NEW DRUG APPROVAL

Brand Name	Sotyktu™
Generic Name	deucravacitinib
Drug Manufacturer	Bristol-Myers Squibb Company

New Drug Approval

FDA approval date: September 9, 2022

Review designation: Standard

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214958

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, manifesting most commonly with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Nail lesions, including pitting and onycholysis, occur in ~80–90% of patients with PsA. About 30% of patients with psoriasis will eventually develop PsA within an average of 7 to 10 years, but there is significant variability in this timeframe. Although it is unclear what risk factors predict a shorter or longer timeframe between the onset of psoriasis and the development of PsA, [one study][1] found that potentially an older age at psoriasis onset may predict a shorter time until PsA.

The incidence of PsA is ~6 per 100,000 per year, and the prevalence is ~1–2 per 1,000 in the general population. The annual incidence of PsA in patients with psoriasis is 2.7%, and the reported prevalence of PsA among patients with psoriasis has varied between 6% and 41%. In the majority of patients, the skin symptoms develop first, followed by the arthritis; however, in some patients the skin and joint symptoms present at the same time, and in 10–15% the arthritis presents first.

It was initially considered a variant of rheumatoid arthritis, but subsequently emerged as a distinct clinical entity. Historically, seronegativity for rheumatoid factor (RF) had been a requirement for the diagnosis; however, over 10% of patients with uncomplicated psoriasis and up to 15% of the normal population have RF present in their serum. Several reports documented positive cyclic citrullinated peptide (CCP) antibodies in PsA patients as well. As a result, the term "usually seronegative" arthritis is most suitable for PsA.

Efficacy

Plaque Psoriasis:
The efficacy and safety of Sotyktu™ 6 mg once daily were assessed in two multicenter, randomized, double-blind, placebo- and active-controlled clinical trials, PSO-1 (NCT03624127) and PSO-2 (NCT03611751) which enrolled subjects 18 years of age and older with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Subjects had a body surface area (BSA) involvement of ≥10%, a Psoriasis Area and Severity Index (PASI) score ≥12, and a static Physician's Global Assessment (sPGA) ≥3 (moderate or severe).
In PSO-1 and PSO-2, efficacy was assessed in 1,684 subjects randomized to either Sotyktu™ (6 mg orally once daily), placebo, or apremilast (30 mg orally twice daily).
Endpoints
Both trials assessed the responses at Week 16 compared to placebo for the two co-primary endpoints:

- proportion of subjects who achieved a sPGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

- The proportion of subjects who achieved at least a 75% improvement in PASI scores from baseline (PASI 75).

Other comparisons between Sotyktu™ and placebo that were secondary endpoints at Week 16:

- The proportion of subjects who achieved PASI 90, PASI 100, sPGA 0, scalp severity PGA (ssPGA) score of 0 (clear) or 1 (almost clear) with at least 2-grade improvement, and Psoriasis Symptoms and Signs Diary (PSSD) Symptom Score of 0 (symptom-free).

Comparisons between Sotyktu™ and apremilast were made for the following secondary endpoints at these time points:

- at Week 16 and Week 24 (PSO-1 and PSO-2), the proportion of subjects who achieved PASI 75, PASI 90, and sPGA 0/1 with at least a 2-grade improvement from baseline.
- at Week 16 (PSO-1 and PSO-2), the proportion of subjects who achieved sPGA 0 and ss-PGA 0/1 with at least a 2-grade improvement from baseline (scalp).

Results: In both trials, the mean age was 47 years, the mean weight was 91 kg, 67% of subjects were male, 13% were Hispanic or Latino, 87% were White, 2% were Black, and 10% were Asian. At baseline, subjects had a median affected BSA of 20% and a median PASI score of 19. The proportion of subjects with sPGA score of 3 (moderate) and 4 (severe) at baseline were 80% and 20%, respectively. Approximately 18% of subjects had a history of psoriatic arthritis. Across both trials, 40% of subjects had received prior phototherapy, 42% were naive to any systemic therapy (including biologic and/or non-biologic treatment), 41% received prior non-biologic systemic treatment, and 35% had received prior biologic therapy. Table 1 presents the efficacy results of Sotyktu™ compared to apremilast and placebo in PSO-1. Table 2 presents the efficacy results in PSO-2.

