CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214958Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214958
PDUFA Goal Date	September 9, 2022
OSE RCM #	2021-1818
Reviewer Name(s)	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	September 8, 2022
Subject	Evaluation of Need for a REMS
Established Name	deucravacitinib
Trade Name	Sotyktu
Name of Applicant	Bristol-Myers Squibb
Therapeutic Class	Tyrosine kinase 2 inhibitor
Formulation(s)	6 mg tablet
Dosing Regimen	1 tablet daily, with or without food

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Sotyktu (deucravacitinib) is necessary to ensure the benefits outweigh its risks. Bristol Myers Squibb, Inc. (Bristol) submitted a New Drug Application (NDA 214958) for deucravacitinib with the proposed indication for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This application is under review in the Division of Dermatology and Dentistry (DDD). The applicant did not submit a REMS with this application.

2. Background

2.1. Product Information

Deucravacitinib, a new molecular entity[a], is a tyrosine kinase 2 inhibitor (TYK2), proposed for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. TYK2, a member of the Janus Kinase (JAK) family, is an intracellular non-receptor kinase that mediates the signaling of the pro-inflammatory cytokines interleukin (IL)-23, IL-12 and Type I interferons. Deucravacitinib binds to the regulatory domain of TYK2 resulting in allosteric inhibition of receptor-mediated activation of TYK2 and its downstream inflammatory and immune responses. Deucravacitinib is proposed as a 6 mg tablet to be taken orally, with or without food, once daily for chronic use[b]. It is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 214958 relevant to this review:

- **09/10/2021:** NDA 214958 submission for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy indication.
- **07/06/2022:** Medical Policy and Program Review Council meeting convened to discuss if the deucravacitinib prescribing information should follow the class labeling for JAK inhibitors. The council recommended class labeling with delineation of adverse reactions specifically observed during the deucravacitinib psoriasis program versus what was seen for other JAK inhibitor products.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug*

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Psoriasis is a chronic inflammatory, immune-mediated skin disorder affecting approximately 7.5 million people in the United States[1,c]. It is characterized by well-demarcated, erythematous scaly plaques on the skin. The plaques are typically found on the elbows, knees, lower back and scalp, but can develop anywhere on the body. Moderate to severe plaque psoriasis is typically defined as involvement of more than 5-10% of the body surface area[2]. Psoriasis can have a fluctuating relapsing course. Flares may be induced by factors such as infections, trauma, smoking and stress. Moderate-to-severe psoriasis can have a profound effect on quality of life, as it has been associated with increased risk of depression, sleep disturbances, social stigma and decreased work productivity[3,d].

3.2. Description of Current Treatment Options

There are numerous therapies available for the treatment of moderate-to-severe plaque psoriasis. The initial decision point when choosing psoriasis therapy is usually between local (topical) and full body (systemic or phototherapy) treatment. Because patients with moderate-to-severe psoriasis typically have more than 5% of their body surface area affected, the sole use of topical agents is not practical and often unsuccessful.[4] Topical agents, such as emollients, corticosteroids, retinoids, vitamin D analogs and calcineurin inhibitors, are often used as adjuncts for resistant, localized lesions in patients who are undergoing systemic treatment or phototherapy. Options for systemic therapy includes retinoids and immunosuppressive or immunomodulatory drugs such as methotrexate, cyclosporine, apremilast and biologic agents.

Biologic agents include the most effective therapies for moderate-to-severe plaque psoriasis.[5] A comparison of biologic therapies approved for the treatment of moderate-to-severe plaque psoriasis is included in the Appendix of this review. Several of the biologic agents were approved with a REMS that consisted of a Medication Guide (MG) and Communication Plan to mitigate the risks of infections and malignancies; this includes etanercept, adalimumab, certolizumab pegol, infliximab and ustekinumab. The REMS for these agents were released in 2011, with the exception of the ustekinumab REMS that was released in 2017. Brodalumab was approved to treat moderate-to-severe plaque psoriasis in 2017 with a REMS to mitigate the risk of suicidal ideation and behavior including completed suicides. The REMS includes prescriber and pharmacy certification, as well as documentation of safe use conditions.

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Non-pharmacological agents are also used in the treatment of moderate-to-severe plaque psoriasis. The use of ultraviolet light in therapeutic doses is used as phototherapy. Phototherapy can be used alone or in combination with saltwater baths. Dietary supplements such as turmeric, vitamin D and zinc have also been used.

