PubMed/MEDLINE, Google Scholar, ScienceDirect, and ClinicalTrials.gov databases, covering the period from January 2015 to March 2026. The following search terms were used, both individually and in various combinations: “psoriasis”, “TYK2 inhibitors”, “allosteric inhibition”, “zasocitinib”, “TAK-279”, and “deucravacitinib”.

Original articles, clinical trials, preclinical studies, and review articles published in English were included, provided they were relevant to the immunological mechanisms of the IL-23/IL-17 pathway and to the evaluation of the efficacy and safety of TYK2 inhibitors. Whenever possible, full-text analysis of the selected articles was performed. In cases where full-text access was not available, information was obtained from abstracts and other available secondary sources.

Exclusion criteria comprised duplicate articles, studies with limited relevance to the topic under investigation, and publications with insufficient data for the extraction of meaningful information.

Study selection was conducted based on the assessment of titles and abstracts, followed by full-text review of accessible articles deemed relevant. The reference lists of included studies were additionally screened (snowballing) to identify relevant studies not captured in the initial search.

Although a formal systematic assessment of risk of bias was not performed, priority was given to randomized clinical trials, advanced-phase studies, and publications in peer-reviewed scientific journals, in order to maximise the robustness of the included evidence.

In total, 44 references were included and considered fundamental for the development of this narrative review.

Pathophysiology and the Role of TYK2

The IL-23/IL-17 Signaling Axis

The understanding of psoriasis as an immune-mediated disease has evolved significantly over the past decades, largely due to the identification of the IL-23/IL-17 axis as a central element in its pathophysiology. This model has replaced the previously Th1-centred perspective, enabling a more integrated understanding of the underlying inflammatory mechanisms. Within this paradigm, activated dendritic cells play a fundamental role by producing IL-23, a cytokine responsible for the survival, expansion, and differentiation of Type 17 helper cells (Th17).[5,24] These cells, in turn, produce effector cytokines such as interleukin 17-A (IL-17A), interleukin-17F (IL-17F), and interleukin-22 (IL-22), which act directly on keratinocytes.

These molecules induce accelerated keratinocyte proliferation and the production of antimicrobial peptides, establishing an inflammatory feedback loop that culminates in the formation of psoriatic plaques.[6]

Beyond cutaneous involvement, this axis also has implications in the systemic inflammation associated with the disease, being involved in several of its comorbidities. It is therefore not surprising that it currently represents one of the main therapeutic targets, forming the basis of some of the most effective biologic therapies available.[4,17]

The JAK-STAT Signaling Pathway

The transmission of extracellular cytokine signals, such as IL-23 and interferons, to the cell nucleus depends on the Janus Kinase–Signal Transducer and Activator of Transcription (JAK–STAT) pathway. This pathway comprises four intracellular tyrosine kinases: Janus Kinase 1 (JAK1), Janus Kinase 2 (JAK2), Janus Kinase 3 (JAK3), and TYK2. These kinases associate with the cytoplasmic tails of cytokine receptors and, upon ligand binding, undergo autophosphorylation, creating docking sites for Signal Transducers and Activators of Transcription (STAT) proteins.[24,26]

In psoriasis, activation of these proteins (particularly STAT3) results in their dimerisation and translocation to the nucleus, where they function as transcription factors for pro-inflammatory genes.[5,24,27] Although essential for both innate and adaptive immunity, chronic dysregulation of this pathway underlies persistent inflammation.[24] The complexity of this system lies in its redundancy: different cytokines utilise distinct combinations of JAKs, making pharmacological selectivity a critical challenge in order to avoid undesirable off-target effects on physiological pathways unrelated to the disease.[24,28]

TYK2: Structure and Function

TYK2 plays a pivotal role in the signalling of key cytokines in psoriasis, mediating responses to IL-23, interleukin-12 (IL-12), and type I interferons (IFN-I). It is critical for the activation and maintenance of the IL-23/IL-17 axis and represents a strategic therapeutic target in the management of the disease.[24,29]

From a structural perspective, TYK2 is composed of seven Janus Homology (JH1–JH7) domains. Among these, a key distinction lies between the catalytic domain (JH1), responsible

for kinase activity, and the pseudokinase domain (JH2), which exerts a regulatory function through allosteric mechanisms.[24,26] This differentiation has direct implications for the development of targeted therapeutic strategies.

