DEUCRAVACITINIB
RISK MANAGEMENT PLAN

Version Number: 2.0

Data-Lock Point for this RMP: 15-Jun-2022

Date of Final Sign-off: 11-Dec-2023

Bristol-Myers Squibb
P.O. Box 4000
Princeton, NJ 08543-4000
USA

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

LIST OF ANNEXES

LIST OF ABBREVIATIONS

Term	Definition
AE(s)	adverse event(s)
aHR	adjusted hazard ratio
AUC	area under the curve
BID	twice daily
BMS	Bristol Myers Squibb
CD	Crohn's disease
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CT	computed tomography
CV	cardiovascular
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EEA	European Economic Area
EEIG	European Economic Interest Grouping
FDA	Food and Drug Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA-Cw6	human leukocyte antigen Cw6
HR	hazard ratio
IFN	interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGRA	interferon-gamma release assay
IL	interleukin
IR	incidence rate
IV	intravenous
JAK	Janus kinase
KLH	keyhole limpet hemocyanin
LTE	long-term extension

Term	Definition
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MSSO	MedDRA Support and Services Organization
N/A	not applicable
NMSC	non-melanoma skin cancer
NOAEL	no-observed-adverse-effect level
OR	odds ratio
p-y	person-years
PASS	post-authorisation safety study
PE	pulmonary embolism
PI	Product Information
PL	Package Leaflet
PsA	psoriatic arthritis
PSORS1	Psoriasis susceptibility 1
PSUR	Periodic Safety Update Report
PT	preferred term
PUVA	psoralen with UVA light
PV	pharmacovigilance
QD	once daily
QOD	once every other day
RA	rheumatoid arthritis
RBC	red blood cell
RHD	recommended human dose
RMP	Risk Management Plan
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SOC	System Organ Class
STAT	signal transducer and activator of transcription
TB	tuberculosis
TDAR	T-cell-dependent antibody response
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor

Term	Definition
TYK2	tyrosine kinase 2
UK	United Kingdom
US	United States
VTE	venous thromboembolic events

EU RISK MANAGEMENT PLAN (RMP) FOR DEUCRAVACITINIB

RMP Version: 2.0

Data-Lock Point for this RMP: 15-Jun-2022

Date of Final Sign-off: 11-Dec-2023

Rationale for submitting an updated RMP: To revise milestone due dates for the Category 3 studies listed in Section 3.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	N/A	V1.3 / 24-Mar-2023
SII Non-clinical part of the safety specification	N/A	V1.3 / 24-Mar-2023
SIII Clinical trial exposure	N/A	V1.3 / 24-Mar-2023
SIV Populations not studied in clinical trials	N/A	V1.3 / 24-Mar-2023
SV Post-authorization experience	Updated with post-authorisation exposure data from PSUR #2	V2.0 / Pending
SVI Additional EU requirements for the safety specification	N/A	V1.3 / 24-Mar-2023
SVII Identified and potential risks	N/A	V1.3 / 24-Mar-2023
SVIII Summary of the safety concerns	N/A	V1.3 / 24-Mar-2023
Part III Pharmacovigilance Plan	Revised milestone due dates for Category 3 studies.	V2.0 / Pending
Part IV Plan for post-authorization efficacy studies	N/A	V1.3 / 24-Mar-2023
Part V Risk Minimization Measures	N/A	V1.3 / 24-Mar-2023
Part VI Summary of the Risk Management Plan	N/A	V1.3 / 24-Mar-2023
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Revised milestone due dates for Category 3 studies.	V2.0 / Pending
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	N/A	V1.3 / 24-Mar-2023

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
ANNEX 4 Specific adverse drug reaction follow-up forms	N/A	V1.3 / 24-Mar-2023
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	N/A	V1.3 / 24-Mar-2023
ANNEX 6 Details of proposed additional risk minimisation activities	N/A	V1.3 / 24-Mar-2023
ANNEX 7 Other supporting data	N/A	V1.3 / 24-Mar-2023
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include V2.0	V2.0 / Pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

Version number: 1.3

Approved with procedure: EMEA/H/C/005755/0005

Date of approval (opinion date): 24-Mar-2023

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler, EU QPPV

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	deucravacitinib
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, selective immunosuppressant (L04AA56)
Marketing Authorisation Applicant	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	SOTYKTU
Marketing authorization procedure	centralized
Brief description of the product	Deucravacitinib is a small molecule that selectively inhibits the TYK2 enzyme. 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 functions in cells. TYK2 mediates signalling of (IL-23, IL-12, and type I IFN, which are naturally occurring cytokines involved in inflammatory and immune responses. Deucravacitinib inhibits the release of proinflammatory cytokines and chemokines.
Hyperlink to the Product Information	Refer to eCTD sequence 0005
Indication(s) in the EEA	**Current:** **Plaque Psoriasis:** SOTYKTU is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. **Proposed:** N/A
Dosage in the EEA	**Current:** **Plaque Psoriasis:** The recommended dose is 6 mg taken orally once daily. **Proposed:** N/A
Pharmaceutical form (s) and strength(s)	**Current:** Film-coated tablet (tablet) Pink, round, biconvex, film-coated tablet of 8 mm diameter, printed with “BMS 895’’, and “6mg” on one side in two lines, plain on the other side. **Proposed:** N/A

Table 1-1: Product Details

Is/will the product be subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Psoriasis

