

Deucravacitinib, an oral, selective tyrosine kinase 2 (TYK2) inhibitor, in moderate to severe plaque psoriasis: malignancies in the phase 3 POETYK PSO-1, PSO-2, and long-term extension (LTE) trials

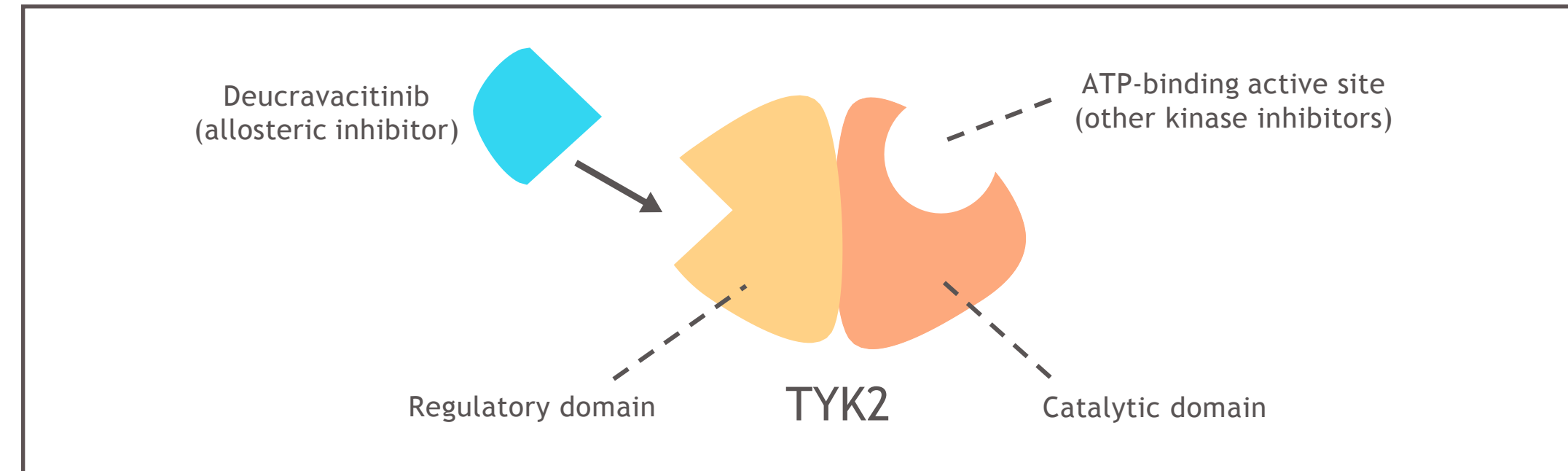
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Background

- Deucravacitinib
 - Novel, oral, selective tyrosine kinase 2 (TYK2) inhibitor with a unique mechanism of action distinct from Janus kinase (JAK) 1/2/3 inhibitors (Figure 1)¹
 - Binds to the TYK2 regulatory domain and inhibits TYK2 via an allosteric mechanism¹
 - ≥100-fold greater selectivity for TYK2 vs JAK 1/3 and ≥2000-fold greater selectivity for TYK2 vs JAK 2 in cells^{1,2}
 - Inhibits TYK2-mediated signaling of cytokines involved in psoriasis pathogenesis (eg, interleukin [IL]-23 and Type I interferons)¹

Figure 1. Mechanism of action of deucravacitinib



ATP, adenosine triphosphate; TYK2, tyrosine kinase 2.

- Patients with psoriasis are at an elevated risk for malignancies, excluding nonmelanoma skin cancer (NMSC), independent of treatment vs patients without psoriasis or the general population³
- The risk of lymphoma in patients with psoriasis has been shown to be higher than the general population,⁴ with the exposure-adjusted incidence rate (EAIR) ranging from 0.04-0.06/100 person-years (PY)
- Certain immunomodulatory agents have been shown to increase the risk of malignancies in clinical trials (eg, briakinumab [anti-IL-12/23p40 antibody]; JAK 1/2/3 inhibitors)⁵
- TYK2 mediates signaling of cytokines, including IL-23, IL-12, and Type I interferons, which may be implicated in tumor immunosurveillance via their effects on promoting natural killer- and T-cell elimination of tumor cells⁶
- However, a loss-of-function TYK2 genetic polymorphism that is protective for development of psoriasis has not been observed to increase malignancy risk⁷
- Nonclinical in vitro and in vivo toxicology data indicate that deucravacitinib is neither genotoxic nor carcinogenic

