Impact of oral, selective, allosteric tyrosine kinase 2 inhibitor, deucravacitinib, on psoriasis in patients with active psoriatic arthritis: results from a phase 2 trial

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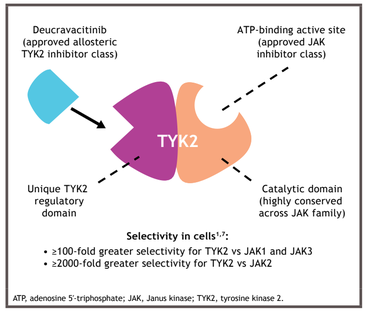
Synopsis

- Tyrosine kinase 2 (TYK2) is an intracellular enzyme that mediates signaling of cytokines (eg, interleukin [IL]-23, IL-12, Type I interferons [IFNs])[1]
  - IL-23 and Type I IFNs are involved in plaque psoriasis (PsO) and psoriatic arthritis (PsA) 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 PsO 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 oral drugs
- Deucravacitinib has shown superiority to apremilast and placebo in a variety of PsO disease activity measures in two phase 3 trials (POETYK PSO-1 and POETYK PSO-2) in patients with moderate to severe PsO[8,9]
- Deucravacitinib was efficacious on multiple measures of arthritis severity compared with placebo in a phase 2 trial in patients with active PsA[10]
  - Patients in the phase 2 PsA trial were required to have ≥1 PsO lesion (≥2 cm); at baseline, >80% of patients had PsO with ≥3% body surface area (BSA) involvement
  - In patients with BSA ≥3% at baseline, a greater proportion of patients achieved ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75) with deucravacitinib treatment (6 mg once daily [QD]: 42.4%, $P = 0.01$; 12 mg QD: 59.6%, $P < 0.0001$) compared with placebo (20.4%) at Week 16

Figure 1. Unique mechanism of action of deucravacitinib



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

Objective

- This post hoc analysis further evaluated the impact of deucravacitinib on PsO in patients with PsA in the phase 2 PsA trial

Methods

Phase 2 PsA study design

- The phase 2, double-blind PsA trial (NCT03881059) enrolled patients with active PsA: PsA diagnosis ≥6 months, meeting Classification Criteria for Psoriatic Arthritis (CASPAR) criteria, and having active disease: ≥3 tender and ≥3 swollen joints, C-reactive protein ≥3 mg/L, and ≥1 PsO lesion (≥2 cm)
  - 203 patients were randomized 1:1:1 to oral placebo, deucravacitinib 6 mg QD, or deucravacitinib 12 mg QD
  - After Week 16 (Part A), patients could enroll in an optional, double-blind, long-term extension trial until Week 52 (Part B)
    - Patients receiving deucravacitinib who achieved minimal disease activity (MDA) at Week 16 continued deucravacitinib treatment, and those who did not achieve MDA were switched to ustekinumab

Phase 3 PsO study design

- The 52-week, phase 3, double-blind PsO trial, POETYK PSO-1 (NCT03624127), enrolled patients with a diagnosis of moderate to severe PsO with a baseline PASI ≥12, static Physician Global Assessment ≥3, and BSA ≥10%
  - 666 patients were randomized 1:2:1 to oral placebo, deucravacitinib 6 mg QD, or apremilast 30 mg twice daily

Study endpoints

- Measurements of PsO disease activity, including mean BSA involvement, mean PASI score, and achievement of treat-to-target PASI and BSA thresholds were evaluated in this analysis
- All *P* values shown are nominal

Results

Baseline patient demographics and disease characteristics

- Baseline patient demographics and baseline disease characteristics were generally similar across treatment groups in the phase 2 trial (**Table 1**)

Table 1. Baseline patient demographics and disease characteristics in the phase 2 PsA trial

