Deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 inhibitor, in moderate to severe plaque psoriasis: absolute PASI outcomes over 52 weeks in the phase 3 POETYK PSO-1 trial

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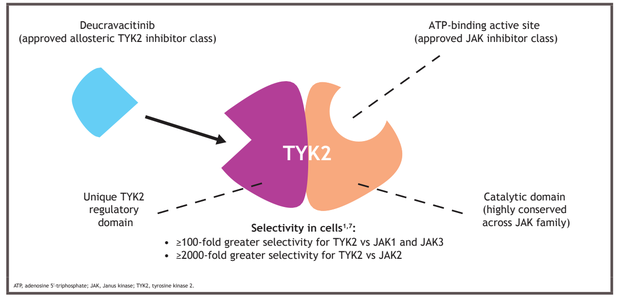
Synopsis

- Tyrosine kinase 2 (TYK2) is an intracellular enzyme that mediates signaling of cytokines (eg, interleukin-23, Type I interferons) that are involved in psoriasis pathogenesis[1]
- Deucravacitinib, an oral, selective, allosteric TYK2 inhibitor, is approved in the US, EU, Japan, 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 regulatory domain of TYK2 rather than to the catalytic domain where Janus kinase (JAK) 1,2,3 inhibitors bind[1,7] (**Figure 1**), representing the first in a new class of small molecules
- In the global, phase 3 POETYK PSO-1 (NCT03624127) and POETYK PSO-2 (NCT03611751) trials, deucravacitinib was significantly more effective compared with placebo and apremilast in patients with moderate to severe plaque psoriasis[8,9]:
  - In both phase 3 trials, significantly greater improvements from baseline in Psoriasis Area and Severity Index (PASI) were achieved with deucravacitinib vs placebo at Week 16 and vs apremilast at Weeks 16 and 24[10]
  - Greater proportions of patients receiving deucravacitinib achieved treat-to-target outcomes of absolute PASI ≤1, ≤2, and ≤5 compared with placebo (Week 16) or apremilast (Week 24) in the pooled analysis[10]

Figure 1. Mechanism of action of deucravacitinib



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

- Treatment outcomes for plaque psoriasis based on the absolute PASI scores achieved are indicative of a patient's disease severity at the time of analysis[11]
  - Achieving absolute PASI thresholds may be more clinically meaningful and relevant in clinical settings than achieving a set percent reduction from baseline in PASI captured by scores such as PASI 75 (≥75% reduction from baseline in PASI)[11,12]
  - Data suggest attainment of an absolute PASI ≤2 represents meaningful improvements in clinical and health-related quality-of-life outcomes and a relevant treat-to-target measure in the real-world setting[11,12]
  - A treat-to-target expert panel has recommended an absolute PASI ≤3 as a treatment goal for psoriasis[13]

Objectives

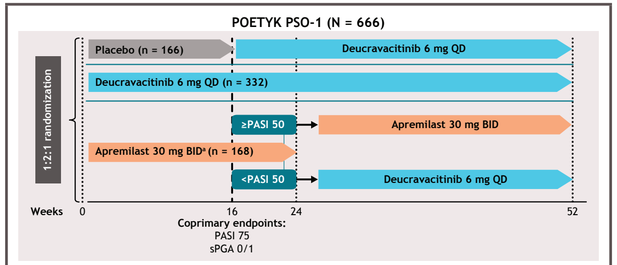
- To compare the efficacy of deucravacitinib vs placebo and apremilast over 16 weeks and apremilast over 24 weeks in mean PASI improvements from baseline and to evaluate absolute PASI thresholds with continuous deucravacitinib treatment from Day 1 through 52 weeks in POETYK PSO-1, which permitted continuous therapy with deucravacitinib for 52 weeks

Methods

Study design

- POETYK PSO-1 was a global, 52-week, phase 3, double-blind trial that randomized patients with moderate to severe plaque psoriasis 1:2:1 to oral placebo, deucravacitinib 6 mg once daily (QD), or apremilast 30 mg twice daily (BID) (**Figure 2**)
- Key eligibility criteria included the following:
  - Age ≥18 years
  - Diagnosis of moderate to severe plaque psoriasis
    - Baseline PASI ≥12, static Physician Global Assessment (sPGA) ≥3, and body surface area (BSA) involvement ≥10%
- Randomization was stratified by geographic region, body weight, and previous biologic use

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; PASI 75, ≥75% reduction from baseline in PASI; QD, once daily; sPGA 0/1, static Physician Global Assessment score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline.