Objective

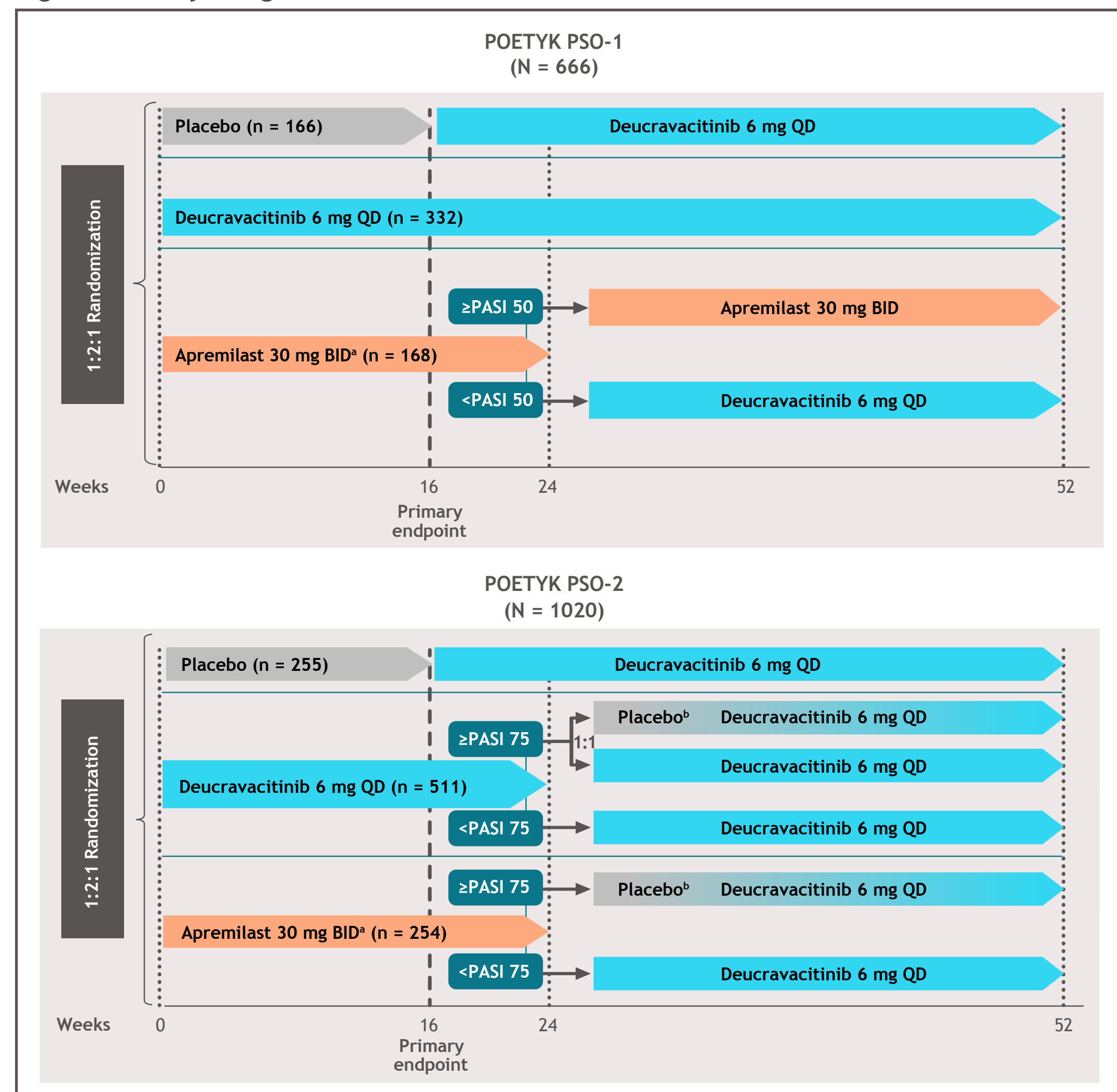
- This analysis assessed the incidence rates of malignancies in patients with psoriasis enrolled in the phase 3 POETYK PSO-1, PSO-2, and long-term extension (LTE) trials

