Deucravacitinib for the Treatment of Psoriatic Disease

Ana Maria Lé1 · Luis Puig2 · Tiago Torres1,3

Accepted: 25 July 2022 / Published online: 12 August 2022
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

Abstract
Psoriasis is an immune-mediated disease, with the interleukin (IL)-23/IL-17 axis currently considered its main pathogenic pathway. Tyrosine kinase 2 (TYK2) is responsible for mediating immune signalling of IL-12, IL-23 and type I interferons, without interfering with other critical systemic functions as other JAK proteins do. This article aims to review the current knowledge on deucravacitinib, a new oral drug that selectively inhibits TYK2, granting it a low risk of off-target effects. After good efficacy and safety results in a phase II, placebo-controlled trial, two phase III, 52-week trials evaluated deucravacitinib 6 mg against placebo and apremilast—an active comparator. POETYK PSO-1 and PSO-2 involved 1688 patients with moderate-to-severe psoriasis. After 16 weeks, in both studies, over 50% of patients treated with deucravacitinib reached PASI75, which was significantly superior to placebo and apremilast. In POETYK PSO-1, these results improved until week 24 and were maintained through week 52, with over 65% of patients achieving PASI75 at this point. A reduction in signs and symptoms was also reported by patients, with greater impact on itch. Deucravacitinib was well tolerated and safe. There were no reports of serious infections, thromboembolic events, or laboratory abnormalities, which are a concern among other JAK inhibitors. Persistent efficacy and consistent safety profiles were reported for up to 2 years. Despite advances in the treatment of psoriasis, namely among biologic agents, an oral, effective and safe new drug can bring several advantages to prescribers and patients. Further investigation is required to understand where to place deucravacitinib among current psoriasis treatment options.

1 Introduction
Psoriasis is a chronic, inflammatory, immune-mediated disease with a high negative impact on patients' quality of life [1]. Psoriasis impairs patients' psychosocial wellbeing and work productivity, as a result of persistent lesions and social stigma [2, 3].

Psoriasis arises from a complex immunological disarray that is still not fully understood. Interleukin (IL)-23/IL-17 signalling pathway is currently considered the main pathogenic pathway [4–6]. Environmental stimuli or loss of self-tolerance via autoantibodies trigger plasmacytoid dendritic cells (DCs) to produce tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). These antinecrotic cytokines recruit neutrophils and macrophages, which induce keratinocyte proliferation and inflammation.

Tyrosine kinase 2 (TYK2) is a member of the Janus kinases family that is responsible for mediating the immune response associated with psoriasis through interleukin (IL)-12, IL-23 and type I interferons (IFN-α and IFN-β).

Deucravacitinib, an oral TYK2 selective inhibitor, has shown a good efficacy and safety profile up to 52 weeks in moderate to severe psoriasis.

This new drug may address the existing unmet need for oral options for psoriasis, but long-term evaluation and comparison trials with biologic agents might determine what place it will take among current therapeutic solutions.
interferon-α (IFN-α). These inflammatory cytokines activate myeloid DCs to release IL-23 and IL-12. IL-23 promotes the proliferation of T helper (Th) 17 and Th22 cells that enhance IL-17 and IL-22 production, respectively. IL-12 induces differentiation of Th1 cells which secrete IFN-γ and TNF-α, expanding the inflammatory cascade [4, 5, 7].

Plaque psoriasis is the most common form of the disease, accounting for 80% of the cases. Most patients have a mild-to-moderate presentation of the disease, which can usually be managed with topical treatments. However, when topical therapy fails to control the disease and in extensive and severe cases, systemic treatment is required [1].

Current systemic therapies include oral conventional options, namely cyclosporine, methotrexate, fumaric acid esters and acitretin, newer targeted oral small molecules such as apremilast and parenteral biologic agents [8]. The efficacy of current oral treatments in psoriasis is generally lower than that of biologics. In addition, conventional systemic therapies are associated with high risk of drug interactions, cumulative organ toxicities (hepatic, pulmonary, hematologic and renal) and potential severe adverse effects, and require extensive analytic monitoring, while apremilast is less extensively monitored, while apremilast is often not well tolerated. Thus, there is still an unmet need for accessible, efficacious and safe therapies for patients with moderate-to-severe psoriasis [1, 9–12].

New small molecules are the subject of recent research. They have the potential to be administered orally or topically, which can be more convenient for some patients [6, 13, 14].

This article aims to review the current knowledge on deucravacitinib, a new oral small molecule that selectively inhibits TYK2, for the treatment of psoriasis.

2 TYK2 Inhibition

Janus kinases (JAKs) are cytoplasmatic proteins involved in cytokine receptor signalling: JAK1, JAK2, JAK3 and TYK2. They act as signal transducers, translating extracellular stimuli into intracellular cascade, which results in altered gene expression. They are constituted by multiple domains. The highly conserved active domain is similar in all JAKs, while the regulatory domain has a specific configuration in each one of them [15].

When a circulating extracellular cytokine binds to its cell receptor, a combination of two members of the JAK family is recruited and phosphorylated. Subsequently, intracellular signal transducer and activator of transcription (STAT) proteins become phosphorylated and activated. This process enables STAT proteins to move into the cell nucleus and modulate gene expression. Each set of JAKs is associated with specific cytokine receptors [15, 16].

All JAKs play an essential role in many immune responses. TYK2 mediates signalling of inflammatory cytokines of both adaptive (IL-12, IL-23) and innate (type I IFNs) immune responses [17]. Unlike TYK2, JAK1, 2 and 3 are also responsible for mediating a series of signals that support broader systemic responses, namely haematopoiesis, myelopoiesis, lipid metabolism and bone regulation. In fact, according to studies with mice models, complete deficiency of JAK1 and JAK2 seems to be incompatible with life, and there are no reports of human beings born with this genetic condition [18–20]. JAK3 inactivating mutations result in immunodeficiency syndromes in both mice and humans, and they present with life-threatening infections in the first months of life [21–23].

