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

Mark Lebwohl,[1] Bruce Strober,[2] Misti Linaberry,[3] Kim Hoyt,[3] Subhashis Banerjee,[3] Renata M Kisa,[3] Nehal N Mehta[4]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Yale University School of Medicine, New Haven, and Central Connecticut Dermatology, Cromwell, CT, USA; [3]Bristol Myers Squibb, Princeton, NJ, USA; [4]The George Washington University School of Medicine, Washington, DC, USA

Synopsis

- Tyrosine kinase 2 (TYK2) is an intracellular enzyme that mediates signaling of cytokines (interleukin-23 and Type I interferons) involved in psoriasis pathogenesis[1]
- Deucravacitinib, an oral, selective, allosteric TYK2 inhibitor, is approved by the US Food and Drug Administration for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy[2] based on results from the phase 3 POETYK PSO-1 and PSO-2 trials[3,4]
- Plaque psoriasis is associated with hypertriglyceridemia and metabolic syndrome,[5,6] and the frequency of hypertriglyceridemia increases with plaque psoriasis severity[7]
  - Triglycerides ≥150 mg/dL are among the clinical characteristics used to identify patients with metabolic syndrome[8]
  - The American Academy of Dermatology recommends that patients with plaque psoriasis be informed about their increased risk of metabolic syndrome and have frequent lipid screenings, especially when the disease is severe[5]
- In clinical trials enrolling patients with moderate to severe plaque psoriasis, treatment with deucravacitinib was associated with slight increases (~10 mg/dL) in mean triglyceride levels in the absence of any changes in mean cholesterol levels[2]
- In the absence of atherosclerotic cardiovascular disease (ASCVD) and diabetes mellitus, the American Academy of Cardiology[9] recommends:
  - Diet and lifestyle optimization in adults with fasting triglycerides ≥150 mg/dL and <500 mg/dL
  - Consideration of initiation or intensification of statin therapy in adults with persistently elevated fasting triglycerides ≥150 mg/dL and <500 mg/dL and a calculated ASCVD risk ≥5%

Objective

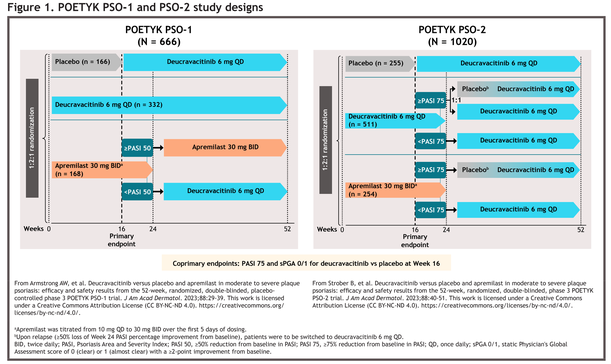
- To report changes in lipid parameters in patients enrolled in POETYK PSO-1 and PSO-2 and treated with:
  - Placebo, deucravacitinib, or apremilast over 16 weeks
  - Deucravacitinib continuously for 52 weeks

Methods

Study designs

- POETYK PSO-1 (NCT03624127) and PSO-2 (NCT03611757) were phase 3, 52-week, double-blind, randomized, placebo- and active comparator (apremilast)-controlled trials conducted globally (**Figure 1**)
  - Enrolled patients with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index [PASI] ≥12; static Physician's Global Assessment [sPGA] ≥3; body surface area involvement ≥10%) were randomized 1:2:1 to oral placebo, deucravacitinib 6 mg once daily, or apremilast 30 mg twice daily during Weeks 0-16
  - Blinded treatment switches occurred at Week 16 and Week 24
    - Patients receiving placebo crossed over to deucravacitinib at Week 16
    - Patients receiving apremilast who failed to meet trial-specific efficacy thresholds in POETYK PSO-1 (≥50% reduction from baseline in PASI [PASI 50]) and in POETYK PSO-2 (≥75% reduction from baseline in PASI [PASI 75]) were switched to deucravacitinib at Week 24
    - Patients receiving deucravacitinib who achieved PASI 75 at Week 24 in POETYK PSO-2 were re-randomized (1:1) to continue deucravacitinib or to switch to placebo (withdrawal); patients receiving apremilast who achieved PASI 75 were switched to placebo