Methods

Study designs

- The study designs for POETYK PSO-1 and POETYK PSO-2 are summarized in Figure 2
- Key eligibility criteria included the following:
 - Age ≥18 years
 - Diagnosis of moderate to severe plaque psoriasis
 - Psoriasis Area and Severity Index (PASI) ≥12
 - Static Physician's Global Assessment (sPGA) ≥3
 - Body surface area involvement ≥10%
 - Patient randomization was stratified by:
 - Geographic region
 - Body weight
 - Prior biologic use
- Coprimary endpoints, deucravacitinib vs placebo (Week 16)
 - ≥75% reduction from baseline in PASI (PASI 75)
 - sPGA score of 0 or 1 (sPGA 0/1)

Figure 2. Study designs



*Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing. *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.

- Patients who completed the PSO-1 or PSO-2 trials could enroll in the LTE trial in which they would receive open-label deucravacitinib 6 mg once daily (N = 1221)
 - >95% of patients completing PSO-1 (517/531) and PSO-2 (703/749) enrolled in the LTE
- Integrated safety pools
 - Placebo-controlled period: pooled data from the PSO-1 and PSO-2 trials evaluated over Weeks 0-16
 - 1-Year Controlled Safety Pool: pooled data from the PSO-1 and PSO-2 trials evaluated over Weeks 0-52
 - Extended Phase 3 Safety Pool: pooled data from the PSO-1, PSO-2, and LTE trials evaluated through June 15, 2021 (date cutoff for analyses)
- Adverse events (AEs) are expressed as:
 - Frequencies
 - EAIRs per 100 PY to adjust for differences in exposures due to treatment switches at Weeks 16 and 24 (Figure 2)

Results

Total exposure beyond 16 weeks

- 1-Year Controlled Safety Pool (Weeks 0-52):
 - Placebo, 240.9 PY
 - Deucravacitinib, 969.0 PY
 - Apremilast, 221.1 PY
- Phase 3 Safety Pool: deucravacitinib, 2166.9 PY (median exposure, 588.0 days); 296 patients received 104 weeks of deucravacitinib

Placebo-controlled period (Weeks 0-16)

- The overall incidence rates for AEs and serious AEs (SAEs) were similar across the 3 treatment groups (Table 1)
 - Most events were mild to moderate in severity
 - The frequency of AEs leading to discontinuation was lower for patients receiving deucravacitinib than for patients receiving placebo or apremilast
 - Nasopharyngitis and upper respiratory tract infection were more common in deucravacitinib-treated patients compared with those who received placebo or apremilast
 - Gastrointestinal events such as nausea and diarrhea were most common in apremilast-treated patients

Table 1. Overall safety summary, Weeks 0-16

AE category	Placebo (n = 419)		Deucravacitinib (n = 842)		Apremilast (n = 422)	
	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY
Any AEs	208 (49.6)	263.2	469 (55.7)	305.7	243 (57.6)	341.3
SAEs	12 (2.9)	9.9	15 (1.8)	6.0	5 (1.2)	4.0
AEs leading to discontinuation	16 (3.8)	13.2	20 (2.4)	8.0	22 (5.2)	17.9
Deaths	1 (0.2) ^a	—	1 (0.1) ^b	—	1 (0.2) ^c	—
Most common AEs (≥5% in any treatment group)						
Nasopharyngitis	36 (8.6)	30.6	76 (9.0)	31.7	37 (8.8)	31.1
Upper respiratory tract infection	17 (4.1)	14.0	46 (5.5)	18.8	17 (4.0)	13.9
Headache	19 (4.5)	16.0	38 (4.5)	15.6	45 (10.7)	39.1
Diarrhea	25 (6.0)	21.3	37 (4.4)	15.2	50 (11.8)	43.9
Nausea	7 (1.7)	5.8	14 (1.7)	5.6	42 (10.0)	36.4

^aOne patient in the placebo group died due to hypertensive cardiovascular disease. This patient had a history of obesity, obstructive sleep apnea, and attention deficit hyperactivity disorder. This death was considered not related to placebo. ^bOne patient in the deucravacitinib group was discontinued from treatment on Day 4 for prohibited medication and was hospitalized on Day 12 after suffering multiple cardiac arrests with resuscitation at home. The patient died the following day in the hospital from heart failure and sepsis as per a family member. No medical records were available. This patient had a history of obesity, rheumatoid arthritis, hypertension, and stroke and had a cardiac pacemaker implanted. This death was considered not related to deucravacitinib. ^cOne patient in the apremilast group died due to lung cancer and a gastrointestinal bleed. This patient had a history of hypertension, type 2 diabetes mellitus, and smoking. This death was considered not related to apremilast. AE, adverse event; EAIR, exposure-adjusted incidence rate; PY, person-years; SAEs, serious adverse events.

