

Deucravacitinib in plaque psoriasis: laboratory parameters through 4 years of treatment in the phase 3 POETYK PSO-1, PSO-2, and LTE trials

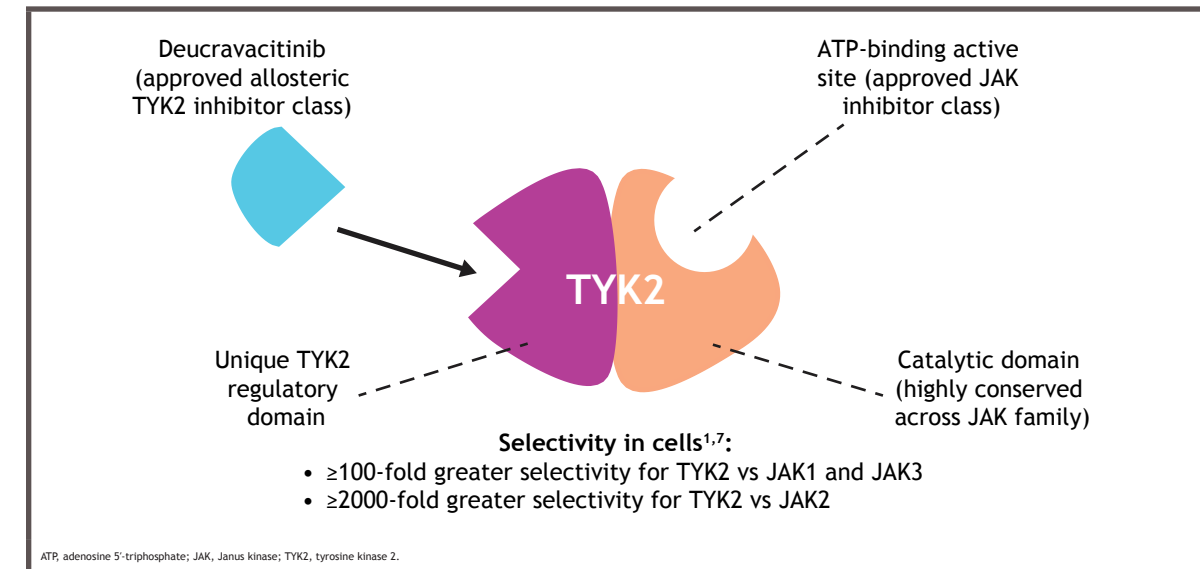
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Background

- Tyrosine kinase 2 (TYK2) is an intracellular enzyme that mediates signaling of select inflammatory cytokines (eg, interleukin [IL]-23, IL-12, Type I interferons [IFNs])¹
 - IL-23 and Type I IFNs are involved in psoriasis pathogenesis¹
- 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 TYK2 regulatory domain rather than to the catalytic domain where Janus kinase (JAK) 1,2,3 inhibitors bind^{1,7} (Figure 1), driving its selectivity for TYK2 and representing the first in a new class of oral drugs

Figure 1. Mechanism of action of deucravacitinib



- Two global, 52-week, phase 3 trials, POETYK PSO-1 (NCT03624127) and POETYK PSO-2 (NCT03611751), demonstrated that deucravacitinib was significantly more efficacious than placebo and apremilast at Week 16 and was well tolerated in patients with moderate to severe plaque psoriasis^{8,9}
- Patients who completed the POETYK PSO-1 and PSO-2 parent trials could enroll in the ongoing POETYK long-term extension (LTE) (NCT04036435) trial and receive open-label deucravacitinib
 - Clinical efficacy was maintained through 1 year in the parent trials and 2 additional years in the POETYK LTE trial (total, 3 years), with no new safety signals observed compared with the first year^{10,11}
 - No clinically meaningful changes from baseline or trends were observed in laboratory parameters through 3 years^{10,11}

Objectives

- To determine whether there were clinically relevant changes in blood laboratory parameters through 4 years (Week 208; data cutoff, November 1, 2023) in deucravacitinib-treated patients with moderate to severe plaque psoriasis in the POETYK PSO-1, PSO-2, and LTE trials
- To evaluate whether deucravacitinib treatment elicits changes in laboratory parameters known to occur with JAK1,2,3 inhibitors

