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REVIEW

Envudeucitinib, a Potent, Next-Generation, Allosteric Inhibitor of TYK2: A Narrative Review

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ABSTRACT

Psoriasis is an immune-mediated inflammatory disease (IMID) impacting more than 40 million people globally and characterized by skin plaques, elevated systemic levels of inflammatory cytokines, and psychosocial burden. Many patients remain undertreated. Available topical and oral treatments are typically less effective than biologic therapies and have safety considerations that may limit long-term use. Tyrosine kinase 2 (TYK2), a Janus kinase (JAK) enzyme, is a validated target in psoriasis and is also being investigated for other IMIDs. TYK2 mediates signaling of interleukin (IL)-23 and IL-17, central proinflammatory cytokines whose dysregulation contributes to chronic inflammation associated with psoriasis, and IL-12 and type I interferons (IFNs). Therefore, selective inhibition of TYK2 offers more targeted immunomodulation vs. broader immunosuppression associated with JAK 1/2/3 inhibition. Envudeucitinib (formerly ESK-001) is a next-generation, oral, allosteric TYK2 inhibitor under investigation for the treatment of psoriasis and systemic lupus erythematosus. Envudeucitinib selectively binds to the unique regulatory domain (JAK homology 2 [JH2]) of TYK2 to induce a conformational change that prevents ATP from binding the catalytic domain (JAK homology 1 [JH1]), thereby inactivating TYK2. This approach avoids adverse events associated with classic JAK inhibition. In preclinical and phase 1 studies,

Prior Publication and Presentation: This review references 3 publications reporting results with envudeucitinib (formerly ESK-001): Ucpinar S, et al. Clin Transl Sci. 2024;17(12):e70094, Blauvelt A, et al. J Am Acad Dermatol. 2026;94(1):57-65, and Papp KA, et al. J Am Acad Dermatol. 2026;94(1):187-95. Additionally, this review includes results reported in a poster at the American Academy of Dermatology (AAD) Annual Meeting 2024 (Ucpinar S, et al. Pharmacokinetic and pharmacodynamic characteristics of ESK-001, an oral allosteric TYK2 inhibitor, in phase 1 healthy volunteer trials [poster 53968]. AAD Annual Meeting; March 8–12, 2024; San Diego, CA, USA) and oral presentation at the European Academy of Dermatology and Venereology 2024 (Tilley MK, et al. ESK-001, an allosteric TYK2 inhibitor, downregulates biomarkers of disease and TYK2 activity: biomarker analysis of phase 2 psoriasis study STRIDE [oral presentation]. European Academy of Dermatology and Venereology; September 25–28, 2024; Amsterdam, the Netherlands).

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oral administration of envudeucitinib twice daily achieved maximal (90% inhibitory concentration [IC_{90}]) TYK2 inhibition over 24 h, highlighting a level of sustained target engagement that distinguishes envudeucitinib from other oral immunomodulators. Envudeucitinib decreased type I IFN gene signatures in whole blood and pSTAT1 in T cells. These findings were corroborated in a phase 2 study in adults with moderate-to-severe plaque psoriasis; envudeucitinib showed maximal TYK2 inhibition at higher doses (40–80 mg daily), patients demonstrated significant and increasing efficacy responses through week 52, and the safety profile was favorable. The efficacy and safety of envudeucitinib are being further evaluated in the ongoing phase 3 ONWARD studies.

