Deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 inhibitor, in moderate to severe plaque psoriasis: evaluation of creatine phosphokinase elevations in the phase 3 POETYK PSO-1 and PSO-2 trials

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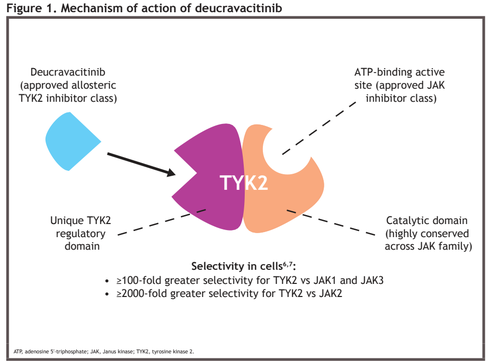
Synopsis

- Deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 (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[1-5]
- Deucravacitinib uniquely binds to the regulatory domain of TYK2 rather than to the catalytic domain where Janus kinase (JAK) 1,2,3 inhibitors bind[6,7] (**Figure 1**), representing the first in a new class of small molecules
- Deucravacitinib was superior to placebo and apremilast in the global phase 3 POETYK PSO-1 (NCT03624127) and POETYK PSO-2 (NCT03611751) trials in moderate to severe plaque psoriasis[8,9]
- Creatine phosphokinase (CPK; also known as creatine kinase) levels can be highly variable, and elevations may result from muscular damage, such as following exercise, muscle injury, myositis, myopathy, and rhabdomyolysis, and from the use of certain prescription drugs and supplements[10,11]
- The clinical significance and exact mechanism of action for elevated CPK levels in response to prescription drugs, such as statins, JAK1,2,3 inhibitors, and HIV therapy, are unclear[12,13]

Figure 1. Mechanism of action of deucravacitinib



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

Objective

- To assess changes in CPK levels from baseline and adverse events (AEs) of CPK elevations and rhabdomyolysis in a pooled analysis of patients treated with deucravacitinib in the POETYK PSO-1 and PSO-2 trials

Methods

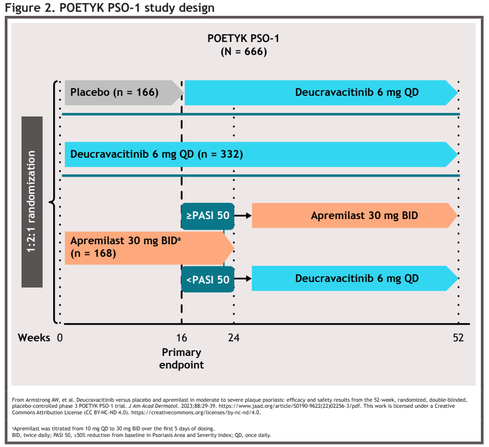
Study designs

- The study designs for POETYK PSO-1 and POETYK PSO-2 are summarized in **Figure 2** and **Figure 3**, respectively
- Key eligibility criteria included the following:
  - Aged ≥18 years
  - Diagnosis of moderate to severe plaque psoriasis
    - Baseline Psoriasis Area and Severity Index (PASI) ≥12, static Physician Global Assessment (sPGA) ≥3, and body surface area involvement ≥10%
- CPK elevation at baseline was not an exclusion criterion

Assessments

- Per protocol, CPK levels were assessed at screening and baseline visits; at Weeks 1, 2, 4, and every 4 weeks thereafter through Week 52; and at the safety follow-up visit (Week 56)
- AEs of CPK elevations and rhabdomyolysis were reported per investigator discretion
- Shifts from baseline in severity grade (Common Terminology Criteria for Adverse Events [CTCAE] version 5) of CPK levels are reported

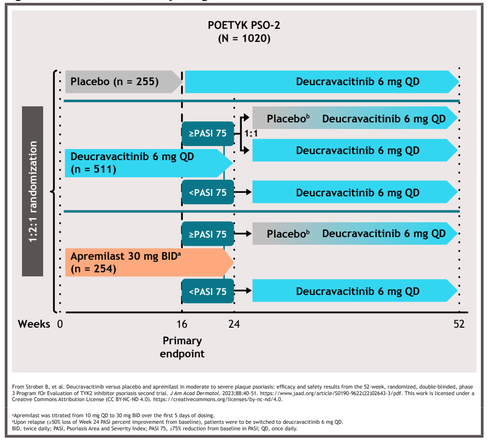
Figure 2. POETYK PSO-1 study design



From Armstrong AW, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. *J Am Acad Dermatol*. 2023;88:29-39. https://www.jaad.org/article/S0190-9622(22)02256-3/pdf. This work is licensed under a Creative Commons Attribution License (CC BY-NC-ND 4.0). https://creativecommons.org/licenses/by-nc-nd/4.0.