Parameter	Placebo (n = 66)	Deucravacitinib 6 mg QD (n = 70)	Deucravacitinib 12 mg QD (n = 67)
Age, mean, y	48.5	50.5	50.5
Female, n (%)	40 (60.6)	30 (42.9)	34 (50.7)
Body mass index, mean, kg/m²	31.2	29.6	30.3
Disease duration since diagnosis, median (range), y	4.5 (0.6-22.9)	5.3 (0.1-42.8)	3.8 (0.6-27.7)
PASDAS, mean (SD)	6.2 (0.9)	6.4 (0.9)	6.1 (0.9)
DAPSA, mean (SD)	42.6 (20.1)	45.0 (17.5)	45.1 (21.0)
Oral steroid use at baseline, n (%)	12 (18.2)	7 (10.0)	6 (9.0)
Mean daily dose, mg	4.4	3.7	3.5
csDMARD use at baseline, n (%)	44 (66.7)	45 (64.3)	43 (64.2)
Methotrexate use at baseline, n (%)	39 (59.1)	35 (50.0)	37 (55.2)
Mean weekly dose, mg	16.7	16.4	16.5
Prior TNF inhibitor use, n (%)	11 (16.7)	12 (17.1)	9 (13.4)

csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA, Disease Activity Index for Psoriatic Arthritis Score; PASDAS, Psoriatic Arthritis Disease Activity Score; PsA, psoriatic arthritis; QD, once daily; SD, standard deviation; TNF, tumor necrosis factor.

- Baseline PsO characteristics were generally comparable across treatment groups, with most patients (≥74%) having BSA ≥3% to <10% or PASI ≤12 (**Table 2**)

Table 2. Baseline PsO characteristics in the phase 2 PsA trial

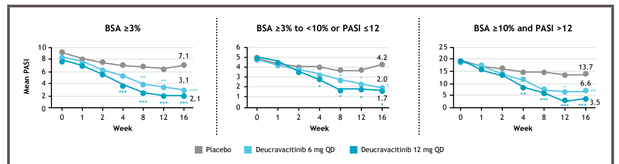
Parameter		Placebo (n = 66)	Deucravacitinib 6 mg QD (n = 70)	Deucravacitinib 12 mg QD (n = 67)
BSA severity	BSA <3%, n (%)	9 (13.6)	11 (15.7)	14 (20.9)
	BSA ≥3% - <10%, n (%)	32 (48.5)	37 (52.8)	29 (43.3)
	BSA ≥10%, n (%)	22 (33.3)	22 (31.4)	23 (34.3)
PASI severity	PASI ≤5, n (%)	30 (45.5)	33 (47.1)	29 (43.3)
	PASI >5 - ≤12, n (%)	18 (27.3)	23 (32.8)	30 (44.8)
	PASI >12, n (%)	15 (22.7)	14 (20.0)	7 (10.4)
	Not reported, n (%)	3 (4.5)	0	1 (1.5)
BSA ≥3%	n (%)	54 (81.8)	59 (84.3)	52 (77.6)
	PASI, mean (SD)	9.1 (7.4)	8.5 (6.8)	7.9 (6.0)
BSA ≥3% to <10% or PASI ≤12	n (%)	49 (74.2)	57 (81.4)	59 (88.1)
	PASI, mean (SD)	4.9 (3.3)	4.8 (3.2)	5.0 (3.2)
BSA ≥10% and PASI >12	n (%)	14 (21.2)	13 (18.6)	7 (10.4)
	PASI, mean (SD)	19.2 (6.3)	18.5 (6.8)	19.2 (8.5)

BSA, body surface area; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsO, plaque psoriasis; QD, once daily; SD, standard deviation.