PLAIN LANGUAGE SUMMARY

Psoriasis, an inflammatory disease that develops when the immune system is overactive in the skin, impacts more than 40 million people globally. Patients with psoriasis have red, scaly, itchy skin plaques and high levels of inflammatory molecules in the blood. Many patients do not receive adequate treatment, highlighting the need for more effective and safer oral therapies. We describe how a new potential oral medicine for psoriasis, envudeucitinib, works. Envudeucitinib targets the tyrosine kinase 2 (TYK2) protein that is involved in the inflammation process associated with psoriasis. When taken twice daily, envudeucitinib achieved strong and sustained inhibition of TYK2 for a full 24 h, which is a distinguishing feature of this therapy. Selective reduction of TYK2 activity, while avoiding effects on other related proteins, may allow for more targeted adjustment of inflammatory signaling associated with psoriasis and may translate to clinical benefit. In early studies, envudeucitinib taken orally twice daily markedly reduced TYK2 activity and the levels of other inflammatory molecules over a 24-h period. These findings were confirmed in a phase 2 study in patients with psoriasis, where envudeucitinib again reduced TYK2 activity. Patients with psoriasis taking envudeucitinib had significant improvements in their skin after 12 weeks of treatment, and these improvements were sustained or continued to improve through 52 weeks of treatment without notable side effects. In summary, envudeucitinib is a new potential oral medication for psoriasis that reduces inflammation with an acceptable safety profile.

Keywords: Autoimmune disease; TYK2; Envudeucitinib; ESK-001; Psoriasis; Next-generation oral

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Key Summary Points

Patients with psoriasis, an immune-mediated inflammatory disease, are frequently undertreated, and available topical and oral treatment options are typically less effective than biologic therapies and have safety and tolerability considerations that may limit long-term use.

Selective inhibition of tyrosine kinase 2 (TYK2), a validated target in psoriasis, offers more targeted immunomodulation and avoids adverse events associated with classic Janus kinase inhibition.

Envudeucitinib (formerly ESK-001) is a next-generation, oral, allosteric TYK2 inhibitor (i.e., selectively binds the unique regulatory domain to prevent ATP from binding the conserved catalytic domain) under investigation for the treatment of psoriasis.

Oral administration of envudeucitinib twice daily achieves maximal TYK2 inhibition over 24 h, and in a phase 2 study of envudeucitinib in adults with moderate-to-severe plaque psoriasis, treatment resulted in significant and increasing efficacy responses through week 52 with a favorable safety profile.

Envudeucitinib combines strong molecular properties with robust clinical efficacy and safety, and is being further evaluated in the ongoing phase 3 ONWARD studies.

INTRODUCTION

An expanding body of evidence underscores that dysregulated cytokine signaling is a driver of psoriasis and a variety of chronic immune-mediated inflammatory diseases (IMIDs) [1–5]. Interleukin (IL)-23 is a central regulatory cytokine that is key to the pathogenesis of psoriasis [6, 7], an IMID that impacts more than 40 million people worldwide [8, 9]. Psoriasis is associated with substantial physical, emotional, and financial burden [10–12]. In addition to erythematous, scaly, pruritic skin plaques [3, 10], patients with psoriasis present with elevated levels of circulating inflammatory cytokines [5, 13] that promote persistent systemic inflammation and are associated with a wide spectrum of comorbidities [14–16], including psoriatic arthritis, cardiovascular disease, and metabolic syndrome [3, 10, 17–19].

Despite considerable advances in the treatment landscape over the past several decades, many patients with psoriasis who are candidates for systemic therapy [20] remain untreated or undertreated [21–23]. In particular, there remains an unmet need for oral therapies with short- and long-term efficacy as well as safety similar to anti–IL-23 and anti–IL-17 biologics [24, 25].

Oral drugs such as methotrexate and cyclosporine have been available for decades, but they are less effective than biologic treatments and limited by monitoring requirements and well-recognized safety concerns [24]. Apremilast, a phosphodiesterase 4 (PDE4) inhibitor approved for the treatment of adults and children (≥ 6 years of age) with plaque psoriasis [26], remains widely used but demonstrates modest clinical efficacy and is associated with gastrointestinal tolerability issues [27–30]. Deucravacitinib is a first-generation allosteric tyrosine kinase 2 (TYK2) inhibitor indicated for the treatment of adults with moderate-to-severe plaque psoriasis [31]. When compared with apremilast, deucravacitinib exhibits improved tolerability, with fewer discontinuations due to adverse events, as well as greater efficacy, with ≥ 75% improvement from baseline in Psoriasis Area and Severity Index score (PASI 75) response rates of approximately 55% vs. 37% at week 16 [32, 33]. While the efficacy of deucravacitinib is lower than that of most injectable IL-23 or IL-17 inhibitors [25], treatment is associated with low discontinuation rates [32, 33] and no Janus kinase (JAK)-associated laboratory abnormalities even with long-term exposure [34].

