


Deucravacitinib: A Novel TYK2 Inhibitor for the Treatment of Moderate-to-Severe Psoriasis

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Abstract

Background: Deucravacitinib is a first-in-class tyrosine kinase 2 (TYK2) inhibitor recently approved for the treatment of adults with moderate-to-severe plaque psoriasis. **Objective:** To discuss the mechanism of action, efficacy, safety, and real-world applications of deucravacitinib for the treatment of psoriasis. **Methods:** Literature on the mechanism of action of deucravacitinib is reviewed. The pivotal clinical studies and long-term extension studies for deucravacitinib are also examined. **Results:** Deucravacitinib is a novel oral TYK2 inhibitor that binds to the regulatory domain of TYK2, a Janus kinase. By inhibiting TYK2, deucravacitinib interferes with signaling of IL-23, IL-12, and type I interferons, cytokines believed to play important roles in psoriasis pathogenesis. Nearly 60% of patients achieve PASI 75 at 16 weeks of treatment; efficacy improves over 24 weeks and is maintained through 2 years of continuous treatment. In a head-to-head comparison, deucravacitinib efficacy was superior to apremilast, an older yet commonly used oral PDE4 inhibitor approved for the treatment of psoriasis. Of note, patients with moderate-to-severe plaque psoriasis with concomitant involvement of the scalp, nails, and/or palms/soles demonstrated good improvement in these high impact areas. Deucravacitinib has an acceptable safety profile and is generally well-tolerated. Small increases in reactivation of herpesvirus infections, including herpes simplex outbreaks, have been reported. Tuberculosis evaluation, but no other blood tests, is recommended prior to initiation of deucravacitinib. Monitoring of triglyceride levels should be conducted for high-risk patients according to local guidelines. **Conclusion:** Deucravacitinib is an effective, safe, and well-tolerated novel oral medication for adults with moderate-to-severe plaque psoriasis.

Keywords

deucravacitinib, tyrosine kinase, TYK2, mechanism of action, psoriasis, review, efficacy, safety

Introduction

Psoriasis is a chronic immune-mediated inflammatory disease that affects up to 8 million adults in the United States.^{1,2} Patients with moderate-to-severe disease often require treatment with systemic medications, including oral and biologic therapies.^{3,4} Innovations in oral therapies have been scant. In 1972, methotrexate, a dihydrofolate reductase inhibitor, was approved for the treatment of severe plaque psoriasis in adults.⁵ Cyclosporine, a calcineurin inhibitor, and acitretin, an oral retinoid, were approved for adults with severe psoriasis in 1997.^{6,7} More recently, apremilast, a phosphodiesterase-4 inhibitor, was approved in 2014 for adults with psoriasis,⁸ and represented a safer treatment option for patients when compared to the previous oral drugs. Apremilast, however, has limited efficacy, so the search for novel, safe, and more effective oral drugs for psoriasis has been pursued. In September 2022, deucravacitinib was approved by the U.S. Food and Drug Administration for adults with moderate-to-severe plaque psoriasis.⁹ Here, the mechanism of action,

efficacy, safety, and real-world applications of deucravacitinib for psoriasis are reviewed in detail.

Tyrosine Kinase 2 Background and Mechanism of Action of Deucravacitinib

Along with JAK1, JAK2, and JAK3, TYK2 is a member of the Janus kinase (JAK) family, enzymes involved in

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transducing inflammatory signals within cells.¹⁰ The first step in this process is binding of a cytokine to the extracellular portion of its receptor.¹¹ These receptors span across cell membranes, with both extracellular and intracellular regions.¹¹ Upon cytokine binding to the extracellular region of the cytokine receptor, the intracellular region undergoes a conformational change. This shape change leads to phosphorylation, or activation, of the JAK enzymes that are attached to the intracellular portion of the cytokine receptor.^{11,12} Activation of JAKs then lead to phosphorylation (activation) of signal transducer and activator of transcription (STAT) proteins, which are also attached to the cytokine receptor/JAK complex.^{11,12} Phosphorylated STAT proteins then dislodge from the complex and migrate to the nucleus, where they bind to DNA regulatory regions.¹² Genes are then transcribed, leading to the further production of inflammatory cytokines and other relevant proteins.^{12,13}