Methods

Study designs

- POETYK PSO-1 and PSO-2 were 52-week, multinational, phase 3, double-blind trials that randomized adults with moderate to severe plaque psoriasis 1:2:1 to oral placebo, deucravacitinib 6 mg once daily, or apremilast 30 mg twice daily
 - Placebo patients crossed over to deucravacitinib at Week 16
 - In POETYK PSO-2, deucravacitinib-treated patients who achieved ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75) at Week 24 were rerandomized 1:1 to continue deucravacitinib treatment or switch to placebo through Week 52
- At Week 52, eligible patients were allowed to enroll in the POETYK LTE trial and receive open-label deucravacitinib 6 mg once daily

Laboratory assessments

- Adverse events (AEs) and treatment discontinuations due to laboratory abnormalities (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) were evaluated through 4 years (Week 208)
 - Safety data were reported as exposure-adjusted incidence rate (EAIR) per 100 person-years (PY) and calculated as 100 × (number of patients with an AE) / (total exposure time for all patients at risk [time to initial AE occurrence for patients with AE + total exposure time for patients without AE])
- Select laboratory parameters of note in the blood that are known to be associated with JAK1,2,3 inhibitors were assessed periodically through 4 years
 - Changes in laboratory parameters assessed included:
 - Hematology: hemoglobin, neutrophils, lymphocytes, platelets
 - Chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, creatine phosphokinase (CPK), total bilirubin, alkaline phosphatase
 - Lipids: total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides

Results

Patients

- A total of 1519 patients received ≥1 dose of deucravacitinib across the parent trials (POETYK PSO-1 and PSO-2) and the POETYK LTE trial
 - Total deucravacitinib exposure through 4 years was 4392.8 PY
 - Median duration of exposure was 185 weeks
 - ≥52 weeks, n = 1203 (79.2%) patients
 - ≥208 weeks, n = 542 (35.7%) patients

- 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/m ²	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

- The most common laboratory abnormality AEs (EAIR ≥1/100 PY) were blood CPK increased (n = 93/1519; EAIR, 2.20) and ALT increased (n = 47/1519; EAIR, 1.08), which resolved spontaneously on continuing treatment with deucravacitinib
- Discontinuations due to laboratory abnormality AEs were low and balanced across treatment groups over the first 52 weeks in the parent trials and continued to be low through 4 years (Table 2)
- No patients discontinued deucravacitinib treatment due to the minimal triglyceride elevations noted below

Table 2. Laboratory abnormality AEs leading to treatment discontinuation through 1 year and 4 years

Parameter	At 1 year (POETYK PSO-1 + PSO-2, Weeks 0-52)			At 4 years (POETYK PSO-1 + PSO-2 + LTE, Weeks 0-208)		
	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 = 4392.8 PY		
Lymphopenia	0	1 (0.1) ^b	0	1 (0.1) ^b	0.02	
Blood CPK increased	0	2 (0.1) ^c	0.2	3 (0.2) ^c	0.1	
Hepatic function abnormal	1 (0.2)	1 (0.1) ^b	0	1 (0.1) ^b	0	
ALT increased	0	0	0	1 (0.1) ^b	0	
AST increased	0	0	1 (0.2)	1 (0.1) ^c	0	

Incidence rates are expressed as EAIR/100 PY to account for variable exposure due to treatment switches at Weeks 16 and 24. ^aThis AE was considered treatment related. ^bThis CPK event was considered treatment related and 1 CPK event was considered not related. ^cThis AE was considered not related to treatment.

- No clinically meaningful mean changes were observed through 4 years (Weeks 0-208) in any of the evaluated hematology (Figure 2), chemistry (Figure 3), or lipid (Figure 4) laboratory parameters
 - Laboratory parameters remained within normal ranges for the vast majority of patients throughout this period
 - As expected, due to comorbidities known to be present in this population, such as obesity and metabolic syndrome,¹² baseline levels of cholesterol and triglycerides were elevated
 - A minimal increase (<10 mg/dL) in the mean change from baseline (150 mg/dL) in serum triglycerides was observed with deucravacitinib during the first year of treatment and was:
 - Not considered clinically relevant
 - Not associated with increases in LDL levels (<3 mg/dL)
 - Stable over time
 - Signature changes in mean laboratory parameters seen with 1 or more JAK1,2,3 inhibitors, such as lymphopenia, anemia, thrombocytopenia, liver enzyme elevations, creatinine increases, and cholesterol increases,¹³ were not observed with deucravacitinib treatment