- Malignancies reported during Weeks 0-16 were:
 - Placebo - 0
 - Deucravacitinib - 1 (malignant sweat gland neoplasm [spiroadenoma] in scalp on Day 30; 0.1%; EAIR: 0.4/100 PY)
 - Apremilast - 2 (squamous cell carcinoma on Day 23, lung adenocarcinoma on Day 105; 0.5%; EAIR: 1.6/100 PY)

1-Year Controlled Safety Pool (Weeks 0-52)

- The overall AE profile was similar over Weeks 0-52 with no increased EAIR of AEs with continued deucravacitinib exposure (Table 2)

Table 2. Overall safety summary, Weeks 0-52

AE category	Placebo (n = 666)		Deucravacitinib (n = 1364)		Apremilast (n = 422)	
	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY
Any AEs	347 (52.1)	217.4	995 (72.9)	229.2	299 (70.9)	281.1
SAEs	14 (2.1)	5.7	55 (4.0)	5.7	9 (2.1)	4.0
AEs leading to discontinuation	23 (3.5)	9.3	43 (3.2)	4.4	26 (6.2)	11.6
Deaths	1 (0.2)	0.4	2 (0.1) ^a	0.2	1 (0.2)	0.4
Most common AEs (EAIR ≥5) in any treatment group						
Nasopharyngitis	54 (8.1)	22.7	229 (16.8)	26.1	54 (12.8)	25.9
Upper respiratory tract infection	33 (5.0)	13.5	124 (9.1)	13.4	27 (6.4)	12.4
Headache	21 (3.2)	8.6	80 (5.9)	8.5	53 (12.6)	26.0
Diarrhea	28 (4.2)	11.5	69 (5.1)	7.3	54 (12.8)	26.5

^aOne additional death was reported between Week 16-52 due to hepatocellular carcinoma in a patient with a history of HCV infection and liver cirrhosis. AEs, adverse events; EAIR, exposure-adjusted incidence rate; PY, person-years; SAEs, serious adverse events.

- Malignancies with deucravacitinib treatment (Week 0-52) are summarized in Table 3