Table 2.1.1-1: Epidemiologic Characteristics of Psoriasis

Psoriasis	
Incidence	Bell et al., using the Rochester Epidemiology Project database in the US, reported an overall incidence of psoriasis of 59.9/100,000 p-y (95% CI: 49.5-70.3).[1] Two European studies used data from primary-care databases and reported incidences of 120-130/100,000 p-y (the Netherlands)[2] and 140/100,000 p-y (UK).[3]
Prevalence	According to current studies, more than 8 million US Americans have psoriasis. 125 million people worldwide-2 to 3 percent of the total population-have psoriasis, according to the World Psoriasis Day consortium.[4,5] The most common form (58-97% of cases) is plaque psoriasis.[6] Nearly one-quarter of people with psoriasis have cases that are considered moderate to severe.
Demographics of the population: age, gender, racial and/or ethnic origin	Although psoriasis occurs worldwide, its prevalence varies. Psoriasis is estimated to affect about 2-4% of the population in western countries.[7,8,9] Important factors in the variation of the prevalence of psoriasis include age, gender, geography, and ethnicity, probably due to genetic and environmental factors. Higher prevalence rates have been reported at higher latitudes, and in Caucasians compared with other ethnic groups.[10] The North-East and South Europe reported higher values than the UK, specifically of 3.73% (95% CI: 3.13-4.32) in Denmark,[11] 4.82% (95% CI: 4.47-5.17)[12] and 8.50% (95% CI: 8.03–8.97) in Norway,[13] 3.10% (95% CI: 2.54-3.66) in Italy,[14] and 5.20% (95% CI: 4.68-5.72) in France.[15] Although it can present at any age, studies have observed a bimodal distribution of adult-onset psoriasis with the first peak ranging from 20-30 years of age and the second peak ranging from 55-60 years of age.[16] Early Onset Psoriasis (Type I) occurs prior to age 40 and accounts for more than 75% of cases.[45] The prevalence of psoriasis is considered to be balanced between the sexes; however, some studies have indicated sex differences in the treatment of psoriasis.[8] In a study spanning three decades (1970-2000), overall age-adjusted incidence has been observed to be higher in males (85.5 per 100,000; 95% CI: 79.5, 91.6) than in females (73.2 per 100,000; 95% CI: 68.0, 78.4; p=0.003). However, age and sex-specific annual incidence in females was highest in the sixth decade of life (90.7 per 100,000) whereas among men, a peak incidence was observed in the seventh decade of life (115.3 per 100,000).[17]
Risk factors for the disease	The prevalence of psoriasis varies with the country, and psoriasis can appear at any age, suggesting that ethnicity, genetic background, and environmental factors affect

Table 2.1.1-1: Epidemiologic Characteristics of Psoriasis

Psoriasis	
	the onset of psoriasis. Extrinsic risk factors such as injuries, air pollution, sun exposure, alcohol, drugs, vaccination, and infection (e.g.: strep throat) have been associated with the development of psoriasis. Intrinsic risk factors can include obesity, metabolic syndrome, mental stress, diabetes mellitus, and hypertension.[18] Genetic factors play a significant role in the pathogenesis of psoriasis. PSORS1, which lies within an approximately 220 kb segment of the major histocompatibility complex on chromosome 6p21, is a major susceptibility locus for psoriasis.[19,20,21] HLA-Cw6 is the susceptibility allele within PSORS1;[22] it is associated with early onset and severe and unstable disease.[27,23] In genetically predisposed individuals, various triggering factors can elicit the disease. In past surveys from 1982 to 2012, the exacerbating factors for the Japanese population were observed to be stress (6.4% to 16.6%), seasonal factors (9.7% to 13.3%), infection (3.5% to 8.3%), sun exposure (1.3% to 3.5%), and β-blockers (0.9% to 2.3%).[24,25,26] Metabolic syndrome is common in patients with psoriasis and obesity is strongly associated with the onset and exacerbation of psoriasis.[27,28,29,30,31,32,33] Patients with psoriasis have a significantly higher prevalence of obesity as well as a higher risk of obesity.[34,35,36] In a meta-analysis, patients with psoriasis showed greater prevalence and incidence of hypertension.[37] This meta-analysis also revealed that severe psoriasis was associated with greater incidence of hypertension. Patients with psoriasis appear to have more severe hypertension. Patients with CD have a 7-times higher risk of developing psoriasis, and psoriasis patients have a 2.9-times higher risk of developing CD, when compared with the general population.[38]
Main treatment options	Mild to moderate psoriasis can be treated topically with a combination of glucocorticoids, vitamin D analogues, and phototherapy. Moderate to severe psoriasis often requires systemic treatment. The presence of comorbidities such as psoriatic arthritis is also highly relevant in treatment selection. Severe psoriasis requires phototherapy or systemic therapies such as retinoids, methotrexate, cyclosporine, apremilast, or biologic immune modifying agents. Biologic agents used in the treatment of psoriasis include the anti-TNF agents adalimumab, etanercept, infliximab, and certolizumab pegol; the anti-IL-12/IL-23 antibody ustekinumab; the anti-IL-23A antibodies risankizumab and guselkumab; the anti-IL-17 antibodies secukinumab and ixekizumab; the anti-IL-17 receptor antibody brodalumab; and the anti-IL-23/IL-39 antibody tildrakizumab.
Mortality and morbidity (natural history)	Severe psoriasis is associated with an increased risk of death from a variety of causes with cardiovascular death being the most common etiology.[39] These patients were also at increased risk of death from infection, kidney disease, and dementia. Patients with severe psoriasis were at increased risk of death from cardiovascular disease (HR = 1.57; 95% CI: 1.26, 1.96), malignancies (HR = 1.41; 95% CI: 1.07, 1.86), chronic lower respiratory disease (HR = 2.08; 95% CI: 1.24-3.48), diabetes (HR = 2.86; 95% CI: 1.08, 7.59), dementia (HR = 3.64; 95% CI: 1.36, 9.72), infection (HR = 1.65; 95% CI: 1.26, 2.18), kidney disease (HR = 4.37; 95% CI: 2.24, 8.53), and unknown/missing causes (HR = 1.44; 95% CI: 1.09, 1.88).[44] The absolute and excess risk of death was highest for cardiovascular disease (61.9 and 3.5 deaths per 1000 p-y, respectively).[44]

