Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 (TYK2) Inhibitor, Versus Placebo and Apremilast in Moderate to Severe Plaque Psoriasis: Onset of Action in the Phase 3 POETYK PSO-1 and PSO-2 Trials

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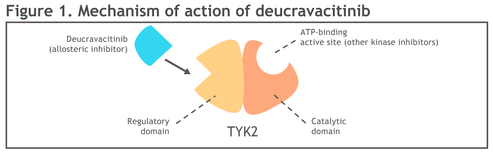
Background

- Deucravacitinib
  - Novel, oral, selective tyrosine kinase 2 (TYK2) inhibitor with a unique mechanism of action distinct from Janus kinase (JAK) 1/2/3 inhibitors[1]
    - Binds to the TYK2 regulatory domain with high selectivity and inhibits TYK2 via an allosteric mechanism (**Figure 1**)[1]
      - ≥100-fold greater selectivity for TYK2 vs JAK 1/3 and ≥2000-fold greater selectivity for TYK2 vs JAK 2[1,2]
    - Inhibits TYK2-mediated signaling of cytokines involved in psoriasis pathogenesis (eg, interleukin 23 [IL-23], IL-12, and Type I interferons)[1]
  - Previously demonstrated good efficacy and tolerability in Phase 2 trials in moderate to severe plaque psoriasis[3] and in active psoriatic arthritis[4]

Figure 1. Mechanism of action of deucravacitinib



ATP, adenosine triphosphate; TYK2, tyrosine kinase 2.

Objective

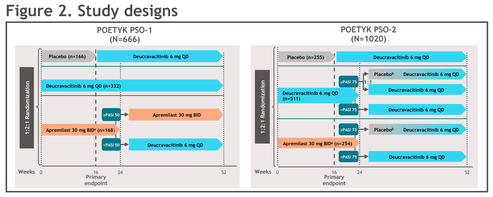
- To assess the onset of action of deucravacitinib using data from the Phase 3 POETYK PSO-1 and PSO-2 trials

Methods

Study designs

- POETYK PSO-1 (NCT03624127) and PSO-2 (NCT03611751) were double-blind, placebo-controlled, 52-week trials that randomized patients with moderate to severe plaque psoriasis (body surface area [BSA] involvement ≥10%, Psoriasis Area and Severity Index [PASI] ≥12, static Physician's Global Assessment [sPGA] score ≥3) 1:2:1 to placebo, deucravacitinib 6 mg once daily, or apremilast 30 mg twice daily (**Figure 2**)
  - Patients were stratified by geographic region, body weight, and prior biologic use
  - Patients receiving placebo switched to deucravacitinib at Week 16 and patients receiving apremilast failing to meet study-specific efficacy thresholds (≥50% reduction from baseline in PASI [PASI 50] score in PSO-1, ≥75% reduction from baseline in PASI [PASI 75] score in PSO-2) switched to deucravacitinib at Week 24
- Coprimary endpoints were the proportion of patients who achieved PASI 75 and sPGA score of 0 or 1 (0/1) responses vs placebo at Week 16

Figure 2. Study designs



[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 50, ≥50% reduction from baseline in Psoriasis Area and Severity Index; PASI 75, ≥75% reduction from baseline in PASI; QD, once daily.

Efficacy analyses

- Onset of action of deucravacitinib was evaluated by:
  - Determining mean change from baseline or percentage change from baseline, adjusted for baseline covariates, in continuous objective and patient-reported efficacy outcomes that are sensitive to change
  - Endpoints analyzed included PASI, BSA, sPGA×BSA, Psoriasis Symptoms and Signs Diary (PSSD) symptom score, and Dermatology Life Quality Index (DLQI) score at Weeks 1, 2, 4, 8, 12, and 16
- Proportions of patients achieving PASI 75 response, ≥90% reduction from baseline in PASI (PASI 90) response, sPGA 0/1, and DLQI 0/1 responses at these time points were also evaluated
- The analyses primarily focused on the onset of action of deucravacitinib vs placebo to help contextualize the outcomes to be expected in clinical practice