Although there are numerous options for treatment, there is no cure for plaque psoriasis. It is a chronic disease that often requires long-term treatment. Current therapies have varying effectiveness in patients and may be associated with limitations related to parental administration, poor adherence, tolerability and safety. An unmet medical need remains for additional therapeutic options, especially oral agents.

4. Benefit Assessment

The efficacy and safety of deucravacitinib for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy was demonstrated in two pivotal Phase 3 trials (**IM011046** [*NCT03624127*]- 154 investigative sites in 11 countries, **IM011047** [*NCT03611751*]- 191 investigative sites in 16 countries). Both studies enrolled adult subjects with moderate-to-severe plaque psoriasis (defined as Psoriasis Area and Severity Index (PASI)[e] ≥ 12, Static Physician's Global Assessment (sPGA)[f] score ≥ 3, and body surface area involvement ≥ 10%) and were required to be candidates for phototherapy or systemic therapy for their psoriasis. The two trials were similar in design: 52-week, multicenter, randomized, double-blind, placebo- and active comparator-controlled trials with apremilast[g] as the comparator. Study IM011047 additionally had a randomized-withdrawal and maintenance period. In both studies, eligible subjects were randomized in a 2:1:1 ratio of deucravacitinib 6 mg QD, placebo, and apremilast 30 mg BID. Trial IM011046 enrolled 666 subjects and consisted of a screening period (up to 4 weeks), a treatment period (52 weeks), and a follow-up period (4 weeks). Trial IM011047 enrolled 1020 subjects and consisted of a screening period (up to 4 weeks), a treatment period (24 weeks), a randomized withdrawal and maintenance period (28 weeks) and a follow-up period (4 weeks). Subjects in both trials had visits at screening, baseline, Weeks 1, 2, 4, and every 4 weeks thereafter until Week 52.

[e] PASI is a ClinRO instrument designed to assess severity and extend of psoriasis (based on lesions). Each component is rated using a 5-point VRS ranging from 0 (none) to 4 (very severe

[f] sPGA is a single item clinician-reported outcome (ClinRO) instrument designed to assess the overall psoriasis severity (based on lesions). Each component is rated using a 5-point verbal rating scale (VRS) ranging from 0 (clear) to 4 (severe).

[g] Apremilast (NDA 206088) is a phosphodiesterase 4 inhibitor that was approved on September 23, 2014 for the treatment of patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Analysis of the co-primary endpoints was assessed for deucravacitinib compared to placebo. The co-primary endpoints were (1) the proportion of subjects who achieve sPGA score of 0 (clear) or 1 (minimal) with at least 2 grade improvement from baseline at Week 16 and (2) the proportion of subjects who achieve PASI 75 (i.e., at least 75% reduction from baseline in PASI score) at Week 16. The results of both Phase 3 studies showed that deucravacitinib was statistically superior to placebo for both co-primary endpoints as detailed below in Table 1.

Table 1: Results for the Co-Primary Endpoints at Week 16-Trials IMO11046 and IMO011047

	Trial IM011046		Trial IM011047	
Endpoint	**DEUC* (N=330)**	**PBO (N=166)**	**DEUC* (N=511)**	**PBO (N=255)**
sPGA 0/1	178 (54%)	12 (7%)	253 (50%)	22 (9%)
Difference (95% CI)[2]	47% (40%, 53%)		42% (36%, 47%)	
P-Value[2]	<0.001		<0.001	
PASI-75	193 (58%)	21 (13%)	271 (53%)	24 (9%)
Difference (95% CI)[2]	46% (39%, 53%)		44% (38%, 49%)	
P-Value[2]	<0.001		<0.001	

Source: DDD Draft Unireview[6]

* Deucravacitinib (DEUC)

Multiple secondary endpoint analysis was conducted comparing deucravacitinib to apremilast, including a Week 16 comparison of PASI-75, PASI-90, and sPGA 0/1 with at least a 2-grade improvement from baseline, as well as comparison of subjects who achieved sPGA 0 and scalp severity-PGA (ss-PGA) 0/1 with at least a 2-grade improvement from baseline. In both trials, deucravacitinib was statistically superior to apremilast ($p<0.001$) for sPGA, PASI and ss-PGA at Week 16.