Despite the broad availability of oral and biologic therapies for psoriasis, there remains a need for novel oral therapeutics that combine high efficacy with favorable safety. Herein, the mechanism of action of a new investigational

oral drug for psoriasis, envudeucitinib (formerly known as ESK-001), is described.

METHODS

This narrative review is supported by a targeted literature search for publications reporting preclinical and clinical evidence for envudeucitinib and/or ESK-001, and publications describing drug characteristics and clinical trial results for other relevant psoriasis treatments (e.g., based on pharmacologic profile, signaling pathway, and clinical development phase). ClinicalTrials.gov was consulted to identify relevant therapies and guide literature search parameters. Formal inclusion/exclusion criteria were not applied given the qualitative nature of this narrative review. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

TYK2

TYK2 is an extensively studied and validated target in psoriasis [32, 33, 35] and is being investigated for multiple other IMIDs, including psoriatic arthritis, systemic lupus erythematosus, and ulcerative colitis [7]. IL-23 is the central regulatory cytokine in the pathogenesis of psoriasis [6, 7]. Dysregulation of IL-23 signaling drives systemic, chronic inflammation characteristic of psoriasis [2, 6]. TYK2 mediates downstream signaling of IL-23 as well as other cytokines, including IL-12 and type I interferons (IFNs) [6, 7, 36, 37]. Through these pathways, TYK2 regulates both type 17 responses (i.e., T helper 17 [Th17] and IL-17A/IL-17F via IL-23) and type 1 IFN responses (i.e., Th1, IFNγ, and tumor necrosis factor alpha via IL-12; Fig. 1) [6, 7, 36, 37]. Thus, inhibition of TYK2 provides comprehensive targeting that reduces both the signaling and production of the proinflammatory cytokines central to psoriasis pathogenesis.

Unlike broader immunosuppression associated with JAK 1/2/3 inhibition, TYK2 inhibition provides more precise immunomodulation of psoriasis-related cytokine signaling while avoiding off-target adverse effects on hematopoietic functions or serum lipid levels [3, 7, 36]. Notably, genetic studies have shown that a loss-of-function variant in *TYK2* (rs34536443 [P1104A]) confers protection against psoriasis and other IMIDs and does not appear to be associated with increased risk of infection or malignancy [38, 39]. Therefore, systemic inhibition of TYK2 is hypothesized to normalize elevated immune-mediated signaling associated with psoriasis and other IMIDs while mitigating safety concerns.

RESULTS

Envudeucitinib Mechanism of Action

Envudeucitinib is a next-generation, oral, allosteric TYK2 inhibitor that combines high selectivity and potency with a well-characterized safety profile (Fig. 2) [40, 41]. It is under investigation for the treatment of psoriasis and other IMIDs. Orthosteric inhibitors with activity against TYK2 (e.g., brepocitinib and ropsacitinib) bind the JAK homology 1 (JH1) domain and compete with the natural substrate, ATP, to occupy the active site [7, 36]. Orthosteric inhibition lacks selectivity as the target JH1 catalytic domain (i.e., the binding site) is highly conserved across all four JAK family members [42]. In contrast, allosteric TYK2 inhibitors such as envudeucitinib achieve selectivity by binding to the pseudokinase JAK homology 2 (JH2) domain, a regulatory site unique to TYK2 [43]. This binding induces a conformational change that prevents the activation of the catalytic JH1 domain, thereby functionally blocking ATP binding and TYK2 signaling [43]. Because the TYK2 JH2 domain is structurally distinct from the JH2 domains of other JAK family members, this allosteric mechanism (indirect inhibition) confers high selectivity for TYK2, preserving JAK 1/2/3 activity and reducing the risk of adverse events associated with classic JAK inhibition (Fig. 2) [42, 44, 45]. Moreover, highly selective TYK2 JH2 inhibition with envudeucitinib effectively suppresses signaling that drives transcriptional activation of downstream proinflammatory genes like