Figure 1. POETYK PSO-1 and PSO-2 study designs



Coprimary endpoints: PASI 75 and sPGA 0/1 for deucravacitinib vs placebo at Week 16

[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 percentage improvement from baseline), patients were to be switched to deucravacitinib 6 mg QD.
BID, twice daily; PASI, Psoriasis Area and Severity Index; PASI 50, ≥50% reduction from baseline in PASI; PASI 75, ≥75% reduction from baseline in PASI; QD, once daily; sPGA 0/1, static Physician's Global Assessment score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline.

Lipid assessments

- Mean total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides are reported:
  - At baseline and Week 16 in patients treated with placebo, deucravacitinib, and apremilast
  - Over multiple time points from baseline to Week 52 in patients who received continuous deucravacitinib
- Changes in cholesterol and triglycerides on laboratory analyses are presented as grade shifts per Common Terminology Criteria for Adverse Events (CTCAE) version 5 (**Table 1**):
  - From baseline to Week 16 in patients treated with placebo, deucravacitinib, and apremilast
  - From baseline to Week 52 in patients who received continuous deucravacitinib treatment

Table 1. CTCAE grades for hypercholesterolemia and hypertriglyceridemia

Grade	Total cholesterol range	Triglyceride range
0	≤ULN[a]	<150 mg/dL (<1.71 mmol/L)
1	>ULN-300 mg/dL; >ULN-7.75 mmol/L	150-300 mg/dL (1.71-3.42 mmol/L)
2	>300-400 mg/dL; >7.75-10.34 mmol/L	>300-500 mg/dL (>3.42-5.7 mmol/L)
3	>400-500 mg/dL; >10.34-12.92 mmol/L	>500-1000 mg/dL (>5.7-11.4 mmol/L)
4	>500 mg/dL; >12.92 mmol/L	>1000 mg/dL (>11.4 mmol/L); life-threatening consequences

[a]Defined in these analyses as 200 mg/dL.
CTCAE, Common Terminology Criteria for Adverse Events; ULN, upper limit of normal.

Results

Patient population

- A total of 666 and 1020 patients were randomized in the POETYK PSO-1 and PSO-2 trials, respectively, and were included in this analysis

Changes in lipid parameters from baseline to Week 16

- Baseline means for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were similar across treatment groups (**Table 2**)
- Mean changes in total cholesterol, HDL cholesterol, and LDL cholesterol were small across treatment groups and not clinically meaningful (**Table 2**)
- Baseline mean triglyceride levels were near the upper limit of normal (ULN; 150 mg/dL) across treatment groups (**Table 2**)
- There were slight increases (~10 mg/dL) in mean triglyceride levels with deucravacitinib treatment (**Table 2**)

Table 2. Changes in lipid parameters from baseline to Week 16 (pooled POETYK PSO-1 and PSO-2)

Parameter	Placebo		Deucravacitinib 6 mg QD		Apremilast 30 mg BID	
	n	Mean (SD/SE[a])	n	Mean (SD/SE[a])	n	Mean (SD/SE[a])
Total cholesterol, mg/dL[b]						
Baseline	419	189.4 (39.03)	842	189.1 (39.24)	422	190.1 (37.15)
Week 16	357	190.4 (38.55)	755	192.5 (40.42)	369	187.8 (36.70)
Change	357	-0.1 (1.27)	755	2.6 (0.97)	369	-2.8 (1.26)
HDL cholesterol, mg/dL						
Baseline	419	49.5 (15.50)	842	50.4 (15.16)	422	50.5 (17.23)
Week 16	357	48.5 (13.49)	755	51.7 (15.80)	369	51.9 (18.46)
Change	357	-0.9 (0.39)	755	0.9 (0.28)	369	0.5 (0.38)
LDL cholesterol, mg/dL						
Baseline	419	110.8 (33.77)	842	109.8 (34.90)	421	111.5 (32.32)
Week 16	347	112.8 (33.37)	733	110.2 (35.97)	360	109.2 (32.37)
Change	347	0.7 (1.15)	733	-0.2 (0.84)	359	-2.5 (1.11)
Triglycerides, mg/dL						
Baseline	419	149.5 (106.77)	842	146.6 (92.04)	422	145.9 (93.81)
Week 16	357	149.8 (88.95)	755	157.1 (104.02)	369	137.7 (80.80)
Change	357	0.4 (4.77)	755	10.3 (3.15)	369	-6.8 (3.24)