Table 2.1.1-1: Epidemiologic Characteristics of Psoriasis

Psoriasis	
	Patients with severe psoriasis are also shown to be at increased risk of thromboembolic events (aHR = 1.26 [95% CI 1.07, 1.47], p = 0.005).[40] Patients with psoriasis have a slightly elevated baseline risk of malignancies, in particular lymphoproliferative diseases. Compared to patients without psoriasis, patients with psoriasis had increased risk for all cancers excluding NMSC (aHR = 1.06, 95% CI 1.02, 1.09) and for lymphoma (aHR = 1.34, 95% CI 1.18, 1.51).[41] Results from two separate meta-analyses also demonstrated patients with psoriasis had higher risk of malignancy compared to non-psoriasis patients, particularly keratinocyte cancer and lymphomas.[42,43] In patients with moderate-to-severe psoriasis, the incidence rate for lymphoma was 0.35 per 1,000 p-y, 0.58 per 1,000 p-y for lung cancer, and 3.53 per 1,000 p-y for NMSC. Compared to patients without psoriasis, moderate-to-severe psoriasis patients demonstrated a strong association for lymphoma (aHR = 1.86, 95% CI: 1.23, 2.80), for lung cancer (aHR = 1.60, 95% CI: 1.14, 2.24), and for NMSC (aHR = 1.61, 95% CI: 1.42, 1.84).[41] In the literature, the incidence rate of serious infections in the psoriasis population is higher compared to the general population. In a study conducted using the national Inpatient Sample from 2002-2012, which represents a 20% sample of all hospitalizations in the US, including 187,246 patients with psoriasis, psoriasis was found to be associated with serious infections (OR = 1.30, 95% CI: 1.28, 1.32). The strongest associations were observed for cellulitis (OR = 3.21, 95% CI: 3.12, 3.30), herpes simplex virus (OR = 2.21, 95% CI: 1.70, 2.89), and fungal infections (OR = 2.02, 95% CI: 1.96, 2.09).[40] In a recent study by Takeshita et al in 2018,[44] risk of herpes zoster in 12,442 patients with moderate-to-severe psoriasis was compared with 954,315 randomly selected patients without psoriasis in a large UK primary care medical record database. Patients with psoriasis had a higher incidence of serious infection than patients without psoriasis; the incidence rate for herpes zoster was highest among patients with moderate to severe disease (incidence rate = 6.47 per 1000 p-y, 95% CI: 5.88, 7.11). Compared to those without psoriasis, patients with moderate-to-severe psoriasis had higher risk of herpes zoster infection (aHR = 1.17, 95% CI: 1.06, 1.30).
Important comorbidities	Comorbidities classically associated with psoriasis are psoriatic arthritis, CD, psychological/psychiatric disorders.[45,46,47] In recent years, the metabolic syndrome as a whole and its individual components have been associated with psoriasis. Gelfand et al. considered psoriasis as an independent factor of cardiovascular risk aggravation.[48] Psoriatic arthritis is a chronic, often progressive, inflammatory arthropathy that can lead to permanent joint damage and severe disability. Psoriatic arthritis is a common comorbidity among patients with psoriasis, affecting 6% to 10% of psoriasis patients overall and 20% to 40% of psoriasis patients with more extensive skin involvement.[49] Binus et al. reported that patients with psoriasis and concomitant inflammatory bowel disease have a higher rate of comorbidities (seronegative arthritis, thyroiditis, diabetes and lymphoma) than patients with psoriasis only, which could be explained by common inflammatory pathways and shared genetic risks.[38] Psoriasis is associated with low self-esteem and prevalence of anxiety and depressive disorders (30% and 60%, respectively).[50,51,52] Recently, a high prevalence of

Table 2.1.1-1: Epidemiologic Characteristics of Psoriasis

Psoriasis	
	alexithymia was observed. About 10% of patients with psoriasis consider the possibility of suicide. Recent data shows that depression and anxiety are mainly found in women with family problems.[53]

2.2 Nonclinical Part of the Safety Specification

The scope and results of the nonclinical toxicity studies support the clinical use of deucravacitinib at the RHD in human subjects with moderate-to-severe psoriasis. Deucravacitinib is pharmacologically active in rats and monkeys and was tolerated following once daily oral dosing for up to 6 months in rats and 9 months in monkeys. Deucravacitinib was not carcinogenic in a 6-month study in rasH2 transgenic mice at doses up to 60 mg/kg/day (185× RHD AUC) or a 2-year study in rats at doses up to 15 mg/kg/day (51× RHD AUC). In addition, there was no evidence of lymphoproliferative disorders or malignancies in the 9-month toxicity study in monkeys (65× RHD AUC).

The lymphoid/immune, hematopoietic, and skin were identified as the main target organs of toxicity, with the following principal effects in the chronic rat and monkey toxicology studies:

1) In rats, several immunomodulatory effects were noted at doses ≥ 5 mg/kg (≥ 9× RHD AUC), including decreased blood lymphocytes and lymphoid cellularity in lymph nodes, decreased spleen and weights, decreased lymphoid cellularity of the splenic white pulp, and decreased T-cell-dependent antibody (IgM and IgG) response (TDAR) to KLH. Decreased TDAR to KLH was also noted in monkeys at ≥ 1 mg/kg (≥ 7× RHD AUC) without decreased blood lymphocytes or microscopic changes in lymphoid tissues.
2) Decreased RBC mass parameters (count, hemoglobin, and hematocrit) and platelets in rats at ≥ 15 mg/kg (≥ 42× RHD AUC) and monkeys at ≥ 1 mg/kg (≥ 7× RHD AUC).
3) Various skin changes (swollen, dry, lesion, flaking, papule, red, white, scab) throughout the body in monkeys were noted at doses ≥ 1 mg/kg (≥ 7× RHD AUC). Skin findings in most monkeys did not require veterinary treatments; others were treated with antibiotics, and/or antiseptic agents. The skin findings generally improved clinically after start of the veterinary treatments and did not result in any preterminal deaths or unscheduled euthanasia.

The above findings were fully or partially reversible following discontinuation of drug administration.

In the pivotal embryo-fetal development studies in rats at doses up to 75 mg/kg/day (266× RHD AUC) and rabbits at doses up to 10 mg/kg/day (total/free 91×/20× RHD AUC, respectively), there was no evidence of teratogenicity or effects on embryo-fetal development. Deucravacitinib had no effects on male rat reproductive parameters or early embryonic development of litters sired by deucravacitinib-treated males at doses up to 50 mg/kg/day (247× RHD AUC). In a female rat fertility study, there were no deucravacitinib-related effects on mating and fertility parameters at doses up to 50 mg/kg/day (171× RHD AUC). In a pre- and post-natal development study in rats, deucravacitinib administered at doses up to 50 mg/kg/day was well tolerated with no maternal

toxicity. Deucravacitinib was associated with transient adverse effects on pup body weight in the preweaning period at 50 mg/kg/day, which recovered postweaning. Based on these results, the maternal NOAEL was considered to be 50 mg/kg/day (110× RHD AUC) and the developmental NOAEL was considered to be 15 mg/kg/day (19× RHD AUC).

The results of these evaluations support the long-term safety of deucravacitinib in humans. Safety specifications for the principal nonclinical findings are summarized in Table 2.2-1. A summary of nonclinical safety is provided in Appendix 2.