[a]Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
BID, twice daily; PASI 50, ≥50% reduction from baseline in Psoriasis Area and Severity Index; QD, once daily.

Figure 3. POETYK PSO-2 study design



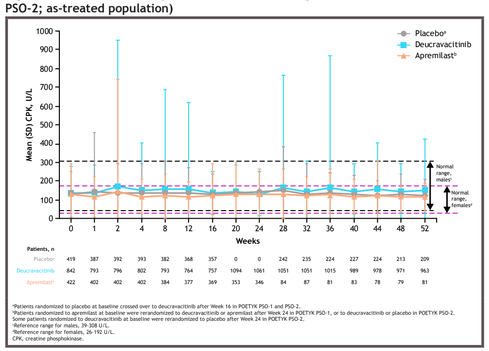
From Strober B, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52 week, randomized, double-blinded, phase 3 Program fOr Evaluation of TYK2 inhibitor psoriasis second trial. *J Am Acad Dermatol*. 2023;88:40-51. https://www.jaad.org/article/S0190-9622(22)02043-3/pdf. This work is licensed under a Creative Commons Attribution License (CC BY-NC-ND 4.0). https://creativecommons.org/licenses/by-nc-nd/4.0.

[a]Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
[b]Upon relapse (≥50% loss of Week 24 PASI percent improvement from baseline), patients were to be switched to deucravacitinib 6 mg QD.
BID, twice daily; PASI, Psoriasis Area and Severity Index; PASI 75, ≥75% reduction from baseline in PASI; QD, once daily.

Results

- The pooled POETYK PSO-1/PSO-2 safety population included 1683 patients randomized to placebo (n = 419), deucravacitinib (n = 842), or apremilast (n = 422)
- At baseline, the proportions of patients with grade ≥1 CPK levels were comparable across the placebo (6.3%), deucravacitinib (5.9%), and apremilast (7.4%) groups
- There were no clinically meaningful increases from baseline through Week 52 in mean CPK levels, and mean changes from baseline at Weeks 16 and 52 were comparable with placebo, deucravacitinib, and apremilast (**Figure 4**)

Figure 4. Mean CPK levels by treatment Weeks 0-52 (pooled POETYK PSO-1 and PSO-2; as-treated population)



[a]Patients randomized to placebo at baseline crossed over to deucravacitinib after Week 16 in POETYK PSO-1 and PSO-2.
[b]Patients randomized to apremilast at baseline were rerandomized to deucravacitinib or apremilast after Week 24 in POETYK PSO-1, or to deucravacitinib or placebo in POETYK PSO-2. Some patients randomized to deucravacitinib at baseline were rerandomized to placebo after Week 24 in POETYK PSO-2.
[c]Reference range for males, 39-308 U/L.
[d]Reference range for females, 26-192 U/L.
CPK, creatine phosphokinase.

- During Weeks 0-16, the proportions of patients who experienced a worsening of CPK level by >1 grade from baseline were comparable across placebo (2.2%), deucravacitinib (2.5%), and apremilast (1.4%) groups (**Table 1**)
- During Weeks 0-52, the proportions of patients who experienced a worsening of CPK level by >1 grade from baseline were slightly increased vs Weeks 0-16 but were comparable across all treatment groups (**Table 2**)
- Most deucravacitinib-treated patients maintained the same or shifted to a lower CPK CTCAE grade from baseline through Week 16 or Week 52 (**Table 1**; **Table 2**)
  - The proportions of patients with a shift to a lower CPK grade in the placebo, deucravacitinib, and apremilast groups, respectively, were 2.9%, 2.0%, and 3.3% through Week 16 and 2.4%, 2.0%, and 2.9% through Week 52