JAKs work in pairs, either homodimerizing, e.g., JAK1/JAK1, or to another JAK, e.g., TYK2/JAK1.¹¹ Importantly, detailed work has shown that certain groups of cytokines signal through different types of JAKs. For example, the cytokines IL-23, IL-12, and type I interferons rely on TYK2 to mediate their pro-inflammatory effects.¹⁴⁻¹⁷ By contrast, another group of cytokines, IL-4, IL-13, and IL-31, signal through JAK1.^{18,19} This concept is important, since JAK inhibitors are now available that have different specificities for each JAK enzyme, with some being more selective than others, such as the TYK2 inhibitor deucravacitinib (approved for psoriasis)⁹ and the JAK1 inhibitor abrocitinib (approved for atopic dermatitis).²⁰ By blocking TYK2, deucravacitinib blocks signaling of IL-23 and IL-12, similar to ustekinumab, a commonly used biologic used to treat psoriasis.²¹

Another important feature of deucravacitinib is its selectivity for binding and inactivating TYK2 (Figure 1), while demonstrating negligible ability to block the other three

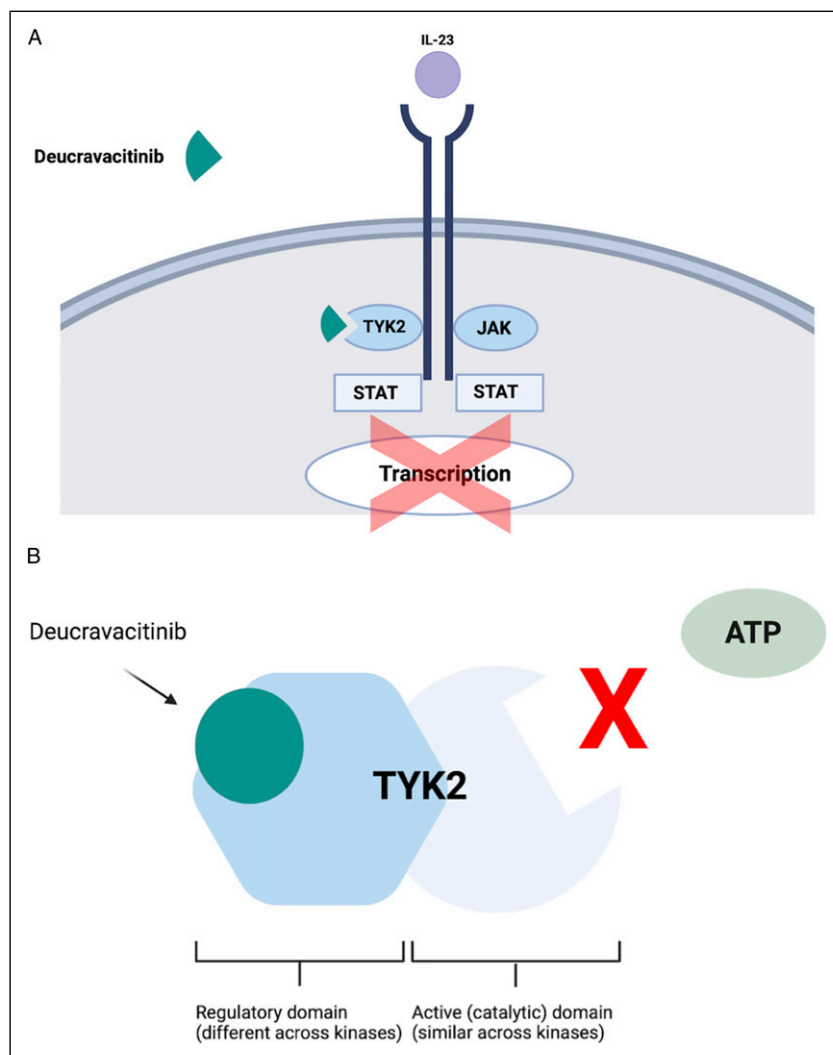


Figure 1. (A-B): Mechanism of action of deucravacitinib.

