Deucravacitinib in plaque psoriasis: 2-year laboratory results from the phase 3 POETYK PSO program

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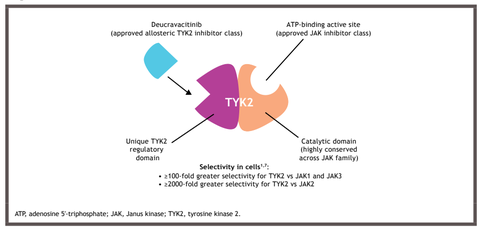
Background

- Tyrosine kinase 2 (TYK2) is an intracellular enzyme that mediates signaling of cytokines (eg, interleukin-23, Type I interferons) that are involved in psoriasis pathogenesis[1]
- Deucravacitinib, an oral, selective, allosteric TYK2 inhibitor, is approved in the US, EU, and other countries for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy[2-6]
- Deucravacitinib uniquely binds to the regulatory domain of TYK2 rather than to the catalytic domain where Janus kinase (JAK) 1,2,3 inhibitors bind[1,7] (**Figure 1**), driving its selectivity and representing the first in a new class of small molecules

Figure 1. Mechanism of action of deucravacitinib



ATP, adenosine 5'-triphosphate; JAK, Janus kinase; TYK2, tyrosine kinase 2.

- The selectivity of deucravacitinib facilitates a more targeted therapeutic approach that avoids signature laboratory changes seen with the JAK1,2,3 inhibitors
  - In phase 2 and phase 3 trials (POETYK PSO-1 and PSO-2) in plaque psoriasis, deucravacitinib treatment did not result in neutropenia, elevated liver enzyme and serum creatinine levels, or dyslipidemia — adverse events that have been associated with JAK1,2,3 inhibitors[8-12]
- Deucravacitinib demonstrated a robust efficacy profile, including superiority to placebo and apremilast and durability and maintenance of response, in two multinational phase 3 trials in patients with moderate to severe plaque psoriasis[10,11,13]
- Patients who completed the POETYK PSO-1 and PSO-2 trials could enroll in the ongoing POETYK long-term extension (LTE) trial

Objectives

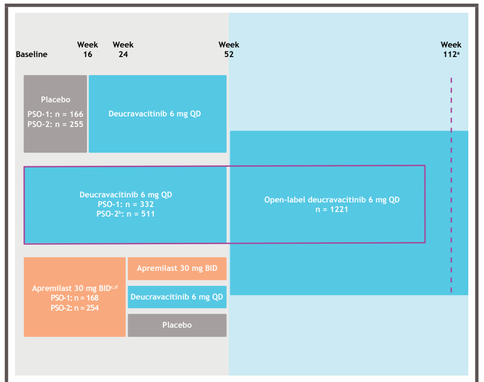
- To determine whether there were any clinically relevant changes in blood laboratory parameters with up to 2 years of deucravacitinib treatment in the POETYK PSO-1, PSO-2, and LTE trials
- To evaluate whether deucravacitinib treatment elicits changes in the blood that are known to occur with JAK1,2,3 inhibitors

Methods

Study designs

- POETYK PSO-1 (NCT03624127) and POETYK PSO-2 (NCT03611751) were 52-week, multinational, phase 3, double-blind trials that randomized patients with moderate to severe plaque psoriasis 1:2:1 to oral placebo, deucravacitinib 6 mg once daily, or apremilast 30 mg twice daily (**Figure 2**)
- At Week 52, eligible patients were able to enroll in the POETYK LTE (NCT04036435) trial and receive open-label deucravacitinib 6 mg once daily for up to 2 years

Figure 2. POETYK PSO-1, PSO-2, and LTE analysis population[a]



[a]Data reported through the 120-day POETYK LTE trial cutoff date of October 1, 2021. [b]In POETYK PSO-2, patients randomized to deucravacitinib on Day 1 who achieved PASI 75 at Week 24 were rerandomized to placebo or deucravacitinib; for patients who were rerandomized to placebo, upon relapse (≥50% loss of Week 24 PASI percent improvement from baseline), they were to cross over to deucravacitinib; however, due to a programming error, these patients continued to receive placebo until Week 52. [c]In POETYK PSO-1, patients who responded to apremilast remained on apremilast. In POETYK PSO-2, patients who responded to apremilast crossed over to placebo and were to cross over to deucravacitinib upon relapse; however, due to a programming error, these patients continued to receive placebo until Week 52. [d]Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
BID, twice daily; LTE, long-term extension; PASI, Psoriasis Area and Severity Index; PASI 75, ≥75% reduction from baseline in PASI; QD, once daily.