Table 1. Shifts in CPK grade from baseline to Week 16 (pooled POETYK PSO-1 and PSO-2)

Parameter	Baseline grade	Grade, Weeks 0-16, n (%)					Total patients
		0	1	2	3	4	
Placebo	0	330 (85.3)	49 (12.7)	6 (1.6)	1 (0.3)	1 (0.3)	387
	1	11 (45.8)	9 (37.5)	3 (12.5)	1 (4.2)	0	24
	2	1 (100)	0	0	0	0	1
	3	0	0	0	1 (100)	0	1
	4	0	0	0	0	0	0
	Total	342	58	9	3	1	413
Deucravacitinib 6 mg QD	0	652 (83.2)	112 (14.3)	10 (1.3)	4 (0.5)	6 (0.8)	784
	1	16 (34.8)	24 (52.2)	5 (10.9)	1 (2.2)	0	46
	2	0	0	2 (100)	0	0	2
	3	1 (100)	0	0	0	0	1
	4	0	0	0	0	0	0
	Total	669	136	17	5	6	833
Apremilast 30 mg BID	0	344 (88.7)	38 (9.8)	4 (1.0)	1 (0.3)	1 (0.3)	388
	1	12 (42.9)	14 (50.0)	2 (7.1)	0	0	28
	2	2 (100)	0	0	0	0	2
	3	0	0	0	1 (100)	0	1
	4	0	0	0	0	0	0
	Total	358	52	6	2	1	419

Light pink shading indicates an increase of 1 grade; dark pink indicates an increase of >1 grade. Light green shading indicates a decrease of 1 grade; dark green indicates a decrease of >1 grade.
BID, twice daily; CPK, creatine phosphokinase; QD, once daily.

Table 2. Shifts in CPK grade from baseline to Week 52 (pooled POETYK PSO-1 and PSO-2)

Parameter	Baseline grade	Grade, Weeks 0-52, n (%)					Total patients
		0	1	2	3	4	
Placebo[a]	0	514 (82.4)	93 (14.9)	12 (1.9)	2 (0.3)	3 (0.5)	624
	1	14 (45.2)	11 (35.5)	5 (16.1)	1 (3.2)	0	31
	2	2 (100)	0	0	0	0	2
	3	0	0	0	1 (100)	0	1
	4	0	0	0	0	0	0
	Total	530	104	17	4	3	658
Deucravacitinib 6 mg QD	0	941 (74.6)	258 (20.4)	39 (3.1)	12 (1.0)	12 (1.0)	1262
	1	23 (28.0)	43 (52.4)	11 (13.4)	4 (4.9)	1 (1.2)	82
	2	1 (25.0)	1 (25.0)	0	2 (50.0)	0	4
	3	0	0	2 (66.7)	1 (33.3)	0	3
	4	0	0	0	0	0	0
	Total	965	302	52	19	13	1351
Apremilast 30 mg BID	0	327 (84.3)	48 (12.4)	8 (2.1)	4 (1.0)	1 (0.3)	388
	1	10 (35.7)	13 (46.4)	3 (10.7)	2 (7.1)	0	28
	2	2 (100)	0	0	0	0	2
	3	0	0	0	1 (100)	0	1
	4	0	0	0	0	0	0
	Total	339	61	11	7	1	419

[a]The placebo group includes patients who received placebo at any time through POETYK PSO-1 and PSO-2.
Light pink shading indicates an increase of 1 grade; dark pink indicates an increase of >1 grade. Light green shading indicates a decrease of 1 grade; dark green indicates a decrease of >1 grade.
BID, twice daily; CPK, creatine phosphokinase; QD, once daily.