Conventional JAK inhibitors (pan-JAK) act at the level of the catalytic domain, which is highly conserved across the different JAKs. This lack of selectivity is associated with relevant adverse effects, particularly haematological abnormalities resulting from the unintended inhibition of JAK2.[27] In contrast, the development of molecules such as Deucravacitinib and Zasocitinib has introduced a distinct approach, based on the allosteric inhibition of the JH2 domain.[24,30,31]

This strategy enables greater selectivity for TYK2, reducing interference with other physiological pathways dependent on the remaining JAKs.[32] In the case of Zasocitinib, the available pharmacological data suggest effective inhibition of inflammatory signalling with a more limited systemic impact.[33]

Thus, selective TYK2 inhibition represents a promising therapeutic approach, aiming to balance efficacy and safety. Emerging data suggest that this class of drugs may constitute a relevant oral alternative to biologic agents, although its definitive positioning will depend on further clinical evidence.[31,34]

Zasocitinib

Chemical Structure and Mechanism of Action

Zasocitinib is a highly selective, small-molecule oral inhibitor designed to target the TYK2 pseudokinase (JH2) domain. Unlike traditional catalytic inhibitors that compete for the ATP-binding site within the JH1 domain, Zasocitinib acts through an allosteric inhibition mechanism.[24,26,32]

From a structural perspective, the molecule was designed to bind to the regulatory JH2 domain, inducing a conformational change that prevents activation of the adjacent catalytic domain. This mechanism enables functional inhibition of TYK2 without directly interfering with the conserved catalytic sites shared among different JAKs.

The clinical relevance of this approach lies in its extreme selectivity: Zasocitinib demonstrates approximately a one-million-fold greater selectivity for the TYK2 JH2 domain

compared with the JH2 domain of JAK1.[32,33] This selectivity enables the inhibition of psoriasis-relevant pathways, such as IL-23 and IFN-I mediated signalling, while preserving physiological functions dependent on other JAKs, particularly those associated with haematopoiesis.

This molecular precision, initially validated by Deucravacitinib, is what allows oral small molecules to achieve higher levels of clinical response in psoriasis.[31]

Pharmacokinetics and Pharmacodynamics

From a pharmacokinetic perspective, Zasocitinib exhibits rapid absorption following oral administration, enabling the attainment of stable plasma concentrations compatible with a once-daily dosing regimen. This aspect is particularly relevant in chronic diseases such as psoriasis, in which the simplicity of the therapeutic regimen may significantly influence treatment adherence.[18,33,35]

With regard to pharmacodynamics, Zasocitinib demonstrates potent and sustained inhibition of IL-23 induced STAT3 phosphorylation, reflecting its direct impact on the Th17 inflammatory pathway. Molecular characterisation studies suggest that this inhibition occurs even at clinically safe concentrations, while maintaining selectivity for TYK2. Importantly, this selectivity translates into reduced interference with other JAK-dependent pathways, such as those mediated by erythropoietin or γc interleukins, which play essential physiological roles.[32,33]

Taken together, these data point to a potentially favourable therapeutic window, combining efficacy in modulating the inflammatory response with minimal systemic off-target effects. This feature distinguishes Zasocitinib from non-selective JAK inhibitors, in which efficacy is often associated with a higher risk of adverse effects, necessitating a more delicate balance between benefit and safety.[28,36]

Preclinical Evidence

The preclinical evidence supporting the development of Zasocitinib is based on studies conducted in both *in vitro* and *in vivo* models of immune-mediated inflammation. In experiments using human cells, the molecule was shown to reduce the production of cytokines such as IL-17 and IL-22 in stimulated T lymphocytes, mimicking the effects of anti–IL-23 monoclonal antibodies.[32,33]

In animal models of psoriasis, particularly the imiquimod-induced inflammation model, the administration of Zasocitinib resulted in a significant reduction in epidermal thickness, inflammatory infiltrate, and the expression of genes associated with the IL-23/IL-17 axis. These findings further support the relevance of TYK2 as a therapeutic target in this context.[32,33]

In addition to efficacy, preclinical data also suggest a favourable safety profile, with no significant alterations observed in haematological parameters, such as red blood cell or platelet counts. This aspect reinforces the safety advantage of allosteric inhibition compared with conventional catalytic inhibition.[26,32]

Clinical Evidence: Results from Trials

Phase I Studies: Safety and Tolerability

Initial Phase I studies were fundamental in establishing the pharmacokinetics and preliminary safety of Zasocitinib in humans. In these single and multiple-ascending dose trials, the molecule demonstrated rapid oral absorption and a half-life compatible with once-daily administration, both of which are relevant for its clinical application.[33] Drug exposure was shown to be dose-proportional in both healthy volunteers and patients with psoriasis, suggesting a predictable pharmacokinetic profile. This characteristic is particularly important in early-phase development, as it facilitates dose selection and optimisation in subsequent clinical studies.