Figure 2. Changes in hematology parameters over 4 years in patients treated with deucravacitinib in POETYK PSO-1 + PSO-2 + LTE

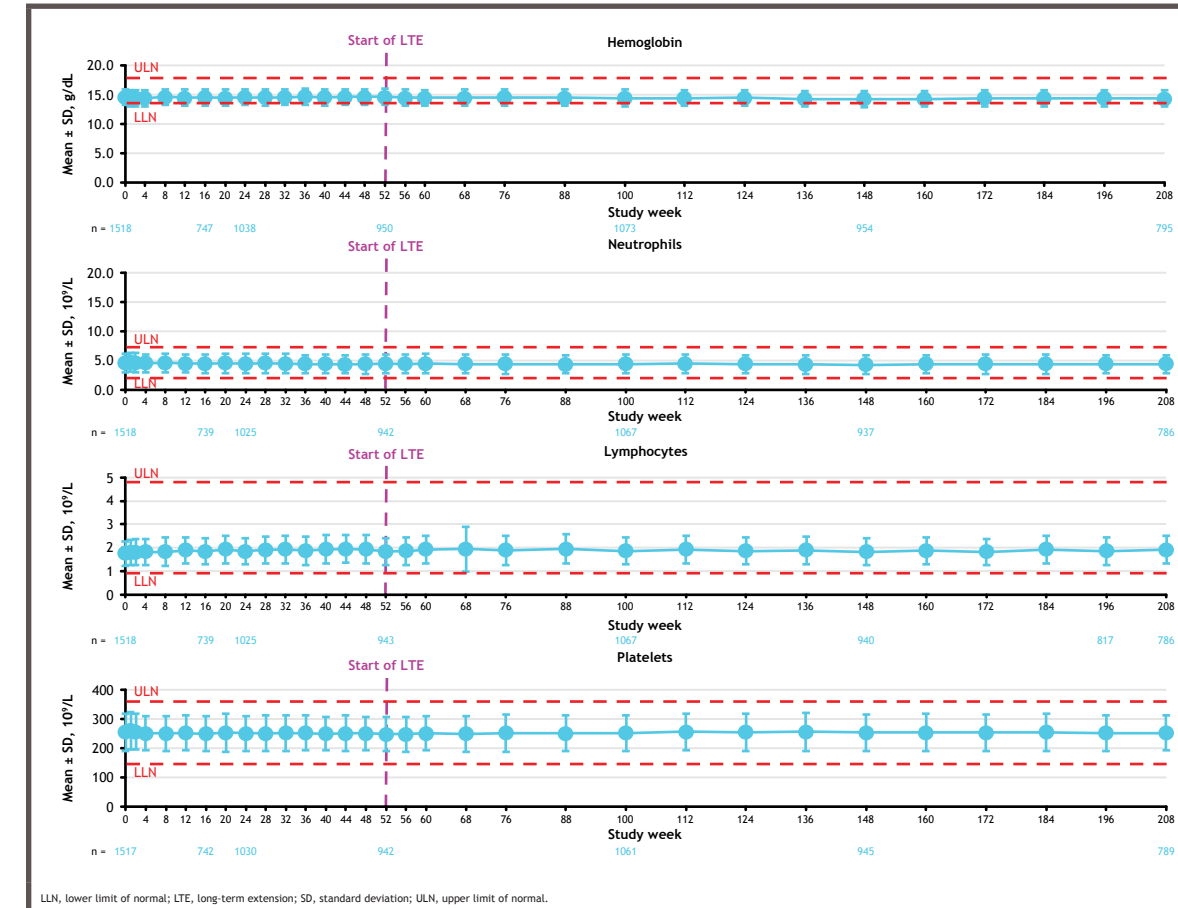


Figure 3. Changes in chemistry parameters over 4 years in patients treated with deucravacitinib in POETYK PSO-1 + PSO-2 + LTE