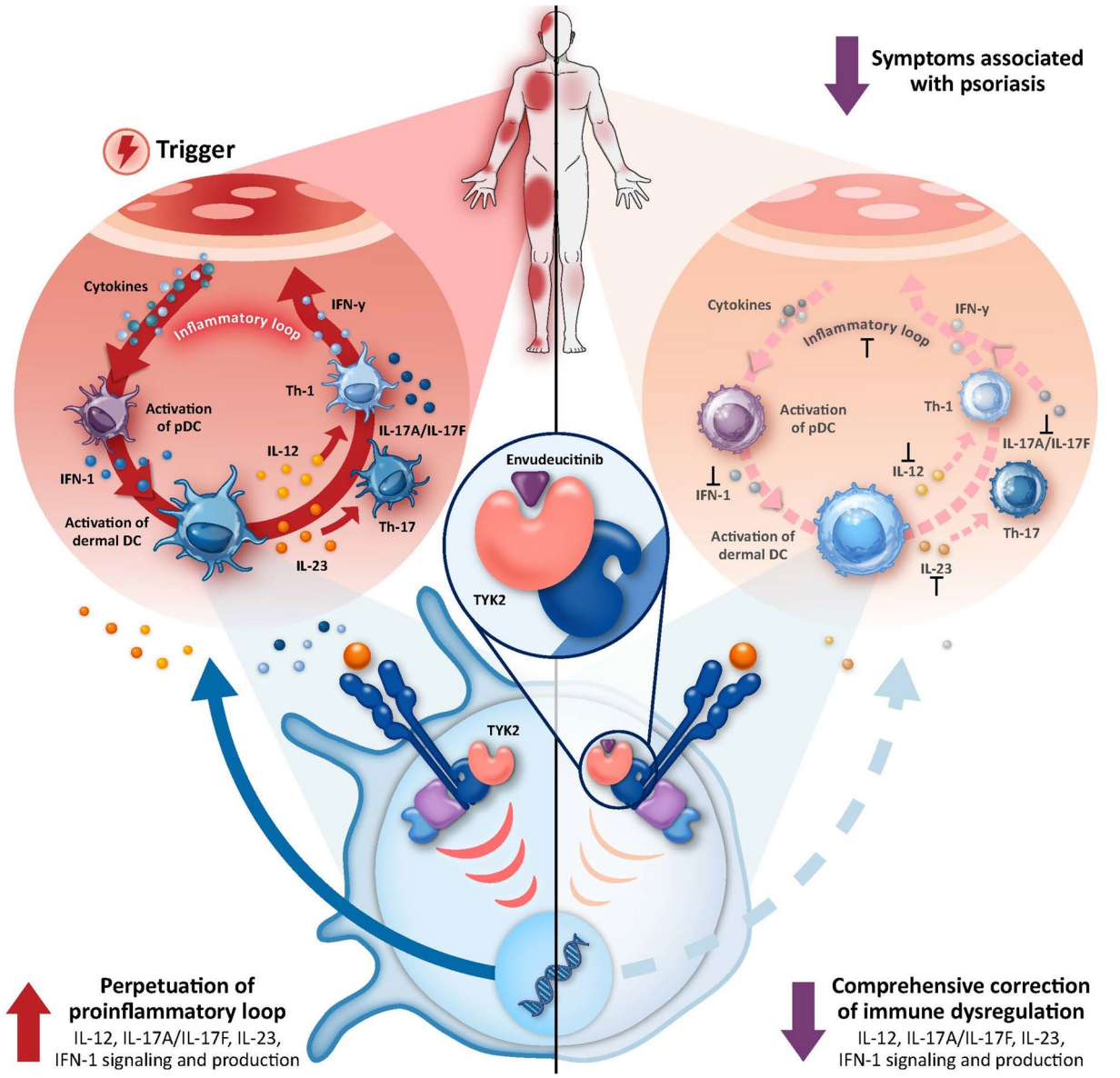

Fig. 1 Proinflammatory signaling in psoriasis and comprehensive correction of immune dysregulation via TYK2 inhibition with envudeucitinib. TYK2 mediates downstream signaling of IL-23 and other cytokines, thereby regulating both Th17 and IL-17A/IL-17F (via IL-23) and type 1 IFN responses (via IL-12), which drive the self-amplifying proinflammatory loop in psoriasis. Inhibition of TYK2 with envudeucitinib provides comprehensive targeting that reduces both the signaling and production of proinflammatory cytokines to correct the immune dysregulation and reduce the clinical signs and symptoms of psoriasis. *DC* dendritic cell, *IFN* interferon, *IL* interleukin, *pDC* plasmacytoid dendritic cell, *Th1/Th17* T helper 1/17, *TYK2* tyrosine kinase 2

IL-23 and *IL-17F* that contribute to psoriasis pathogenesis [40, 41], and returns lesional skin levels of key cytokines (e.g., IFN signature [46], IL-17A/IL-17F, IL-22, IL-23A, and IL-36A) and disease-related biomarkers (e.g., human beta-defensin 4A [DEFB4A], keratin 16 [KRT16], and S100 calcium binding protein A9 [S100A9]) to nonlesional levels [47]. Thus, allosteric TYK2 inhibition with envudeucitinib provides precise yet comprehensive targeting to reduce