members of the JAK family at relevant pharmacokinetic drug levels.²² This selectivity is imparted due to its binding in the unique regulatory region of TYK2 as opposed to the enzymatic region of the enzyme, which is a relatively conserved region of all four JAKs (Figure 1).^{15,23–25} Therefore, drug binding to the enzymatic region of a JAK often leads to at least some cross-inactivation of all four JAKs, i.e., less specificity. Selectivity for TYK2 also is the reason deucravacitinib has not been categorized with other types of JAK inhibitors, which all have boxed warnings related to safety (see below);²⁰ deucravacitinib currently has no boxed warnings. Indeed, it has been designated a first-in-class drug as a selective TYK2 inhibitor.⁹

Efficacy of Deucravacitinib

Phase 3 Trials

Three phase 3 clinical trials have examined the efficacy of deucravacitinib in adults with moderate-to-severe plaque psoriasis: two pivotal trials (POETYK PSO-1 and POETYK PSO-2)^{26,27} and one long-term extension trial (POETYK PSO-LTE).²⁸ POETYK PSO-1 and POETYK PSO-2 enrolled individuals ≥ 18 years old with moderate-to-severe psoriasis for 6 months prior to screening.^{29,30} Patients were randomized to deucravacitinib 6 mg daily, placebo, or apremilast 30 mg twice a day on day 1.

The coprimary end points were achievement of $\geq 75\%$ reduction from baseline in PASI (PASI 75) and sPGA 0/1 (clear/almost clear) with a ≥ 2 -point improvement from baseline for deucravacitinib versus placebo at Week 16. Key secondary end points included achievement of $\geq 90\%$ and 100% reductions from baseline in PASI (PASI 90 and PASI 100) at Weeks 16 and 24. In POETYK PSO-1 and POETYK PSO-2, clinical responses with deucravacitinib were also compared to apremilast for primary and secondary endpoints. A head-to-head comparison with an established therapy like apremilast was critical to understanding how the efficacy of deucravacitinib compared to an existing oral treatment commonly used for psoriasis.

Efficacy of Deucravacitinib: Results from POETYK PSO-1 and POETYK PSO-2

In both trials, a majority of patients had received prior systemic treatment for psoriasis (63% in POETYK PSO-1; 54% in POETYK PSO-2).^{29,30} Deucravacitinib demonstrated superior PASI 75 and sPGA 0/1 response rates compared to apremilast and placebo at Week 16 (Figure 2).^{29,30} In POETYK PSO-1, 58% of patients on deucravacitinib achieved PASI 75 at Week 16, compared to 35% of patients on apremilast and 13% of patients on placebo.²⁹ A total of 54% of patients on deucravacitinib achieved sPGA 0/1 at Week 16, compared to 32% of patients on apremilast and 7% of patients on placebo.²⁹

Deucravacitinib was also superior to apremilast in PASI 90 response rates at Weeks 16 and 24 in both trials.^{29,30} PASI 90

responses with deucravacitinib were 27% and 32% at Weeks 16 and 24, respectively, compared to 18% and 20% with apremilast, in POETYK PSO-2.³⁰ PASI 100 response rates for deucravacitinib were 14% and 10% in POETYK PSO-1 and POETYK PSO-2, respectively, compared to 1% and 1% for placebo at Week 16 ($P < .001$).^{29,30} Notably, deucravacitinib is the first oral therapy for moderate-to-severe plaque psoriasis to include PASI 100 data at Week 16 in its label.^{5–9}

Deucravacitinib had similar efficacy among different patient sub-groups, including those with varying demographics, baseline disease activity, and prior treatment history. More specifically, on post-hoc analysis, there were no identified differences in PASI 75 responses with deucravacitinib among patient subgroups based on age, gender, race, body weight, baseline disease severity or prior systemic therapy use.^{31–33}

Over time, PASI response rates remained stable through 1 year for patients on deucravacitinib (Figure 3). In POETYK PSO-1, 65% of patients achieved PASI 75 at Week 52 (compared to 69% at Week 24).³⁴ Similarly, 44% of patients achieved PASI 90 at Week 52 (compared to 42% at Week 24). Nearly one in five patients (19%) achieved PASI 100 at Week 52.³⁴