JAK1 can pair with all other JAKs, being associated with type I IFN-α/β (JAK1-TYK2), IFN-γ (JAK1-JAK2) and IL-6 (JAK1/JAK2-TYK2) receptors. JAK3 only pairs with JAK1 and they become activated by IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 receptors, being crucial in lymphocyte function [15, 16].

The JAK2 pair (JAK2-JAK2) plays an important role in erythropoiesis and myelopoiesis signalling as it is connected to the receptor of erythropoietin, thrombopoietin and granulocyte macrophage-colony stimulating factor. The JAK2-TYK2 pair is triggered by IL-12 and IL-23 (Fig. 1) [15, 16].

In line with this knowledge, JAK 1, 2 and 3 inhibitors such as tofacitinib (JAK 1/3), baricitinib (JAK 1/2) and ruxolitinib (JAK 1/2) raised safety concerns due to reports of important adverse effects like cytopenia, dyslipidaemia, gastric perforation, thromboembolic events and infections, namely herpes zoster [24–29]. Their clinical research in psoriasis has, therefore, been abandoned, mostly due to their unfavourable efficacy/safety ratio [30].

TYK2 participates almost exclusively in immune cytokine signalling pathways. Mouse models with TYK2 deficiency have a compromised immune cytokine signalling which results in a mild immunodeficiency phenotype. According to published case reports, human patients with TYK2 homozygous mutations present a higher susceptibility to mycobacterial and viral infections. Concomitantly, hyper-IgE syndrome occurred in some of the cases, depending on which one of five null mutations was present. These findings were attributed to impairment of the IL-23 pathway [31–33].

Considering TYK2 is involved in the signalling process of IFN-α, IL-12 and IL-23, it was accepted as a viable therapeutic target for psoriasis [34].

A study with mouse models suggested that TYK2 inactivation provides protection from multiple autoimmune diseases, including psoriasis. An association between TYK2 gene and psoriasis susceptibility was also reported in a genome-wide association study [35]. This evidence was the starting point for researching TYK2 as a potential therapeutic target for psoriasis [31].

Δ Adis
Deucravacitinib for Psoriatic Disease

3 Deucravacitinib

Deucravacitinib is a new oral small molecule that selectively inhibits TYK2 by uniquely binding to the TYK2 regulatory pseudokinase (JH2) domain (allosteric inhibition). By not binding to the conserved active domain (competitive inhibitors), like other JAK inhibitors, deucravacitinib is considerably more selective to TYK2 than to the other JAKs. Other JAK inhibitors like tofacitinib, upadacitinib and baricitinib variably inhibit JAK 1, 2 and 3, but not TYK2. The use of deucravacitinib in psoriatic patients decreases IL-23 pathway biomarkers in lesional skin towards non-lesional levels and normalizes IFN and IL-12 pathway genes, without affecting JAK 1, 2 and 3 biomarkers. Through this mechanism of action, deucravacitinib blocks IL-12, IL-23 and type I interferon downstream signalling, without interfering with JAK2-dependent hematopoietic functions [17, 36]. Preclinical studies initially showed its efficacy in mouse models with lupus erythematosus and inflammatory bowel disease [37–39].

3.1 Phase I Trial

Deucravacitinib’s safety and good tolerability was shown in a phase I trial involving 108 healthy participants (ClinicalTrials.gov identifier: NCT02534636) [40]. For approximately 3 months, there were no reports of serious adverse effects and non-serious adverse events were evenly described in the active and the placebo groups (75% and 76%, respectively). Headache, nausea, rash and upper tract respiratory infections were the most frequently reported side effects [40].

Another phase I study was later developed to determine whether deucravacitinib had a clinically relevant effect on electrocardiographic parameters. A single oral dose of deucravacitinib 12 mg (therapeutic dose) or 36 mg (supratherapeutic dose) did not produce clinically relevant changes on
the corrected QT interval or other measured parameters in healthy adults [41].

3.2 Phase II Trials

A phase II multicentre, double-blind, placebo-controlled trial was conducted in 267 adult patients with moderate-to-severe psoriasis (NCT02931838) [42]. All 267 patients presented a Psoriasis Area Severity Index (PASI) score ≥12 or higher, a Physician’s Global Assessment (PGA) score ≥2 and a body surface area (BSA) of 10% or worse. They were randomized into six arms, one corresponding to placebo and the other five evaluating different doses of oral deucravacitinib (3 mg every other day, 3 mg each day, 3 mg twice a day, 6 mg twice a day and 12 mg each day). At the end of 12 weeks of treatment, patients treated with deucravacitinib in a dose of 3 mg daily or higher achieved significantly greater rates of PASI75 (achieving 75% improvement in PASI from baseline) than with placebo. PASI75 was achieved in 39% of patients on 3 mg of deucravacitinib daily (p < 0.001 vs placebo). Among the groups treated with doses of 3 mg twice daily or higher, over 60% of patients reached a PASI75 response (p < 0.001 vs placebo) [42].

Additionally, the Dermatology Life Quality Index (DLQI) questionnaire was used to assess symptom-related discomfort and impact on daily functioning. A greater percentage of patients in the groups receiving 3 mg of deucravacitinib twice daily, 6 mg twice daily, or 12 mg daily presented a DLQI score of 0 or 1 (normal or near-normal quality of life) in comparison to the placebo group (42%, 60% and 64% in the respective deucravacitinib groups vs 4% in the placebo one—95% confidence intervals of 20–54, 38–71 and 41–74, respectively) [42].

