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 ORIGINAL ARTICLE

Selective Tyrosine Kinase 2 (TYK2) Inhibition in Plaque Psoriasis

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ABSTRACT

Members of the Janus kinase (JAK) superfamily, comprising tyrosine kinase 2 (TYK2) and JAK1, JAK2, and JAK3, mediate signaling by cytokines (eg, interleukin [IL]-23) involved in psoriasis pathogenesis. Binding of IL-23 to its receptor activates TYK2 and JAK2, which trigger signal transducer and activator of transcription (STAT) translocation to the nucleus to regulate target gene transcription, including genes of proinflammatory mediators such as IL-17. Physiologically, TYK2 solely mediates immune function, whereas JAK1,2,3 mediate broad systemic and immune functions. Inhibition of individual JAK family members is being evaluated in many dermatologic indications, including psoriasis. Selective TYK2 inhibition is therefore expected to be associated with few adverse effects in patients with psoriasis. People with genetic mutations leading to loss of function of TYK2 are protected from the development of psoriasis without an increased risk of infections or malignancies. In contrast, treatments with JAK1,2,3 inhibitors are associated with various systemic effects. We review the unique allosteric mechanism of action of the selective TYK2 inhibitor, deucravacitinib, which binds to the TYK2 regulatory (pseudokinase) domain, and the mechanisms of action of JAK1,2,3 inhibitors, which bind to the adenosine 5'-triphosphate-binding active (catalytic) site in the kinase domains of JAK1,2,3. Deucravacitinib, which is approved for the treatment of moderate to severe plaque psoriasis in adults in the United States and several other countries, represents a novel, targeted systemic treatment approach with a favorable safety profile.

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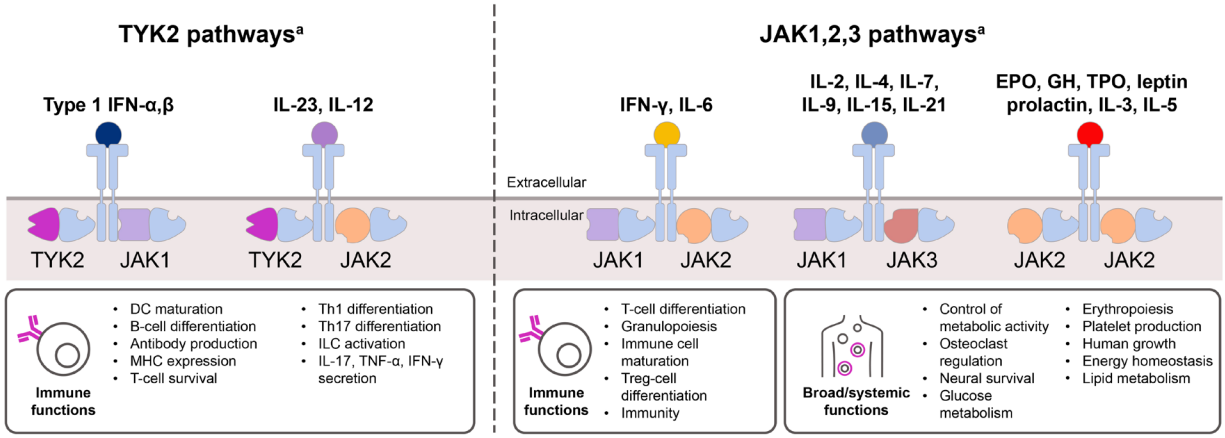
INTRODUCTION

The Janus kinase (JAK) family members, tyrosine kinase 2 (TYK2), JAK1, JAK2, and JAK3, are related nonreceptor tyrosine kinases that are associated with the cytoplasmic domains of cytokine receptors.[1,2] TYK2 solely mediates select immune functions; in contrast, JAK1,2,3 mediate broad systemic and immune functions (Figure 1).[1] JAK family members function predominantly as heterodimers and rarely as heterotrimers (JAK2 also functions as a homodimer), with specific pairings dictating their downstream effects.[1,2] The complex protein TYK2 has multiple domains, including a kinase or catalytic domain (also known as the Janus homology 1, or JH1, domain) and a pseudokinase or regulatory domain (also known as the JH2 domain), which lacks catalytic activity but plays an important role in regulating receptor-mediated activation of the catalytic domain via autoinhibitory interactions.[3,4]

TYK2 is involved in a key axis of inflammation in psoriasis (Figure 2),[5] mediating signaling by interleukin (IL)-12, IL-23, and Type I interferons (IFNs).[6-15] IL-23 stimulates T-helper 17 cells to produce IL-17, which then stimulates keratinocyte proliferation and epidermal hyperplasia. As other immune cells are attracted to the area, the inflammatory process is potentiated.[5] Support for TYK2 playing a central role in the inflammatory process comes from TYK2 loss-of-function genetic mutations shown to be associated with a reduced risk of developing immune-mediated inflammatory diseases (IMIDs) such as psoriasis.[16]