Improvements in PsO as measured by PASI

- Absolute mean PASI scores decreased over 16 weeks and were greater with deucravacitinib vs placebo (**Figure 2**)
  - Differences in the deucravacitinib treatment group compared with the placebo group were observed as early as Week 4 regardless of PsO severity

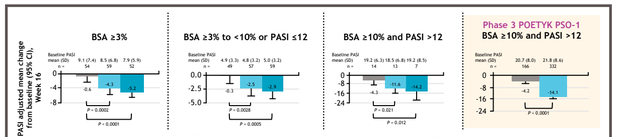
Figure 2. Absolute mean PASI over time by PsO severity at baseline



*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ mean change from baseline nominal *P* values vs placebo. Modified baseline observation carried forward method was used to handle missing data. Adjusted means and *P* values were derived from an analysis of covariance model with factors for body weight and TNFi use and the baseline value as a covariate.
BSA, body surface area; PASI, Psoriasis Area and Severity Index; PsO, plaque psoriasis; QD, once daily; TNFi, tumor necrosis factor inhibitor.

- At Week 16, significant decreases from baseline in mean PASI score were observed with deucravacitinib treatment regardless of PsO severity (**Figure 3**)
  - These significant changes in PASI were observed in the baseline BSA ≥3% to <10% or PASI ≤12 PsO population, even with very low baseline PASI scores
  - Improvements in PASI at Week 16 in patients with baseline BSA ≥10% and PASI >12 were comparable in the phase 2 PsA trial (6 mg QD and 12 mg QD) and in the phase 3 POETYK PSO-1 trial (6 mg QD)

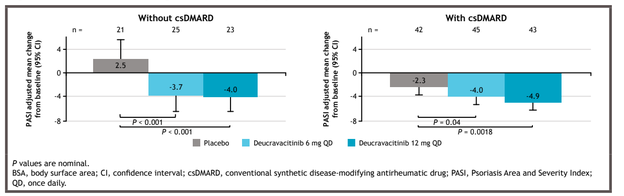
Figure 3. PASI mean change from baseline at Week 16 in phase 2 PsA and phase 3 PsO POETYK PSO-1 trials



P values are nominal. *Modified* baseline observation carried forward method was used to handle missing data; adjusted means, 95% CI, and *P* values were derived from an analysis of covariance model with factors for phase 2 PsA (body weight and TNFi use) and phase 3 PsO POETYK PSO-1 (geographic region, body weight, and prior biologic use) and the baseline value as a covariate.
BSA, body surface area; CI, confidence interval; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsO, plaque psoriasis; QD, once daily; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

- Significant decreases from baseline in PASI were observed with deucravacitinib treatment vs placebo in both patients without background conventional synthetic disease-modifying antirheumatic drug (csDMARD) use and those with csDMARD use (**Figure 4**)
- In patients with baseline BSA ≥10% and PASI >12, a significantly greater proportion of patients achieved PASI 75 with deucravacitinib treatment compared with placebo in both the phase 2 PsA trial (deucravacitinib 6 mg: 61.5%, 12 mg: 71.4% vs placebo: 7.1%; $P < 0.01$ for both) and phase 3 POETYK PSO-1 trial (deucravacitinib 6 mg: 58.4% vs placebo: 12.7%, $P < 0.0001$)

Figure 4. PASI mean change at Week 16 by csDMARD use (BSA ≥3% at baseline)

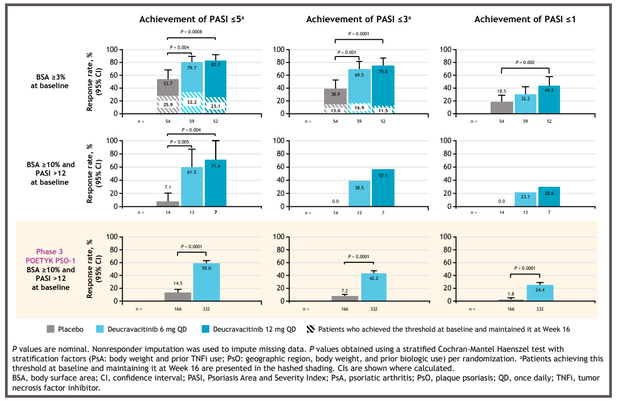


P values are nominal.
BSA, body surface area; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; PASI, Psoriasis Area and Severity Index; QD, once daily.