A post-hoc analysis of this phase II trial evaluated the impact of deucravacitinib on patient-reported quality of life. The percentage of patients achieving a DLQI 0/1 in the three highest dosage groups combined increased through weeks 4–12. Improvement in quality of life followed a similar pattern of response to treatment to that of the clinical outcomes [43].

Regarding safety data, the percentage of patients with reported adverse events ranged from 55% in the group treated with 3 mg each day to 80% in the group on 6 mg twice a day, whereas the placebo group presented the lowest rate of adverse effects (51%). The most common were nasopharyngitis, headache and diarrhoea. Acne was reported only in the active treatment groups (n = 8), with four cases (9%) in the highest dose arm. Only four patients reported serious adverse effects and they belonged either to the placebo group or to groups treated with the lowest doses of deucravacitinib. No cases of herpes zoster infection, tuberculosis, opportunistic infections or cardiovascular events were reported during the 12-week period of the trial [42].

3.3 Phase III Trials

Two large, phase III, double-blinded, 52-week trials on plaque psoriasis were recently completed: NCT03624127 (POETYK PSO-1) and NCT03611751 (POETYK PSO-2) [44, 44].

In POETYK PSO-1, 666 patients with moderate to severe plaque psoriasis (BSA ≥10%, PASI ≥12, PGA ≥3) were randomly assigned to deucravacitinib 6 mg once daily, placebo or an active comparator in a 2:1:1 proportion. The first group maintained the same dose of 6 mg once a day for 52 weeks, while the placebo group switched to deucravacitinib 6 mg once a day after 16 weeks. In the active comparator group, patients were treated with apremilast 30 mg twice a day, titrated from 10 mg over the first 5 days. At the end of 24 weeks, PASI response was evaluated and patients reaching PASI50 were maintained on apremilast. All patients from this arm who did not reach PASI50 at this point were switched to deucravacitinib treatment [44].

POETYK PSO-2 involved 1022 patients with moderate to severe plaque psoriasis who were also randomly assigned to one of three different arms. Patients assigned to receive placebo switched to deucravacitinib 6 mg once a day after 16 weeks. The other two groups started with deucravacitinib 6 mg daily or with apremilast 30 mg twice a day, titrated up from 10 mg over the first 5 days. POETYK PSO-2 included a randomized withdrawal phase in which patients originally randomized to deucravacitinib who had achieved PASI75 response at week 24 were re-randomized 1:1 to placebo or deucravacitinib, whereas those who did not achieve PASI75 response at week 24 continued being treated with deucravacitinib. Regarding patients on apremilast for the first 24 weeks, those who achieved PASI75 were maintained under the same treatment, while those who did not were started on deucravacitinib [45].

According to POETYK PSO-1 results at the end of 16 weeks, response rates were significantly higher with deucravacitinib versus placebo and apremilast regarding PASI75 (58.4% vs 12.7% vs 35.1%, respectively; p < 0.0001) and PGA 0/1 (53.6% vs 7.2% vs 32.1%, respectively; p < 0.0001) [45, 45] (Table 1).

At week 16, there were more deucravacitinib patients—versus placebo and apremilast patients—achieving an absolute PASI ≤1 (PSO-1: 24.4%, 1.8%, 10.1%, respectively) and ≤5 (PSO-1: 59.3%, 14.5%, 35.7%, respectively) [46].

Deucravacitinib-treated patients reported greater quality of life improvement in comparison with other groups, with a significantly greater DLQI 0/1 response rate at week 16 (41.0%) versus patients who received placebo (10.6%; p < 0.0001) or apremilast (28.6%; p = 0.0088) [44].

These responses were maintained throughout week 52 in the deucravacitinib group in POETYK PSO-1, with 65.1% of patients achieving PASI75 response and 52.7% a PGA of
Deucravacitinib for Psoriatic Disease

Patients who switched from placebo to deucravacitinib at week 16 had PASI75 and PGA 0/1 responses at week 52 comparable to those observed in patients who received continuous deucravacitinib treatment from day 1 [44] (Table 1).

POETYK PSO-2 obtained similar results: 53.6% of patients in the deucravacitinib arm achieved PASI75 at week 16 in comparison with 9.4% (p < 0.0001) of patients receiving placebo and 40.2% (p = 0.0003) of those receiving apremilast [45] (Table 1). Among deucravacitinib-treated patients who achieved PASI75 at week 24 and were re-randomized to continue treatment, responses were maintained at week 52 in the most patients (PASI75 of 80.4%) [45]. Information regarding patients who switched to placebo is still unavailable.

Efficacy outcomes on scalp psoriasis were separately analysed in both POETYK studies. Significantly more patients receiving deucravacitinib achieved scalp-specific PGA 0/1 and Psoriasis Scalp Severity Index (PSSI 90), in comparison with placebo and apremilast. At the end of 16 weeks, 70.8% of deucravacitinib-treated patients in POEYK PSO-1 and 60.3% in POETYK PSO-2 reached scalp-specific-PGA 0/1 (p < 0.0001) [47].

Daily evolution of symptoms (burning, itch, pain, skin tightness, stinging) and signs (bleeding, cracking, dryness, redness, scaling, shedding or flaking) was also evaluated during these trials by using a patient-reported numerical scale ranging from 0 (absent) to 10 (worst imaginable) [48]. At week 16, in both POETYK PSO-1 and POETYK PSO-2, patients treated with deucravacitinib experienced significantly greater improvements in mean change from baseline in symptom scores (−32.0 vs −6.3 for placebo and −23.7 for apremilast in POETYK PSO-1 and −31.3 vs −3.2 for placebo and −23.0 for apremilast in POETYK PSO-2; p < 0.0001 for each) and sign scores (−34.3 vs −7.7 for placebo and −25.4 for apremilast in POETYK PSO-1 and −35.0 vs −6.3 for placebo and −26.5 for apremilast in POETYK PSO-2; p < 0.0001 for each). The greatest improvements in psoriasis symptoms were observed for itch and skin tightness [48].