Laboratory assessments

- Pooled POETYK PSO-1 + PSO-2 data over Weeks 0–52 and pooled POETYK PSO-1 + PSO-2 + LTE data over Weeks 0–100 are presented
- Changes in laboratory parameters that are known to be affected by JAK1,2,3 inhibitors[7] were evaluated in blood over time:
  - Hematologic parameters: lymphocytes, neutrophils, platelets, and hemoglobin
  - Lipid parameter: total cholesterol
  - Chemistry parameters: creatinine, creatine phosphokinase (CPK), and alanine aminotransferase (ALT)
- Incidences of grade ≥3 laboratory abnormalities (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) and treatment discontinuations due to laboratory abnormalities were also evaluated through Week 100

Results

Patient population

- This analysis included 1519 patients who received ≥1 dose of deucravacitinib in POETYK PSO-1, PSO-2, and/or LTE through the data cutoff date of October 1, 2021
  - Total deucravacitinib exposure was 2482.0 person-years (PY)
- In total, 1179 (77.6%) and 584 (38.4%) patients had ≥52 weeks and ≥104 weeks, respectively, of continuous deucravacitinib exposure at the data cutoff date
  - Median duration of exposure was 682.0 days (97 weeks)
- Baseline patient demographics and disease characteristics are presented in **Table 1**

Table 1. Baseline patient demographics and disease characteristics

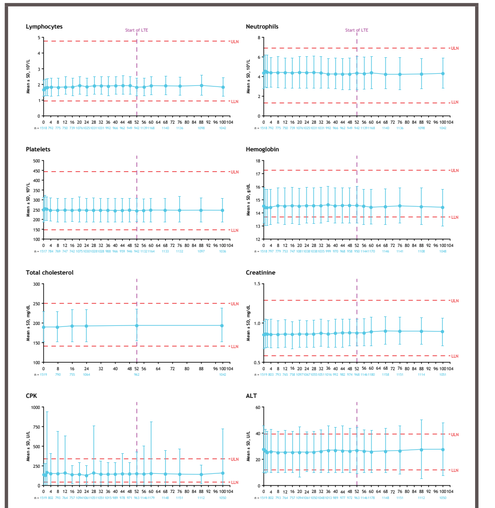
Parameter	POETYK PSO-1 + PSO-2 + LTE Deucravacitinib (N = 1519)
Age, mean (SD), y	46.6 (13.4)
Weight, mean (SD), kg	90.6 (21.6)
Body mass index, mean (SD), kg/m²	30.5 (6.8)
Female, n (%)	493 (32.5)
Race, n (%)	
White	1325 (87.2)
Asian	153 (10.1)
Black or African American	23 (1.5)
Other	18 (1.2)
Age at disease onset, mean (SD), y	28.8 (14.9)
Disease duration, mean (SD), y	18.7 (12.7)
PASI score, mean (SD)	21.1 (8.1)
sPGA score, n (%)	
3 (moderate)	1211 (79.7)
4 (severe)	308 (20.3)
BSA involvement, mean (SD), %	26.2 (15.8)

BSA, body surface area; LTE, long-term extension; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician Global Assessment.

Laboratory assessments

- No clinically meaningful changes were observed over Weeks 0–100 in any of the evaluated laboratory parameters in the pooled POETYK PSO-1/PSO-2/LTE population (**Figure 3**)
  - Laboratory parameters remained within normal ranges for most patients throughout this period
- Grade ≥3 laboratory abnormalities were rare (**Table 2**)
  - Frequencies of individual events were comparable across groups over the first 52 weeks (POETYK PSO-1 and PSO-2), and no increases were seen with deucravacitinib treatment through Week 100 in the POETYK LTE trial
  - Grade ≥3 CPK elevations occurred rarely, were mostly transient, and were observed at a similar incidence in each treatment group over the first 52 weeks; almost all were related to recent physical exertion, and none was serious
- Discontinuations due to laboratory abnormalities were low and balanced across treatment groups over the first 52 weeks and were also low through Week 100 in the POETYK LTE (**Table 3**)
  - ALT elevations in deucravacitinib-treated patients (**Table 2**) were predominantly transient, and none was serious or resulted in treatment discontinuation

Figure 3. Changes in hematologic, lipid, and chemistry parameters over 2 years in patients receiving deucravacitinib in POETYK PSO-1 + PSO-2 + LTE



ALT, alanine aminotransferase; CPK, creatine phosphokinase; LLN, lower limit of normal; LTE, long-term extension; SD, standard deviation; ULN, upper limit of normal.