Table 2.2-1: Summary of Significant Nonclinical Safety Findings

Key Safety Findings	Relevance to human usage
Skin Findings A variety of skin findings (swollen, dry, lesion, flaking, papule, red, white, scab) located throughout the body were noted in the chronic monkey study at doses ≥ 7× RHD AUC. The skin changes were monitorable and improved following antibiotic and/or antiseptic treatments, and were present in the context of deucravacitinib-mediated immunomodulation.	Skin findings (eg, folliculitis, acne, or acneiform dermatitis) were observed in clinical studies in healthy subjects and infrequently in patients with moderate-to-severe plaque psoriasis. The skin findings were mild or moderate in severity, reversible, and rarely led to discontinuation of study treatment. Based on the nature of the events observed, the skin findings are not anticipated to impact the benefit-risk balance of the product or have implications for public health; therefore, they are not classified as an important risk for deucravacitinib.
Decreased RBC Mass Parameters and Platelets Decreased RBC mass parameters (count, hemoglobin, and hematocrit) and platelets were noted in rats at doses ≥ 42× RHD AUC, and monkeys at doses ≥ 7× RHD AUC. These changes were monitorable and reversible.	Based on the available data from the deucravacitinib Phase 1 to 3 studies, there is no clinical evidence to suggest that deucravacitinib alters RBC or platelet counts.
Decreased TDAR to KLH Immunization Decreased TDAR (IgM and IgG) to immunization with KLH in rats at doses ≥ 9× RHD AUC, and monkeys at doses ≥ 7× RHD AUC. Decreased TDAR responses are consistent with the contributions of Type I IFNs and IL-12/23 to the antigen-induced antibody responses. However, although diminished, the KLH-induced IgM and IgG antibody responses were still evident, indicating that responses to the primary or recall responses were still maintained in rats and monkeys, and were fully reversible during post-dose recovery in rats.	To date, no vaccination studies in humans have been completed with deucravacitinib.

2.3 Clinical Trial Exposure

Deucravacitinib has been studied in a comprehensive clinical development program in Phase 1, 2, and 3 studies. An overview of the deucravacitinib clinical program summarized in this RMP supporting the safe and effective use of deucravacitinib is in Table 2.3-1.

Table 2.3-1: Deucravacitinib Clinical Studies in Adults with Psoriasis Supporting Safety Analyses in the RMP

Study Number	Study Title	Number Treated Subjects
IM011046	A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis	665
IM011047	A Multi-Center, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled Phase 3 Study with Randomized Withdrawal and Retreatment to Evaluate the Efficacy and Safety of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis	1,018
IM011075	An Open-Label, Multi-Center Extension Study to Characterize the Long-Term Safety and Efficacy of BMS-986165 in Subjects with Moderate-to-Severe Plaque Psoriasis	1,221
IM011011	A Multi-Center, Randomized, Double-Blind, Placebo-controlled, Parallel Group Phase 2 Study to Evaluate the Clinical Efficacy and Safety of BMS-986165 in Subjects with Moderate to Severe Psoriasis	267

Exposure to deucravacitinib is derived from the key Phase 3 studies (IM011046, IM011047, and IM011075) in moderate-to-severe psoriasis. The **Controlled Safety Pool** comprises the 2 pivotal, Phase 3 studies (IM011046 and IM011047) which evaluated the use of deucravacitinib in adult subjects with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Both studies had similar designs (identical up to Week 24), with the same comparators, identical eligibility criteria, the same co-primary endpoints, and many of the same secondary endpoints. Both studies were double-blind and placebo-controlled through Week 16, apremilast-controlled through Week 24, and were 52 weeks in treatment duration. The **Phase 3 Safety Pool** comprises the two pivotal Phase 3 psoriasis studies and long-term safety data in subjects from these two studies enrolled in the long-term extension study (IM011075) as of the safety cutoff date. Subjects were eligible regardless of assigned treatment in the pivotal Phase 3 studies and may have received deucravacitinib, placebo, and/or apremilast as per protocol.

The exposure tables are as follows:

- Table 2.3-2 presents overall duration of exposure for the Controlled Safety Pool (Week 0-52)
- Table 2.3-3 presents overall duration of exposure for the Phase 3 Safety Pool (Week 0 - safety cutoff date [15-Jun-2022])
- Table 2.3-4 presents exposure by sex, age group, and race for the Controlled Safety Pool (Week 0-16)
- Table 2.3-5 presents exposure by sex, age group, and race for the Controlled Safety Pool (Week 0-52)
- Table 2.3-6 presents exposure by sex, age group, and race for the Phase 3 Safety Pool (Week 0 - safety cutoff date [15-Jun-2022])

Table 2.3-2: Duration of Exposure (Psoriasis) - Controlled Safety Pool Week 0 Through 52 - As-treated Population in Studies IM011046 and IM011047

Statistic	BMS-986165 6 mg QD N = 1364	Placebo N = 666	Apremilast N = 422
DURATION OF EXPOSURE (DAYS)			
N	1364	666	422
MEAN (SD)	259.5 (100.60)	132.1 (49.59)	191.4 (96.81)
MEDIAN	252.0	113.0	168.0
MIN, MAX	1, 400	1, 210	3, 392
TOTAL EXPOSURE IN PATIENT-YEARS	969.0	240.9	221.1
AT LEAST ONE DOSE (%)	1364 (100)	666 (100)	422 (100)
AT LEAST 16 WEEKS OF TOTAL EXPOSURE (%)	1257 (92.2)	581 (87.2)	370 (87.7)
EXPOSURE IN MONTHS (%)			
< 4	107 (7.8)	77 (11.6)	52 (12.3)
4 - < 6	96 (7.0)	375 (56.3)	67 (15.9)
6 - < 12	641 (47.0)	214 (32.1)	221 (52.4)
>= 12	520 (38.1)	0 (0.0)	82 (19.4)

Exposure is summarized according to the number of subjects exposed to each treatment and includes all exposure up to Week 52.
Total exposure in patient-years is calculated as the sum of exposure from all subjects divided by 365.25.
Includes data from IM011046 and IM011047.
Program Source: /gbs/prod/clin/programs/im/011/pso/fda/rpt/rt-ex-exdsum1rmp-v01.sas 08AUG2021:10:16

Table 2.3-3: Duration of Exposure (Psoriasis) - Phase 3 Safety Pool Week 0 Through Safety Cutoff Date - As-treated Population in Studies IM011046, IM011047, and IM011075

Statistic	BMS-986165 6 mg QD N = 1519
DURATION OF EXPOSURE (DAYS)	
N	1519
MEAN (SD)	784.1 (378.53)
MEDIAN	932.0
MIN, MAX	1, 1467
TOTAL EXPOSURE IN PATIENT-YEARS	3260.7
AT LEAST ONE DOSE (%)	1519 (100)
AT LEAST 16 WEEKS OF TOTAL EXPOSURE (%)	1407 (92.6)
EXPOSURE IN MONTHS (%)	
< 4	111 (7.3)
4 - < 6	64 (4.2)
6 - < 12	136 (9.0)
12 - < 18	75 (4.9)
18 - < 22	57 (3.8)
22 - < 26	130 (8.6)
26 - < 30	113 (7.4)
30 - < 34	314 (20.7)
34 - < 38	396 (26.1)
38 - < 42	81 (5.3)
42 - < 46	39 (2.6)
46 - < 50	3 (0.2)
>= 50	0

Exposure is summarized according to the number of subjects exposed to BMS-986165 6 mg QD only.
Total exposure in patient-years is calculated as the sum of exposure from all subjects divided by 365.25.
Includes subjects who were assigned to BMS-986165 in IM011046, IM011047, or IM011075.
Includes data from IM011046, IM011047, and IM011075 (Safety Cutoff Date = 15JUN2022).