[a]SD is reported for baseline and Week 16 means; SE is reported for mean change from baseline.
[b]Total cholesterol = HDL + LDL + 20% triglycerides.
BID, twice daily; HDL, high-density lipoprotein; LDL, low-density lipoprotein; QD, once daily; SD, standard deviation; SE, standard error.

- Worsening of hypercholesterolemia was observed with comparable frequency among patients treated with placebo, deucravacitinib, and apremilast (10.6%, 11.7%, and 8.4%, respectively); nearly all shifts were 1 grade (**Table 3**)
- Most deucravacitinib-treated patients maintained the same or shifted to a lower grade of hypercholesterolemia from baseline to Week 16 (**Table 3**)

Table 3. Shifts in grade of hypercholesterolemia from baseline to Week 16 (pooled POETYK PSO-1 and PSO-2)

Parameter	Baseline grade	Grade at Week 16, n (%)					Total patients
		0	1	2	3	4	
Placebo	0	182 (82.7)	38 (17.3)	0 (0.0)	0 (0.0)	0 (0.0)	220
	1	31 (22.8)	105 (77.2)	0 (0.0)	0 (0.0)	0 (0.0)	136
	2	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	Total	213	144	0	0	0	357
Deucravacitinib 6 mg QD	0	387 (82.5)	81 (17.3)	1 (0.2)	0 (0.0)	0 (0.0)	469
	1	64 (22.7)	212 (75.2)	6 (2.1)	0 (0.0)	0 (0.0)	282
	2	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	4
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	Total	451	297	7	0	0	755
Apremilast 30 mg BID	0	205 (87.2)	30 (12.8)	0 (0.0)	0 (0.0)	0 (0.0)	235
	1	41 (31.1)	90 (68.2)	1 (0.8)	0 (0.0)	0 (0.0)	132
	2	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	2
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	Total	246	122	1	0	0	369

Light pink shading indicates a shift of 1 grade; dark pink shading indicates a shift of >1 grade.
BID, twice daily; QD, once daily.

- Grade ≥3 hypertriglyceridemia occurred in several patients in each treatment group at Week 16 (**Table 4**)
- Worsening shifts in hypertriglyceridemia >1 grade were observed in 1.4%, 1.2%, and 0.3% of patients treated with placebo, deucravacitinib, and apremilast, respectively (**Table 4**)
- Most deucravacitinib-treated patients maintained the same or shifted to a lower grade of hypertriglyceridemia from baseline to Week 16 (**Table 4**)
  - Of the 34 deucravacitinib-treated patients with grade 2 or 3 hypertriglyceridemia at baseline, 19 improved to grade 0 or 1 at Week 16
- No patient exhibited pancreatitis or a major adverse cardiovascular event associated with grade 4 hypertriglyceridemia
- No adverse event related to increased triglycerides was reported as serious or led to treatment discontinuation

Table 4. Shifts in grade of hypertriglyceridemia from baseline to Week 16 (pooled POETYK PSO-1 and PSO-2)