Long-Term Efficacy of Deucravacitinib: Results from POETYK PSO-LTE

Patients who completed treatment through Week 52 in either POETYK PSO-1 or POETYK PSO-2 were eligible to enroll in the long-term extension trial, POETYK PSO-LTE.³⁵ All enrolled patients, regardless of treatment arm in the parent study, were blindly switched to open-label deucravacitinib at the start of POETYK PSO-LTE. Among all patients enrolled in POETYK PSO-LTE, PASI 75 and sPGA 0/1 response rates were 78% and 59%, respectively, at 2 years, compared to 67% and 52% at 1 year, using nonresponder imputation.^{35,36} Of note, long-term extension efficacy data may be inflated as patients who lose response or are unable to tolerate the medication may be more likely to discontinue treatment, which may raise the proportion of responders. A *post-hoc* sub-analysis of patients who received 2 years of continuous deucravacitinib treatment showed a PASI 75 response rate of 82% using nonresponder imputation (Figure 4).³⁶

Efficacy of Deucravacitinib in High Impact Areas

A subset of patients with moderate-to-severe psoriasis in POETYK PSO-1 and POETYK PSO-2 had concomitant disease in high impact areas, e.g., scalp, fingernails, and palms/soles.^{9,37} Deucravacitinib efficacy within these specific body areas was also assessed. In POETYK PSO-1, significantly more patients who had baseline moderate-to-severe scalp disease achieved clear or almost clear scalp (scalp-specific Physician's Global Assessment [ss-PGA] 0/1) at Week 16 when treated with deucravacitinib, compared to those treated with apremilast ($P < .001$)