The pathogenesis of psoriasis involves complex interactions among 1) proinflammatory cytokines, including IL-17, IL-23, IL-12, IL-19, tumor necrosis factor (TNF), and Type I IFNs (eg, IFN-α)[1,3]; 2) immune cells, including T cells and dendritic cells[3]; and 3) keratinocytes.[17] Some of these proinflammatory cytokines are regulated by JAK family members such as TYK2.[2,18] Extracellular binding of a cytokine to its receptor activates the associated intracellular JAK family members to activate signal transducers and activators of transcription (STATs). Activated STATs

FIGURE 1. TYK2 pathways and JAK1,2,3 pathways involve specific pairings of JAK family members that mediate specific sets of cytokine signals to control different downstream functions.[1]

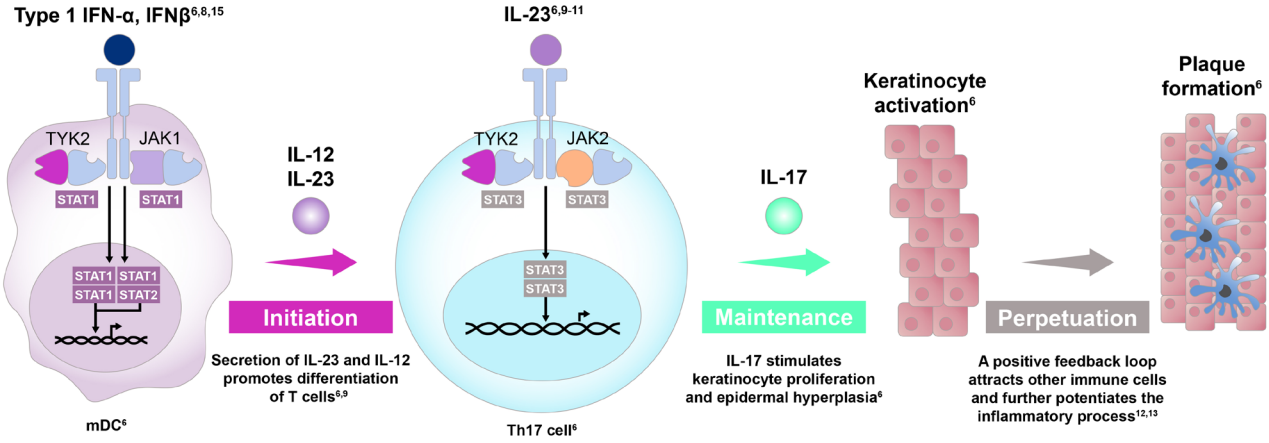


DC, dendritic cell; EPO, erythropoietin; GH, growth hormone; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; JAK, Janus kinase; MHC, major histocompatibility complex; Th, T helper; TNF, tumor necrosis factor; TPO, thrombopoietin; Treg cell, regulatory T cell; TYK2, tyrosine kinase 2. [a]List of cytokines and effects modulated by different JAK/JAK and TYK2/JAK pairs is not exhaustive. Adapted by permission from BMJ Publishing Group Limited. *Ann Rheum Dis*, Baker KF and Isaacs JD, 77, 175-187, 2023 with permission from BMJ Publishing Group Ltd.

dimerize and translocate from the cytoplasm to the nucleus to regulate the transcription of numerous target genes, resulting in increased expression of proinflammatory mediators such as IL-17.[1,2]