Preliminary safety results suggested a good tolerability and safety profile in both trials. The most reported adverse effects were nasopharyngitis, upper respiratory tract infections, headache and diarrhoea [45]. According to peer-reviewed data from POETYK PSO-1, herpes zoster infections occurred at a low rate in the deucravacitinib arm (n = 5) and all cases were mild to moderate. Acne was reported in 15 out of 531 patients on deucravacitinib against 0 among placebo and apremilast groups [46]. Serious adverse events were more frequent with placebo (5.5%) than apremilast (2.4%) or deucravacitinib (2.1%) at week 16. Discontinuation due to adverse effects over weeks 0 to 52 were lower with deucravacitinib versus placebo and apremilast [46]. Changes from baseline levels of standard hematologic parameters (lymphocytes, neutrophils, platelets and haemoglobin) and chemistry parameters including lipid panel and creatine phosphokinase (CPK) were globally not clinically relevant from weeks 0 to 16 in both POETYK PSO-1 and 2 [44, 49].

At the end of the 52-week POETYK PSO-1 and 2, 1221 patients were switched to an open-label deucravacitinib extension trial for up to 240 weeks. Recently, data concerning long-term extension (LTE) results was presented [50].

From week 0 to 60 of POETYK PSO-LTE (NCT04036435), patients who were already on deucravacitinib at week 0 kept improving (PASI75 from 70.8 to 79.4% and PASI90 from 43.6% to 50.7%). Patients who switched

### Table 1

| Endpoint (16 weeks) | Trial          | Deucravacitinib 6 mg once a day (%) | Placebo (%) | Apremilast (%) |
|--------------------|---------------|-------------------------------------|-------------|----------------|
| PASI75             | POETYK PSO-1  | 58.4                                | 12.7        | 35.1           |
|                    | POETYK PSO-2  | 53.6                                | 9.4         | 40.2           |
| PGA 0/1            | POETYK PSO-1  | 53.6                                | 7.2         | 32.1           |
|                    | POETYK PSO-2  | 50.3                                | 8.6         | 34.3           |
| ss-PGA 0/1         | POETYK PSO-1  | 70.8                                | 17.4        | 39.1           |
|                    | POETYK PSO-2  | 60.3                                | 17.3        | 37.3           |
| DLQI 0/1           | POETYK PSO-1  | 40.7                                | 10.6        | 28.6           |
|                    | POETYK PSO-2  | 38.0                                | 9.8         | 23.1           |

POETYK PSO-1 (n = 666) and POETYK PSO-2 (n = 1020)

PASI75 at least a 75% improvement from baseline in Psoriasis Area and Severity Index scores, PGA 0/1 Physician’s Global Assessment score of clear or almost clear; ss-PGA 0/1 scalp-specific Physician’s Global Assessment score of clear or almost clear in those with ss-PGA of at least 3 (moderate) at baseline; DLQI Dermatology Life Quality Index 0/1 scores reflect no effect at all on patient’s life in patients with a baseline DLQI score of ≥ 2

△ Adis
from apremilast to deucravacitinib at week 0 also clinically improved (PASI75 from 73.8 to 87.1% and PASI90 from 40.0 to 62.9%) [50].

Aside from COVID-19, the safety profile was consistent across POETYK PSO-1, PSO-2 and LTE. An increase in serious infections was observed, which is attributable to COVID-19 infections due to the ongoing pandemic [50].

A smaller, phase III, 52-week, open-label, single-arm, clinical trial with 80 Japanese patients with moderate-to-severe psoriasis (NCT03924427) was also recently completed, with no published results to date.

### 3.4 Psoriatic Arthritis

There is also emerging data suggesting good efficacy and safety results of deucravacitinib in patients with active psoriatic arthritis. A total of 203 patients with psoriatic arthritis were randomized 1:1:1 to placebo, deucravacitinib 6 mg once a day and deucravacitinib 12 mg once a day in a double-blind phase II trial (NCT03881059). American College of Rheumatology-20 (ACR-20) response at week 16 was considered the primary endpoint, which refers to an improvement from baseline in the number of tender and swollen joints and patient’s pain, among other parameters. ACR-20 response was significantly higher with deucravacitinib 6 mg once a day (52.9%; \( p = 0.0134 \)) and 12 mg once a day (62.7%; \( p = 0.0004 \)) against the placebo (31.8%). Higher numbers of patients treated with deucravacitinib versus placebo also achieved enthesitis and dactylitis resolution. Adverse events were more frequently reported at both deucravacitinib doses (65.7%) compared with placebo (42.4%). The most common ones in deucravacitinib-treated patients were nasopharyngitis, upper respiratory tract infections, sinusitis, bronchitis, rash, diarrhoea and headache. Acne was reported in 2 of 70 (2.9%) patients in the 6-mg, once-a-day deucravacitinib group, 1 of 67 (1.5%) in the 12-mg, once-a-day group and dermatitis acneiform was reported in 2 of 70 (2.9%) and 2 of 67 (3.0%), respectively. No placebo patients developed acne or dermatitis acneiform [51].

Phase III studies are currently in the recruiting phase (NCT04908202 and NCT04908189) (Table 2) [52].

### 4 Discussion

Systemic therapies for psoriatic disease have evolved rapidly in recent years, and several highly effective biologic drugs have been developed. However, there is still an unmet need for effective and safe oral therapies, as conventional systemic treatments are associated with important side effects, long-term toxicity and drug interactions. Apremilast, a new targeted small molecule, is only moderately effective [9–12].