With regard to safety, Zasocitinib was generally well tolerated, with no serious adverse events reported. In addition, no clinically relevant changes were observed in haematological, lipid, or creatine phosphokinase parameters, which are commonly monitored in therapies targeting the JAK pathway.[33,35]

These findings confirm, in a clinical setting, the high selectivity of TYK2 over other Janus kinases (JAK1/2/3) that had been predicted in preclinical models, thereby avoiding the systemic adverse effects associated with first-generation JAK inhibitors.[32,33]

Phase II Trials: Efficacy and Safety

The phase IIb clinical trial represented a pivotal milestone in demonstrating the efficacy of Zasocitinib in moderate-to-severe plaque psoriasis. In this randomised, double-blind, placebo-controlled study, 259 patients were enrolled and assigned to five treatment arms: placebo and

doses of 2 mg, 5 mg, 15 mg, and 30 mg, administered once daily over a 12-week period.[35] The results demonstrated a statistically significant and clinically robust dose-dependent response.

In the group receiving the 30 mg dose, 67% of patients achieved the primary endpoint of PASI 75, compared with only 6% in the placebo group. This trend was maintained for more stringent endpoints, with 46% of patients achieving PASI 90 and 33% reaching PASI 100.[35] These findings are consistent with recent reviews highlighting the promising efficacy of emerging oral therapies.[37]

In addition, assessment using the Physician's Global Assessment (PGA) reinforced these findings, with 52% of patients in the highest-dose group achieving a score of 0 or 1, indicative of clear or almost clear skin.[35] These findings support the potential of the molecule to induce deep remissions comparable to those observed with some biological agents.[38]

Regarding safety in this trial, most adverse events were of mild to moderate severity. COVID-19 infection, acne/acneiform dermatitis and diarrhea were reported as the most frequent adverse events.[35]

It is important to note that, in contrast to what has been observed with non-selective JAK inhibitors, no clinically meaningful laboratory abnormalities were observed in haematological or lipid parameters, nor were MACE or venous thromboembolism reported during the study period.[28,36] This absence of severe systemic toxicity suggests that high selectivity for the JH2 domain may overcome the historical limitations of catalytic inhibitors, providing a safer therapeutic window for the chronic treatment of psoriasis.[24,33]

Ongoing Phase III Programs (LATITUDE-PsO)

At present, definitive confirmation of the therapeutic value of Zasocitinib relies on the global Phase III programme, designated LATITUDE-PsO. This programme comprises two multicentre studies with identical designs, LATITUDE-PsO-1[39] and LATITUDE-PsO-2[40], ensuring the reproducibility of efficacy and safety data required for regulatory submission. These trials were designed to evaluate clinical efficacy and long-term safety in a large cohort of more than 1700 patients with moderate-to-severe psoriasis.

Recently reported Phase III results from the LATITUDE-PsO programme strongly suggest the efficacy and safety of Zasocitinib, based on company-reported data.[42] In the LATITUDE PsO-1 and PsO-2 studies, Zasocitinib demonstrated superiority over both placebo and Apremilast,

with approximately 70% of patients achieving static Physician´s Global Assessment (sPGA) 0/1 at week 16.

PASI 90 response rates ranged from 52% to 61%, while PASI 100 rates ranged from 25% to 33%, indicating a level of efficacy exceeding that of currently available oral therapies. An early onset of action was also observed, with differences versus placebo evident as early as week 4, as well as sustained response in more than 90% of responders through week 60. The safety profile remained overall consistent with that observed in Phase II studies, with no new significant safety signals identified.[42]

In parallel, a direct head-to-head comparative study with Deucravacitinib[41] is currently underway, with the aim of clarifying the relative positioning of these two molecules within the same therapeutic class. This type of comparison will be particularly relevant in determining whether pharmacological differences, such as the degree of selectivity for the TYK2 JH2 domain, translate into clinically meaningful advantages.

Discussion

Comparison with Deucravacitinib

The introduction of Deucravacitinib represented a significant milestone in the oral treatment of psoriasis, demonstrating that selective TYK2 inhibition can achieve levels of efficacy superior to those previously observed with small molecules such as Apremilast.[22,30,43]

However, available data suggest that there may still be room for further optimisation within this pharmacological class.