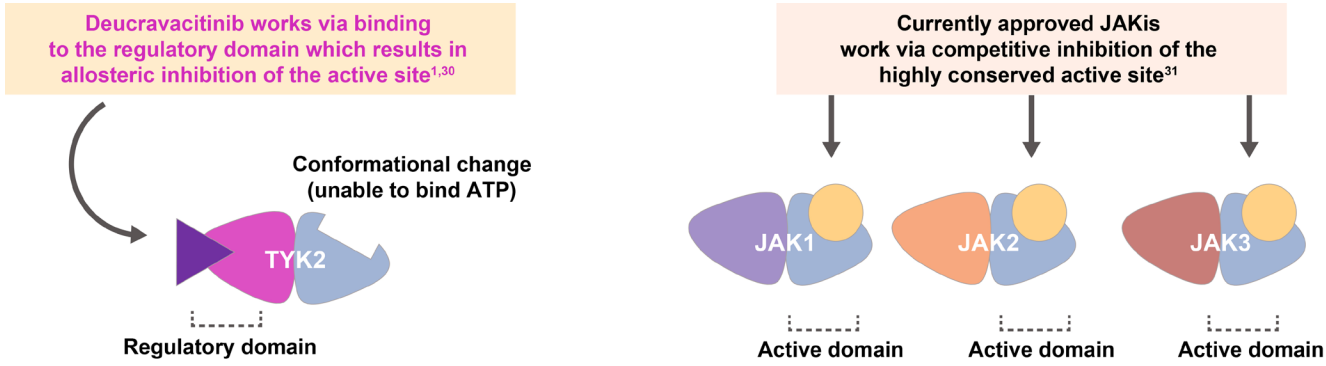
Systemic treatment of moderate to severe plaque psoriasis with targeted therapies has focused primarily on direct inhibition of IL-17, IL-23, and TNF with biologic agents[1,17] and inhibition of phosphodiesterase-4.[19] The monoclonal antibodies brodalumab, ixekizumab, bimekizumab, and secukinumab target IL-17; guselkumab, tildrakizumab, and risankizumab target IL-23; ustekinumab targets IL-12/23; and adalimumab, etanercept, infliximab, and certolizumab pegol target TNF-α, while the small molecule apremilast targets phosphodiesterase-4.[19,20] Targeting the JAK-STAT pathway is a current focus of research in dermatologic conditions. JAK1,2,3 inhibitors nonselectively bind to the adenosine 5'-triphosphate (ATP)-binding site on the catalytic domain of JAK1,2,3 and are not highly selective for any of the superfamily members, including TYK2.[21,22] JAK1,2,3 inhibitors are approved by the US Food and Drug Administration for use in dermatologic indications such as psoriatic arthritis, alopecia areata, atopic dermatitis, and vitiligo, as well as in additional disease states such as rheumatoid arthritis, ulcerative colitis, Crohn's disease, myelofibrosis, polycythemia vera, and graft versus host disease.[23]

FIGURE 2. TYK2 mediates a key axis of inflammation in psoriasis.[5]



IFN, interferon; IL, interleukin; JAK, Janus kinase; mDC, myeloid dendritic cell; STAT, signal transducer and activator of transcription; Th17, T-helper 17; TYK2, tyrosine kinase 2. Adapted with permission from Gonciarz et al. *Immunotherapy.* 2021;13:1135-1150.

FIGURE 3. Mechanism of action and binding location of deucravacitinib compared with JAK1,2,3 inhibitors.[22]

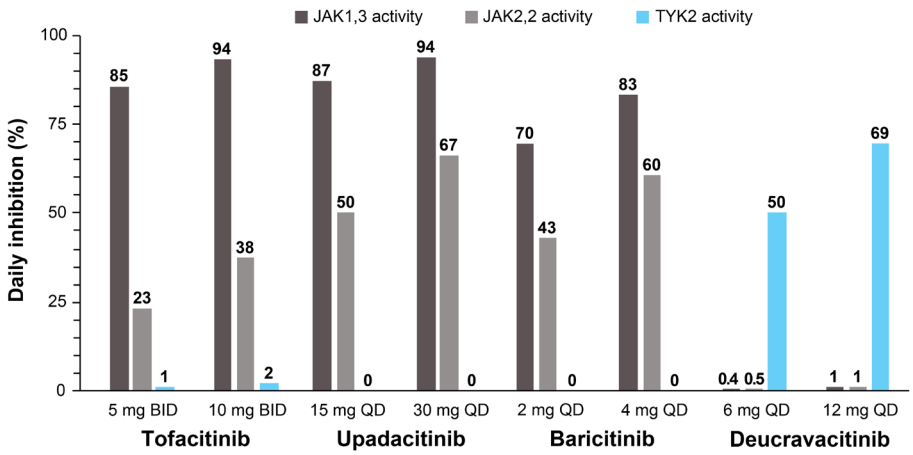


ATP, adenosine 5'-triphosphate; JAK, Janus kinase; JAKi, Janus kinase inhibitor; TYK2, tyrosine kinase 2. Reprinted from *J Am Acad Dermatol*, Krueger JG, McInnes IB, Blauvelt A, Tyrosine kinase 2 and Janus kinase-signal transducer and activator of transcription signaling and inhibition in plaque psoriasis, 86, 148-157, Copyright 2022, with permission from Elsevier.