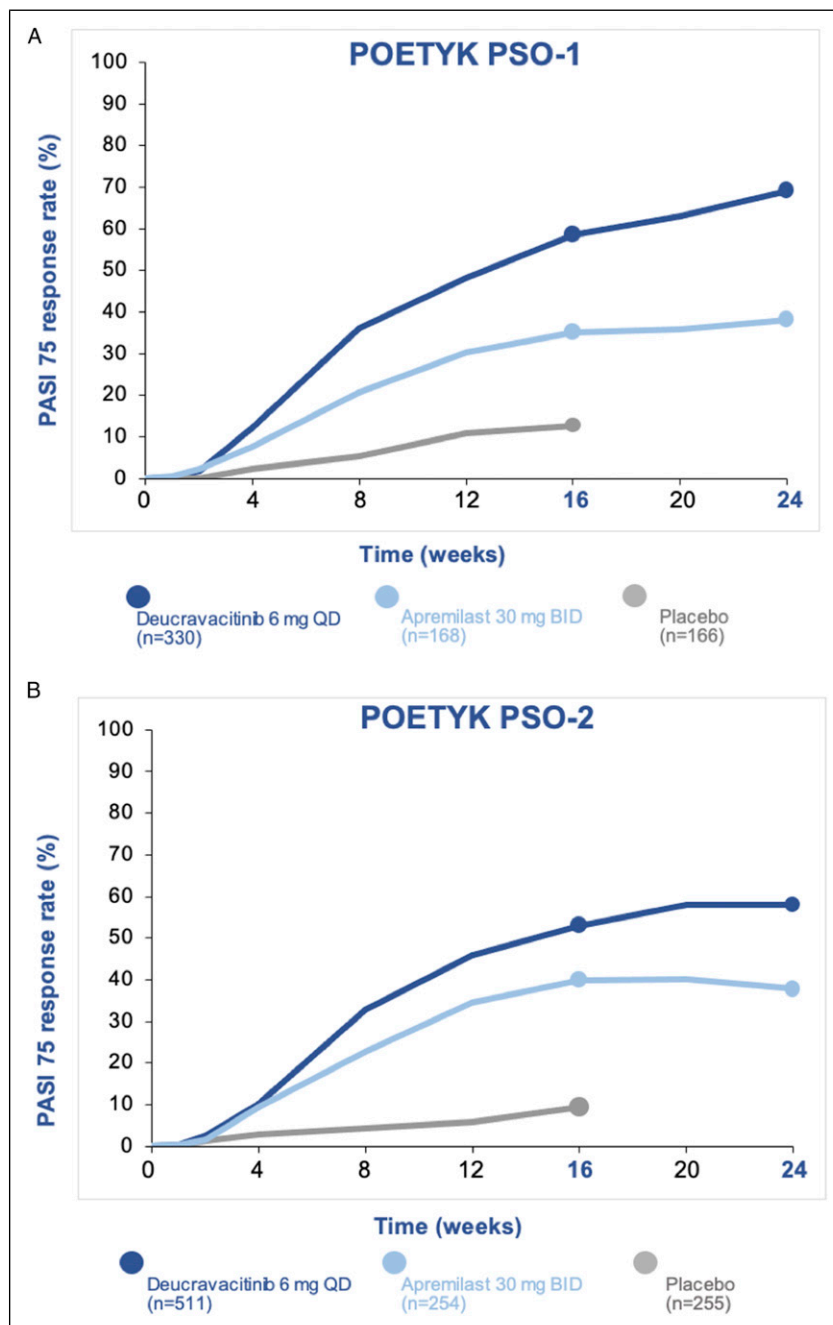


Figure 2. (A-B): PASI 75 response rates in the POETYK PSO-1 and POETYK PSO-2 trials.

and placebo ($P < .001$).²⁹ A small number of patients in both trials had concomitant moderate-to-severe nail psoriasis at baseline.^{29,30} In a pooled analysis of POETYK PSO-1 and POETYK PSO-2, the Physician's Global Assessment of fingernails (PGA-F) score of 0 (clear) or 1 (almost clear) response at Week 16 was greater for deucravacitinib versus placebo ($P = .0272$) using nonresponder imputation.³⁸ Similarly, few patients had concomitant moderate-to-severe palmoplantar psoriasis at baseline.^{29,30} In a pooled analysis, significantly more patients receiving deucravacitinib versus placebo achieved palmoplantar

Physician's Global Assessment (pp-PGA) of 0/1 (clear/almost clear) at Week 16 ($P = .0052$) using nonresponder imputation.³⁹

Safety of Deucravacitinib

Safety of Deucravacitinib: Safety Data from POETYK PSO-1 and POETYK PSO-2

Deucravacitinib was well-tolerated; rates of headache, diarrhea, and nausea were similar or lower than in patients treated

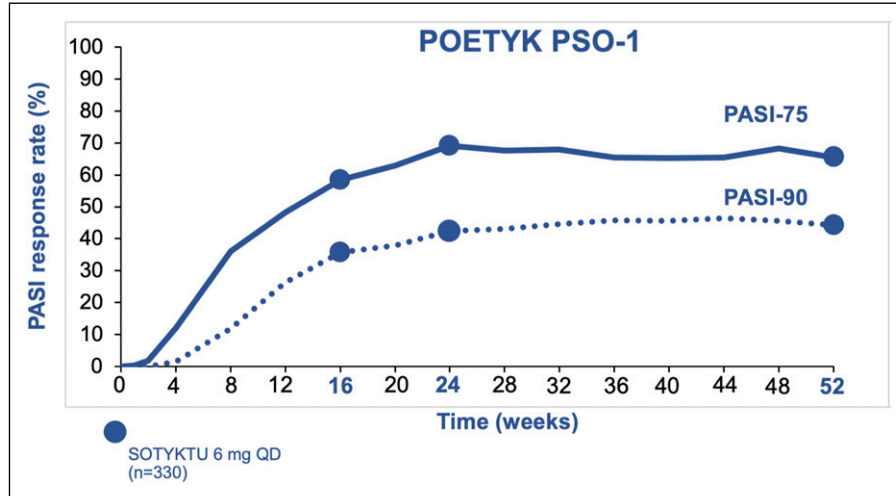


Figure 3. PASI 75 and PASI 90 response rates at 1 year of treatment with deucravacitinib.