Outcomes

- Mean percent change from baseline in PASI scores over time was determined using a modified baseline-observation-carried-forward (mBOCF) approach
  - The baseline observation was carried forward for patients who discontinued treatment due to lack of efficacy or adverse events
- The proportions of patients achieving absolute PASI thresholds of ≤1, ≤2, ≤3, ≤4, and ≤5 were determined using nonresponder imputation (NRI)
- Outcomes were compared between the deucravacitinib and apremilast groups at Week 24:
  - Percent change from baseline in PASI used an analysis of covariance model with factors for geographic region, body weight, and prior biologic use and the baseline value as a covariate
  - PASI threshold response rates were compared using a Cochran-Mantel-Haenszel test with stratification factors for geographic region, body weight, and prior biologic use
- Percent change from baseline in PASI and PASI thresholds was reported for the deucravacitinib group through Week 52

Results

Baseline patient demographics and disease characteristics

- Mean baseline PASI was similar across treatment groups (**Table 1**)

Table 1. Baseline patient demographics and disease characteristics

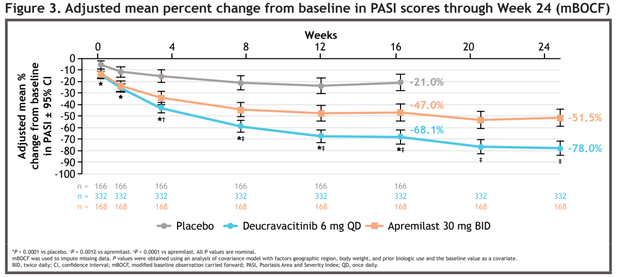
Parameter	Placebo (n = 166)	Deucravacitinib (n = 332)	Apremilast (n = 168)
Age, mean (SD), y	47.9 (14.0)	45.9 (13.7)	44.7 (12.1)
Weight, mean (SD), kg	89.1 (22.3)	87.9 (21.8)	87.5 (21.1)
Female, n (%)	53 (31.9)	102 (30.7)	58 (34.5)
Race, n (%)			
White	128 (77.1)	267 (80.4)	139 (82.7)
Asian	34 (20.5)	59 (17.8)	28 (16.7)
Other	4 (2.4)	6 (1.8)	1 (0.6)
Disease duration, mean (SD), y	17.3 (12.8)	17.1 (12.4)	17.7 (11.8)
Prior systemic therapy, n (%)			
Biologic	63 (38.0)	130 (39.2)	66 (39.3)
No prior systemic therapy	57 (34.3)	132 (39.8)	59 (35.1)
PASI score, mean (SD)	20.7 (8.0)	21.8 (8.6)	21.4 (9.0)
sPGA score, n (%)			
3 (moderate)	128 (77.1)	257 (77.4)	139 (82.7)
4 (severe)	37 (22.3)	75 (22.6)	29 (17.3)
BSA involvement, mean (SD), %	25.3 (16.9)	26.6 (15.9)	26.6 (16.1)
PSSD symptom score, mean (SD)	51.4 (26.8)	51.7 (25.2)	56.2 (25.2)
DLQI score, mean (SD)	11.4 (6.6)	12.0 (6.7)	12.4 (6.8)

BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptoms and Signs Diary; SD, standard deviation; sPGA, static Physician Global Assessment.

Mean percent change from baseline in PASI scores

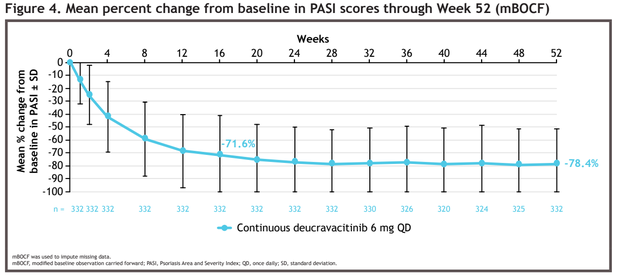
- Patients treated with deucravacitinib had significantly greater mean reduction from baseline in PASI vs placebo (Week 16: -68.1% vs -21.0%; $P < 0.0001$) and vs apremilast (Week 16: -68.1% vs -47.0%; Week 24: -78.0% vs -51.5%; $P < 0.0001$ for both; **Figure 3**)
  - Improvements with deucravacitinib compared with apremilast were seen as early as Week 4 and compared with placebo as early as Week 1
- Patients treated with continuous deucravacitinib maintained mean reduction in PASI scores through Week 52 (-78.4%) (**Figure 4**)