Table 2. CTCAE grades 3 and 4 abnormalities in laboratory parameters over 1 year and 2 years

		At 1 year (POETYK PSO-1 + PSO-2, Weeks 0-52)						At 2 years (POETYK PSO-1 + PSO-2 + LTE, Weeks 0-100)	
		Placebo (n = 666)		Deucravacitinib (n = 1364)		Apremilast (n = 422)		Deucravacitinib (n = 1519)	
Parameter	Grade	Baseline n (%)	Week 52 n (%)	Baseline n (%)	Week 52 n (%)	Baseline n (%)	Week 52 n (%)	Baseline n (%)	Week 100 n (%)
Lymphocyte count decreased	3	0	1 (0.2)[a]	0	2 (0.1)[b]	0	1 (0.2)[c]	0	2 (0.1)[d]
	4	0	0	0	0	0	0	0	0
Neutrophil count decreased	3	0	1 (0.2)[a]	1 (0.1)[b]	4 (0.3)[b]	0	0	1 (0.1)[d]	5 (0.3)[d]
	4	0	1 (0.2)[a]	0	0	0	1 (0.2)[c]	0	1 (0.1)[d]
Platelet count decreased	3	0	1 (0.2)[a]	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
Anemia	3	0	0	0	0	0	1 (0.2)[c]	0	1 (0.1)[d]
	4	0	0	0	0	0	0	0	0
High cholesterol	3	0	0	0	1 (0.1)[f]	0	0	0	1 (0.1)[d]
	4	0	0	0	0	0	0	0	0
Creatinine increased	3	0	0	0	0	0	0	0	0
	4	0	0	0	0	0	0	0	0
CPK increased	3	1 (0.2)[a]	4 (0.6)[a]	3 (0.2)[b]	19 (1.4)[b]	1 (0.2)[c]	7 (1.7)[c]	3 (0.2)[c]	25 (1.7)[f]
	4	0	3 (0.5)[a]	0	13 (1.0)[b]	0	1 (0.2)[c]	0	26 (1.7)[f]
ALT increased	3	2 (0.3)[a]	0	1 (0.1)[b]	4 (0.3)[b]	0	0	1 (0.1)[c]	10 (0.7)[f]
	4	0	0	0	0	0	0	0	0

[a]n = 658. [b]n = 1351. [c]n = 418. [d]n = 1503. [e]n = 657. [f]n = 1317. [g]n = 1454. [h]n = 419. [i]n = 1504.
ALT, alanine aminotransferase; CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; LTE, long-term extension.

Table 3. Laboratory abnormality adverse events leading to treatment discontinuation over 1 year and 2 years

	At 1 year (POETYK PSO-1 + PSO-2, Weeks 0-52)						At 2 years (POETYK PSO-1 + PSO-2 + LTE, Weeks 0-100)	
	Placebo (n = 666) Total exposure = 240.9 PY		Deucravacitinib (n = 1364) Total exposure = 969.0 PY		Apremilast (n = 422) Total exposure = 221.1 PY		Deucravacitinib (n = 1519) Total exposure = 2482.0 PY	
Parameter	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY[a]	n (%)	EAIR/ 100 PY[a]	n (%)	EAIR/ 100 PY[a]
Lymphopenia	0	0.0	1 (0.1)	0.1	0	0.0	1 (0.1)	0.0
Blood CPK increased	0	0.0	2 (0.1)	0.2	1 (0.2)	0.4	3 (0.2)	0.1
Hepatic function abnormal	1 (0.2)[b]	0.4	1 (0.1)[c]	0.1	0	0.0	1 (0.1)	0.0
AST increased	0	0.0	0	0.0	1 (0.2)	0.4	0	0.0

[a]Incidences are expressed as EAIRs per 100 PY to account for variable exposure due to treatment switches at Weeks 16 and 24. [b]The patient who received placebo during Weeks 0-16 had ALT >3x ULN on Days 1 and 8; total bilirubin levels remained in the normal range. The patient discontinued placebo and ALT levels improved. [c]The patient who received deucravacitinib during Weeks 0-16 had ALT and AST elevations ≥3x ULN and bilirubin elevation >2x ULN on Day 58. Deucravacitinib treatment was discontinued and ALT, AST, and bilirubin levels improved.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; EAIR, exposure-adjusted incidence rate; LTE, long-term extension; PY, person-years; ULN, upper limit of normal.

Conclusions

- In the large, phase 3 POETYK PSO-1, PSO-2, and LTE trials in patients with moderate to severe plaque psoriasis, no trends or clinically meaningful changes in multiple hematologic, lipid, and chemistry parameters were observed in 1519 patients with 2482.0 PY of deucravacitinib exposure
  - Signature laboratory changes associated with JAK1,2,3 inhibitors were not observed over 2 years of deucravacitinib exposure
- CTCAE grade ≥3 laboratory abnormalities and treatment discontinuations due to laboratory abnormalities in deucravacitinib-treated patients were rare and were comparable to incidence rates observed with placebo and apremilast over the first 52 weeks
- Deucravacitinib, a once-daily oral drug, has the potential to become a treatment of choice and new standard of care for patients who require systemic therapy for their moderate to severe plaque psoriasis

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