Based on the deucravacitinib Phase 3 study results, the clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness.[h]

5. Risk Assessment & Safe-Use Conditions

The primary safety analysis consists of data from 1364 subjects who received at least one dose of deucravacitinib 6 mg during either of the two Phase 3 clinical trials (IM011046, IM011047). Supportive safety data from the long-term extension trial (IM011075) is also provided.

Four deaths (2 deucravacitinib, 1 placebo, 1 apremilast) were reported in the primary safety pool, and 6 were reported during the long-term extension (LTE) trial (June 15, 2021 safety data cutoff date). The four deaths in the Phase 3 trials were attributed to cardiovascular causes (cardiac arrest, cardiac failure

[h] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

in the setting of sepsis)[2], cancer[1] and unknown cause [1]. In the LTE trial, 5 of the 6 deaths were due to COVID-19 and 1 to ruptured thoracic aortic aneurysm. The clinical reviewer stated that all of the subjects who died of COVID-19 had existing comorbidities that are associated with increased mortality from severe COVID-19 infection. Additionally, she stated that excluding deaths due to COVID-19, the proportion of deaths is comparable to the rate observed for most approved psoriasis products.[7]

The incidence of serious adverse events (SAEs) was similar across the treatment groups (1.8% deucravacitinib, 2.9% placebo, 1.2% apremilast). The most frequently reported SAEs were infections and infestations, which will be discussed in section 5.1 of this review. Table 2 below displays the SAEs in the Phase 3 trials by system organ class (SOC).

Table 2: Serious AEs by SOC in Phase 3 Trials- IM011046, IM011047

	DEUC*	Placebo	Apremilast
	N=842	N= 419	N=422
SYSTEM ORGAN CLASS	n (%)	n (%)	n (%)
Total Subjects with an Event	15 (1.8)	12 (2.9)	5 (1.2)
Infections & Infestations	5 (0.6)	2 (0.5)	2 (0.5)
Cardiac	3 (0.4)	3 (0.7)	1 (0.2)
Renal & urinary	2 (0.2)	0	0
Gastrointestinal	1 (0.1)	1 (0.2)	2 (0.5)
Immune system	1 (0.1)	0	0
Injury, poisoning & procedural complications	1 (0.1)	2 (0.5)	0
Metabolism and nutrition	1 (0.1)	0	0
Nervous system	1 (0.1)	0	1 (0.2)
Respiratory, thoracic	1 (0.1)	1 (0.2)	0
Vascular	1 (0.1)	1 (0.2)	0
Congenital, familial, genetic	0	0	1 (0.2)
General & admin site	0	2 (0.5)	0
Neoplasms	0	0	1 (0.2)
Psychiatric	0	1 (0.2)	0
Skin & subcutaneous	0	1 (0.2)	0

* deucravacitinib (DEUC)

5.1. Serious Infections

During the placebo and apremilast-controlled period of the Phase 3 trials (Week 0-16), serious infections were reported in 5 (0.6%) subjects treated with deucravacitinib , 2 (0.5%) subjects treated with placebo [cellulitis, diverticulitis] and 2 (0.5%) subjects treated with apremilast [cellulitis, polymicrobial diabetic foot wound]. The serious infections in the deucravacitinib subjects included sepsis, streptococcal

bacteremia, diverticulitis, upper respiratory infection and pyelonephritis. To capture infections that occurred outside of the placebo and apremilast-controlled period of the Phase 3 trials, analyses were performed for deucravacitinib -treated subjects that included those who switched treatment during the trials. After 52-weeks of exposure, 17/1364 (1.2%) deucravacitinib treated subjects experienced serious infections including pneumonia, COVID-19, pharyngotonsillitis, carbuncle, anal abscess, mononucleosis, vascular graft infection and purulence with pancreatitis. The clinical reviewer stated that due to confounding factors and limited exposure, it is difficult to attribute all the serious infections to deucravacitinib use. The risk of serious infections will be included in the Warnings and Precautions (Section 5.2) and Adverse Reactions (Section 6.1) sections of the deucravacitinib prescribing information. Additionally, the applicant proposed a Medication Guide (MG) that includes the risk of infections as a possible side effect of deucravacitinib treatment.

5.2. Lymphoma

One deucravacitinib treated subject in the Phase 3 trials and three in the LTE study (as of the October 1, 2021 safety update cut-off date) reported lymphoma. The clinical reviewer stated that although the events were few, the exposure-adjusted incidence rate of lymphoma observed with deucravacitinib during the clinical development program (0.1/100 person-years [PY]) was noticeably higher than published rates observed in patients with psoriasis (0.04-0.06/100 PY). The clinical reviewer noted that each case included multiple, differing confounding factors, so causality is uncertain. The risk of malignancies, including lymphoma, will be conveyed in the Warnings and Precautions (Section 5.7) of the deucravacitinib prescribing information.