Program Source: /gbs/prod/clin/programs/im/011/ebr25-euir/d180/rpt/rt-ex-exdsum2rmp-v02.sas 05OCT2022:17:41

Table 2.3-4: Clinical Exposure by Sex, Age Group, and Race - Controlled Safety Pool Week 0 Through 16 - As-treated Population in Studies IM011046 and IM011047

	BMS-986165 6 mg QD N = 842		Placebo N = 419		Apremilast N = 422	
Category	n (%)	P-Y	n (%)	P-Y	n (%)	P-Y
SEX						
MALE	566 (67.2)	165.4	292 (69.7)	83.0	267 (63.3)	76.6
FEMALE	276 (32.8)	80.2	127 (30.3)	34.9	155 (36.7)	43.8
AGE CATEGORIZATION						
18 - < 40	270 (32.1)	78.2	125 (29.8)	35.2	148 (35.1)	42.7
40 - < 65	492 (58.4)	143.8	243 (58.0)	67.8	236 (55.9)	67.0
65 - < 75	67 (8.0)	20.2	45 (10.7)	13.2	34 (8.1)	9.6
75 - < 85	13 (1.5)	3.4	6 (1.4)	1.6	4 (0.9)	1.2
>= 85	0		0		0	
RACE						
WHITE	740 (87.9)	216.6	359 (85.7)	101.0	368 (87.2)	105.1
BLACK OR AFRICAN AMERICAN	10 (1.2)	2.7	12 (2.9)	3.4	10 (2.4)	2.6
ASIAN	83 (9.9)	24.1	41 (9.8)	11.7	40 (9.5)	11.6
OTHER	9 (1.1)	2.2	7 (1.7)	1.9	4 (0.9)	1.3

Exposure is summarized according to the number of subjects exposed to each treatment and includes all exposure up to Week 16.
Total exposure in patient-years is calculated as the sum of exposure from all subjects divided by 365.25.
Includes data from IM011046 and IM011047.
Program Source: /gbs/prod/clin/programs/im/011/pso/fda/rpt/rt-ex-exsa1rmp-v02.sas 08AUG2021:10:25

Table 2.3-5: Clinical Exposure by Sex, Age Group, and Race - Controlled Safety Pool Week 0 Through 52 - As-treated Population in Studies IM011046 and IM011047

	BMS-986165 6 mg QD N = 1364		Placebo N = 666		Apremilast N = 422	
Category	n (%)	P-Y	n (%)	P-Y	n (%)	P-Y
SEX						
MALE	931 (68.3)	666.5	437 (65.6)	156.6	267 (63.3)	140.5
FEMALE	433 (31.7)	302.5	229 (34.4)	84.3	155 (36.7)	80.6
AGE CATEGORIZATION						
18 - < 40	440 (32.3)	306.3	204 (30.6)	72.6	148 (35.1)	76.5
40 - < 65	791 (58.0)	570.9	383 (57.5)	139.2	236 (55.9)	125.1
65 - < 75	114 (8.4)	79.5	71 (10.7)	26.7	34 (8.1)	17.3
75 - < 85	19 (1.4)	12.2	8 (1.2)	2.4	4 (0.9)	2.2
>= 85	0		0		0	
RACE						
WHITE	1188 (87.1)	839.2	590 (88.6)	215.5	368 (87.2)	191.9
BLACK OR AFRICAN AMERICAN	20 (1.5)	13.9	16 (2.4)	5.4	10 (2.4)	4.1
ASIAN	139 (10.2)	106.1	51 (7.7)	17.1	40 (9.5)	23.5
OTHER	17 (1.2)	9.8	9 (1.4)	2.9	4 (0.9)	1.6

Exposure is summarized according to the number of subjects exposed to each treatment and includes all exposure up to Week 52.
Total exposure in patient-years is calculated as the sum of exposure from all subjects divided by 365.25.
Includes data from IM011046 and IM011047.
Program Source: /gbs/prod/clin/programs/im/011/pso/fda/rpt/rt-ex-exsa2rmp-v02.sas 08AUG2021:10:27

Table 2.3-6: Clinical Exposure by Sex, Age Group, and Race - Phase 3 Safety Pool Week 0 Through Safety Cutoff Date - As-treated Population in Studies IM011046, IM011047, and IM011075

Category	BMS-986165 6 mg QD N = 1519 n (%)	P-Y
SEX		
MALE	1026 (67.5)	2219.8
FEMALE	493 (32.5)	1040.9
AGE CATEGORIZATION		
18 - < 40	483 (31.8)	986.8
40 - < 65	884 (58.2)	1952.1
65 - < 75	131 (8.6)	282.7
75 - < 85	21 (1.4)	39.0
>= 85	0	
RACE		
WHITE	1325 (87.2)	2819.2
BLACK OR AFRICAN AMERICAN	23 (1.5)	45.7
ASIAN	153 (10.1)	359.1
OTHER	18 (1.2)	36.7

Exposure is summarized according to the number of subjects exposed to BMS-986165 6 mg QD only.
Total exposure in patient-years is calculated as the sum of exposure from all subjects divided by 365.25.
Includes subjects who were assigned to BMS-986165 in IM011046, IM011047, or IM011075.
Includes data from IM011046, IM011047, and IM011075 (Safety Cutoff Date = 15JUN2022).