Unlike JAK1,2,3 inhibitors (which are not approved for use in psoriasis), deucravacitinib, an oral, selective, allosteric TYK2 inhibitor, is approved in the United States, European Union, Japan, and other countries for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.[24-29] Deucravacitinib selectively binds to the regulatory (pseudokinase) domain of TYK2 and locks the kinase in its native inactive state,[3,4,30,31] preventing receptor-mediated TYK2 activation and downstream signal transduction (Figure 3).[22] Deucravacitinib is highly selective for TYK2 at clinically relevant doses.[21] This mechanism of action differs from that of nonselective, orthosteric, oral TYK2 inhibitors such as ropsacitinib (PF-06826647), which binds to the active site of TYK2 and JAK2 and was shown to be more efficacious than placebo and was well tolerated in a phase 2b study of moderate to severe plaque psoriasis.[32] Similarly, a second nonselective, orthosteric, oral TYK2 inhibitor brepocitinib (PF-06700841), which binds to the active site of TYK2, JAK1, and JAK2, was also more efficacious than placebo and was well tolerated in a phase 2a study of patients with moderate to severe plaque psoriasis.[33] Given the differences in signaling across TYK2 and JAK1,2,3, coupled with the different mechanisms of action and downstream effects of TYK2 and JAK1,2,3, selective, allosteric inhibition of TYK2 is expected to have a different safety profile compared with nonselective inhibition of JAK1,2,3.[2,30,34]

The objectives of this review are to introduce a new pharmacologic class of oral, selective, allosteric inhibitors targeting the regulatory domain of TYK2; to describe how the mechanism of action, efficacy, safety, and tolerability profiles

FIGURE 4. Deucravacitinib, an allosteric TYK2 inhibitor, is highly selective for TYK2 versus JAK1,2,3 inhibitors (tofacitinib, upadacitinib, and baricitinib) at their clinically relevant doses.[21]



BID, twice daily; JAK, Janus kinase; QD, once daily; TYK2, tyrosine kinase 2. From Chimalakonda A, et al. Selectivity profile of the tyrosine kinase 2 inhibitor deucravacitinib compared with Janus kinase 1/2/3 inhibitors. *Dermatol Ther (Heidelb).* 2021;11:1763-1776. https://doi.org/10/1007/s13555-021-00596-8. This work is licensed under a Creative Commons Attribution License (CC BY-NC-ND 2.0). https://creativecommons.org/licenses/by-nc/2.0.

of the only approved TYK2 inhibitor deucravacitinib differ from those of JAK1,2,3 inhibitors; and to summarize clinical data from phase 3 trials of deucravacitinib for the treatment of adults with moderate to severe plaque psoriasis.

Mechanism of Action and Profile of Deucravacitinib

Deucravacitinib is highly selective for the regulatory pseudokinase (JH2) domain of TYK2 and shows negligible activity against JAK1,2,3.[3,4,21] The TYK2 pseudokinase domain is structurally unique to TYK2, making deucravacitinib highly selective for TYK2.[3,4] Binding of deucravacitinib to the pseudokinase domain results in a conformational change to the TYK2 active site and allosterically inhibits its ability to bind ATP and phosphorylate its target (Figure 3).[4,22]

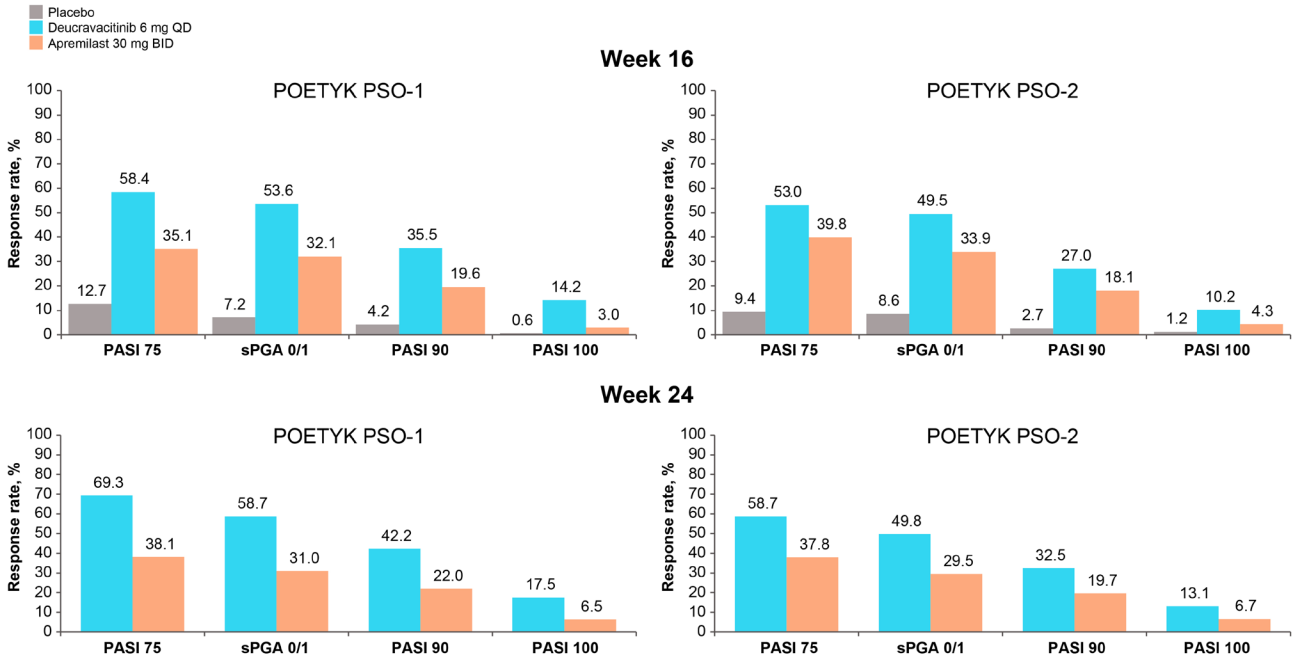
At physiologically relevant concentrations, deucravacitinib demonstrated ≥100-fold greater selectivity for TYK2 pathways versus JAK1,3 pathways and ≥2000-fold greater selectivity for TYK2 pathways versus JAK2 pathways in cellular assays.[3] In a simulation analysis, at clinically relevant doses of 6 mg and 12 mg once daily, the daily average percent inhibition of TYK2 by deucravacitinib was ≥50%, while TYK2 inhibition by clinically relevant doses of JAK1,2,3 inhibitors was ≤2% (Figure 4).[21] Conversely, the simulated daily average percent inhibition of JAK1,2,3 by deucravacitinib was ≤1%; the average percent inhibition of JAK1,3 by JAK1,3 inhibitors was ≥70% and of JAK2,2 by JAK2,2 inhibitors was 23% to 67%.[21]