In addition to the Warnings and Precautions for infections and malignancies, the deucravacitinib prescribing information will include a Limitation of Use that states deucravacitinib is not recommended for use in combination with (b) (4) other potent immunosuppressants. In the Phase 3 trials potential subjects who were currently using biologics, systemic conventional therapies, phototherapy or topical therapy were excluded from the trials.

6. Expected Postmarket Use

Deucravacitinib is expected to be taken by patients orally, with or without food, once daily in the outpatient setting. Per the applicant, deucravacitinib can be given as initial systemic therapy in patients naïve to psoriasis treatment. In most cases it will be prescribed by specialists, such as dermatologists. These clinicians will likely have experience with immunomodulatory psoriasis therapies and are knowledgeable about the associated risks of JAK inhibition. Healthcare providers can counsel patients at the point of care regarding the observed risks of serious infections and malignancies, such as lymphoma. The adult psoriasis patient population will likely be able to recognize symptoms associated with these potential adverse effects and take necessary actions to manage them.

7. Risk Management Activities Proposed by the Applicant

The applicant states that safety concerns relevant to deucravacitinib can be managed with routine risk minimization measures, i.e., the United States Prescribing Information (USPI). Additionally, the applicant proposes a Medication Guide to communicate risks of deucravacitinib treatment to patients.

7.1. Other Proposed Risk Management Activities

The applicant proposes postmarketing pharmacoepidemiology studies to further assess the safety profile of deucravacitinib:

- (b) (4) Long-term safety observational study in patients treated with deucravacitinib
- (b) (4) deucravacitinib pregnancy exposure and follow-up study
- IM011075 ongoing study- Extension of the Phase 3 trials to characterize long-term safety

Reviewer's Comments: *We note that these activities proposed by the applicant are outside of the scope of this REMS review and defer to DDD and Division of Pharmacovigilance and Epidemiology.*

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the Clinical Reviewer recommends approval of deucravacitinib for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Moderate-to-severe plaque psoriasis is a chronic, inflammatory, immune-mediated skin disorder that can have a profound effect on patient's quality of life. The benefits of treatment with deucravacitinib were demonstrated by meeting the co-primary endpoints of the proportion of subjects who achieved a sPGA score of 0 (clear) or 1 (minimal) with at least 2 grade improvement from baseline at Week 16 and the proportion of subjects who achieved PASI 75 at Week 16.

The safety profile for deucravacitinib is similar to that of the biologic psoriasis agents with JAK inhibition.[8] Treatment-emergent serious infections and lymphoma were observed during the clinical trials. The proposed label includes a Warning and Precaution for the increased risk of infection and potential risk of malignancies due to JAK inhibition. Additionally, the proposed MG includes the risk of infections as a possible side effect of deucravacitinib treatment. The DDD has determined that a post-marketing requirement (PMR) to evaluate the long-term safety of deucravacitinib is necessary, as well as 2 pediatric, 2 pregnancy and 1 lactation PMR.

The healthcare providers who are likely to prescribe deucravacitinib should be familiar with immunomodulatory psoriasis therapies and knowledgeable about the potential risks related to JAK inhibition. The REMS that mitigated the risks of infections and malignancies for etanercept, adalimumab, certolizumab, infliximab and ustekinumab were released because the CP activities were completed and

the REMS assessments demonstrated that healthcare professionals understood the key risk messages. Since the likely prescribers of deucravacitinib and the aforementioned agents are the same, prescribers should be aware and knowledgeable about the risks. Therefore, based on the data currently available, DRM and DDD agree that a REMS is not necessary to ensure the benefits outweigh the risks of deucravacitinib.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks for deucravacitinib. In general, healthcare providers who treat moderate-to-severe plaque psoriasis with immunomodulatory agents are familiar with the risks of serious infections and malignancies, such as lymphoma, that can result from JAK inhibition. These healthcare providers will likely be specialists and understand the importance of patient monitoring. At the time of this review, labeling is ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] Warycha MA, What is Psoriasis? CareMount Medical 2018-2021. What is Psoriasis?– Healthcare Services in New York | Multi-Specialty Practices (caremountmedical.com)