- AEs of CPK elevations were reported in 1.2%, 2.7%, and 0.7% of patients treated with placebo, deucravacitinib, and apremilast, respectively, through Week 16 (**Table 3**)
- The exposure-adjusted incidence rates (EAIRs) for AEs of CPK elevations were comparable across treatment arms through Week 52 (4.5/100 person-years [PY], 4.7/100 PY, and 3.6/100 PY for patients treated with placebo, deucravacitinib, and apremilast, respectively) (**Table 3**)
- Two patients treated with deucravacitinib (0.2/100 PY) and 1 patient treated with apremilast (0.4/100 PY) discontinued due to AEs of CPK elevations (**Table 3**)
  - One patient treated with deucravacitinib had a high CPK level at screening (1796 U/L; grade 3) and the other had a high CPK level at baseline (1503 U/L; grade 2); levels fluctuated until the date of discontinuation (2557 U/L and 1863 U/L; 761 U/L [Day 297] and 360 U/L [Day 283] greater than screening/baseline, respectively)
    - One of the 2 patients had exercised within 7 days before the elevated CPK event
    - Neither patient reported potential signs or symptoms of elevated CPK, including pain, muscle aches/myalgias, weakness, muscle cramps, or muscle swelling
  - The apremilast-treated patient had a normal CPK level at baseline (182 U/L) that rose to 11,878 U/L; the patient reported exercising within 7 days before the elevated CPK event, and the study drug was discontinued on Day 18
    - The patient did not report potential signs or symptoms of elevated CPK, including pain, muscle aches/myalgias, weakness, muscle cramps, or muscle swelling

Table 3. Summary of AEs of CPK elevations (pooled POETYK PSO-1 and PSO-2)

Parameter	POETYK PSO-1 and PSO-2: Weeks 0-16						POETYK PSO-1 and PSO-2: Weeks 0-52					
	Placebo (n = 419)		Deucravacitinib (n = 842)		Apremilast (n = 422)		Placebo[a] (n = 666)		Deucravacitinib (n = 1364)		Apremilast (n = 422)	
	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY	n (%)	EAIR/ 100 PY
AEs of CPK elevations	5 (1.2)	4.1	23 (2.7)	9.3	3 (0.7)	2.4	11 (1.7)	4.5	45 (3.3)	4.7	8 (1.9)	3.6
Serious AEs	0	--	0	--	0	--	0	--	0	--	0	--
CPK elevations that led to discontinuation	0	--	0	--	1 (0.2)	--	0	--	2 (1.0)	0.2	1 (0.2)	0.4

Note: EAIRs are presented only for those preferred terms where there was at least 1 event.
[a]The placebo group includes patients who received placebo at any time through POETYK PSO-1 and PSO-2.
AE, adverse event; CPK, creatine phosphokinase; EAIR, exposure-adjusted incidence rate; PY, person-years.

- Five patients treated with deucravacitinib had CPK levels >10,000 U/L during the trial; all elevations were transient and CPK levels returned to baseline at subsequent visits on continued treatment with the drug; all 5 patients had exercised within 7 days before the event, and none discontinued treatment (**Table 4**)
- One patient treated with apremilast had CPK levels >10,000 U/L during the trial, and the study drug was discontinued on Day 18; the patient had exercised within 7 days before the event (**Table 4**)

Table 4. Narratives of patients with CPK levels >10,000 U/L by treatment group

Patient	Treatment received	Baseline level (grade)	Event CPK level (grade)	CPK elevation reported as AE	Led to discontinuation	Treatment interruption	Exercised within 7 days of event	Outcome
Patient 1 (26 years old/male)	Deucravacitinib	106 U/L (grade 0)	22,000 U/L (grade 4; Day 254)	No	No	No	Yes	Completed study (grade 0 CPK at EOS); enrolled in the LTE
Patient 2 (35 years old/male)	Deucravacitinib	96 U/L (grade 0)	14,707 U/L (grade 4; Day 60)	Yes (mild, not related to study drug per investigator)	No	No	Yes	Lost to follow-up (grade 0 CPK at EOS)
Patient 3 (37 years old/male)	Deucravacitinib	282 U/L (grade 0)	12,270 U/L (grade 4; Day 85)	No	No	No	Yes	Withdrew; no longer wished to participate (grade 0 CPK at EOS)
Patient 4 (31 years old/ female)	Deucravacitinib	96 U/L (grade 0)	21,020 U/L (grade 4; Day 15)	No; AE of rhabdomyolysis reported (mild; related to study drug per investigator), associated with event	No	Yes, study drug interrupted for 6 days	Yes; patient had initiated intense exercise regimen 7 days prior and exercised the day before the event	Completed study (grade 0 CPK at EOS); enrolled in the LTE
Patient 5 (32 years old/male)	Deucravacitinib	155 U/L (grade 0)	17,902 U/L (grade 4; Day 197)	No; AE of muscle injury reported (post-workout; moderate, not related to study drug per investigator), associated with event	No	No	Yes	Completed study (grade 0 CPK at EOS); enrolled in the LTE
Patient 6 (40 years old/male)	Apremilast	182 U/L (grade 0)	11,878 U/L (grade 4; Day 15)	Yes (moderate; not related to study drug per investigator); AE of increased AST reported (mild; related to study drug per investigator), associated with event	Yes	Yes; study drug was discontinued on Day 18	Yes	Withdrew (grade 0 CPK at EOS)