The TYK2 signaling pathway influences a select group of immune-signaling molecules and is not implicated in broad systemic effects, unlike the pathways that mediate JAK1,2,3 signaling.[3,35] Selective inhibition of TYK2 by deucravacitinib inhibits IL-23 and Type I IFN signaling,[36] the key pathways involved in psoriasis pathogenesis (Figure 2).[5] Selective TYK2 inhibition by deucravacitinib also inhibits IL-12 signaling[36]; while IL-12 was initially thought to be a key driver in psoriasis pathogenesis, its role remains undetermined. Furthermore, in genome-wide association studies, patients with partial or near loss-of-function polymorphism of TYK2 exhibited a decreased risk of IMIDs such as psoriasis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Crohn's disease, and ulcerative colitis, as mentioned above.[16]

Clinical Efficacy of Deucravacitinib

In the 52-week, global, pivotal phase 3 POETYK PSO-1 and POETYK PSO-2 trials (NCT03624127 and NCT03611751, respectively) conducted in patients with moderate to severe plaque psoriasis, deucravacitinib was compared with placebo and an active control, the phosphodiesterase-4 inhibitor apremilast.[34,37] As shown in (Figure 5), patients in POETYK PSO-1

FIGURE 5. Summary of efficacy up to 24 weeks in the POETYK PSO trials.[34,37]



PASI 75/90/100, ≥75%/≥90%/100% reduction from baseline in Psoriasis Area and Severity Index; sPGA 0/1, static Physician Global Assessment score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline. POETYK PSO-1: From Armstrong AW, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. *J Am Acad Dermatol.* 2023;88:29-39. https://www.jaad.org/action/showPdf?pii=S0190-9622%2822%2902256-3. This work is licensed under a Creative Commons Attribution License (CC BY-NC-ND 4.0). https://creativecommons.org/licenses/by-nc-nd/4.0/. POETYK PSO-2: Adapted from Strober B, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 POETYK PSO-2 trial. *J Am Acad Dermatol.* 2023;88:40-51. https://www.jaad.org/action/showPdf?pii=S0190-9622%2822%2902643-3. This work is licensed under a Creative Commons Attribution License (CC BY-NC-ND 4.0). https://creativecommons.org/licenses/by-nc-nd/4.0/.

TABLE 1.