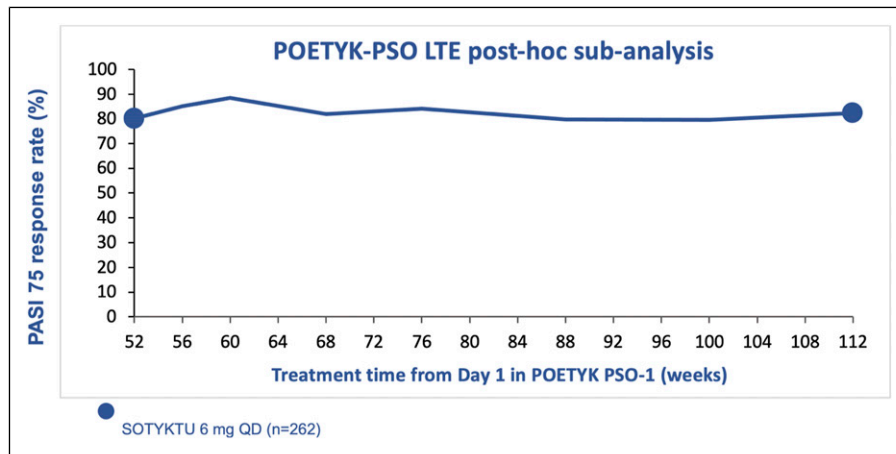


Figure 4. PASI 75 response rates through 2 years of continuous treatment with deucravacitinib.

with either placebo or apremilast at Week 16 (headache: deucravacitinib 4.5%, placebo 4.5%, apremilast 10.7%; diarrhea: deucravacitinib 4.4%, placebo 6.0%, apremilast 11.8%; nausea: deucravacitinib 1.7%, placebo 1.7%, apremilast 10.0%).⁴⁰

In pooled Week 16 safety data of POETYK PSO-1 and POETYK PSO-2, patients on deucravacitinib had relatively low frequencies of upper respiratory tract infections (URI), increased blood creatine phosphokinase, herpes simplex infections, mouth ulcers, folliculitis, and acne, with slight increases in frequencies of these events compared to patients on placebo;^{9,40} most of these events were mild and did not require treatment discontinuation.

Deucravacitinib had the lowest discontinuation rates due to adverse events (AE) at 16 weeks (2.4%) compared to apremilast

(5.2%) and placebo (3.8%).⁴⁰ Discontinuation rates due to AEs remained lower for patients on deucravacitinib (4.4%) compared to patients on apremilast (11.6%) and placebo (9.4%) through 52 weeks of treatment.⁴⁰ Incidence (reported as exposure adjusted incident rate [EAIR] per 100 patient years [PY]) of headache, diarrhea and nausea remained significantly lower for deucravacitinib vs apremilast (headache 8.5 vs 26.0; diarrhea 7.3 vs 26.5; nausea 2.1 vs 22.9) at Week 52.⁴⁰

The incidence of specific AEs of interest, including non-melanoma skin cancer (NMSC), malignancies, serious infections, arterial thromboembolic events, venous thromboembolism events (VTE), and major cardiovascular events (MACE) were low and similar among the deucravacitinib, apremilast, and placebo arms at Week 52 (Figure 5).^{9,36,40} Serious adverse events (SAE) occurred at low

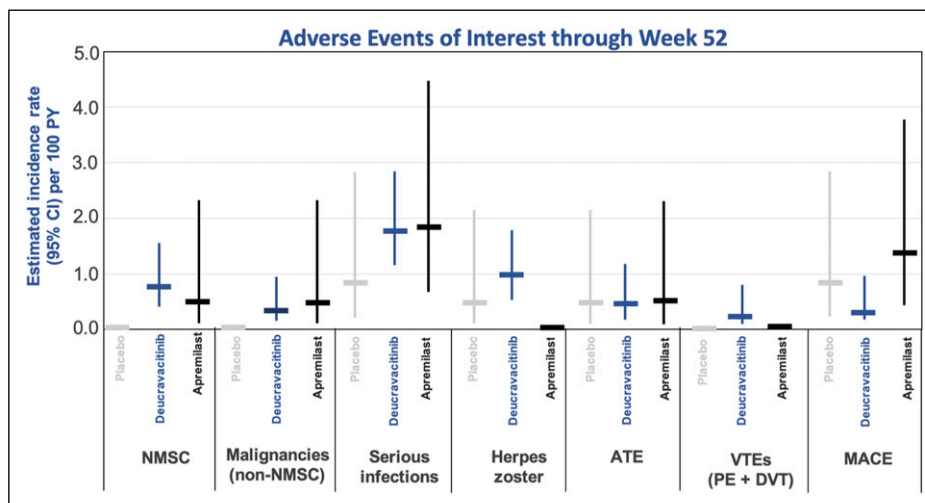


Figure 5. Adverse events of interest through week 52: pooled analysis of POETYK PSO-1 and POETYK PSO-2. NMSC, non-melanoma skin cancer; ATE, arteriothrombotic event; VTE, venous thromboembolism event; PE, pulmonary embolism; DVT, deep vein thrombosis; MACE, major adverse cardiovascular event.