AE, adverse event; AST, aspartate aminotransferase; CPK, creatine phosphokinase; EOS, end of study; LTE, long-term extension.

- Two patients treated with deucravacitinib had AEs of rhabdomyolysis; neither patient received specific treatment nor had sequelae due to the event
  - **31 years old/female (patient 4 in Table 4):** Day 15; mild, related to study drug per the investigator
    - Intensive exercise training was initiated within the first week of treatment, and the patient reported exercise the day before the event
    - Associated myalgia was reported with concurrent elevations of CPK (21,020 U/L; grade 4), alanine aminotransferase (ALT) (<2 × upper limit of normal [ULN]), aspartate aminotransferase (AST) (>5 × ULN), and lactate dehydrogenase (LDH) (>3 × ULN)
    - The study drug was interrupted for 6 days
    - All laboratory values normalized (AST, LDH) or improved (ALT, CPK) by the next visit
    - The event resolved without treatment, and the patient completed the trial and enrolled in the POETYK long-term extension (LTE) trial without any AEs of CPK elevation or recurrence of rhabdomyolysis reported
  - **64 years old/male:** Day 189; severe, not related to study drug per the investigator
    - In the setting of serious AEs of right lower leg arterial thrombosis with resultant ischemic compartment syndrome and hepatitis (severe, not related to study drug per the investigator) that required hospitalization
    - Relevant history: hypertension, chronic obstructive pulmonary disease, obesity (body mass index, 30 kg/m^2), ~34 pack/year smoker, unknown family history of cardiovascular disease, no known previous peripheral arterial disease
    - Computerized tomography angiogram revealed thrombosed 6.0 cm right popliteal artery aneurysm, 3.2 cm left popliteal artery aneurysm, 3.0 cm infrarenal abdominal aortic aneurysm, ectatic right common iliac artery, and thrombosed left tibioperoneal trunk with reconstitution
    - The patient had concurrent elevated AST (>10 × ULN) with reported hepatitis, considered related to lower leg ischemia and resultant rhabdomyolysis
    - CPK levels were within normal range throughout the study, but supporting laboratory test results were not specified in the available hospital documents
    - The study drug was discontinued
    - Patient received surgical intervention for underlying events; rhabdomyolysis and hepatitis resolved without treatment

Conclusions

- In the POETYK PSO-1 and PSO-2 trials, the EAIRs for AEs of CPK elevations over the 52-week trial period were comparable with deucravacitinib treatment (4.7/100 PY) vs placebo (4.5/100 PY) and apremilast (3.6/100 PY)
- No clinically meaningful increases from baseline in mean CPK levels were observed with deucravacitinib
- The vast majority of patients treated with deucravacitinib maintained their baseline CPK grade or shifted to a lower grade through Weeks 16 and 52
- Discontinuations due to AEs of CPK elevations were infrequent and comparable across treatment groups
- Five patients treated with deucravacitinib had CPK levels >10,000 U/L
  - Only 1 patient who had a CPK level >10,000 U/L had an AE, which was mild and unrelated to the study drug
  - All CPK levels >10,000 U/L decreased by the next laboratory draw, and all ultimately returned to normal ranges; all were associated with recent physical exertion
- Two deucravacitinib-treated patients had AEs of rhabdomyolysis
  - One patient experienced the event following initiation of intensive exercise training
  - One patient experienced the event in association with hospitalization for ischemic limb compartment syndrome following popliteal artery thrombosis in an underlying popliteal aneurysm and peripheral arterial disease; the event was not associated with elevated CPK levels
- These data provide important context for the risk of CPK elevations in patients with moderate to severe plaque psoriasis treated with deucravacitinib

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