Summary of Pooled Adverse Events Over 1 Year in the POETYK PSO Trials[a]

	Placebo, n=666 Total PY=240.9		Deucravacitinib, n=1364 Total PY=969.0		Apremilast, n=422 Total PY=221.1	
	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)
AE category						
Any AEs	347 (52.1)	217.4 (195.7, 241.5)	995 (72.9)	229.2 (215.4, 243.9)	299 (70.9)	281.1 (250.9, 314.8)
Serious AEs	14 (2.1)	5.7 (3.4, 9.6)	55 (4.0)	5.7 (4.4, 7.4)	9 (2.1)	4.0 (2.1, 7.7)
AEs leading to discontinuation	23 (3.5)	9.3 (6.2, 14.0)	43 (3.2)	4.4 (3.3, 5.9)	26 (6.2)	11.6 (7.9, 17.1)
Deaths	1 (0.2)	0.4	2 (0.1)[b]	0.2	1 (0.2)	0.4
Most common AEs (≥2%) in any treatment group						
Nasopharyngitis	54 (8.1)	22.7 (17.4, 29.7)	229 (16.8)	26.1 (23.0, 29.8)	54 (12.8)	25.9 (19.9, 33.9)
Upper respiratory tract infection	33 (5.0)	13.5 (9.6, 19.1)	124 (9.1)	13.4 (11.3, 16.0)	27 (6.4)	12.4 (8.5, 18.0)
Headache	21 (3.2)	8.6 (5.6, 13.1)	80 (5.9)	8.5 (6.8, 10.5)	53 (12.6)	26.0 (19.9, 34.0)
Diarrhoea	28 (4.2)	11.5 (7.9, 16.7)	69 (5.1)	7.3 (5.7, 9.2)	54 (12.8)	26.5 (20.3, 34.6)
Arthralgia	21 (3.2)	8.5 (5.6, 13.1)	55 (4.0)	5.7 (4.4, 7.4)	17 (4.0)	7.7 (4.8, 12.3)
Blood CPK increased	11 (1.7)	4.5 (2.5, 8.1)	45 (3.3)	4.7 (3.5, 6.3)	8 (1.9)	3.6 (1.8, 7.1)
Pharyngitis	4 (0.6)	1.6 (0.6, 4.3)	41 (3.0)	4.2 (3.1, 5.8)	5 (1.2)	2.2 (0.9, 5.4)
Hypertension	5 (0.8)	2.0 (0.8, 4.8)	39 (2.9)	4.0 (3.0, 5.5)	16 (3.8)	7.2 (4.4, 11.8)
Viral upper respiratory tract infection	6 (0.9)	2.4 (1.1, 5.4)	30 (2.2)	3.1 (2.2, 4.4)	3 (0.7)	1.3 (0.4, 4.1)
Acne	1 (0.2)	0.4 (0.1, 2.8)	28 (2.1)	2.9 (2.0, 4.2)	0	0
Oral herpes	2 (0.3)	0.8 (0.2, 3.2)	28 (2.1)	2.9 (2.0, 4.2)	2 (0.5)	0.9 (0.2, 3.5)
Psoriasis	31 (4.7)	12.8 (9.0, 18.2)	29 (2.1)	3.0 (2.1, 4.3)	10 (2.4)	4.5 (2.4, 8.3)
Urinary tract infection	8 (1.2)	3.2 (1.6, 6.5)	29 (2.1)	3.0 (2.1, 4.3)	4 (0.9)	1.8 (0.7, 4.7)
Back pain	8 (1.2)	3.2 (1.6, 6.4)	27 (2.0)	2.8 (1.9, 4.0)	17 (4.0)	7.7 (4.8, 12.3)
Bronchitis	4 (0.6)	1.6 (0.6, 4.3)	27 (2.0)	2.8 (1.9, 4.0)	5 (1.2)	2.2 (0.9, 5.3)
Folliculitis	0	0	27 (2.0)	2.8 (1.9, 4.0)	2 (0.5)	0.9 (0.2, 3.5)
Rhinitis	5 (0.8)	2.0 (0.8, 4.8)	26 (1.9)	2.7 (1.8, 3.9)	11 (2.6)	5.0 (2.7, 8.9)
Nausea	10 (1.5)	4.0 (2.2, 7.5)	20 (1.5)	2.1 (1.3, 3.2)	47 (11.1)	22.9 (17.2, 30.5)
Vomiting	7 (1.1)	2.8 (1.3, 5.9)	18 (1.3)	1.8 (1.2, 2.9)	9 (2.1)	4.0 (2.1, 7.7)
Myalgia	3 (0.5)	1.2 (0.4, 3.7)	13 (1.0)	1.3 (0.8, 2.3)	11 (2.6)	4.9 (2.7, 8.9)

[a]Includes patients who received the agent after treatment switches. [b]One additional death was reported at day 298 due to hepatocellular carcinoma in a patient with a history of hepatitis C virus infection and liver cirrhosis. This death was not considered to be drug-related by the investigator. AE, adverse event; CI, confidence interval; CPK, creatine phosphokinase; EAIR, exposure-adjusted incidence rate; PY, person-years.

TABLE 2.