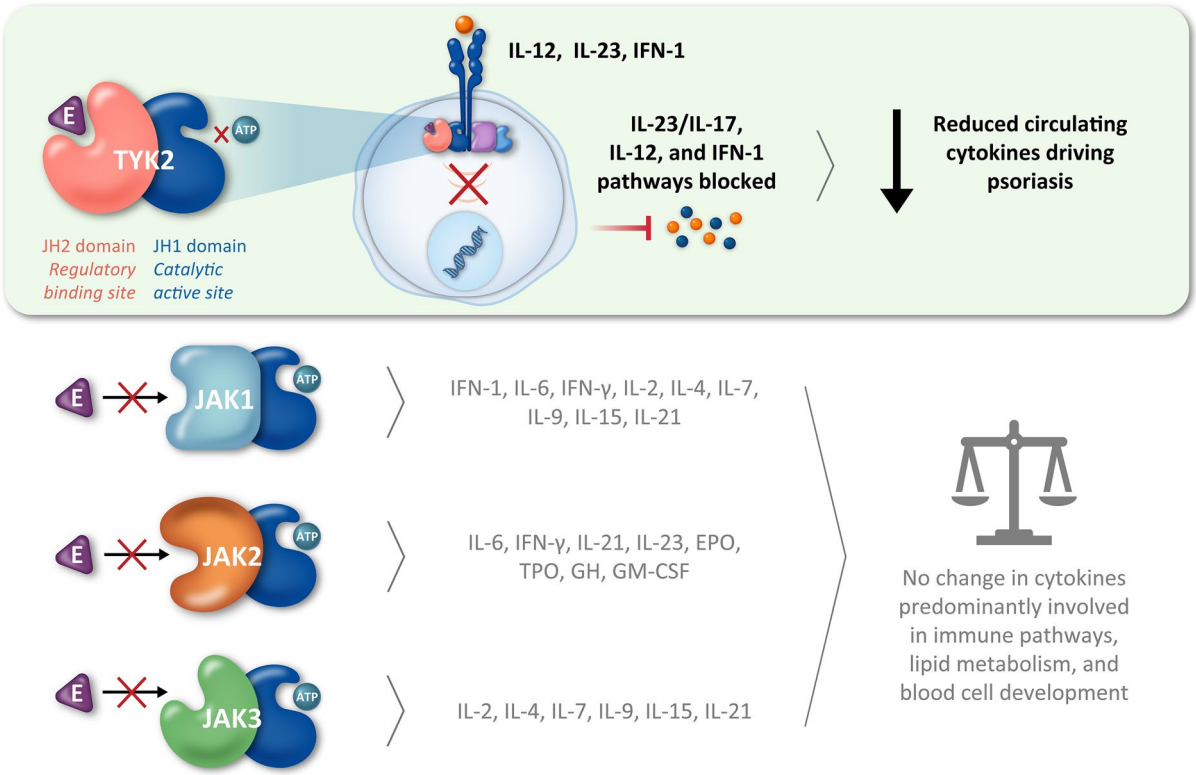

Fig. 2 Allosteric TYK2 inhibition confers selectivity to minimize off-target effects. Envudeucitinib is a next-generation, oral, allosteric TYK2 inhibitor that binds selectively to the pseudokinase JH2 domain, a regulatory site unique to TYK2, to inactivate the catalytic TYK2 JH1 domain while preserving JAK 1/2/3 signaling activity. Inhibition of TYK2 reduces production and inflammatory signaling of cytokines associated with psoriasis without affecting cytokines involved in immune pathways, lipid metabolism, and blood cell development. *E* envudeucitinib, *EPO* erythropoietin, *GH* growth hormone, *GM-CSF* granulocyte-monocyte colony-stimulating factor, *IFN* interferon, *IL* interleukin, *JAK 1/2/3* Janus kinase 1/2/3, *JH1/JH2* JAK homology 1/2, *TPO* thrombopoietin, *TYK2* tyrosine kinase 2

both production and signaling of relevant disease-associated cytokines (Fig. 1).

Envudeucitinib Molecular Characteristics

The molecular structure of envudeucitinib [48] builds upon the molecular structure of first-generation TYK2 inhibitors like deucravacitinib and confers distinct metabolic and pharmacologic properties that contribute to its efficacy and safety profile (Fig. 3). Envudeucitinib includes a deuterated methyl triazole moiety that may enhance its metabolic stability by reducing cytochrome P450 1A2 (CYP1A2)-mediated