Table 1: Efficacy Results in Adults with Moderate to Severe Plaque Psoriasis (NRI[a]) in PSO-1

Endpoint	Sotyktu™ (N=330) n (%)	Placebo (N=166) n (%)	Apremilast (N =168) n (%)	Difference, % (95% CI)[b]	
				Difference from Placebo	Difference from Apremilast
sPGA response of 0/1 (clear or almost clear)					
Week 16[c]	178 (54)	12 (7)	54 (32)	47 (40, 53)	22 (13, 30)
Week 24	194 (59)	-	52 (31)	-	27 (19, 36)
sPGA response of 0					
Week 16	58 (18)	1 (1)	8 (5)	17 (13, 21)	13 (8, 18)
PASI 75 response					
Week 16[c]	193 (58)	21 (13)	59 (35)	46 (39, 53)	23 (14, 32)
Week 24	228(69)	-	64 (38)	-	31 (22, 40)
PASI 90 response					
Week 16	118 (36)	7 (4)	33 (20)	32 (26, 38)	16 (8, 24)
Week 24	140 (42)	-	37 (22)	-	20 (12, 28)
PASI 100 response					
Week 16	47 (14)	1 (1)	-	14 (10, 18)	-
ss-PGA response of 0/1 (scalp)[d]	**(N=209)**	**(N=121)**	**(N=110)**		
Week 16	147 (70)	21 (17)	43 (39)	53 (44, 62)	30 (19, 41)

CI = Confidence interval ;
PASI = Psoriasis Area and Severity Index ;
sPGA = Static Physician Global Assessment ;
ssPGA = Scalp Specific Physician's Global Assessment
[a] NRI = Non-Responder Imputation

[b] Adjusted difference in proportions is the weighted average of the treatment differences across region, body weight and prior biologic use with the Cochran-Mantel-Haenszel weights.

[c] Co-primary endpoints comparing Sotyktu™ to placebo [d] Includes only subjects with baseline ss-PGA score of ≥ 3

Table 2: Efficacy Results in Adults with Moderate to Severe Plaque Psoriasis (NRI[a]) in PSO-2					
Endpoint	Sotyktu™ (N=511) n (%)	**Placebo (N=255) n (%)**	**Apremilast (N=254) n (%)**	**Difference, % (95% CI)[b]**	
				Difference from Placebo	**Difference from Apremilast**
sPGA response of 0/1 (clear or almost clear)					
Week 16[c]	253 (50)	22 (9)	86 (34)	41 (35, 46)	16 (9, 23)
Week 24	251 (49)	-	75 (30)	-	20 (13, 27)
sPGA response of 0					
Week 16	80 (16)	3 (1)	16 (6)	14 (11, 18)	9 (5, 14)
PASI 75 response					
Week 16[c]	271 (53)	24 (9)	101 (40)	44 (38, 49)	13 (6, 21)
Week 24	296 (58)	-	96 (38)	-	20 (13, 27)
PASI 90 response					
Week 16	138 (27)	7 (3)	46 (18)	24 (20, 29)	9 (3, 15)
Week 24	164 (32)	-	50 (20)	-	13 (6, 19)
PASI 100 response					
Week 16	52 (10%)	3 (1)	-	9 (6, 12)	-
ss-PGA response of 0/1 (scalp)[d]	**(N=305)**	**(N=173)**	**(N=166)**		
Week 16	182 (60)	30 (17)	61 (37)	42 (34, 50)	23 (14, 33)

CI = Confidence interval;
PASI = Psoriasis Area and Severity Index ;
sPGA = Static Physician Global Assessment; ss-
PGA = Scalp Specific Physician's Global Assessment
[a] NRI = Non-Responder Imputation
[b] Adjusted difference in proportions is the weighted average of the treatment differences across region, body weight and prior biologic use with the Cochran-Mantel-Haenszel weights.
[c] Co-primary endpoints comparing Sotyktu™ to placebo
[d] Includes only subjects with baseline ss-PGA score of ≥ 3.

Examination of age, gender, race, body weight, baseline disease severity, and prior systemic therapy did not identify differences in response to Sotyktu™ at Week 16 among these subgroups.

