Deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 inhibitor, in plaque psoriasis: 3-year Psoriasis Area and Severity Index (PASI) outcomes in the long-term extension of the phase 3 POETYK PSO-1 and PSO-2 trials

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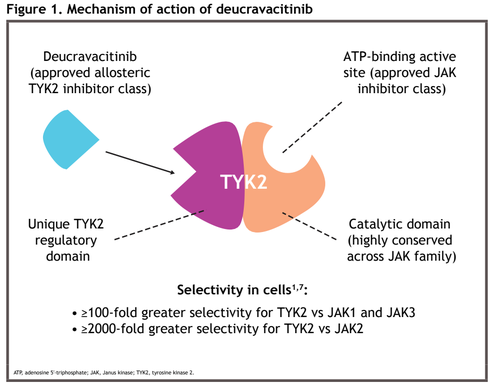
Background

- Tyrosine kinase 2 (TYK2) is an intracellular enzyme that mediates signaling of select inflammatory cytokines (eg, interleukin [IL]-23, IL-12, Type I interferons [IFNs])[1]
  - IL-23 and Type I IFNs are involved in psoriasis 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 plaque psoriasis who are candidates for systemic therapy[2,6]
- Deucravacitinib uniquely binds to the TYK2 regulatory domain rather than to the catalytic domain where Janus kinase (JAK) 1,2,3 inhibitors bind[1,7] (**Figure 1**), driving its selectivity for TYK2 and representing the first in a new class of oral drugs

Figure 1. Mechanism of action of deucravacitinib



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

- Two phase 3 trials, POETYK PSO-1 and PSO-2, demonstrated that in patients with moderate to severe plaque psoriasis:
  - Deucravacitinib (6 mg once daily [QD]) was significantly more efficacious than placebo and apremilast at Week 16 based on the coprimary endpoints of ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75) and static Physician Global Assessment score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline (sPGA 0/1)[8,9]
  - The drug was well tolerated[8,9]
  - Clinical responses were maintained through Week 52 in patients who received continuous deucravacitinib treatment from baseline[10]
- Patients treated with deucravacitinib could continue on to the POETYK long-term extension (LTE) trial and receive open-label deucravacitinib 6 mg QD
  - Data have been previously presented demonstrating maintenance of long-term efficacy responses and consistent safety profile for a total of 3 years (Week 148; data cutoff, June 15, 2022) of continuous deucravacitinib treatment[11]
- The standard efficacy outcome measure of PASI 75 is inclusive of all improvements from baseline ≥75% (ie, ≥75% to 100%)
  - It may be beneficial to show more granularity of PASI 75 responses, such as improvements in nonoverlapping 5% increments within PASI 75

Objectives

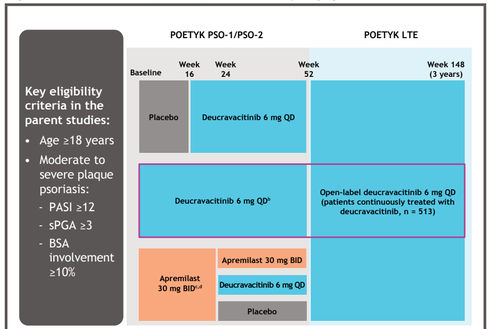
- To evaluate the efficacy of continuous deucravacitinib treatment for up to 3 years (Week 148) based on:
  - Achievement of various treat-to-target absolute PASI thresholds
  - Improvements from baseline in PASI scores at different efficacy bands

Methods

Study designs

- POETYK PSO-1 (NCT03624127) and POETYK PSO-2 (NCT03611751) were global, 52-week, phase 3, double-blind trials that randomized adults with moderate to severe plaque psoriasis 1:2:1 to oral placebo, deucravacitinib 6 mg QD, or apremilast 30 mg twice daily (BID) (**Figure 2**)
- At Week 52, eligible patients were able to enroll in the POETYK LTE (NCT04036435) trial and receive open-label deucravacitinib 6 mg QD, as mentioned above

Figure 2. POETYK PSO-1, PSO-2, and LTE analysis populations[a]



[a]Includes patients with ≥1 dose of deucravacitinib 6 mg QD, n = 1519. [b]In POETYK PSO-2, patients randomized to deucravacitinib on Day 1 who achieved PASI 75 at Week 24 were rerandomized to deucravacitinib or placebo; for patients who were rerandomized to placebo, upon relapse (≥50% loss of PASI percent improvement from baseline), they were to cross over to deucravacitinib; however, due to a programming error, these patients continued to receive placebo until Week 52. [c]In POETYK PSO-1, patients who responded to apremilast remained on apremilast. In POETYK PSO-2, patients who responded to apremilast crossed over to placebo and were to cross over to deucravacitinib upon relapse; however, due to a programming error, these patients continued to receive placebo until Week 52. [d]Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
BID, twice daily; BSA, body surface area; LTE, long-term extension; PASI, Psoriasis Area and Severity Index; PASI 75, ≥75% reduction from baseline in PASI; QD, once daily; sPGA, static Physician Global Assessment.