JAK inhibitors have been of particular interest due to their ability to target multiple cytokines simultaneously. JAK inhibitors, as a class, although proven to be effective in the treatment of psoriasis, are also associated with some off-target effects that translate into changes in laboratory parameters (haemoglobin, platelets, neutrophils, lipid panel, creatine phosphokinase), higher risk of infections, malignancy and thromboembolic events. Available evidence suggests that these unwanted effects are a consequence of JAK 1, 2 and 3 pathways inhibition. Therefore, due to safety concerns with JAK 1, 2 and 3 inhibitors, interest has shifted to more selective inhibition of TYK2. At clinically relevant doses and exposures, deucravacitinib demonstrates highly selective inhibition of TYK2 [30, 34, 36].

Deucravacitinib, a novel oral TYK2 selective inhibitor, has shown a good efficacy and safety profile in moderate to severe psoriasis trials. A phase II study showed that a daily dose of at least 3 mg was necessary to accomplish efficacy purposes. Considering higher rates of adverse effects in the 6-mg twice-a-day group, 6 mg once a day was the dose chosen for phase III studies [42].

### Table 2 Ongoing and recently concluded phase III clinical trials of deucravacitinib for psoriasis

| Clinical trial* | Objective | Phase | Status          |
|----------------|-----------|-------|-----------------|
| NCT04036435 (POETYK PSO-LTE) | Long-term (240 weeks) efficacy and safety for psoriasis | Phase III | Active, not recruiting |
| NCT04772079 | Efficacy and safety in adolescents with psoriasis (12–18 years old) | Phase III | Recruiting |
| NCT04908202 | Efficacy and safety in psoriatic arthritis | Phase III | Recruiting |
| NCT04908189 | Efficacy and safety in psoriatic arthritis | Phase III | Recruiting |
| NCT04167462 (POETYK-PSO-3) | Efficacy and safety in psoriasis against placebo (apremilast) | Phase III | Completed |
| NCT03611751 (POETYK-PSO-2) | Efficacy and safety in psoriasis against placebo and active comparator (apremilast) | Phase III | Completed |
| NCT03624127 (POETYK-PSO-1) | Efficacy and safety in psoriasis against placebo and active comparator (apremilast) | Phase III | Completed |
| NCT03924427 (POETYK PSO-4) | Efficacy and safety in psoriasis against placebo | Phase III | Completed |

*ClinicalTrials.gov identifier
Phase III trials evaluated deucravacitinib 6 mg versus placebo and apremilast as active comparator. Deucravacitinib showed superior and faster improvement of psoriasis lesions than placebo and apremilast. The clinical response improved through week 24 and was maintained in patients who were under treatment thorough week 52. The impact on scalp psoriasis was separately analysed with even stronger efficacy outcomes.

A subjective reduction in signs and symptoms was also noted. The greatest symptom improvement was consistently observed for the itch domain; this may be particularly meaningful to patients given the prevalence and burden of this symptom. The positive repercussion of this therapy on patients’ quality of life was also superior compared with apremilast and placebo.

Deucravacitinib was globally well tolerated and safe. In contrast, tolerability is often a cause of discontinuation for both conventional agents and apremilast. Nasopharyngitis and upper respiratory tract infections were the most frequently reported adverse events. Acne was first described in the active treatment groups of the phase II study, with greater incidence in the arms with the highest doses. It has been suggested to be a consequence of commensal bacteria proliferation allowed by cytokine inhibition [42]. Results of phase III studies using deucravacitinib 6 mg a day report this adverse effect as uncommon. A higher selectivity for TYK2 versus JAK 1, 2 and 3 reduces the chance of off-target effects, and the reported safety profile was consistent with its mechanism of action. There was no description of herpes zoster, opportunistic infections, thromboembolic events, or hematologic and lipid laboratory abnormalities, in contrast to trials of JAK 1, 2 and 3 inhibitors in psoriasis and other diseases [24–28]. Additionally, no clinically significant laboratory parameter abnormalities were observed with deucravacitinib treatment, suggesting that routine laboratory monitoring during deucravacitinib treatment may not be warranted.

Deucravacitinib demonstrated persistent efficacy and consistent safety profiles in patients with psoriasis for up to 2 years. Information from the POETYK PSO-2 trial regarding patients who responded to deucravacitinib and were re-randomized to placebo is still unavailable. These results will be essential to evaluate time until relapse after drug withdrawal. Currently available oral drugs have not been able to induce a long maintenance of clinical response after drug withdrawal, as we have seen with IL-23 inhibitor biologic agents [53]. Being an IL-23 inhibitor as well, if deucravacitinib demonstrates this phenomena it would greatly impact clinical practice.

Deucravacitinib clinical efficacy in psoriatic arthritis is under research, with promising results in a phase II study. It is also being studied for lupus, ulcerative colitis and Crohn’s disease. Moreover, this compound’s positive phase III data led to an increased interest in molecules targeting the TYK2 JH2 domain, and several companies are announcing phase I and II studies with other highly selective TYK2 inhibitors [54].

At this point, biologic therapies offer effective, safe and convenient options for psoriatic patients. However, oral options bring some advantages, such as no risk of immunogenicity or injection-site reactions, easier transportation and storage and may be more comfortable for patients who prefer an oral treatment they can take at home or for those with trypanophobia. Although they do not need expert personnel drug administration or patient training, treatment response might be easily compromised as a result of incorrect adherence [55]. Further pharmacoeconomic studies are required. The role of deucravacitinib in the treatment landscape for psoriasis is still to be determined. It will probably be used as a first-line agent, but also after biologic exposure, since at least one third of the POETYK PSO-1 and POETYK PSO-2 study population had prior biologic exposure. In addition to clinical data, price and regulatory factors are likely to be decisive in defining the place of deucravacitinib in the treatment of psoriasis.