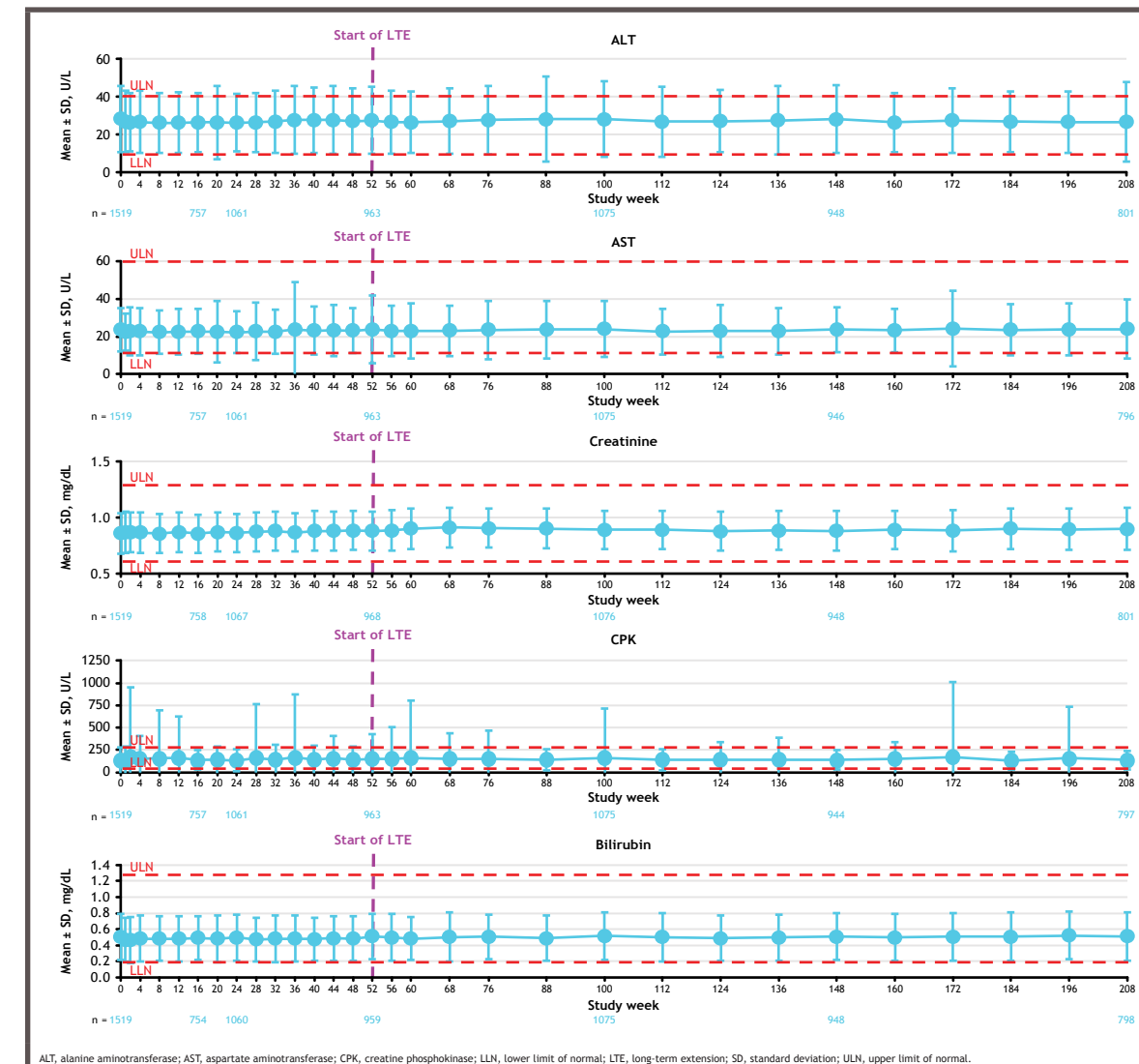
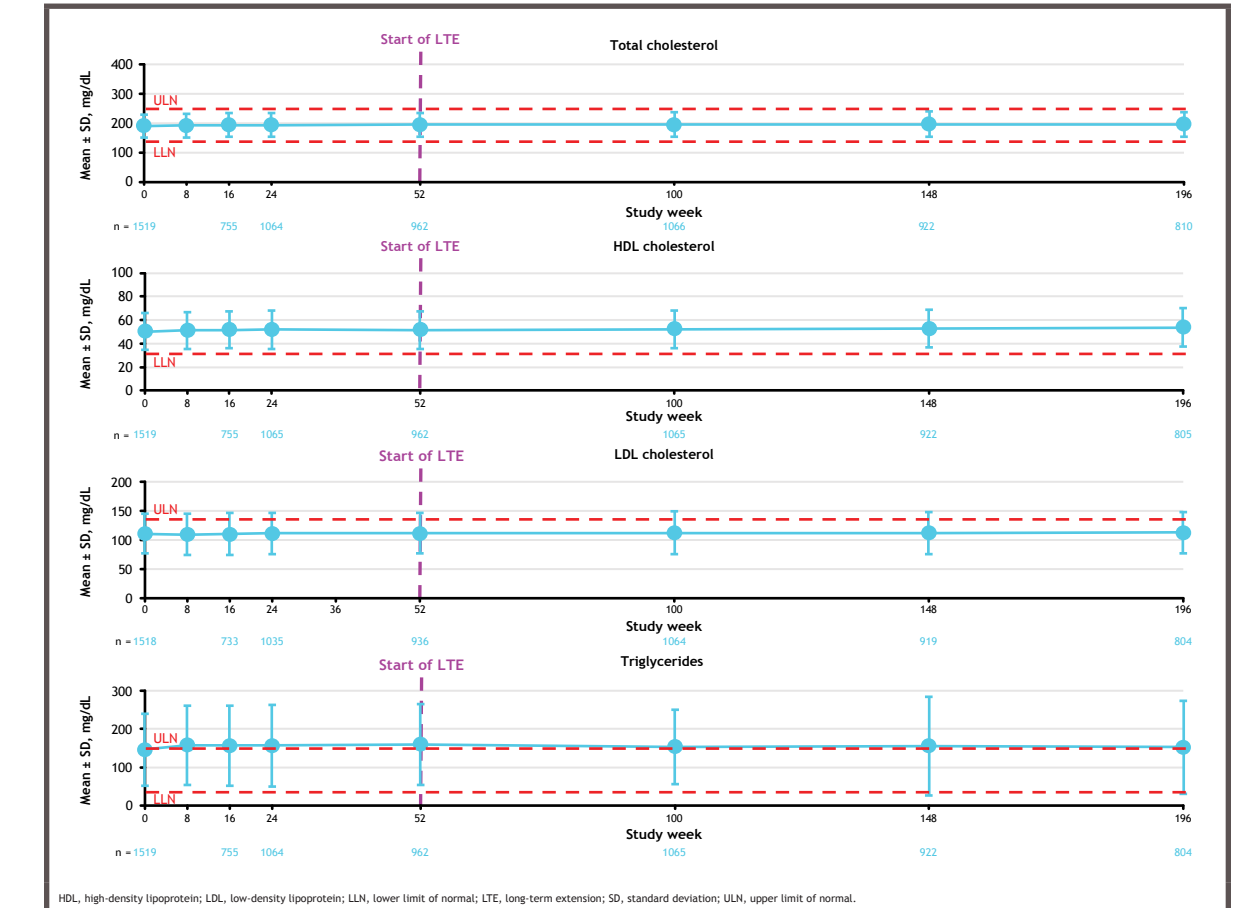


Figure 4. Changes in lipid parameters over 4 years in patients treated with deucravacitinib in POETYK PSO-1 + PSO-2 + LTE



Conclusions

- In the global, phase 3 POETYK PSO-1, PSO-2, and LTE trials in patients with plaque psoriasis, no trends or clinically meaningful mean changes from baseline in hematology, chemistry, or lipid (including triglycerides) laboratory parameters were observed in 1519 patients with 4392.8 PY of deucravacitinib exposure
 - Signature changes in mean values of laboratory analytes observed with JAK1,2,3 inhibitors (eg, increased cholesterol, creatinine, serum transaminases, CPK levels, cytopenias)¹³ were not observed over 4 years of deucravacitinib treatment
- Discontinuations due to laboratory abnormalities were rare (7 events) through 4 years of deucravacitinib treatment
- The laboratory parameter profile further supports the selectivity of deucravacitinib for TYK2 and highlights that the JAK1,2,3 pathways are not impacted by selective, allosteric TYK2 inhibition

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