demethylation, mitigating potential metabolite-driven off-target effects, and maximizing the pharmacodynamic response. Moreover, the presence of a cyclopropyl carboxamide group on envudeucitinib is hypothesized to reduce human ether-a-go-go-related gene (hERG) and cardiac repolarization-associated safety concerns [49, 50]. Taken together, these next-generation molecular characteristics were predicted to confer elevated permeability, rapid absorption, and a linear pharmacokinetic/pharmacodynamic relationship with no dose-limiting effect. Indeed, preclinical and phase 1 studies demonstrated that envudeucitinib twice daily achieves maximal TYK2 target inhibition (90% inhibitory concentration [IC_{90}]) at clinically relevant doses over 24 h [40], highlighting

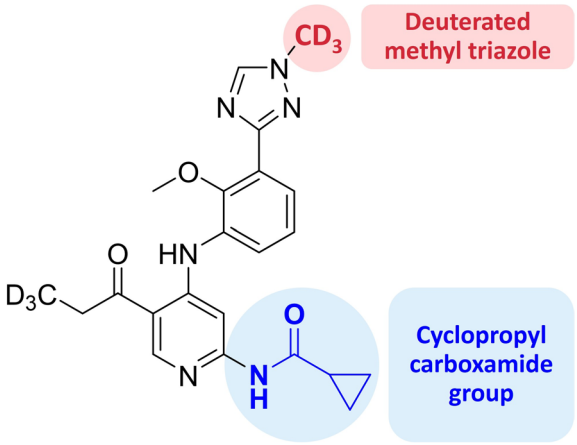

Fig. 3 Envudeucitinib structure. Envudeucitinib is a next-generation, allosteric TYK2 inhibitor that includes a deuterated methyl triazole moiety (red) hypothesized to enhance metabolic stability, mitigate metabolite-driven off-target effects, and maximize pharmacodynamic response. The cyclopropyl carboxamide group (blue) is hypothesized to reduce hERG and cardiac repolarization-associated safety concerns. *hERG* human ether-a-go-go-related gene, *TYK2* tyrosine kinase 2

a level of sustained target engagement that distinguishes envudeucitinib from other licensed oral immunomodulators [45].