[2] Feldman, SR, In: UpToDate, Dellavalle RP, Duffin KC, Ofori AO (Eds), UpToDate, Waltham, MS (Accessed on July 11, 2022). Treatment of psoriasis in adults - UpToDate

[3] Kupetsky EA, Keller M. Psoriasis vulgaris: an evidence-based guide for primary care. J AM Board Fam Med 2013;26:787-801

[4] Feldman, SR, In: UpToDate, Dellavalle RP, Duffin KC, Ofori AO (Eds), UpToDate, Waltham, MS (Accessed on July 11, 2022). Treatment of psoriasis in adults - UpToDate

[5] Feldman, SR, In: UpToDate, Dellavalle RP, Duffin KC, Ofori AO (Eds), UpToDate, Waltham, MS (Accessed on August 3, 2022). Treatment of psoriasis in adults - UpToDate

[6] Division of Dermatology and Dentistry. Draft Unireview for Sotyktu (Deucravacitinib), NDA 214958, August 18, 2022.

[7,8] Division of Dermatology and Dentistry. Draft Unireview for Sotyktu (Deucravacitinib), NDA 214958, August 19, 2022.

10.2 FDA Approved Biologic Treatments for Moderate-to Severe Psoriasis

Product Trade Name (Generic) Year of Approval	Mechanism of Action	Indication	Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Biologic Treatments for Moderate-to Severe Psoriasis					
Skyrizi (risankizumab) 2019	IL-23 inhibitor	moderate-to-severe plaque psoriasis, psoriatic arthritis, Crohn's disease	SC and IV injections	hypersensitivity reactions, infections, TB, hepatotoxicity in Crohn's treatment	MG, IFU
Ilumya (tildrakizumab) 2018	IL-23 inhibitor	moderate-to-severe plaque psoriasis	SC injection	hypersensitivity reactions, infections, TB	MG
Siliq (brodalumab) 2017	IL-17A receptor antagonist	moderate-to-severe plaque psoriasis in pts who failed to respond or lost response to other systemic therapies	SC injection	SIB, infections, TB, Crohn's disease	REMS for SIB, boxed warning for SIB, MG, IFU
Tremfya (guselkumab) 2017	IL-23 inhibitor	moderate-to-severe plaque psoriasis, psoriatic arthritis	SC injection	hypersensitivity reactions, infections, TB	MG, IFU
Taltz (ixekizumab) 2016	IL-17A inhibitor	Moderate-to-severe plaque, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis	SC injection	Infections, TB, hypersensitivity, IBD	MG
Cosentyx (secukinumab) 2015	IL-17A inhibitor	Moderate-to-severe plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, enthesitis-related arthritis	SC injection	Infections, TB, IBD, hypersensitivity reactions	MG, IFU
Stelara (ustekinumab) 2009	IL-12 and 23 inhibitor	Moderate-to-severe plaque psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis	SC and IV injections	Infections, TB, malignancies, hypersensitivity reactions, Posterior reversible encephalopathy syndrome	MG

Cimzia (certolizumab) 2008	TNF-alpha inhibitor	Crohn's disease, moderate-to-severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, moderate-to-severe plaque psoriasis	SC injection	Infections, malignancies, heart failure, hypersensitivity reactions, neurologic reactions, hematological reactions	Boxed warning for serious infections, TB, lymphoma and other malignancies; MG, IFU
Humira (adalimumab) 2002	TNF-alpha inhibitor	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, uveitis	SC injection	Infections, malignancies, anaphylaxis or hypersensitivity reactions, demyelinating disease, heart failure	Boxed warning for serious infections and malignancy; MG, IFU
Remicade (infliximab) 1998	TNF-alpha inhibitor	Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis	IV injection	Infections, malignancies, hepatotoxicity, heart failure, cytopenias, hypersensitivity, demyelinating disease, cardiovascular/cerebrovascular reactions	Boxed warning for serious infections and malignancy; MG
Enbrel (etanercept) 1998	TNF-alpha inhibitor	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis	SC injection	Infections, demyelinating disease, lymphoma, heart failure, anaphylaxis or allergic reactions	Boxed warning for serious infections and malignancies; MG, IFU
Other Treatments: phototherapy, topical treatments, non-biologic therapies, dietary supplements (turmeric, St. John's wort, fish oil, vitamin D, zinc, aloe vera)					

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