Efficacy outcomes

- Analyses were conducted at 3 years (Week 148; data cutoff, June 15, 2022) in patients treated continuously with deucravacitinib from Day 1 of POETYK PSO-1 and POETYK PSO-2 and included:
  - Mean change from baseline in PASI scores
  - Proportions of patients who achieved reduction from baseline in PASI scores per the following ranges: 75% to <80%, 80% to <85%, 85% to <90%, 90% to <95%, and 95% to ≤100%; each range, or band, is nonoverlapping
  - Proportions of patients who achieved treat-to-target absolute PASI thresholds of ≤1, ≤2, ≤3, ≤4, and ≤5
  - Proportions of patients who achieved PASI score bands of >1 to ≤3 and >3 to ≤5

Statistical analysis

- Mean changes from baseline in PASI scores were imputed for missing data by the modified baseline observation carried forward (mBOCF) method: the baseline observation was carried forward for patients who discontinued due to lack of efficacy or an adverse event; for all other reasons, the last valid observation was carried forward for missing data
- Consistent with recommendations for assessing long-term efficacy outcomes in psoriasis clinical trials,[12] two methods for imputation of missing binary data were used as sensitivity analyses in addition to observed values
  - **Modified nonresponder imputation (mNRI)[13]:** patients who either discontinued prior to Week 148 or completed 148 weeks of treatment were included; patients with missing data who discontinued treatment due to worsening of psoriasis were imputed as nonresponders; all other missing data were imputed by multiple imputation
  - **Treatment failure rules (TFR)[14]:** patients who discontinued treatment due to lack of efficacy or worsening of psoriasis were imputed as nonresponders; all other missing data were not imputed

Results

Patients

- 513 patients received continuous treatment with deucravacitinib from Day 1 to Week 52 in the 2 trials and entered the POETYK LTE trial
- Baseline patient demographics and disease characteristics are shown in **Table 1**

Table 1. Baseline patient demographics and disease characteristics

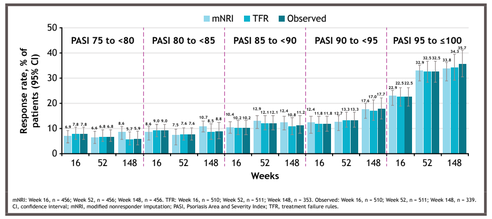
Parameter	Patients receiving continuous deucravacitinib (n = 513)
Age, mean (SD), y	46.9 (13.3)
Weight, mean (SD), kg	89.9 (22.2)
Female, n (%)	159 (31.0)
Race, n (%)	
White	440 (85.8)
Asian	64 (12.5)
Black or African American	5 (1.0)
Other	4 (0.8)
Age at disease onset, mean (SD), y	29.0 (14.7)
Disease duration, mean (SD), y	18.8 (12.6)
PASI score, mean (SD)	21.1 (7.9)
sPGA score, n (%)	
3 (moderate)	401 (78.2)
4 (severe)	112 (21.8)
BSA involvement, mean (SD), %	26.9 (15.8)

BSA, body surface area; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician Global Assessment.

PASI bands

- The proportions of patients achieving PASI 75 to <80, 80 to <85, 85 to <90, 90 to <95, and 95 to ≤100 were either increased or maintained from Week 16 through Week 52 and subsequently through Week 148 (**Figure 3**)
  - Response rates were similar whether using observed values or using mNRI and TFR data imputation methodologies

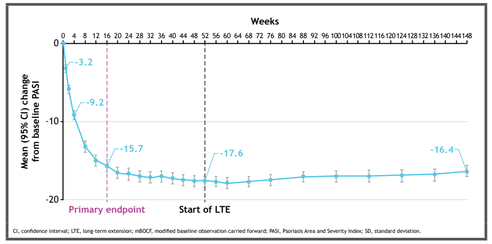
Figure 3. Proportions of patients achieving target PASI bands over time with continuous deucravacitinib treatment



mNRI: Week 16, n = 456; Week 52, n = 456; Week 148, n = 456. TFR: Week 16, n = 510; Week 52, n = 511; Week 148, n = 353. Observed: Week 16, n = 510; Week 52, n = 511; Week 148, n = 339.
CI, confidence interval; mNRI, modified nonresponder imputation; PASI, Psoriasis Area and Severity Index; TFR, treatment failure rules.