Envudeucitinib Phase 1 Pharmacokinetics and Pharmacodynamics

Two randomized, double-blinded, placebo-controlled, phase 1 studies, a first-in-human single- and multiple-ascending dose study (ACTRN12621000011886) and a multiple-dose study (NCT05431634), evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of envudeucitinib in healthy participants [40]. Envudeucitinib demonstrated a favorable pharmacokinetic profile characterized by rapid absorption, an elimination half-life of approximately 8 h, a dose-proportional increase in exposure, minimal renal clearance, and low interindividual variability [40]. Envudeucitinib is primarily cleared through hepatic metabolism [51], and food interaction studies indicate that envudeucitinib may be taken with or without food [40]. Completed in vitro and clinical drug–drug interaction (DDI) studies demonstrated a low potential for clinically relevant DDI with envudeucitinib (data on file).

Studies evaluating absorption, distribution, metabolism, and excretion of envudeucitinib in healthy volunteers identified one major and seven minor metabolites (data on file). The major metabolite is pharmacologically inactive with no significant off-target effects; minor metabolites contribute minimally to the overall pharmacologic activity of envudeucitinib (data on file). Further, in vitro and clinical DDI studies indicate that the major metabolite has minimal potential for DDI interactions. Collectively, these findings support a favorable and differentiated safety profile for envudeucitinib in clinical studies conducted to date.

RNA sequencing of whole blood from healthy participants demonstrated that envudeucitinib dose dependently decreased type I IFN gene signatures and sialic acid binding Ig-like lectin 1 *(SIGLEC1*, or *CD169*) gene expression [40]. *SIGLEC1* expression is a novel biomarker to assess TYK2 target inhibition [41], and its expression and protein levels are known markers of severity in several IMIDs [52, 53]. Additionally, envudeucitinib dose dependently reduced phosphorylated signal transducer and activator of transcription 1 (*pSTAT1*) expression in T cells isolated from whole blood and stimulated with IFNα ex vivo [40]. Findings from the pharmacokinetic and biomarker studies informed dose selection for the phase 2 STRIDE study of envudeucitinib in psoriasis.

Envudeucitinib Phase 2 Clinical Efficacy, Safety, and Pharmacokinetics

STRIDE (NCT05600036; EudraCT number, 2022-002633-34) was a randomized, double-blinded, placebo-controlled, phase 2, dose-ranging study of envudeucitinib in adults with moderate-to-severe plaque psoriasis [41]. The study included dose arms ranging from 10 mg once daily to 40 mg twice daily, which demonstrated the

greatest efficacy among evaluated doses [41]. In STRIDE, patients receiving orally administered envudeucitinib 40 mg twice daily ($n=39$) showed significant, robust, dose-dependent PASI 75, PASI 90, and PASI 100 responses at week 12 (64%, 39%, and 15%, respectively, vs. 0% for all PASI endpoints with placebo) [41], and a significantly higher percentage of patients receiving envudeucitinib 40 mg twice daily vs. placebo achieved a static Physician's Global Assessment (sPGA) score of 0 or 1 (59% vs. 8%) [41]. Patients receiving envudeucitinib 40 mg twice daily also showed improvement in patient-reported outcomes including Dermatology Life Quality Index and pruritus numerical rating scale [41]. Efficacy improved and was sustained throughout all time points leading to week 52 during the open-label extension period; patients with moderate-to-severe plaque psoriasis receiving envudeucitinib 40 mg twice daily for the entirety of the trial period ($n=80$) reached PASI 75, PASI 90, and PASI 100 rates of 78%, 61%, and 39%, respectively, at week 52 [54]. Similarly, continued treatment with envudeucitinib led to progressive improvements in sPGA, pruritus, and Dermatology Life Quality Index score up to week 52 [54].

In STRIDE, during 12 weeks of treatment and 4 weeks off treatment, envudeucitinib was found to be generally safe and well tolerated, with no dose-limiting safety findings [41]. The most frequent treatment-emergent adverse events across all patients treated with envudeucitinib ($N=189$) were headache (6.3%), upper respiratory tract infection (5.3%), and nasopharyngitis (3.7%); 2.6% of patients had treatment-emergent adverse events leading to treatment discontinuation [41]. Envudeucitinib continued to be well tolerated through 52 weeks of treatment, with a low rate of study drug discontinuation, no new safety findings, and no emerging clinically relevant signals [54]. Importantly, safety issues reported for classic JAK 1/2/3 inhibitors (e.g., major adverse cardiovascular events or laboratory abnormalities [7, 36]) were not observed with envudeucitinib treatment in the phase 2 program [41, 54].