Results

Baseline patient demographics and disease characteristics

- Baseline patient demographics and disease characteristics, including PASI, PSSD symptom score, DLQI, BSA, and sPGA×BSA, were similar across treatment groups in both trials and representative of a population with moderate to severe plaque psoriasis (**Table 1**)

Table 1. Baseline patient demographics and disease characteristics

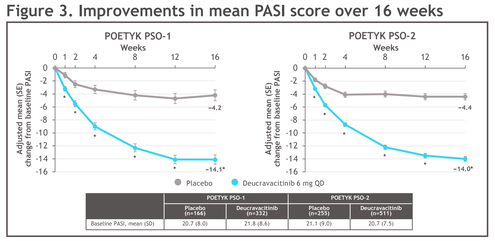
	POETYK PSO-1		POETYK PSO-2	
	Placebo (n=166)	Deucravacitinib (n=332)	Placebo (n=255)	Deucravacitinib (n=511)
Age, y, mean (SD)	47.9 (14.0)	45.9 (13.7)	47.3 (13.6)	46.9 (13.4)
Weight, kg, mean (SD)	89.1 (22.3)	87.9 (21.8)	91.5 (20.2)	92.3 (21.9)
Female, n (%)	53 (31.9)	102 (30.7)	74 (29.0)	175 (34.2)
Race, n (%)				
White	128 (77.1)	267 (80.4)	232 (91.0)	474 (92.8)
Asian	34 (20.5)	59 (17.8)	8 (3.1)	24 (4.7)
Other	4 (2.4)	6 (1.8)	15 (5.9)	13 (2.6)
Disease duration, y, mean (SD)	17.3 (12.8)	17.1 (12.4)	19.9 (12.8)	19.6 (12.9)
Prior systemic treatment use, n (%)				
Biologic	63 (38.0)	130 (39.2)	83 (32.5)	165 (32.3)
No prior systemic therapy	57 (34.3)	132 (39.8)	116 (45.5)	237 (46.4)
sPGA, n (%)				
3 = moderate	128 (77.1)	257 (77.4)	217 (85.1)	408 (79.8)
4 = severe	37 (22.3)	75 (22.6)	38 (14.9)	103 (20.2)
PASI, mean (SD)	20.7 (8.0)	21.8 (8.6)	21.1 (9.0)	20.7 (7.5)
BSA, %, mean (SD)	25.3 (16.9)	26.6 (15.9)	25.3 (15.7)	26.3 (15.8)
sPGAxBSA, mean (SD)	82.1 (57.3)	86.9 (56.1)	81.1 (56.3)	85.0 (54.6)
PSSD symptom score,[a] mean (SD)	51.4 (26.8)	51.7 (25.2)	50.1 (24.8)	52.3 (26.3)
DLQI, mean (SD)	11.4 (6.6)	12.0 (6.7)	11.8 (6.8)	11.8 (6.5)

[a]PSSD symptom score is the average severity of 5 symptoms (itch, pain, burning, stinging, and skin tightness) over the previous 24 h scored on a scale ranging from 0 (absent) to 100 (worst).
BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptoms and Signs Diary; sPGA, static Physician's Global Assessment.

Efficacy

- Deucravacitinib treatment was associated with significantly larger mean changes from baseline in PASI vs placebo as early as Week 1 in both trials (*P*<0.0001; **Figure 3**)
- Significantly larger mean percentage changes from baseline in PASI were seen in the deucravacitinib group vs the placebo group as early as Week 1 in both trials (*P*<0.001; **Figure 4**)
  - Approximately 40% improvement was seen by Week 4 in the deucravacitinib group in both trials

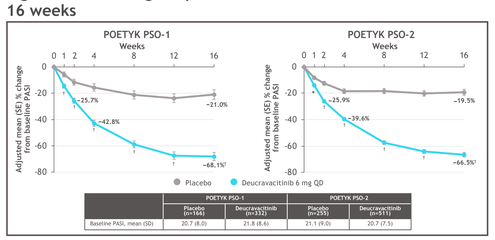
Figure 3. Improvements in mean PASI score over 16 weeks