Summary of Pooled Adverse Events of Interest Over 1 Year in the POETYK PSO Trials

Adverse event	Placebo, n=666 Total PY=240.9		Deucravacitinib, n=1364 Total PY=969.0		Apremilast, n=422 Total PY=221.1	
	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)
Infections						
Serious infections	2 (0.3)	0.8 (0.2, 3.2)	17 (1.2)	1.7 (1.1, 2.8)	4 (0.9)	1.8 (0.7, 4.7)
Herpes zoster	1 (0.2)	0.4 (0.1, 2.8)	9 (0.7)	0.9 (0.5, 1.8)	0	0
Adjudicated MACE	3 (0.5)	1.2 (0.4, 3.7)	3 (0.2)	0.3 (0.1, 0.9)	2 (0.5)	0.9 (0.2, 3.5)
Venous thromboembolic and peripheral arterial thromboembolic events						
Venous thromboembolic events[a]	0	0	2 (0.1)	0.2 (0.1, 0.8)	0	0
Peripheral arterial thromboembolic events	1 (0.2)	0.4 (0.1, 2.8)	2 (0.1)	0.2 (0.1, 0.8)	1 (0.2)	0.4 (0.1, 3.1)
Malignancies						
NMSC[b]	0	0	7 (0.5)	0.7 (0.3, 1.5)	1 (0.2)	0.4 (0.1, 3.1)
Malignancies excluding NMSC	0	0	3 (0.2)	0.3 (0.1, 0.9)	1 (0.2)	0.4 (0.1, 3.1)
Breast cancer[c]	0	0	1 (0.1)	0.1 (0.0, 0.7)	0	0
Hepatocellular carcinoma[d]	0	0	1 (0.1)	0.1 (0.0, 0.7)	0	0
Lung adenocarcinoma	0	0	0	0	1 (0.2)	0.4 (0.1, 3.1)
Hodgkin's disease[e]	0	0	1 (0.1)	0.1 (0.0, 0.7)	0	0
Skin events						
Acne	1 (0.2)	0.4 (0.1, 2.8)	28 (2.1)	2.9 (2.0, 4.2)	0	0
Folliculitis	0	0	27 (2.0)	2.8 (1.9, 4.0)	2 (0.5)	0.9 (0.2, 3.5)
Adjudicated suicidal ideation	1 (0.2)	0.4 (0.1, 2.8)	1 (0.1)	0.1 (0.0, 0.7)	1 (0.2)	0.4 (0.1, 3.1)

Total exposure: deucravacitinib, 969.0 PY; placebo, 240.9 PY; apremilast, 221.1 PY. Most placebo-related data were obtained over weeks 0-16. [a]A 19-year-old female patient discontinued deucravacitinib after 4 days of treatment due to a rash, and 12 days later developed thrombosis in the radial vein after peripheral cannulation for intravenous antibiotic therapy for a streptococcal infection. The thrombosis resolved with anticoagulant therapy. A 48-year-old male patient with multiple cardiovascular risk factors developed acute dissecting ascending aortic aneurysm on day 338 of deucravacitinib treatment, with coincident pulmonary artery thrombus/embolism but without confirmed evidence of deep vein thrombosis. Deucravacitinib treatment was briefly interrupted during surgery, and the patient subsequently enrolled in the long-term deucravacitinib extension trial, without recurrence of a venous thromboembolic event. Neither of these events was considered related to treatment by the investigator. [b]Four patients in the deucravacitinib group had basal cell carcinoma, and 1 patient each had squamous cell carcinoma, squamous cell carcinoma of the skin, and malignant sweat gland neoplasm. One patient had squamous cell carcinoma in the apremilast group. [c]A 64-year-old female with a family history of malignancy (mother had breast cancer) received apremilast over weeks 0-24 and deucravacitinib over weeks 24-52. This patient was diagnosed with breast cancer on day 341 and discontinued from the study due to breast cancer on day 360, with the last dose of deucravacitinib received on day 342. This event was considered not related to study treatment. [d]A 54-year-old male, who was a former smoker (16 packs/years; none in the past 6 years) with type 2 diabetes mellitus, a history of latent tuberculosis (2017; treated), and hepatitis C, was randomized to deucravacitinib treatment. This patient was diagnosed with hepatocellular carcinoma and a pancreatic mass on day 224, and the patient died on day 298. This event was considered unrelated to deucravacitinib treatment by the investigator. [e]A 48-year-old male with a history of type 2 diabetes mellitus, dyslipidemia, and hypertension was randomized to deucravacitinib treatment. At week 8, this patient was diagnosed with anemia and thrombocytopenia and, at week 20, had worsening cough, fatigue, anemia, and an unintended 29 lb weight loss. This patient was diagnosed with classical Hodgkin's lymphoma at week 25 based on lymph node biopsy for enlarged lymph nodes. The latent period of diagnosis was considered too short to attribute causality to deucravacitinib treatment, especially given complete blood count abnormalities detected at week 8. CI, confidence interval; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PY, person-years.