5 Conclusion

Deucravacitinib has the potential to become an efficacious, safe and well-tolerated treatment for patients with moderate to severe psoriasis. Evaluation of longer-term response, maintenance of clinical response after drug withdrawal and comparison trials with biologic agents are important missing steps to understand this drug’s positioning in psoriasis treatment.

Declarations

Author contributions AML, LP and TT had the idea for the article, performed the literature search and data analysis, and drafted and critically revised the work.

Funding No funding was received for the preparation of this manuscript.

Availability of data and material Not applicable.

Code availability Not applicable.

Consent to participate/publish Not applicable.

Conflict of interest Ana Maria Lé has no conflicts of interest. Luis Puig has served as a scientific adviser and/or clinical study investigator for, or has received consultancy and/or speaker’s honoraria from and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Bristol Myers Squibb,
Celgene, Fresenius-Kabi, Janssen, JS BIOCAD, LEO Pharma, Lilly, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanoit and UCB. Tiago Torres has received consultancy and/or speaker’s honoraria from and/or participated in clinical trials sponsored by AbbVie, Amgen, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius-Kabi, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sanoit-Genzyme, Sandoz and UCB.

Ethics approval Not applicable.

References

1. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. JAMA J Am Med Assoc. 2020;323(19):1945–60. https://doi.org/10.1001/jama.2020.4006.

2. Gerdes S, Körber A, Biermann M, Karnthaler C, Reinhardt M. Absolute and relative psoriasis area and severity index (PASI) treatment goals and their association with health-related quality of life. J Dermatol Treat. 2020;31(5):470–5. https://doi.org/10.1080/09546634.2020.1746734.

3. Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation Survey Data 2003–2011. PLoS One. 2012;7(12):e52935. https://doi.org/10.1371/journal.pone.0052935.

4. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/TH17 immune axis in the pathogenesis and treatment of psoriasis. J Immunol. 2018;201(6):3085–95. https://doi.org/10.4049/jimmunol.1800013.

5. Girolomoni G, Strohal R, Puig L, et al. The role of IL-23 and IL-17 in psoriasis. J Dermatol Treat. 2020;31(5):470–5. https://doi.org/10.1080/09546634.2020.1746734.

6. Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation Survey Data 2003–2011. PLoS One. 2012;7(12):e52935. https://doi.org/10.1371/journal.pone.0052935.

7. Bergboer J, Zeeuwen P, Schalkwijk J. Genetics of psoriasis: evidence for epistatic interaction between skin barrier abnormalities and immune deviation. J Investig Dermatol. 2012;132(10):2320–31. https://doi.org/10.1038/jid.2012.167.

8. Boehncke W, Schön MP. Psoriasis. Lancet. 2015;386(9997):983–94. https://doi.org/10.1016/s0140-6736(14)63425-6.

9. Dogra S, Jain A, Kanwar AJ. Efficacy and safety of acitretin in three fixed doses of 25, 35 and 50 mg in adult patients with severe plaque type psoriasis: a randomized, double blind, parallel group, dose ranging study. J Eur Acad Dermatol Venereol. 2013;27(3):305–11. https://doi.org/10.1111/j.1468-3083.2012.04464.x.

10. Papp K, Reich K, Leonard CL, Kirkic L, Griffiths CEM. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). J Am Dermatol. 2015;73(1):37–49. https://doi.org/10.1016/j.jaad.2015.03.049.

11. Warren RB, Mrowietz U, Von KR, et al. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2016;389(10068):528–37. https://doi.org/10.1016/s0140-6736(16)32127-4.

12. Rosmarin DM, Lebwohl M, Elewski BE, Gottlieb AB. Cyclosporine and psoriasis: 2008 National Psoriasis Foundation * Consensus Conference. J Am Dermatol. 2010;62(5):838–53. https://doi.org/10.1016/j.jaad.2009.05.017.

13. Torres T, Filipe P. Small molecules in the treatment of psoriasis. Drug Dev Res. 2015;76(June):215–27. https://doi.org/10.1002/ddr.21263.

14. Le AM, Torres T. New topical therapies for psoriasis. Am J Clin Dermatol. 2022;23(1):13–24. https://doi.org/10.1007/s40257-021-00649-w.

15. Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK–STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. Drugs. 2017;77(5):521–46. https://doi.org/10.1007/s40265-017-0701-9.

16. Ghoreshi K, Laurence A, O’Shea JJ. Janus kinases in immune cell signaling. Immunol Rev. 2009;223(1):273–87. https://doi.org/10.1111/j.1600-065x.2008.00754.x.

17. Catlett JM, Hu Y, Gao L, Banerjee S, Gordon K, Krueger JG. Molecular and clinical effects of selective tyrosine kinase 2 inhibition with deucravacitinib in psoriasis. J Allergy Clin Immunol. 2021. https://doi.org/10.1016/j.jaci.2021.11.001.

18. Rodig SJ, Meraz MA, White JM, et al. Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. Cell. 1998;93(3):373–83. https://doi.org/10.1016/s0092-8674(00)81166-6.

19. Eletto D, Burns SO, Angulo I, et al. Biologic Jak1 mutations in immunodeficient patient with mycobacterial infection. Nat Commun. 2016;7(13992):1–12. https://doi.org/10.1038/ncomms13992.

20. Park SO, Wamsley HL, Bae K, et al. Conditional deletion of Jak2 reveals an essential role in hematopoiesis throughout mouse ontogeny: implications for Jak2 inhibition in humans. PLoS One. 2013;8(3):1–13. https://doi.org/10.1371/journal.pone.0059675.