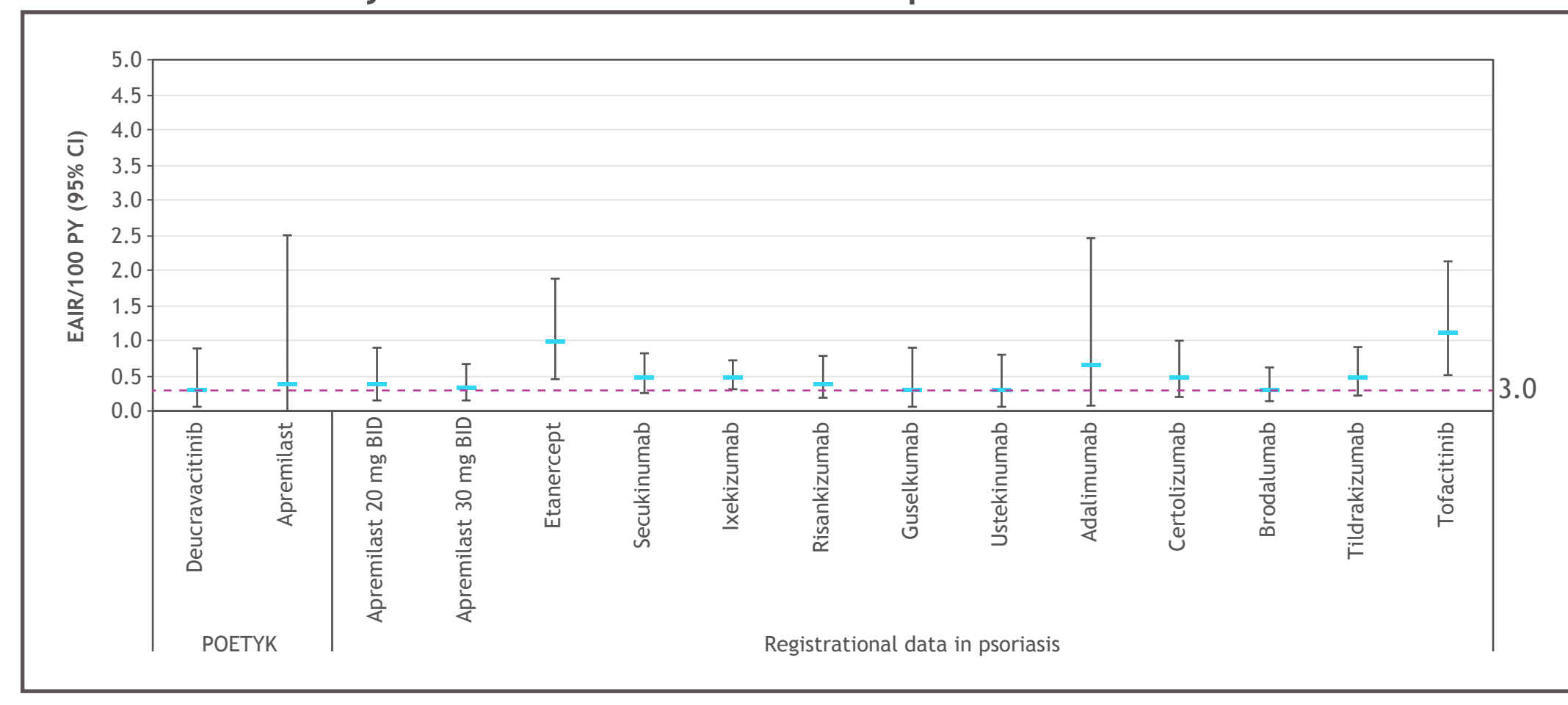
- NMSCs = 7
 - Resolved with minimally invasive treatment
 - Basal to squamous cell carcinoma ratio, 2:1
- Non-NMSCs = 3 (all distinct types)
- Most patients had risk factors for disease, including age, sun exposure, previous occurrence of cancer, long-term smoking, and/or previous exposure to phototherapy
- Observed malignancy rates in the deucravacitinib phase 3 trials were similar to rates reported in clinical trials of other antipsoriatic treatments (Figure 3)

Table 3. Malignancies - Weeks 0-52

Malignancy by type, n (%), EAIR	Pooled POETYK PSO-1 and PSO-2, Weeks 0-52		
	Placebo (n = 666)	Deucravacitinib (n = 1364)	Apremilast (n = 422)
Total malignancies	0	10 (0.7%, 1.0/100 PY)	2 (0.5%, 0.9/100 PY)
NMSC	0	7 (0.5%, 0.7/100 PY)	1 (0.2%, 0.4/100 PY)
Malignancies excluding NMSC	0	3 (0.2%, 0.3/100 PY)	1 (0.2%, 0.4/100 PY)
Breast cancer	0	1 ^a (0.1%, 0.1/100 PY)	0
Hepatocellular carcinoma	0	1 ^b (0.1%, 0.1/100 PY)	0
Lung adenocarcinoma	0	0	1 ^c (0.2%, 0.4/100 PY)
Hodgkin disease	0	1 ^d (0.1%, 0.1/100 PY)	0

^a64-year-old White obese female with family history of breast cancer, history of multiple immunosuppressive treatments, including anti-IL-17, anti-TNF, and methotrexate, and treatment with apremilast for the first 24 weeks, was diagnosed with breast cancer on Day 341 while on deucravacitinib. Treatment was discontinued. This malignancy was not considered related to drug. ^b54-year-old Asian male with history of hepatitis C and liver cirrhosis was diagnosed with hepatocellular carcinoma on Day 224. Treatment was discontinued. This malignancy was not considered related to drug. ^c74-year-old White male with 50 pack/year smoking history and prior anti-TNF and anti-IL-17 treatments was diagnosed with lung adenocarcinoma on Day 109. Treatment was discontinued. This malignancy was not considered related to drug. ^dSee brief narrative below. EAIR, exposure-adjusted incidence rate; IL, interleukin; NMSC, nonmelanoma skin cancer; PY, person-years; TNF, tumor necrosis factor.