Maintenance and Durability of Response

In PSO-1, among subjects who received Sotyktu™ and had sPGA 0/1 response at Week 24, the sPGA 0/1 response at Week 52 was 78% (151/194). Among subjects who received Sotyktu™ and had PASI 75 response at Week 24, the PASI 75 response at Week 52 was 82% (187/228). Among subjects who received Sotyktu™ and had PASI 90 response at Week 24, the PASI 90 response at Week 52 was 74% (103/140).

In PSO-2, to evaluate maintenance and durability of response, subjects who were originally randomized to Sotyktu™ and were PASI 75 responders at Week 24, were re-randomized to either continue treatment on Sotyktu™ or be withdrawn from therapy (i.e., receive placebo).
For subjects who were re-randomized and had a sPGA score of 0 or 1 at Week 24, 70% (83/118) of subjects who continued on Sotyktu™ maintained this response (sPGA 0 or 1) at Week 52 compared to 24% (28/119) of subjects who were re-randomized to placebo. In addition, at Week 52, 80% (119/148) of subjects who continued on Sotyktu™ maintained PASI 75 compared to 31% (47/150) of subjects who were withdrawn from Sotyktu™. For sPGA 0 or 1 responders at Week 24 who were re-randomized to treatment withdrawal (i.e., placebo), the median time to loss of sPGA score of 0 or 1 was approximately 8 weeks. For PASI 75 responders at Week 24 who were re-randomized to treatment withdrawal (i.e., placebo), the median time to loss of PASI 75 was approximately 12 weeks.
Patient Reported Outcomes
A greater proportion of subjects treated with Sotyktu™ compared to placebo achieved Psoriasis Symptoms and Signs Diary (PSSD) symptom score of 0 (absence of itch, pain, burning, stinging, and skin tightness) at Week 16 (8% in Sotyktu™ vs. 1% in placebo) in both trials.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥ 1%) are upper respiratory infections, blood creatine phosphokinase increased, herpes simplex, mouth ulcers, folliculitis, and acne.

WARNINGS & PRECAUTIONS

- **Hypersensitivity**: Hypersensitivity reactions such as angioedema have been reported. Discontinue if a clinically significant hypersensitivity reaction occurs.
- **Infections:** Sotyktu™ may increase the risk of infection. Avoid use in patients with active or serious infection. If a serious infection develops, discontinue Sotyktu™ until the infection resolves.
- **Tuberculosis**: Evaluate for TB prior to initiating treatment with Sotyktu™.
- Malignancy: Malignancies including lymphomas were observed in clinical trials with Sotyktu™ (deucravacitinib).
- Rhabdomyolysis and elevated CPK.
- Laboratory Abnormalities: Periodically evaluate serum triglycerides. Evaluate liver enzymes at baseline and thereafter in patients with known or suspected liver disease.
- Immunizations: Avoid use with live vaccines.
- Potential Risks Related to JAK Inhibition: It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer) were observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in rheumatoid arthritis (RA) patients. Sotyktu™ is not approved for use in RA.

CONTRAINDICATIONS

Known hypersensitivity to deucravacitinib or any of the excipients in Sotyktu™.

Clinical Pharmacology

MECHANISMS OF ACTION

NEW DRUG APPROVAL

Deucravacitinib is an inhibitor of tyrosine kinase 2 (TYK2). TYK2 is a member of the Janus kinase (JAK) family. Deucravacitinib binds to the regulatory domain of TYK2, stabilizing an inhibitory interaction between the regulatory and the catalytic domains of the enzyme. This results in allosteric inhibition of receptor-mediated activation of TYK2, and its downstream activation of Signal Transducers and Activators of Transcription (STATs) as shown in cell-based assays. JAK kinases, including TYK2, function as pairs of homo- or heterodimers in the JAK-STAT pathways. TYK2 pairs with JAK1 to mediate multiple cytokine pathways and pairs with JAK2 to transmit signals as shown in cell-based assays. The precise mechanism linking inhibition of TYK2 enzyme to therapeutic effectiveness in the treatment of adults with moderate-to-severe plaque psoriasis is not currently known.

Dose & Administration

ADULTS

Recommended dosage is 6 mg orally once daily, with or without food.

PEDIATRICS

The safety and effectiveness of Sotyktu™ in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dose adjustment required.

HEPATIC IMPAIRMENT

Sotyktu™ is not recommended for use in patients with severe hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 6 mg