Improvements in PsO as measured by achievement of disease thresholds

- At Week 16, a greater proportion of patients treated with deucravacitinib compared with placebo achieved treat-to-target PASI thresholds of ≤5, ≤3, and ≤1 both in patients with baseline BSA ≥3% and patients with baseline BSA ≥10% and PASI >12 (**Figure 5**)
  - The achievement of PASI thresholds at Week 16 in patients with baseline BSA ≥10% and PASI >12 were comparable in the phase 2 PsA trial (6 mg QD and 12 mg QD) and in the phase 3 POETYK PSO-1 trial (6 mg QD)

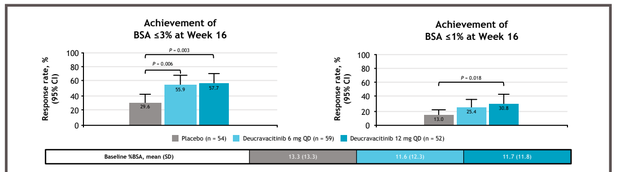
Figure 5. Achievement of PASI thresholds at Week 16 in phase 2 PsA and phase 3 PsO POETYK PSO-1 trials



P values are nominal. Nonresponder imputation was used to impute missing data. *P* values obtained using a stratified Cochran-Mantel Haenszel test with stratification factors (PsA: body weight and prior TNFi use; PsO: geographic region, body weight, and prior biologic use) per randomization. [a]Patients achieving this threshold at baseline and maintaining it at Week 16 are presented in the hashed shading. CIs are shown where calculated.
BSA, body surface area; CI, confidence interval; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsO, plaque psoriasis; QD, once daily; TNFi, tumor necrosis factor inhibitor.

- In patients with baseline BSA ≥3%, a greater proportion of patients treated with deucravacitinib vs placebo achieved a BSA ≤3% and BSA ≤1% at Week 16 (**Figure 6**)

Figure 6. Achievement of BSA thresholds and mean change in BSA over time (in patients with BSA ≥3% at baseline)

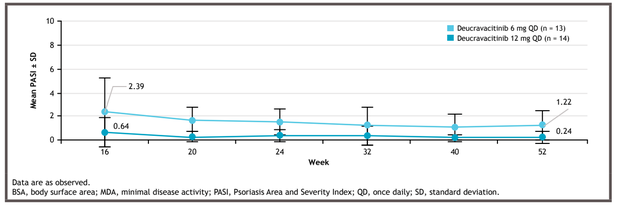


P value obtained using a stratified Cochran-Mantel Haenszel test with stratification factors (body weight and prior TNFi use) per randomization.
BSA, body surface area; CI, confidence interval; QD, once daily; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

Improvements in PsO through Week 52

- In patients with baseline BSA ≥3%, decreases in mean PASI score at Week 16 were maintained through 52 weeks in patients who continued treatment with deucravacitinib after achieving MDA (**Figure 7**)

Figure 7. Mean PASI scores in patients who achieved MDA at Week 16 and remained on deucravacitinib: Weeks 16 through 52 (BSA ≥3% at baseline)



Data are as observed.
BSA, body surface area; MDA, minimal disease activity; PASI, Psoriasis Area and Severity Index; QD, once daily; SD, standard deviation.

Conclusions

- Deucravacitinib was efficacious compared with placebo in improving PsO in patients with PsA
- Treatment with deucravacitinib significantly improved PsO in patients with PsA, regardless of baseline PsO severity and background csDMARD use
- Improvement in the subgroup of patients with baseline BSA ≥10% and PASI >12 in the PsA trial was comparable to that observed in the phase 3 POETYK PSO-1 trial in patients with baseline BSA ≥10% and PASI >12
- A greater number of patients treated with deucravacitinib achieved treat-to-target absolute PASI and BSA thresholds compared with patients receiving placebo
- Decreases in PASI score at Week 16 were maintained up to Week 52 in patients who continued treatment with deucravacitinib after achieving MDA

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