Program Source: /gbs/prod/clin/programs/im/011/ebr25-euir/d180/rpt/rt-ex-exsa3rmp-v03.sas 05OCT2022:17:41

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Program

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered for inclusion as missing information?	Rationale (if not included as missing information)
Nonplaque psoriasis (ie, guttate, inverse, pustular, erythrodermic, or drug-induced psoriasis)	The pivotal clinical studies were designed to evaluate efficacy and safety of deucravacitinib in plaque psoriasis only	No	This population is excluded from the label.
Chronic bacterial infection / HBV infection / HCV infection / HIV-1 or -2 infection / TB infection	Deucravacitinib is an immunomodulator, which may increase the risk of serious infections	No	Serious infection is included as an important potential risk (see Section 2.7.3.1), with routine risk minimization measures in place.
Immunocompromised or concomitant use of systemic immunosuppressants	Deucravacitinib is an immunomodulator, which may increase the risk of serious infections	No	Serious infection is included as an important potential risk (see Section 2.7.3.1), with routine risk minimization measures in place.
Malignancy or a history of malignancy within the previous 5 years (other than resected cutaneous basal cell or squamous cell carcinoma, or carcinoma of cervix in situ that has been treated with no evidence of recurrence)	Deucravacitinib is an immunomodulator, which may increase the risk of malignancy	No	Malignancy is included as an important potential risk (see Section 2.7.3.1), with routine risk minimization measures in place.
Concomitant live vaccines	Deucravacitinib is an immunomodulator; therefore, concomitant use of live vaccines was prohibited	No	Serious infection is included as an important potential risk (see Section 2.7.3.1), with routine risk minimization measures in place.
< 18 years old	Safety and efficacy of deucravacitinib in pediatric subjects have not been evaluated	No	This population is excluded from the label.
Pregnant	Reproductive risk potential has not been comprehensively	Yes	N/A

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered for inclusion as missing information?	Rationale (if not included as missing information)
	evaluated in humans; no evidence of teratogenicity or effects on development in rats and rabbits		
Lactating	It is not known whether deucravacitinib passes into human milk; it was shown to be present in the milk of lactating rats	Yes	N/A
Renal impairment	This patient population was excluded from the pivotal clinical studies.	No	An independent clinical study (IM011061) has been conducted for subjects with renal impairment.
Hepatic impairment	This patient population was excluded from the pivotal clinical studies.	No	An independent clinical study (IM011062) has been conducted for subjects with hepatic impairment.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program for deucravacitinib is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Post-marketing safety monitoring and epidemiology studies will support the identification of these reactions.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities:	
Patients with hepatobiliary disorders	**Phase 3 Safety Pool**[a]: 102 subjects (~265.2 p-y)
Patients with renal disorders	**Phase 3 Safety Pool**[a]: Nephrolithiasis: 37 subjects (~96.2 p-y) Chronic kidney disease: 9 subjects (~23.4 p-y) Renal cyst: 8 subjects (~20.8 p-y) Diabetic nephropathy: 2 subjects (~5.2 p-y) Renal failure: 2 subjects (~5.2 p-y) Glomerulonephritis: 1 subject (~2.6 p-y) Glomerulonephritis acute: 1 subject (~2.6 p-y) Hydronephrosis: 1 subject (~2.6 p-y) Nephropathy: 1 subject (~2.6 p-y) Renal disorder: 1 subject (~2.6 p-y) Renal impairment: 1 subject (~2.6 p-y) Single functional kidney: 1 subject (~2.6 p-y)
Patients with cardiac disorders	**Phase 3 Safety Pool**[a]: 157 subjects (~408.2 p-y)
Immunocompromised patients	Not included in the clinical development program
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	No formal clinical studies conducted
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not applicable

[a] Exposure in p-y estimated using the median duration of exposure of 2.6 p-y in the Phase 3 Safety Pool (see Table 2.3-3)

2.5 Post-Authorization Experience

Deucravacitinib was first approved on 09-Sep-2022 in the US for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Based on PV activities conducted by BMS, postmarketing safety data are consistent with the established deucravacitinib clinical trial safety data. Due to the short time after the first approval worldwide, no post-authorisation exposure estimates are available.

Deucravacitinib postmarketing data are subject to continued PV monitoring and reporting as per applicable safety reporting requirements. Continuous safety monitoring ensures that updated safety information is available in a timely manner and that any future changes to the benefit-risk profile of deucravacitinib are appropriately managed and reported.

2.5.1 Post-authorisation Exposure

2.5.1.1 Method Used to Calculate Exposure

There is no readily available information on the number of patients treated with marketed deucravacitinib; however, an estimate of patient exposure can be derived from available sales figures and free goods and samples dispensed. For samples, the total number of packs dispensed is not recorded, only the number of patients who received them. Therefore, the amount dispensed assumes the minimum of one 30 count pack/patient of 6 mg tablets.

Internal sales, free goods, and sample figures are available for the cumulative and interval periods. Sales/shipment/dispensation data consist of all shipments of the Company's product to all applicable countries and includes commercial and free-of-charge units (as applicable). The data are used to determine the units (eg, milligram) of a product sold/dispensed to a geography to estimate the number of person-years of exposure. For deucravacitinib, a daily dose of 6 mg was used for exposure calculations, as it is assumed that one 6 mg tablet per day is taken during treatment, per the currently approved psoriasis indication.

2.5.1.2 Exposure

Patient exposure can be estimated based on sales data and free goods and samples dispensed and the assumptions described. An estimated 12,040,248 mg were sold/dispensed from 09-Sep-2022 through 08-Sep-2023. The cumulative exposure is estimated to be:

(12,040,248 mg ÷ 6 mg/day) ÷ 365.25 days/year = 5494 person-years.

This estimate of the number of person-years should be interpreted with caution given the limitations of the available sales/dispensation data.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Deucravacitinib does not cross the blood-brain barrier, does not elicit central nervous system activity, and has a low risk of abuse liability/drug dependence. In the clinical studies of psoriasis, there were no clinical features of mu or kappa receptor agonism (eg, euphoria, dysphoria, lethargy, persistent sedation) and no withdrawal symptoms typical of drugs with abuse potential in the 30-day follow-up period after stopping deucravacitinib.[54]

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP are summarized in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	None
Important potential risks	Serious infections
	Malignancies
	MACE
	VTE (DVT/PE)
Missing information	Use in pregnancy and lactation
	Long-term safety

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Deucravacitinib has a safety profile that is reflected in the Summary of Product Characteristics (SmPC) under Sections 4.4 and 4.8. New safety findings that are not categorized as either important identified or potential risks in the list of safety concerns will be described, as applicable.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk-benefit impacts of included risks are provided in Table 2.7.1.2-1.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	**Risk-Benefit Impact**
Important identified risks	None
Important potential risks	
Serious infections	Deucravacitinib may increase the risk of serious infections. In the 2 pivotal, controlled, Phase 3 psoriasis studies (IM011046 and IM011047), pneumonia was the most common serious infection in deucravacitinib-treated subjects.
Malignancies	The potential role of deucravacitinib in the development of malignancies is unclear. Limited data are available on the long-term safety of deucravacitinib.
MACE	Cumulative data do not suggest an increased risk of MACE in patients treated with deucravacitinib. However, it is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of MACE were observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in RA patients 50 years of age and older with at least one CV risk factor.
VTE (DVT/PE)	Cumulative data do not suggest an increased risk of VTE (DVT/PE) in patients treated with deucravacitinib. However, it is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of DVT and PE were

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
	observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in RA patients 50 years of age and older with at least one CV risk factor.
Missing Information	
Use in pregnancy and lactation	There are no adequate and well-controlled studies of deucravacitinib use in pregnant or lactating women. The limited data on the use of deucravacitinib in pregnant women are insufficient to inform on drug-associated risk. It is not known whether deucravacitinib passes into human milk.
Long-term safety	There are limited data on the long-term safety of deucravacitinib.