Figure 3. EAIRs for non-NMSC malignancies in deucravacitinib-treated patients from Weeks 0-52 vs in 1-year clinical trials of other antipsoriatic treatments²¹⁻²²



BID, twice daily; EAIR, exposure-adjusted incidence rate; NMSC, nonmelanoma skin cancer; PY, person-years.

Extended Phase 3 Safety Pool (1-Year Controlled Safety Pool + LTE)

- The EAIRs for AEs, SAEs, and AEs leading to discontinuation for deucravacitinib in the Extended Phase 3 Safety Pool were similar to those during Weeks 0-52 (Table 4)
 - The increase in EAIR for SAEs was primarily due to COVID-related SAEs attributed to the timing of the COVID-19 pandemic
 - Consistent with background rates of COVID-19 infection and mortality, 5 of the 6 additional deaths that occurred in the deucravacitinib group during the LTE were related to COVID-19; the other death was due to a ruptured thoracic aortic aneurysm (details provided in the poster by Mark Lebwohl et al presented at this meeting)

Malignancies with deucravacitinib treatment

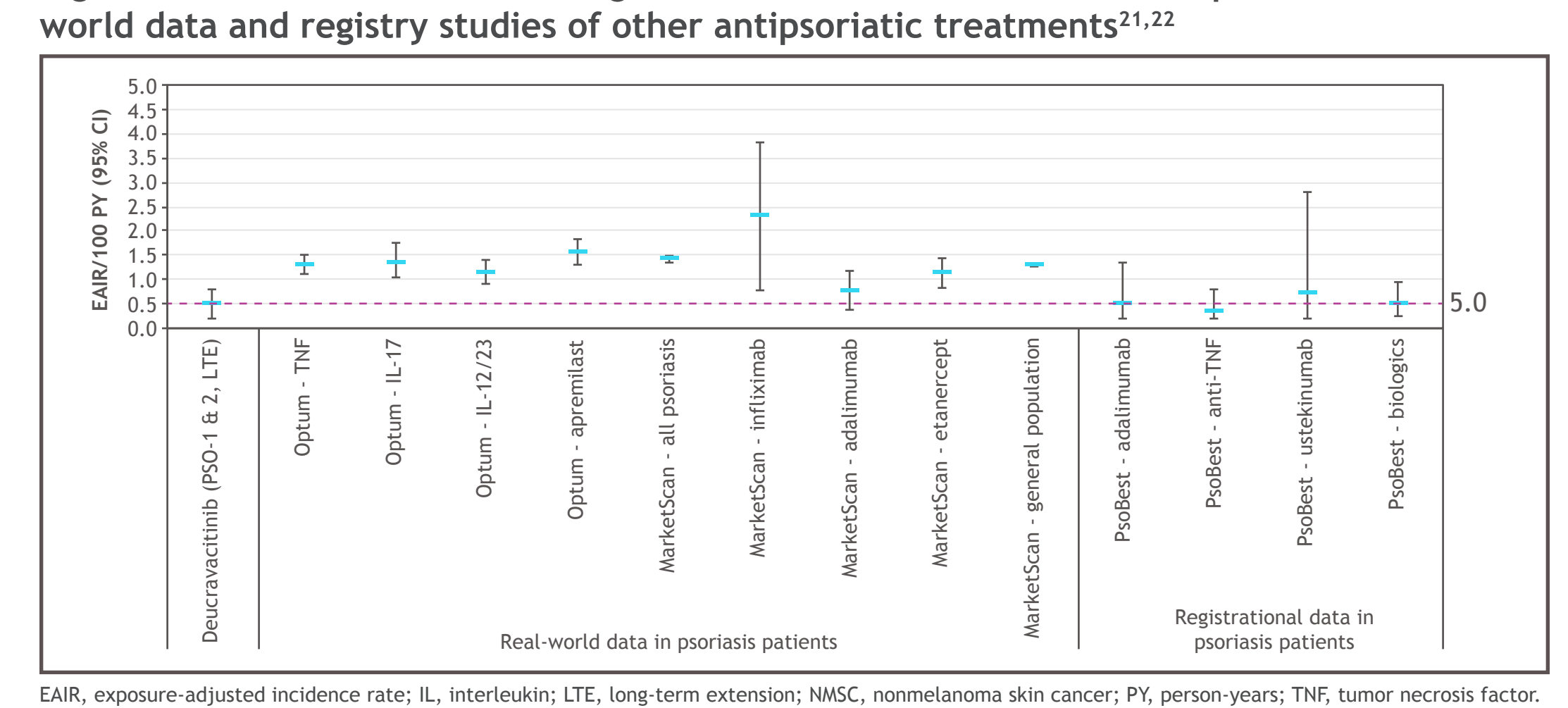
- Total: 19 (EAIR: 0.9/100 PY)
 - Rates were similar to those from Weeks 0-52
 - The rates were consistent with observed rates in clinical trials of other antipsoriatic agents and with observed rates in real-world psoriasis patients receiving antipsoriatic treatments (Figure 4)
 - Rates were comparable to real-world populations of psoriasis
 - Based on the US Surveillance, Epidemiology and End Results database (standardized incidence ratio: 1.1; 95% CI: 0.5-1.9)⁷ 2 patients had basal cell carcinoma and squamous cell carcinoma
- NMSCs: 10 (ratio of basal cell carcinoma to squamous cell carcinoma, 7:4); EAIR: 0.5/100 PY
 - 2 patients had both basal cell carcinoma and squamous cell carcinoma
- Non-NMSCs: 10 malignancies (EAIR: 0.5/100 PY)
 - 2 cases of breast cancer, 2 cases of melanoma, 1 case of colon cancer, 1 case of hepatocellular carcinoma, and 1 case of acute promyelocytic leukemia were reported
 - Of note, 3 cases of lymphoma were reported in the Extended Phase 3 Safety Pool with deucravacitinib (EAIR: 0.1/100 PY)
 - 1-Year Controlled Safety Pool: One Hodgkin's lymphoma diagnosed in a 46-year-old White male at 6 months in PSO-1; worsening anemia by Week 8; the latent period of lymphoma diagnosis in this patient may be too short to attribute causality to the drug treatment
 - LTE: One nodal marginal zone non-Hodgkin's lymphoma in a 72-year-old White male in the LTE (77 weeks exposure); past history of multiple basal cell and squamous cell carcinomas, phototherapy; low B-cell and Th counts at baseline and throughout study; marginal zone non-Hodgkin's lymphoma not being typically associated with immuno-suppression or viral infections, the role of deucravacitinib is uncertain
 - LTE: One low-grade follicular non-Hodgkin's lymphoma in 58-year-old White male in the LTE (98 weeks exposure); history of heavy smoking for long duration (known risk factor), prior exposure to efalizumab and ustekinumab; follicular lymphoma not typically associated with immunosuppression or viral infections, role of deucravacitinib unclear