	POETYK PSO-1		POETYK PSO-2	
	Placebo (n=166)	Deucravacitinib (n=332)	Placebo (n=255)	Deucravacitinib (n=511)
Baseline PASI, mean (SD)	20.7 (8.0)	21.8 (8.6)	21.1 (9.0)	20.7 (7.5)

*P<0.0001 vs placebo.
Modified baseline observation carried forward was used to impute missing data.
PASI, Psoriasis Area and Severity Index; QD, once daily.

Figure 4. Percentage improvements in mean PASI score over 16 weeks

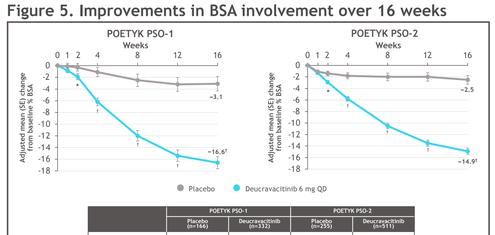


	POETYK PSO-1		POETYK PSO-2	
	Placebo (n=166)	Deucravacitinib (n=332)	Placebo (n=255)	Deucravacitinib (n=511)
Baseline PASI, mean (SD)	20.7 (8.0)	21.8 (8.6)	21.1 (9.0)	20.7 (7.5)

*P<0.001 vs placebo. †P<0.0001 vs placebo.
Modified baseline observation carried forward was used to impute missing data.
PASI, Psoriasis Area and Severity Index; QD, once daily.

- Significantly larger mean changes from baseline in BSA percentage involvement were observed in the deucravacitinib group vs the placebo group by Week 2 (*P*<0.01; **Figure 5**)
- Treatment with deucravacitinib resulted in significantly larger mean changes from baseline vs placebo in sPGA×BSA by Week 1 in both trials (*P*<0.01; **Figure 6**)

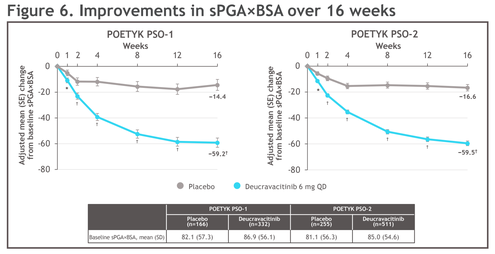
Figure 5. Improvements in BSA involvement over 16 weeks



	POETYK PSO-1		POETYK PSO-2	
	Placebo (n=166)	Deucravacitinib (n=332)	Placebo (n=255)	Deucravacitinib (n=511)
Baseline BSA, %, mean (SD)	25.3 (16.9)	26.6 (15.9)	25.3 (15.7)	26.3 (15.8)

*P<0.01 vs placebo. †P<0.0001 vs placebo.
Modified baseline observation carried forward was used to impute missing data.
BSA, body surface area; QD, once daily.

Figure 6. Improvements in sPGA×BSA over 16 weeks

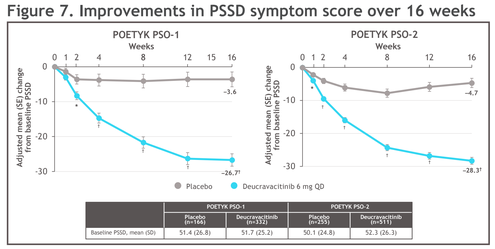


	POETYK PSO-1		POETYK PSO-2	
	Placebo (n=166)	Deucravacitinib (n=332)	Placebo (n=255)	Deucravacitinib (n=511)
Baseline sPGA×BSA, mean (SD)	82.1 (57.3)	86.9 (56.1)	81.1 (56.3)	85.0 (54.6)

*P<0.01 vs placebo. †P<0.0001 vs placebo.
Modified baseline observation carried forward was used to impute missing data.
BSA, body surface area; QD, once daily; sPGA, static Physician's Global Assessment.