Figure 3. Adjusted mean percent change from baseline in PASI scores through Week 24 (mBOCF)



*P < 0.0001 vs placebo. †P = 0.0012 vs apremilast. ‡P < 0.0001 vs apremilast. All P values are nominal.
mBOCF was used to impute missing data. P values were obtained using an analysis of covariance model with factors geographic region, body weight, and prior biologic use and the baseline value as a covariate.
BID, twice daily; CI, confidence interval; mBOCF, modified baseline observation carried forward; PASI, Psoriasis Area and Severity Index; QD, once daily.

Figure 4. Mean percent change from baseline in PASI scores through Week 52 (mBOCF)

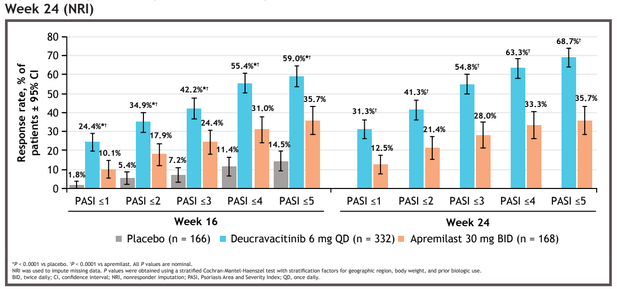


mBOCF was used to impute missing data.
mBOCF, modified baseline observation carried forward; PASI, Psoriasis Area and Severity Index; QD, once daily; SD, standard deviation.

Achievement of absolute PASI thresholds

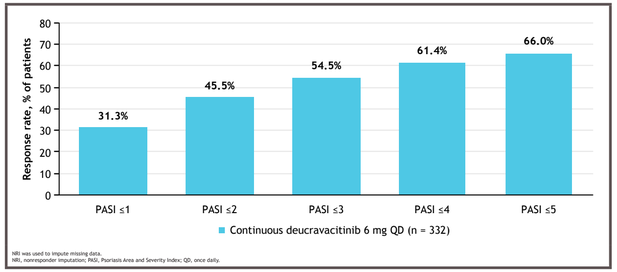
- Significantly higher proportions of patients treated with deucravacitinib achieved absolute PASI thresholds of ≤1, ≤2, ≤3, ≤4, and ≤5 vs placebo (Week 16) and apremilast (Week 16 and Week 24) (**Figure 5**)
- Response rates were maintained through Week 52 with continuous deucravacitinib treatment (**Figure 6**)

Figure 5. Proportion of patients achieving different absolute PASI thresholds at Week 16 and at Week 24 (NRI)



*P < 0.0001 vs placebo. †P < 0.0001 vs apremilast. All P values are nominal.
NRI was used to impute missing data. P values were obtained using a stratified Cochran-Mantel-Haenszel test with stratification factors for geographic region, body weight, and prior biologic use.
BID, twice daily; CI, confidence interval; NRI, nonresponder imputation; PASI, Psoriasis Area and Severity Index; QD, once daily.

Figure 6. Proportion of patients achieving different absolute PASI thresholds at Week 52 (NRI)



NRI was used to impute missing data.
NRI, nonresponder imputation; PASI, Psoriasis Area and Severity Index; QD, once daily.

Conclusions

- In POETYK PSO-1, patients with moderate to severe plaque psoriasis treated with deucravacitinib achieved clinically meaningful and treat-to-target absolute PASI outcomes that were superior to placebo over 16 weeks and apremilast over 24 weeks and maintained through 52 weeks
  - Significantly greater improvements from baseline PASI were achieved with deucravacitinib treatment vs placebo and apremilast at Week 16 and vs apremilast at Week 24, and these improvements were maintained through Week 52
  - Significantly higher proportions of patients treated with deucravacitinib achieved treat-to-target thresholds of absolute PASI ≤1, ≤2, ≤3, ≤4, and ≤5 vs placebo (Week 16) and apremilast (Week 16 and Week 24)
  - Patients receiving continuous deucravacitinib maintained absolute PASI ≤1, ≤2, ≤3, ≤4, and ≤5 at Week 52
- These findings suggest that deucravacitinib, an oral, once-daily drug, has the potential to become a treatment of choice for patients with moderate to severe plaque psoriasis

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