- From a mean (standard deviation [SD]) baseline PASI score of 21.1 (7.9) (**Figure 4**):
  - Improvements were observed beginning at Week 1 (-3.2)
  - Maintained or increased response rates were seen from Week 16 (-15.7) through Week 52 (-17.6)
  - Persistence of responses occurred from Week 52 through Week 148 (-16.4)

Figure 4. Mean change from baseline (mean [SD], 21.1 [7.9]) in PASI score (mBOCF) with continuous deucravacitinib treatment (n = 513)

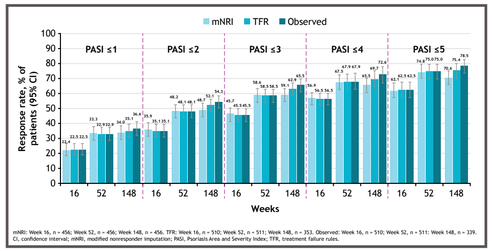


CI, confidence interval; LTE, long-term extension; mBOCF, modified baseline observation carried forward; PASI, Psoriasis Area and Severity Index; SD, standard deviation.

Absolute PASI thresholds and bands

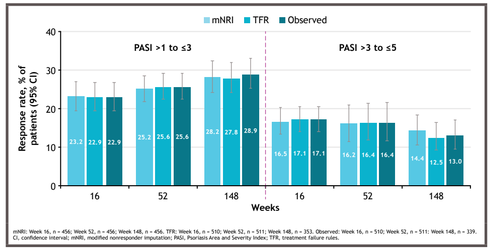
- For the proportions of patients achieving treat-to-target absolute PASI thresholds of ≤1, ≤2, ≤3, ≤4, and ≤5 (**Figure 5**) and PASI improvement bands of >1 to ≤3 and >3 to ≤5 (**Figure 6**):
  - Response rates were either increased or overall maintained from Week 16 through Week 52
  - Response rates persisted from Week 52 through Week 148
  - The somewhat lower response rates at Week 148 vs Week 52 in the PASI >3 to ≤5 band were possibly due to shifts to the higher stringency PASI ≤3 scores at Week 148 (**Figure 6**)
- The proportions of patients achieving PASI thresholds and bands of absolute PASI values were similar whether using observed values or using mNRI and TFR data imputation methodologies

Figure 5. Proportions of patients achieving absolute PASI thresholds over time



mNRI: Week 16, n = 456; Week 52, n = 456; Week 148, n = 456. TFR: Week 16, n = 510; Week 52, n = 511; Week 148, n = 353. Observed: Week 16, n = 510; Week 52, n = 511; Week 148, n = 339.
CI, confidence interval; mNRI, modified nonresponder imputation; PASI, Psoriasis Area and Severity Index; TFR, treatment failure rules.

Figure 6. Proportions of patients achieving PASI improvement bands over time



mNRI: Week 16, n = 456; Week 52, n = 456; Week 148, n = 456. TFR: Week 16, n = 510; Week 52, n = 511; Week 148, n = 353. Observed: Week 16, n = 510; Week 52, n = 511; Week 148, n = 339.
CI, confidence interval; mNRI, modified nonresponder imputation; PASI, Psoriasis Area and Severity Index; TFR, treatment failure rules.

Conclusions

- Patients who received continuous deucravacitinib treatment for up to 3 years (POETYK PSO-1 or PSO-2 and POETYK LTE) achieved clinically meaningful as well as treat-to-target PASI outcomes
  - Mean change from baseline in PASI scores showed improvement in psoriasis severity through Week 16, with efficacy being improved or maintained through Week 52 and then through Week 148
    - Deucravacitinib had an onset of action as early as Week 1
  - Substantial proportions of patients achieved PASI bands (75 to <80, 80 to <85, 85 to <90, 90 to <95, and 95 to ≤100), absolute PASI thresholds (≤1, ≤2, ≤3, ≤4, and ≤5), and PASI improvement bands (>1 to ≤3 and >3 to ≤5) through Week 148
    - Overall, the proportions of patients achieving PASI and absolute PASI thresholds and bands were increased or maintained from Week 16 through Week 52 and then through Week 148
- Deucravacitinib, a once-daily oral drug, has the potential to become a treatment of choice for patients with moderate to severe plaque psoriasis, with the ability to achieve treatment targets over at least 3 years (Week 148)

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Disclosures

- **LSG:** Consultant, advisory board member, and/or speaker: AbbVie, Amgen, Arcutis, Aslan, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dermira, Galderma, Incyte, Janssen, Leo Pharma, Lilly, Novartis, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB
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