and similar rates among the deucravacitinib, placebo, and apremilast groups through 52 weeks (EAIR per 100 PY 5.7, 5.7, and 4.0, respectively).⁴⁰

Long-Term Safety of Deucravacitinib: Safety Data from POETYK PSO-LTE

Treatment with deucravacitinib was well-tolerated through 2 years and had lower rates of AEs compared to 52 weeks of treatment on pooled safety data from POETYK PSO-1, POETYK PSO-2, and POETYK PSO-LTE.³⁵ At 2 years of treatment with deucravacitinib, the EAIR per 100 PY of AEs leading to discontinuation was lower compared to 1 year of treatment (2.8 vs 4.4).³⁵ Rates of SAEs remained low and stable through 2 years (EAIR 6.2 per 100 PY) compared to 1 year (EAIR 5.7 per 100 PY).³⁵ The EAIR per 100 PY for AEs of interest were also reported through 2 years of treatment. The EAIRs per 100 PY for serious infections for patients receiving deucravacitinib were 1.7 at 1 year and 2.6 at 2 years.³⁵ The EAIRs per 100 PY were 0.9 at year 1 and 0.7 at year 2 for herpes zoster infection; 0.3 and 0.4, respectively, for MACE; 0.2 and 0.1, respectively, for VTE; and 1.0 and 0.9, respectively, for total malignancies.³⁵ The EAIRs per 100 PY of NMSC were 0.7 and 0.4 and 1 and 2 years, respectively.³² The EAIRs per 100 PY of malignancies excluding NMSC were 0.3 and 0.5 and 1 year and 2 years, respectively.³⁵

Laboratory Parameters: Results from POETYK PSO-1 and POETYK PSO-2

In pooled laboratory data from POETYK PSO-1 and POETYK PSO-2, there were no abnormalities in hematologic parameters at Week 16.⁴¹ The most commonly

reported laboratory AE in all 3 treatment groups was elevated blood creatine phosphokinase, which was typically associated with recent exercise and resolved without intervention in most cases.^{29,30} While most patients had normal triglyceride levels, some patients experienced increases in triglycerides.⁴¹ Rates of grade ≥ 3 triglyceride abnormalities at Week 16 were similar among the three treatment groups (grade 3: deucravacitinib 1.6%, placebo 1.5%, apremilast 2.0%; grade 4: deucravacitinib 0.2%, placebo 0%, apremilast 0.2%), and the majority of these did not lead to discontinuation from the study.⁴¹ The mean increase in triglycerides in the deucravacitinib group was approximately 10 mg/dL higher than the placebo group,⁴¹ but the clinical significance of this increase is uncertain. Currently, there is no universal recommendation for triglyceride monitoring in patients on deucravacitinib, but, in general, lipid evaluation with primary care providers is recommended for at-risk patients.

Real-World Applications

Which Patients are Appropriate for Deucravacitinib?

Deucravacitinib is a novel oral medication that is among the first-line treatments for adults with moderate-to-severe plaque psoriasis. It is an effective option for patients who are not interested in injectable biologic medications or have contraindications to biologics (Table 1). It would also be an appropriate treatment option for those who have demonstrated an inadequate response to or not tolerated apremilast. Deucravacitinib has similar efficacy regardless of baseline disease severity or prior systemic therapy use,^{31,32} making it an appealing option for both biologic-naïve and biologic-experienced patients (Table 1).

Table 1. Real-World Applications of Deucravacitinib.

Patients that may be appropriate for deucravacitinib	Potential candidates for treatment with deucravacitinib include biologic naïve patients, biologic experienced patients, patients with contraindications to biologic therapy, needle averse patients, patients interested in oral therapy, or patients with BMI >30 kg/m ² .
Dosing and administration	Deucravacitinib 6 mg is a once daily oral tablet that requires no dose titration. It can be taken with or without food. There are no known drug interactions with deucravacitinib; however, patient should avoid live vaccines while on deucravacitinib and update vaccination status prior to initiating therapy, when possible.
Monitoring recommendations	All patients should undergo tuberculosis (TB) evaluation prior to starting deucravacitinib. Patients with latent TB should be initiated on anti-tuberculosis therapy prior to or concurrent to starting deucravacitinib. If a patient has active TB, consider consultation with infectious disease specialists. Consider evaluation of baseline lipids. For patients with known or suspected liver disease, liver function enzymes and hepatitis serologies should be evaluated at baseline. Those with known liver disease should be monitored with liver function enzymes throughout treatment with deucravacitinib, according to routine patient management.