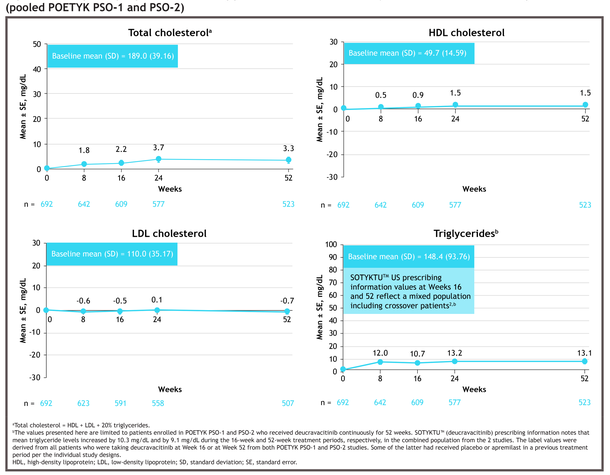
Parameter	Baseline grade	Grade at Week 16, n (%)					Total patients
		0	1	2	3	4	
Placebo	0	195 (86.7)	26 (11.6)	4 (1.8)	0 (0.0)	0 (0.0)	225
	1	37 (35.9)	56 (54.4)	9 (8.7)	1 (1.0)	0 (0.0)	103
	2	4 (15.4)	14 (53.8)	7 (26.9)	1 (3.8)	0 (0.0)	26
	3	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	2
	4	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1
	Total	236	98	20	3	0	357
Deucravacitinib 6 mg QD	0	381 (78.2)	99 (20.3)	6 (1.2)	1 (0.2)	0 (0.0)	487
	1	66 (28.3)	135 (57.9)	31 (13.3)	1 (0.4)	0 (0.0)	233
	2	2 (6.7)	16 (53.3)	7 (23.3)	4 (13.3)	1 (3.3)	30
	3	0 (0.0)	1 (25.0)	2 (50.0)	1 (25.0)	0 (0.0)	4
	4	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1
	Total	449	251	47	7	1	755
Apremilast 30 mg BID	0	210 (87.5)	29 (12.1)	1 (0.4)	0 (0.0)	0 (0.0)	240
	1	42 (40.4)	56 (53.8)	6 (5.8)	0 (0.0)	0 (0.0)	104
	2	2 (8.7)	12 (52.2)	7 (30.4)	2 (8.7)	0 (0.0)	23
	3	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	2
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	Total	254	97	16	2	0	369

Light pink shading indicates a shift of 1 grade; dark pink shading indicates a shift of >1 grade.
BID, twice daily; QD, once daily.

Changes in lipid parameters in patients treated with deucravacitinib continuously from baseline to Week 52

- Mean changes in total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides among patients treated with deucravacitinib continuously for 52 weeks were small and not clinically meaningful (**Figure 2**)
- The exposure-adjusted incidence rate (EAIR) for "blood cholesterol increased" as an adverse event over Weeks 0-52 was 0.2/100 person-years (PY) with deucravacitinib compared with 0.4/100 PY with placebo and 0 with apremilast
- The EAIR for "blood triglycerides increased" as an adverse event over Weeks 0-52 was 1.0/100 PY with deucravacitinib compared with 0.4/100 PY with placebo and 1.3/100 PY with apremilast
- No patient discontinued deucravacitinib due to a lipid-related adverse event

Figure 2. Change in lipid parameters among patients treated continuously with deucravacitinib during Weeks 0-52 (pooled POETYK PSO-1 and PSO-2)



[a]Total cholesterol = HDL + LDL + 20% triglycerides.
[b]The values presented here are limited to patients enrolled in POETYK PSO-1 and PSO-2 who received deucravacitinib continuously for 52 weeks. SOTYKTU™ (deucravacitinib) prescribing information notes that mean triglyceride levels increased by 10.3 mg/dL and by 9.1 mg/dL during the 16-week and 52-week treatment periods, respectively, in the combined population from the 2 studies. The label values were derived from all patients who were taking deucravacitinib at Week 16 or at Week 52 from both POETYK PSO-1 and PSO-2 studies. Some of the latter had received placebo or apremilast in a previous treatment period per the individual study designs.
HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; SE, standard error.