21. Nosaka T, Van Deursen JMA, Tripp RA, et al. Defective lymphoid development in mice lacking Jak3. Science. 1995;270(5237):800–2. https://doi.org/10.1126/science.270.5237.800.

22. Russell SM, Tayebi N, Nakajima H, et al. Mutation of Jak3 in a patient with SCID: essential role of Jak3 in lymphoid development. Science. 1995;270(4):7–10.

23. Cornejo MG, Boggot TJ, Mercher T. The International Journal of Biochemistry JAK3: a two-faced player in hematological disorders. Int J Biochem Cell Biol. 2009;41:2376–9. https://doi.org/10.1016/j.biocel.2009.09.004.

24. Winthrop KL, Park SH, Gul A, et al. Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. Ann Rheum Dis. 2016;75(6):1133–8. https://doi.org/10.1136/annrheumdis-2015-207319.

25. Harrington R, Al Nokhatha SA, Conway R. JAK inhibitors in rheumatoid arthritis: an evidence-based review on the emerging clinical data. J Inflamm Res. 2020;13:519–31. https://doi.org/10.2147/JIR.S219586.

26. Mease P, Charles-Schoeman C, Cohen S, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis. 2020;79(11):1400–13. https://doi.org/10.1136/annrheumdis-2019-207671.

27. Winthrop KL, Lebwohl M, Cohen AD, et al. Herpes zoster in psoriasis patients treated with tofacitinib. J Am Acad Dermatol. 2017;77(2):302–9. https://doi.org/10.1016/j.jaad.2017.03.023.

28. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. Br J Dermatol. 2015;173:949–61. https://doi.org/10.1111/bjd.14018.
Deucravacitinib for Psoriatic Disease

29. Dong Z, Ye X, Chen C, Wang R, Liu D, Xu X, Zhou X. Thromboembolic events in Janus kinase inhibitors: a pharmacovigilance study from 2012 to 2021 based on the Food and Drug Administration's Adverse Event Reporting System. Br J Clin Pharmacol. 2022. https://doi.org/10.1111/bcp.15361 (Epub ahead of print).

30. Nogueira M, Puig L, Torres T. JAK inhibitors for treatment of psoriasis: focus on selective TYK2 inhibitors. Drugs. 2020;80(4):341–52. https://doi.org/10.1007/s40265-020-01261-8.

31. Dendrou CA, Cortes A, Shipman L, et al. Resolving TYK2 locus genotype-to-phenotype differences in autoimmunity. Sci Transl Med. 2016;8:363. https://doi.org/10.1126/scitranslmed.aag1974.

32. Kreins AY, Ciancanelli MJ, Okada S, et al. Human TYK2 deficiency: mycobacterial and viral infections without hyper-IgE syndrome. J Exp Med. 2015;212(10):1641–62. https://doi.org/10.1084/jem.20140280.

33. Kilic SS, Hacimustafaoglu M, Boisson-Dupuis S, et al. A patient with tyrosine kinase 2 deficiency without hyper-IgE syndrome. J Pediatr. 2012;160(6):1055–7. https://doi.org/10.1016/j.jpeds.2012.01.056.

34. Jo CE, Goordial M, Beecker J. Review treatment of dermatologic conditions: the evolution of JAK inhibitors. Int J Dermatol. 2021. https://doi.org/10.1111/ijd.15605.

35. Strange A, Capon F, Spencer CCA, et al. Genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet. 2010;42(11):985–90. https://doi.org/10.1038/ng.694.

36. Chimalakonda A, Burke J, Cheng L, et al. Selectivity profile of the tyrosine kinase 2 inhibitor deucravacitinib compared with janus kinase 1/2 inhibitors. Dermatol Ther (Heidelb). 2021;11(5):1763–76. https://doi.org/10.1007/s13555-021-00596-8.

37. Gillooly K, Zhang Y, Yang X, Zupa-Fernandez A, Cheng L, Strnad J, Cunningham M, Heimrich E, Zhou X, Chen J, Chaudhry C, Li S, McIntyre K, Carman J, Moslin R, Wroblewski S, Weinstein D, Burke J, Gillooly K, Zhang Y, Yang X, Zupa-Fernandez A, Cheng L, Strnad BJ. BMS-986165 is a highly potent and selective allos teric inhibitor of TYK2, blocks IL-12, IL-23 and type I interferon signaling and provides for robust efficacy in preclinical models of systemic lupus erythematosus and inflammatory bowel disease. Arthritis Rheumatol. 2016;68(Suppl 10). https://acrabstracts.org/abstract/bms-986165-is-a-highly-potent-and-selective-allos-teric-inhibitor-of-tyk2-blocks-il-12-il-23-and-type-i-interferon-signaling-and-provides-for-robust-efficacy-in-preclinical-models-of-systemic-lupus-e/. Accessed Oct 5.

38. Tokarski JS, Zupa-Fernandez A, Tredup JA, et al. Tyrosine kinase 2-mediated signal transduction in T lymphocytes is blocked by pharmacological stabilization of its pseudokinase domain. J Biol Chem. 2015;290(17):11061–74. https://doi.org/10.1074/jbc.M114.619502.

39. Wroblewski ST, Moslin R, Lin S, et al. Highly selective inhibition of tyrosine kinase 2 (TYK2) for the treatment of autoimmune diseases: discovery of the allos teric inhibitor BMS-986165. J Med Chem. 2019;2(62):8973–95. https://doi.org/10.1021/acs.jmedchem.9b00444.

40. Catlett I, Aras U, Liu Y, Bei D, et al. SAT0226 A first-in-human, study of BMS-986165, a selective, potent, allos teric small molecule inhibitor of tyrosine kinase 2 [abstract]. Ann Rheum Dis. 2017;76:859. https://doi.org/10.1136/annrheumdis-2017-eular.3036.