The results of the phase IIb trial of Zasocitinib demonstrate a robust, dose-dependent clinical response, with PASI 75 rates of approximately 67% at 12 weeks with the 30 mg dose.[35] In comparison, pivotal trials of Deucravacitinib report PASI 75 response rates in the range of 53–58% at 16 weeks.[22,43]

Although this difference suggests a potential increase in efficacy, it is important to emphasise that these comparisons are indirect and inherently limited by methodological differences between trials, including variations in inclusion criteria, baseline disease severity, and endpoint definitions, which may compromise the validity of robust comparative inferences.[44]

Furthermore, the apparently faster onset of action observed with Zasocitinib may reflect pharmacodynamic differences related to its greater potency and higher selectivity for the TYK2 JH2 domain. However, only ongoing head-to-head comparative trials will allow a rigorous determination of whether this advantage translates into consistent and clinically meaningful superiority.[41]

Implications of Allosteric TYK2 Inhibition

The key innovation of selective TYK2 inhibitors lies in their ability to modulate the JAK-STAT pathway through an allosteric mechanism, thereby avoiding inhibition of the catalytic domain that is highly conserved among different JAKs.[27,30] This approach represents an attempt to dissociate immunomodulatory efficacy from systemic toxicity, one of the major challenges associated with non-selective JAK inhibitors.

Available data suggest that Zasocitinib maintains a favourable short-term safety profile, with no evidence of haematological abnormalities, dyslipidaemia, or increased thromboembolic events, effects that have historically limited the use of conventional JAK inhibitors.[33,35] However, these findings should be interpreted with caution. Prior experience with drugs in this class indicates that rare but clinically relevant adverse events may only emerge following prolonged exposure and in more heterogeneous patient populations.[28,36]

Thus, while allosteric TYK2 inhibition represents a significant conceptual advance, it remains uncertain whether this selectivity will translate into a consistent long-term safety benefit. Confirmation of this potential will depend on data from extension studies and real-world clinical evidence.

Positioning Zasocitinib in the Treatment Algorithm

The positioning of Zasocitinib within the therapeutic algorithm for psoriasis should be considered in light of multiple factors, including efficacy, safety, patient preferences, and cost.

Currently, biological agents remain the reference standard in terms of efficacy, particularly in achieving PASI 90 and PASI 100 responses.[13,14] However, the need for parenteral administration and the associated costs may limit their acceptance and accessibility in certain settings.

In this context, Zasocitinib may represent a valuable therapeutic alternative for selected patients with moderate-to-severe psoriasis who do not respond to or cannot tolerate conventional systemic therapies, prefer to avoid injectable treatments, or value simple oral treatment regimens.[18]

Nevertheless, its earlier integration into the therapeutic algorithm will depend on confirmation of its comparative efficacy versus biologics and the demonstration of a robust long-term safety profile.

Limitations of Current Evidence

The interpretation of the available data on Zasocitinib should take into account several important limitations.

First, although robust Phase III results have recently been reported, the clinical evidence remains incomplete, as these data have not yet been fully published in peer-reviewed scientific journals and long-term follow-up remains limited.[33,42]

Second, the absence of direct comparisons with established biological agents makes it difficult to determine the drug's true therapeutic positioning. Indirect comparisons across clinical trials are inherently limited by methodological differences, including variations in inclusion criteria, baseline disease severity, and endpoint definitions.

Additionally, despite recent Phase III data, the available follow-up period remains relatively short, limiting the assessment of rare adverse events and long-term sustained efficacy, factors that are particularly relevant in a chronic disease such as psoriasis.[33,35]

Future Perspectives

The development of Zasocitinib is aligned with a growing trend toward the refinement of immunomodulatory therapies, with a particular focus on molecular selectivity and optimisation of the benefit–risk profile. This approach reflects an effort to bring the efficacy of oral small molecules closer to that achieved with biological agents, while maintaining the convenience of oral administration.

Recently reported Phase III trial results further support this potential, suggesting that Zasocitinib may represent a meaningful advancement in the oral treatment of psoriasis, helping to narrow the efficacy gap compared with biological agents.[33,42]

Nevertheless, its adoption in clinical practice will depend not only on clinical outcomes but also on factors such as cost, accessibility, and its eventual incorporation into international recommendations and guidelines. In addition, real-world experience will be crucial in clarifying its long-term safety profile and patterns of use.

Conclusions

Psoriasis is a chronic, systemic inflammatory disease with a significant impact on patients' quality of life and is associated with a broad spectrum of comorbidities. Despite the therapeutic advances achieved with biological agents, there remains an important unmet clinical need for oral treatments that combine high efficacy with a favourable safety profile and greater convenience for patients.