- Most patients treated with deucravacitinib continuously for 52 weeks maintained the same or shifted to a lower grade of hypercholesterolemia from baseline to Week 52 (**Table 5**)
  - There was one 2-grade increase in hypercholesterolemia from baseline to Week 52

Table 5. Shifts in grade of hypercholesterolemia among patients treated continuously with deucravacitinib during Weeks 0-52 (pooled POETYK PSO-1 and PSO-2)

Parameter	Baseline grade	Grade at Week 52, n (%)					Total patients
		0	1	2	3	4	
Deucravacitinib 6 mg QD	0	253 (80.8)	59 (18.8)	1 (0.3)	0 (0.0)	0 (0.0)	313
	1	45 (21.4)	161 (76.7)	4 (1.9)	0 (0.0)	0 (0.0)	210
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0
	Total	298	220	5	0	0	523

Light pink shading indicates a shift of 1 grade; dark pink shading indicates a shift of >1 grade.
QD, once daily.

- Most patients treated with deucravacitinib continuously for 52 weeks maintained the same or shifted to a lower grade of hypertriglyceridemia from baseline to Week 52 (**Table 6**)
  - Grade ≥3 hypertriglyceridemia events were rare and were limited to those with elevated triglycerides at baseline
  - Shifts >1 grade were observed in 1.9% of patients

Table 6. Shifts in grade of hypertriglyceridemia among patients treated continuously with deucravacitinib during Weeks 0-52 (pooled POETYK PSO-1 and PSO-2)

Parameter	Baseline grade	Grade at Week 52, n (%)					Total patients
		0	1	2	3	4	
Deucravacitinib 6 mg QD	0	241 (73.0)	84 (25.5)	5 (1.5)	0 (0.0)	0 (0.0)	330
	1	49 (29.9)	97 (59.1)	14 (8.5)	4 (2.4)	0 (0.0)	164
	2	1 (4.0)	10 (40.0)	12 (48.0)	1 (4.0)	1 (4.0)	25
	3	0 (0.0)	2 (66.7)	0 (0.0)	1 (33.3)	0 (0.0)	3
	4	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1
	Total	291	193	32	6	1	523

Light pink shading indicates a shift of 1 grade; dark pink shading indicates a shift of >1 grade.
QD, once daily.

Conclusions

- In the phase 3 POETYK PSO-1 and PSO-2 trials, mean changes in the lipid panel from baseline to Week 16 were minimal across the placebo, deucravacitinib, and apremilast groups, and none was clinically meaningful
  - A 10.3 mg/dL increase in mean triglyceride levels from a baseline mean of 146.6 mg/dL in the deucravacitinib group was accompanied by very few worsening shifts in hypertriglyceridemia >1 grade per CTCAE
- A large majority of patients treated continuously with deucravacitinib for 52 weeks maintained their baseline grade or shifted to a lower grade of hypercholesterolemia or hypertriglyceridemia at Week 52
  - Fewer than 2% of patients had worsening shifts >1 grade from baseline to Week 52
  - No patient discontinued deucravacitinib due to a lipid-related adverse event
- Clinical guidelines recommend diet and lifestyle optimization for most low-risk adults with fasting triglycerides ≥150 mg/dL and <500 mg/dL, with consideration of initiation or intensification of pharmacotherapy in those with persistent elevations and a calculated ASCVD risk ≥5%[9]
  - These guidelines would apply to most patients with moderate to severe plaque psoriasis due to the high incidence of hypertriglyceridemia/metabolic syndrome in these patients

References

1. Burke JR, et al. *Sci Trans Med*. 2019;11:eaaw1736. 2. SOTYKTU™ (deucravacitinib) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; September 2022. 3. Armstrong AW, et al. *J Am Acad Dermatol*. 2023;88:29-39. 4. Strober B, et al. *J Am Acad Dermatol*. 2023;88:40-51. 5. Elmets CA, et al. *J Am Acad Dermatol*. 2019;80:1073-1113. 6. Tekla M, et al. *J Am Acad Dermatol*. 2021;84:1329-1338. 7. Langan SM, et al. *J Invest Dermatol*. 2012;132:556-562. 8. Grundy SM, et al. *Circulation*. 2004;109:433-438. 9. Virani SS, et al. *J Am Coll Cardiol*. 2021;78:960-993.

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Email for Mark Lebwohl, MD: lebwohl@aol.com