and PSO-2 who received deucravacitinib had significantly higher rates of achieving ≥75%, ≥90%, and 100% reductions from baseline in Psoriasis Area and Severity Index (PASI) as well as a static Physician Global Assessment score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline at weeks 16 and 24 compared with placebo and apremilast.[34]

Clinical Safety of Deucravacitinib

Patients with long-term exposure to deucravacitinib did not exhibit increased rates of adverse events reported with JAK1,2,3 inhibition, such as malignancies and cardiovascular events.[34,37] Total adjusted drug exposure across the POETYK PSO-1 and PSO-2 trials was 969.0 person-years for deucravacitinib, 240.9 person-years for placebo, and 221.1 person-years for apremilast. Adverse events reported for up to 1 year in the pooled POETYK PSO trials are summarized in (Table 1).[34,37] Adverse events of interest were infrequent with deucravacitinib and generally comparable to placebo and apremilast (Table 2). Serious infections and herpes zoster events were more common with deucravacitinib than with placebo; however, the incidence rates of these events were low in each treatment group. No clinically meaningful changes in mean levels of laboratory parameters were observed with deucravacitinib treatment for up to 1 year.

Long-term Safety and Efficacy of Deucravacitinib

POETYK long-term extension (LTE) (NCT04036435) is an ongoing, open-label trial designed to evaluate the long-term safety and efficacy of deucravacitinib in adults with moderate to severe plaque psoriasis.[38] Patients were eligible to enter the POETYK LTE trial and receive deucravacitinib 6 mg once daily after completing week 52 of POETYK PSO-1 or PSO-2.[38] The 2-year safety profile of deucravacitinib in POETYK LTE was consistent with the 1-year profile in POETYK PSO-1 or PSO-2, with no new or emerging safety signals identified.[38] Clinical efficacy was maintained over 2 years.[38] POETYK LTE will continue to evaluate the long-term safety and efficacy of deucravacitinib for an additional 5 years beyond the parent trials.

Mechanism of Action and Profile of JAK1,2,3 Inhibitors

Currently approved JAK1,2,3 inhibitors block the JAK1,2,3 ATP-binding active (catalytic) sites, as mentioned above.[2,3,22] JAK-STAT pathways mediate downstream signaling of multiple Type I and Type II cytokines.[39] Generally, JAK1 mediates lymphocyte development and IL-6 signaling, JAK2 mediates hematopoiesis and metabolic regulation, and JAK3 mediates lymphopoiesis and immune function.[2,23] JAK1,2,3 inhibition/deficiency is implicated in dysfunctional hematopoiesis, lipid metabolism abnormalities, and immunodeficiency due to dysregulation of T cells, B lymphocytes, and natural killer cells.[23] Systemic effects of JAK1,2,3 inhibition in clinical trials include dyslipidemia, serious and opportunistic infections, anemia, neutropenia, thrombocytopenia, major adverse cardiovascular events (MACE), venous thromboembolic events, and malignancies.[2,39-41]

JAK1,2,3 inhibitors are not approved for plaque psoriasis, despite showing efficacy in clinical trials.[22,42] Two phase 3 trials demonstrated that oral tofacitinib 5 mg and 10 mg twice daily was superior to placebo,[43] and an additional phase 3 trial demonstrated that oral tofacitinib 10 mg twice daily was noninferior to subcutaneous etanercept 50 mg twice weekly and superior to placebo.[44] However, increased infections (especially herpes zoster), MACE, malignancy, and lipid abnormalities were reported with tofacitinib (Figure 1). Although these trials did not assess long-term safety, the randomized Oral Rheumatoid Arthritis Trial (ORAL) Surveillance (median follow-up, 4 years) reported that MACE and malignancy occurred more often in patients ≥50 years of age with at least one additional cardiovascular risk factor who were receiving tofacitinib 5 mg or 10 mg twice daily compared with a TNF inhibitor (adalimumab 40 mg every 2 weeks or etanercept 50 mg once weekly).[45]

CONCLUSION

TYK2 plays a major role in cytokine signaling in psoriasis pathogenesis. Selective, allosteric TYK2 inhibition effectively blocks this cytokine signaling, while minimizing systemic effects associated with JAK1,2,3 inhibition. Deucravacitinib, the only selective TYK2 inhibitor approved for the treatment of plaque psoriasis, is efficacious and well tolerated in patients with moderate to severe plaque psoriasis. Further clinical evaluation of this and other TYK2 inhibitors will provide additional insights about the role of selective TYK2 inhibition in psoriasis and other IMIDs.

DISCLOSURES

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