Furthermore, it is an appropriate option regardless of patient weight (Table 1).^{31,32} Ongoing clinical trials are investigating the efficacy of deucravacitinib in treating psoriatic arthritis.⁴²

Dosing and Administration of Deucravacitinib

Deucravacitinib is a once daily 6 mg oral tablet that does not require dose titration or dose adjustments (Table 1).⁹ Patients can take deucravacitinib with or without meals,⁹ which provides flexibility for patients and can increase adherence. There are no known medication interactions with deucravacitinib (Table 1).⁹ However, live vaccines should be avoided while taking deucravacitinib,⁹ and when possible, as with other systemic immunosuppressive medications, patients might consider updating immunizations according to current immunization guidelines prior to initiating therapy (Table 1).

Monitoring Recommendations

Prior to starting deucravacitinib, all patients should undergo tuberculosis (TB) evaluation. This recommendation stems from the fact that deucravacitinib can interfere with signaling and function of IL-12,²⁹ a cytokine known to play a role in fighting granulomatous infections.⁴³ If the patient has latent TB, the patient should be considered for anti-tuberculosis therapy prior to or concurrent to starting deucravacitinib. If the patient has active TB, deucravacitinib should not be started, and consultation with infectious disease specialists is advisable (Table 1).⁹ Baseline evaluation of lipids (fasting) can be considered for patients who do not have a prior available assessment of baseline lipids. While there is no additional universal recommendation for triglyceride monitoring, patients with unmanaged hypertriglyceridemia should follow-up with their primary care providers such that they can receive periodic triglyceride evaluation according to clinical guidelines for hyperlipidemia (Table 1).⁹

If a patient has known or suspected liver disease, liver enzymes and hepatitis serologies should be evaluated at baseline prior to starting deucravacitinib. Those with known liver disease should then be monitored with liver function enzymes during deucravacitinib therapy, according to routine patient management (Table 1).⁹ Deucravacitinib is not recommended for patients with severe hepatic impairment or with chronic hepatitis B virus or hepatitis C virus infection.⁹

Counseling Patients on Deucravacitinib

Before starting a patient on deucravacitinib, the risks, benefits and treatment alternatives should be discussed while emphasizing the overall tolerability and safety of deucravacitinib therapy. Patients should be reminded not to crush or cut deucravacitinib tablets. Patients can expect to see improvement in their skin as early as 4 weeks, which can continue to improve with continuous treatment through Week 24.^{29,30} At this time, there is insufficient data to support the use of deucravacitinib in pregnant or breastfeeding women.⁹ Patients can be counseled on the superior efficacy of deucravacitinib as compared to apremilast, though it should be noted there is a lack of head-to-head studies comparing deucravacitinib to other oral therapies for psoriasis.

Combination Use

Deucravacitinib can be used as monotherapy to treat moderate-to-severe psoriasis but may also be used as part of combination therapy. In real-world clinical practices, as with other systemic medications, deucravacitinib is often used with adjunctive topical therapies to achieve greater clearance of plaques. In patients with recalcitrant severe plaque psoriasis, considerations may be given to using deucravacitinib in combination with another systemic agent. However, there are little data with this combination use, and further studies are necessary to understand the efficacy and safety of this approach.

Conclusion

Development and approval of deucravacitinib, a novel first-in-class TYK2 inhibitor, represents a major breakthrough for oral therapies to treat psoriasis. Overall, deucravacitinib has been shown to be an effective oral agent with an acceptable safety profile and good tolerability through 2 years of use. Efficacy has also been shown to be superior to apremilast in head-to-head studies, which positions this drug to become the gold standard oral therapy for patients with plaque psoriasis.

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Consent

Participants provided written informed consent.

Ethical Statement

Ethical Approval

This research did not require IRB approval/ethical approval because data reviewed are publicly available.

ORCID iDs

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