41. Chimalakonda A, Singhal S, Darbenzio R, et al. Lack of electrocardiographic effects of deucravacinib in healthy subjects. Clin Pharmacol Drug Dev. 2022;11(4):442–53. https://doi.org/10.1002/cpdd.1056.

42. Papp K, Gordon K, Thaçi D, Morita A, Gooderham M, Foley P, Girgis IG, Kundi SBS. Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. N Engl J Med. 2018;379:1313–21. https://doi.org/10.1056/NEJMoa1806382.

43. Thaçi D, Strober B, Gordon KB, Foley P, Gooderham M, Morita A, Papp KA, Puig L, Menter MA, Colombo MJ, Elbez Y, Kisa RM, Ye J, Napoli AA, Wei L, Banerjee S, Merola JF, Gottlieb AB. Deucravacitinib in moderate to severe psoriasis: clinical and quality-of-life outcomes in a phase 2 trial. Dermatol Ther. 2022. https://doi.org/10.1007/s13555-021-00649-y (Epub ahead of print).

44. Armstrong AW, Gooderham M, Warren RB, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blind, placebo-controlled phase 3 POETYK PSO-1 trial. J Am Acad Dermatol. 2022. https://doi.org/10.1016/j.jaad.2022.07.002.

45. Warren R, Armstrong A, Gooderham M, Strober B, et al. Abstract N° 2857—deucravacitinib, an oral, selective tyrosine kinase 2 inhibitor, in moderate to severe plaque psoriasis: 52-week efficacy results from the phase 3 POETYK PSO-1 and POETYK PSO-2 trials. EADV 30th Congr. Published online 2021:1–2. https://s3.eu-central-1.amazonaws.com/cst.eadv/eadv2021/abstracts/26128.html.pdf.

46. Lebowohl M, Gooderham M, Warren RB, et al. Deucravacitinib, an oral, selective tyrosine kinase 2 (TYK2) inhibitor, versus placebo and apremilast in moderate to severe plaque psoriasis: achievement of absolute PASI thresholds in the phase 3 POETYK PSO-1 and PSO-2 trials [poster]. Am Acad Dermatology Annu Meet March 25–29 2022, Boston.

47. Blauvelt A, Rich P, Sofen H, et al. Abstract N° 999—deucravacitinib, an oral, selective tyrosine kinase 2 (TYK2) inhibitor, versus placebo and apremilast in scalp psoriasis: analysis of the phase 3 POETYK PSO-1 and POETYK PSO-2 trials. EADV 30th Congr. Published online 2021. https://s3.eu-central-1.amazonaws.com/cst.eadv/eadv2021/abstracts/24270.html.pdf.

48. Armstrong A, Strober B, Gordon KB, et al. Abstract N°: 2127—deucravacitinib improves psoriasis symptoms and signs diary domain scores in patients with moderate to severe plaque psoriasis: results from the phase 3 POETYK PSO-1 and POETYK PSO-2 studies. EADV 30th Congr. https://s3.eu-central-1.amazonaws.com/cst.eadv/eadv2021/abstracts/25398.html.pdf.

49. Thaçi D, Gordon KB, Gooderham M, et al. Abstract N°: 1108—deucravacitinib, an oral, selective tyrosine kinase 2 (TYK2) inhibitor, compared with placebo and apremilast in moderate to severe plaque psoriasis: integrated laboratory parameter results from the phase 3 POETYK PSO-1 and POETYK PSO-2. EADV 30th Congr. Published online 2021. https://s3.eu-central-1.amazonaws.com/cst.eadv/eadv2021/abstracts/24379.html.pdf.

50. Warren RB, Sofen H, Ifamuku S, et al. Poster—Deucravacitinib long-term efficacy and safety in plaque psoriasis: 2-year results from the phase 3 POETYK PSO program. In: Presented at European Academy of Dermatology and Venereology (EADV) Spring Symposium.

51. Mease PJ, Deodhar AA, van der Heijde D, et al. Efficacy and safety of selective TYK2 inhibitor, deucravacinib, in a phase II trial in psoriatic arthritis. Ann Rheum Dis. 2022. https://doi.org/10.1136/annrheumdis-2021-221664.

52. Mease P, Deodhar A, van der Heijde D, Behrens F, Kivitz A, Kim J, Singhal S, Nowak M, Barnerjee S. Efficacy and safety of deucravacinib (BMS-986165), an oral, selective tyrosine kinase 2 inhibitor, in patients with active psoriatic arthritis: results from a phase 2, randomized, double-blind, placebo-controlled trial [abstract]. Arthritis Rheumatol. 2020;72(10). https://acrabstracts.org/abstract/efficacy-and-safety-of-deucravacinib-bms-986165-an-oral-selective-tyrosine-kine-2-inhibitor-in-patients-with-active-psoriatic-arthritis-results-from-a-phase-2-randomized-double-blind-placebo/. Accessed Dec 22, 2021.
53. Gordon KB, Armstrong AW, Foley P, et al. Guselkumab efficacy after withdrawal is associated with suppression of serum IL-23-regulated IL-17 and IL-22 in psoriasis: VOYAGE 2 study. J Investig Dermatol. 2019. https://doi.org/10.1016/j.jid.2019.05.016.

54. He X, Chen X, Zhang H, Xie T, Ye XY. Selective TYK2 inhibitors as potential therapeutic agents: a patent review (2019–2021). Expert Opin Ther Pat. 2019;29(2):137–49. https://doi.org/10.1080/13543776.2019.1567713.

55. Abduelmula A, Gooderham MJ. TYK2 inhibition: changing the treatment landscape for psoriasis? Expert Rev Clin Immunol. 2021. https://doi.org/10.1080/1744666X.2022.2008240.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.