2.7.2 New Safety Concerns and Reclassification with an Updated RMP

This in an initial RMP. All safety concerns are new, and none are reclassified.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important potential risks and missing information are listed below. There are currently no important identified risks.

Important Potential Risks

- Serious infections
- Malignancies
- MACE
- VTE (DVT/PE)

Missing Information

- Use in pregnancy and lactation
- Long-term safety

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Table 2.7.3.1-1: Important Potential Risk: Serious Infections

Important Potential Risk: Serious Infections	
Potential mechanisms	Deucravacitinib is associated with specific cytokine receptors and catalyzes the phosphorylation of STAT proteins downstream of these receptors including the receptors for p40-containing cytokines, IL-12, and IL-23, as well as IFN receptor. P40-containing cytokines are involved in epithelial immune defense, such as activation of immune cells. Type 1 interferons play a critical role in immune responses to viruses. Therefore, based on its mechanism of action, deucravacitinib may increase the risk of serious infections.

Table 2.7.3.1-1: Important Potential Risk: Serious Infections

Important Potential Risk: Serious Infections

Evidence source and strength of evidence

Deucravacitinib has the potential to increase the risk of serious infections, based on its mechanism of action of selective TYK2 inhibition. Although serious infections have been reported in patients treated with deucravacitinib in clinical trials, available cumulative information does not suggest an increased risk of serious infection in patients treated with deucravacitinib.

Characterization of Risk

Controlled Safety Pool

During Week 0-16 in the Controlled Safety Pool (Studies IM011046 and IM011047), the overall incidence of infections (SOC infections and infestations) was higher in the deucravacitinib group (29.1%) than the placebo (21.5%) and apremilast (22%) groups; however, the incidence of serious infection was low and similar across treatment groups (deucravacitinib: 0.6%, placebo: 0.5%, apremilast: 0.5%). The majority of infection-related AEs were of the upper respiratory tract. The majority of the infections were mild or moderate in severity.

n (%) [IR per 100 P-Y]	Deucravacitinib (N = 842)	Placebo (N = 419)	Apremilast (N = 422)
Infection AEs	245 (29.1) [116.0]	90 (21.5) [83.7]	93 (22.0) [84.8]
Infection SAEs	5 (0.6) [2.0]	2 (0.5) [1.6]	2 (0.5) [1.6]
Infections leading to discontinuation	2 (0.2) [0.8]	2 (0.5) [1.6]	1 (0.2) [0.8]

The infection SAEs with deucravacitinib included diverticulitis, pyelonephritis, sepsis, streptococcal bacteremia, and upper respiratory tract infection. One of these cases (sepsis) was fatal: a 75-year-old white female with hypertension, history of cerebrovascular accident, pacemaker placement, rheumatoid arthritis, and obesity was discontinued from treatment with deucravacitinib on Day 4 due to a prohibited concomitant medication (leflunomide). The subject was hospitalized on Day 12 after multiple episodes of cardiac arrest with resuscitation and died the following day. A family member reported that death was due to heart failure and sepsis (medical records not provided).

The incidence of infection-related AEs leading to treatment discontinuation was low and similar across the treatment groups; the infections leading to treatment discontinuation in the deucravacitinib group were folliculitis and pneumonia.

There were 7 subjects with influenza AEs (deucravacitinib 0.5%; placebo 0.7%; apremilast 0%); none of these AEs was confirmed to be influenza by the Infection Adjudication Committee.

The frequency of herpes zoster was low and similar between the deucravacitinib (0.2%; 0.8/100 p-y) and placebo groups (0.2%; 0.8/100 p-y), and there were no reports of herpes zoster in the apremilast group. None of these events was serious, disseminated or led to discontinuation, and all resolved with usual medical care.

There were no reports of TB in any treatment group. There were no opportunistic infections in the deucravacitinib or placebo groups; there was 1 subject with an AE of blastocystis infection in the apremilast group that was not confirmed to be an opportunistic infection by the Infection Adjudication Committee.

Table 2.7.3.1-1: Important Potential Risk: Serious Infections

Important Potential Risk: Serious Infections

Phase 3 Safety Pool

In the Phase 3 Safety Pool (Studies IM011046, IM011047, and IM011075), which included 1,519 subjects who received deucravacitinib with 3,261 p-y of exposure, the IR of infections was 54.6 per 100 p-y and the IR of serious infections was 2.4 per 100 p-y. There was no observed clinically meaningful difference in the type of reported events with longer exposure. The majority of infections were mild or moderate in severity.

n (IR per 100 P-Y)	Deucravacitinib (N = 1519)
Infection AEs	903 (54.6)
Infection SAEs	76 (2.4)
Infections leading to discontinuation	11 (0.3)

In the Phase 3 Safety Pool, 276 subjects who received deucravacitinib had a COVID19-related AE. The majority of cases were not severe or serious and did not lead to treatment discontinuation. A total of 52 subjects had a serious infection related to COVID-19, including 7 fatal cases. The majority of subjects with an SAE related to COVID-19, including all deaths, had risk factors for severe COVID-19, such as elderly age, obesity, smoking, cardiovascular disease, diabetes, and lung disease. The long-term extension study (IM011075) coincided with the COVID-19 pandemic.

As described above, there was a death due to heart failure and sepsis during Week 0-16 and 7 deaths due to COVID-19. There were no additional deaths with deucravacitinib for which the cause was infection.

Infections leading to discontinuation of deucravacitinib included COVID-19 (6), COVID-19 pneumonia, folliculitis, pneumonia, postoperative wound infection, and pulmonary TB.

A total of 33 subjects who were treated with deucravacitinib had an influenza-related AE; 17 subjects (0.5/100 p-y) had an event that was confirmed to be influenza by the Infection Adjudication Committee.

There were 20 subjects with a herpes zoster event (0.6/100 p-y). The risk of herpes zoster did not increase with increasing treatment duration of deucravacitinib. None of the herpes zoster cases were serious, systemic, or led to treatment discontinuation.