Selective TYK2 inhibition, through allosteric mechanisms, represents an innovative therapeutic strategy that enables modulation of key inflammatory pathways involved in the pathogenesis of psoriasis, while minimising the adverse effects associated with non-selective JAK inhibition. In this context, Zasocitinib emerges as a next-generation inhibitor, with clinical evidence demonstrating robust efficacy and a promising safety profile in the short to medium term.

However, the currently available evidence is predominantly based on Phase II studies and recently reported Phase III data that have not yet been fully published in peer-reviewed journals, which limits their interpretation and generalisability. Confirmation of its comparative efficacy versus existing therapies, as well as characterisation of its long-term safety profile, will be essential to define its definitive positioning within the therapeutic algorithm.

In summary, Zasocitinib represents a promising option for the treatment of moderate-to-severe psoriasis, with the potential to redefine the role of oral therapies. Its integration into clinical practice will depend on the consolidation of available evidence, including real-world data and direct comparative studies with existing treatments.

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Appendix

Tables

Table I: Completed clinical trials investigating Zasocitinib for the treatment of Plaque Psoriasis.

Trial	Study Design	Endpoints	Main results disclosed	Main adverse events
Phase I trial[32]	Open-label, single and multiple ascending dose study in healthy volunteers and patients.	Primary: Safety, tolerability, and pharmacokinetics. Secondary: TYK2 JH2 domain binding affinity.	Demonstrated high allosteric selectivity for TYK2 over other JAK kinases; well-tolerated with dose-proportional exposure.	No signals of hematological toxicity, thromboembolism, or clinically significant laboratory shifts.
Phase IIb trial[35]	Randomized, double-blind, placebo-controlled trial. N=259 (Mean baseline PASI >18). Doses: 2, 5, 15, and 30 mg q.d. for 12 weeks.	Primary: PASI 75 at week 12. Secondary: PASI 90, PASI 100 and sPGA 0/1.	30 mg dose**:** 67% achieved PASI 75; 46% achieved PASI 90; 33% achieved PASI 100. Statistical significance reached for all doses ≥5 mg.	COVID-19 infection; Acne and acneiform dermatitis; Diarrhea

Table II: Efficacy results at week 12 in the Phase IIb Trial of Zasocitinib[35].

Endpoint	Placebo (n=52)	2 mg (n=50)	5 mg (n=52)	15 mg (n=53)	30 mg (n=52)
PASI 75, No. (%)	3 (6)	9 (18)	23 (44)	36 (68)	35 (67)
PASI 90, No. (%)	0	4 (8)	11 (21)	24 (45)	24 (46)
PASI 100, No. (%)	0	1 (2)	5 (10)	8 (15)	17 (33)
PGA score of 0 or 1, No. (%)	2 (4)	5 (10)	14 (27)	26 (49)	27 (52)

Note: PASI measures the extent and severity of psoriasis; PASI 75/90/100 represent a 75%, 90%, or 100% reduction from baseline. PGA score of 0 or 1 indicates "clear" or "almost clear" skin. Data adapted from Armstrong et al. (2024).

Table III: Pivotal Phase III clinical trials and key efficacy results of Zasocitinib.

ClinicalTrials.gov identifier	Title/Program	Enrollment (n)	Status	Key efficacy results (week 16)
NCT06088043[39]	**LATITUDE-PsO-1**: A Study About How Well TAK-279 Works and Its Safety in Participants With Moderate-to-severe Plaque Psoriasis During 52 Weeks of Treatment	693 (actual)	Completed	sPGA 0/1: 71.4% vs 10.7% (placebo) vs 32.1% (apremilast); PASI 90: 61.3% PASI 100: 33,4%
NCT06108544[40]	**LATITUDE-PsO-2**: A Study About How Well TAK-279 Works and Its Safety in Participants With Moderate-to-severe Plaque Psoriasis	1108 (actual)	Completed	sPGA 0/1: 69.2% vs 12.6% (placebo) vs 29.7% (apremilast); PASI 90: 51.9% PASI: 25.2%
NCT06973291[41]	A Study Comparing Zasocitinib (TAK-279) With Deucravacitinib in Adults With Plaque Psoriasis	606 (actual)	Active, Not Recruiting	Ongoing (results not yet available)

Note: Data for LATITUDE-PsO-1 and LATITUDE-PsO-2 derived from Takeda Pharmaceutical Company press release (2026).

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