- Deucravacitinib-treated individuals experienced significantly larger mean changes from baseline in PSSD symptom score vs placebo by Week 2 in PSO-1 and as early as Week 1 in PSO-2 (*P*<0.01 for both; **Figure 7**)

Figure 7. Improvements in PSSD symptom score over 16 weeks

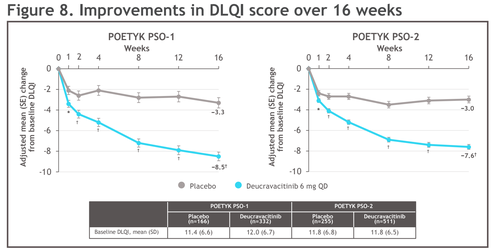


	POETYK PSO-1		POETYK PSO-2	
	Placebo (n=166)	Deucravacitinib (n=332)	Placebo (n=255)	Deucravacitinib (n=511)
Baseline PSSD, mean (SD)	51.4 (26.8)	51.7 (25.2)	50.1 (24.8)	52.3 (26.3)

*P<0.01 vs placebo. †P<0.0001 vs placebo.
Modified baseline observation carried forward was used to impute missing data.
PSSD, Psoriasis Symptoms and Signs Diary; QD, once daily.

- Significantly larger mean changes from baseline in DLQI were seen with the deucravacitinib group vs the placebo group by Week 1 (*P*<0.05) in both trials (**Figure 8**)

Figure 8. Improvements in DLQI score over 16 weeks

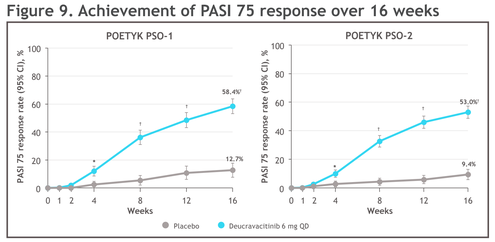


	POETYK PSO-1		POETYK PSO-2	
	Placebo (n=166)	Deucravacitinib (n=332)	Placebo (n=255)	Deucravacitinib (n=511)
Baseline DLQI, mean (SD)	11.4 (6.6)	12.0 (6.7)	11.8 (6.8)	11.8 (6.5)

*P<0.05 vs placebo. †P<0.0001 vs placebo.
Modified baseline observation carried forward was used to impute missing data.
DLQI, Dermatology Life Quality Index; QD, once daily.

- In both trials, significantly higher proportions of patients achieved PASI 75 responses in the deucravacitinib group vs the placebo group by Week 4 (*P*<0.001; **Figure 9**)

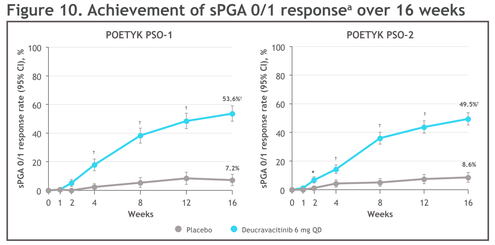
Figure 9. Achievement of PASI 75 response over 16 weeks



*P<0.001 vs placebo. †P<0.0001 vs placebo.
Modified baseline observation carried forward was used to impute missing data.
PASI 75, ≥75% reduction from baseline in Psoriasis Area and Severity Index; QD, once daily.