A strong pharmacokinetic/pharmacodynamic relationship for envudeucitinib was reconfirmed in this phase 2 study. Envudeucitinib demonstrated consistent, dose-proportional linear kinetics with low interindividual variability in patients with psoriasis [41], affirming its predictability and readiness for phase 3 evaluation. Transcriptomic analysis of blood showed dose-dependent reductions in *SIGLEC1* expression with envudeucitinib as early as week 2, with maximal TYK2 inhibition observed at higher doses (40 mg daily and 40 mg twice daily) [41]. These findings provide clinical evidence of robust target engagement in patients. At the highest dose evaluated (40 mg twice daily), envudeucitinib maintained plasma concentrations above the biomarker-defined TYK2 inhibition threshold throughout the dosing interval [41], supporting sustained target inhibition over 24 h. Consistent with these systemic effects, treatment with envudeucitinib was also associated with normalization of IL-23 and IL-17F expression in lesional skin to levels observed in nonlesional skin [41].

Together, these preclinical, phase 1, and phase 2 data demonstrate that envudeucitinib provides highly selective and maximal TYK2 inhibition, supporting it as a promising new drug for psoriasis. By achieving full target engagement without compromising safety, envudeucitinib may offer efficacy comparable to biologics (e.g., IL-23 and IL-17 inhibitors) in an oral formulation.

DISCUSSION

Existing oral agents for the treatment of psoriasis have suboptimal efficacy and are limited by safety/tolerability considerations [24, 29], indicating the need and opportunity for next-generation oral treatments. Allosteric inhibition of TYK2, a validated target in psoriasis and other IMIDs such as psoriatic arthritis and systemic lupus erythematosus [7], allows for precise and safe upstream targeting of a comprehensive array of relevant proinflammatory cytokines [7, 36]. Envudeucitinib is a next-generation, oral, allosteric TYK2 inhibitor that combines high potency and maximal TYK2

inhibition over 24 h when dosed twice daily; these characteristics should enable robust efficacy combined with a well-tolerated safety profile. Phase 2 and open-label extension data support the potential clinically meaningful and durable benefit of envudeucitinib in the treatment of psoriasis and other IMIDs. The ongoing phase 3 ONWARD program will evaluate the long-term efficacy and safety of envudeucitinib in patients with moderate-to-severe plaque psoriasis (ONWARD1 [NCT06586112], ONWARD2 [NCT06588738], and ONWARD3 [NCT06846541]).

Limitations of this review include the need for phase 3 and longer-term evaluations to draw definitive conclusions on the efficacy and safety of envudeucitinib in patients. Additionally, direct (e.g., head-to-head) and formal indirect (e.g., meta-analyses) comparisons of oral agents for the treatment of psoriasis are not presently available.

CONCLUSION

Envudeucitinib's high potency, sustained TYK2 inhibition, and favorable pharmacokinetic/pharmacodynamic characteristics make it a promising next-generation oral therapeutic option in psoriasis and other IMIDs.

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Data Availability. The datasets generated during and/or analyzed during the study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. April W Armstrong has served as a research investigator, scientific adviser, or speaker for AbbVie, Alumis Inc., Bristol Myers Squibb, Eli Lilly, Galderma, Johnson & Johnson, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, Sun, Takeda, and UCB Pharma. James G Krueger has received institutional grant support from AbbVie, Amgen, Artax Biopharma, Avillion, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, ONO-Pharma, Oruka Therapeutics, Pfizer, Provectus, Regeneron, SUDO Bio, Takeda, UCB Pharma, Ventyx, Vitae, and Zomagen; and has received fees for consulting from AbbVie, Allergan, Almirall, Alumis Inc., Amgen, Artax Biopharma, Aristea, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Calliditas, CSL Behring, Eli Lilly, Escalier, Evommune, Incyte, Innovaderm, Janssen, Kymera Therapeutics, Kyowa Kirin, MC2 Therapeutics,

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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