Table 4. Overall safety summary, Phase 3 Safety Pool

AE category	Weeks 0-52 (1-Year Safety Pool)		Extended Phase 3 Safety Pool	
	n (%)	EAIR/100 PY	n (%)	EAIR/100 PY
AEs	995 (72.9)	229.2	1188 (78.2)	162.1
SAEs	55 (4.0)	5.7	130 (8.6)	6.2
Discontinued treatment due to AEs	43 (3.2)	4.4	66 (4.3)	3.0
Deaths	2 (0.1)	0.2	8 (0.5)	0.4

AE, adverse event; EAIR, exposure-adjusted incidence rate; PY, person-years; SAEs, serious adverse events.

Figure 4. EAIRs for non-NMSC malignancies in deucravacitinib-treated patients vs real-world data and registry studies of other antipsoriatic treatments^{21,22}



EAIR, exposure-adjusted incidence rate; IL, interleukin; LTE, long-term extension; NMSC, nonmelanoma skin cancer; PY, person-years; TNF, tumor necrosis factor.

Conclusions

- NMSCs: Low rates with deucravacitinib treatment, with the ratio of basal cell carcinoma:squamous cell carcinoma being maintained >1
- Non-NMSCs: The EAIRs of non-NMSC malignancies in patients treated with deucravacitinib in the POETYK PSO-1, PSO-2, and LTE trials were comparable to rates reported in the literature for rates in clinical trials with approved immunomodulators in psoriasis and in age-matched patients with moderate to severe psoriasis in the real world
- The malignancy rate was not increased over time with longer deucravacitinib exposure
- There did not appear to be an increased risk of malignancy with deucravacitinib treatment in the POETYK trials

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