- The proportion of patients achieving sPGA 0/1 response was significantly higher in the deucravacitinib group vs the placebo group by Week 4 in PSO-1 (*P*<0.0001) and by Week 2 in PSO-2 (*P*<0.001; **Figure 10**)

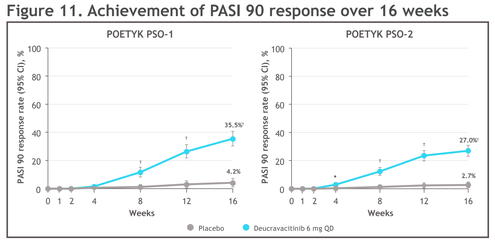
Figure 10. Achievement of sPGA 0/1 response[a] over 16 weeks



[a]Response defined as sPGA score of 0 or 1 with ≥2-point improvement from baseline.
*P<0.001 vs placebo. †P<0.0001 vs placebo.
Nonresponder imputation was used to impute missing data.
sPGA 0/1, static Physician's Global Assessment score of 0 or 1; QD, once daily.

- PASI 90 response rates were significantly higher in the deucravacitinib group vs the placebo group by Week 8 in PSO-1 (*P*<0.0001) and Week 4 in PSO-2 (*P*<0.05; **Figure 11**)

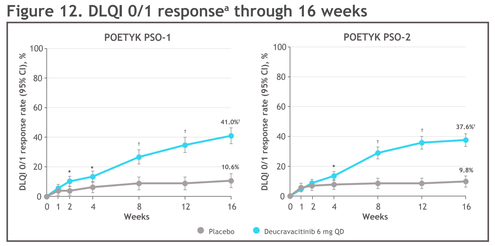
Figure 11. Achievement of PASI 90 response over 16 weeks



*P<0.05 vs placebo. †P<0.0001 vs placebo.
Nonresponder imputation was used to impute missing data.
PASI 90, ≥90% reduction from baseline in Psoriasis Area and Severity Index; QD, once daily.

- The proportion of patients achieving DLQI 0/1 response was significantly higher in the deucravacitinib group vs the placebo group by Week 2 in PSO-1 and by Week 4 in PSO-2 (**Figure 12**)

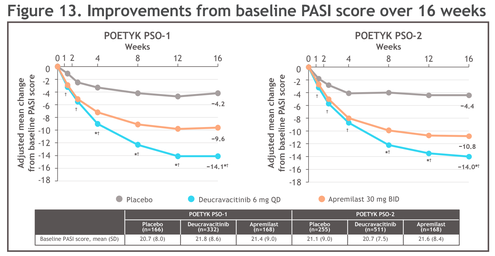
Figure 12. DLQI 0/1 response[a] through 16 weeks



[a]Among patients with baseline DLQI score ≥2.
*P<0.05 vs placebo. †P<0.0001 vs placebo.
Nonresponder imputation was used to impute missing data.
DLQI 0/1, Dermatology Life Quality Index score of 0 or 1; QD, once daily.

- In both trials, the superiority of deucravacitinib vs apremilast was observed as early as Week 4 for change from baseline in PASI (**Figure 13**) and all other endpoints assessed (data not shown)

Figure 13. Improvements from baseline PASI score over 16 weeks



	POETYK PSO-1			POETYK PSO-2		
	Placebo (n=166)	Deucravacitinib (n=332)	Apremilast (n=168)	Placebo (n=255)	Deucravacitinib (n=511)	Apremilast (n=168)
Baseline PASI score, mean (SD)	20.7 (8.0)	21.8 (8.6)	21.4 (9.0)	21.1 (9.0)	20.7 (7.5)	21.6 (8.4)

*P≤0.0019 vs apremilast. †P<0.0001 vs placebo.
Modified baseline observation carried forward was used to impute missing data.
BID, twice daily; PASI, Psoriasis Area and Severity Index; QD, once daily.

Conclusions

- In the Phase 3 POETYK PSO-1 and PSO-2 trials, oral deucravacitinib had a rapid onset of action and improved objective and patient-reported efficacy outcomes compared with placebo as early as Week 1
- These findings suggest that deucravacitinib treatment provides rapid relief of signs and symptoms in patients with moderate to severe plaque psoriasis
- Taken together with the primary results from the Phase 3 POETYK trials, deucravacitinib, a once-daily, oral, selective TYK2 inhibitor, has the potential to become a valuable treatment of choice and new standard of care for patients with moderate to severe plaque psoriasis

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Relationships and Activities

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