There were no serious or systemic opportunistic infections in subjects who received deucravacitinib. There was 1 report of opportunistic infection: a non-serious AE of CMV infection of the gastrointestinal tract of moderate severity that did not result in treatment discontinuation. The Infection Adjudication Committee assessed that it was a case of CMV primary infection in an immunocompetent host. One case of active TB has been reported in the Phase 3 Safety Pool as of the data cutoff date. A subject [redacted] in the long-term extension study (IM011075) had a positive IGRA (protocol manda ed) on Day 380 of the study and was found to have an infiltrate in the right upper lobe of the lung consistent with TB on CT scan. The subject did not exhibit symptoms of TB, and the event was considered to be of moderate severity and not related to study treatment by the investigator.

Phase 2 Study

Table 2.7.3.1-1: Important Potential Risk: Serious Infections

Important Potential Risk: Serious Infections	
	In Study IM011011,[55] the frequency of events in the SOC of Infections and Infestations were as follows: placebo: 13.3%; deucravacitinib 3 mg QOD: 13.6%; 3 mg QD: 22.7%; 3 mg BID: 40.0%; 6 mg BID: 46.7%; 12 mg QD: 29.5%. The most common events were nasopharyngitis and upper respiratory tract infection. All but 1 infection was mild to moderate in intensity; there was 1 bacterial infection of severe intensity on Day 19 (6 mg BID). One infection led to discontinuation of study medication: nasal herpes of moderate intensity on Day 4 (12 mg QD). There was 1 SAE of infection (rotavirus enteritis), which did not result in discontinuation. Oral or nasal herpes simplex infections were reported in 6 of the 267 treated subjects (2.2%), all of whom received deucravacitinib; 5 of these subjects were in the 2 highest dose groups of 6 mg BID and 12 mg QD. There were no instances of dissemination. There were no reports of herpes zoster.

Table 2.7.3.1-1: Important Potential Risk: Serious Infections

Important Potential Risk: Serious Infections	
Risk factors and risk groups	Psoriasis has been shown to increase the risk of serious infection. Other risk factors for the development of serious infection include clinically significant metabolic and endocrine disorders such as diabetes, obesity, thyroid disorders, cardiovascular disorders, and renal and hepatic disorders; advanced age; and the concomitant use of corticosteroids and other immunosuppressants.
Preventability	Most infections can be easily recognized and managed by appropriate diagnostic procedures, dose interruption and treatment. Infections can be minimized by appropriate patient selection by considering factors such as previous history of infections, assessment of risks for chronic or latent infections, and age. Prior to initiating treatment with deucravacitinib, patients should be evaluated for TB infection. Deucravacitinib should not be administered to subjects who have evidence of a clinically important active infection or active TB. Additional information is provided in the SmPC.
Impact on the risk-benefit balance of the product	In clinical studies of deucravacitinib, the incidence of serious infection was low and similar to placebo. There is no increased risk of serious infection when treatment duration of deucravacitinib is increased. Influenza, herpes zoster, TB and opportunistic infections were infrequent and all non-serious. With early recognition and appropriate management of infections, the benefits of deucravacitinib outweigh the potential risk.
Public health impact	Serious infections have been infrequent in patients receiving deucravacitinib. With risk minimization by labeling, and early recognition and appropriate management, the public health impact on the psoriasis population is low.
MedDRA terms	MedDRA SOC - Infections and infestations

Table 2.7.3.1-2: Important Potential Risk: Malignancies

Important Potential Risk: Malignancies	
Potential mechanisms	Deucravacitinib may affect the risk of malignancies, given its immunomodulatory nature. Drugs that are immunomodulators may diminish immune surveillance and thereby increase the risk for development of malignancies. Mechanistic studies to evaluate the role of TYK2 in malignancies are inconclusive.
Evidence source and strength of evidence	As with any modulator of the immune system, there is a theoretical risk of increased malignancy with deucravacitinib. Although malignancies have been reported in patients treated with deucravacitinib in clinical trials, available cumulative information does not suggest an increased risk of malignancy in patients treated with deucravacitinib.
Characterization of risk	**Controlled Safety Pool** During Week 0-16 in the Controlled Safety Pool (Studies IM011046 and IM011047), malignancies were reported in 1 subject in the deucravacitinib group (0.1%; malignant sweat gland neoplasm), 0 subjects in the placebo group (0%), and 2 subjects in the apremilast group (0.5%; lung adenocarcinoma [fatal] and squamous cell carcinoma).

Table 2.7.3.1-2: Important Potential Risk: Malignancies

Important Potential Risk: Malignancies

Phase 3 Safety Pool

In the Phase 3 Safety Pool (Studies IM011046, IM011047, and IM011075), which included 1,519 subjects who received deucravacitinib with 3,261 p-y of exposure, malignancies were reported in 1.9% of subjects (29 subjects) for an IR of 0.9 per 100 p-y. Fourteen subjects (0.9%) had a NMSC for an IR of 0.4 per 100 p-y. Malignancies excluding NMSC were reported in 16 subjects (1.1%) for an IR of 0.5 per 100 p-y. The reported events are shown in the table below.

n (IR per 100 p-y)	Deucravacitinib (N = 1519; 3261 p-y)
Total Malignancies	**29 (0.9)**
Malignancies excluding NMSC	16 (0.5)
Solid tumors	12 (0.4)
Breast cancer[a]	3 (0.1)
Malignant melanoma	2 (0.1)
Colorectal cancer	1 (0.0)
Colon cancer	1 (0.0)
Hepatocellular carcinoma	1 (0.0)
Lung adenocarcinoma	1 (0.0)
Pancreatic carcinoma	1 (0.0)
Squamous cell carcinoma of the tongue	1 (0.0)
Ovarian germ cell teratoma[b]	1 (0.0)
Hematologic	4 (0.1)
Acute promyelocytic leukaemia	1 (0.0)
Lymphoma	3 (0.1)
B-cell lymphoma	1 (0.0)
Hodgkin's disease	1 (0.0)
Nodal marginal zone B-cell lymphoma	1 (0.0)
NMSC[c]	14 (0.4)
Basal cell carcinoma	10 (0.3)
Squamous cell carcinoma[d]	4 (0.1)
Keratoacanthoma	1 (0.0)
Malignant sweat gland neoplasm	1 (0.0)

Table 2.7.3.1-2: Important Potential Risk: Malignancies

Important Potential Risk: Malignancies	
	[a] Includes preferred terms of Breast cancer, Intraductal proliferative breast lesion, and Invasive ductal breast carcinoma [b] Was determined to be benign. [c] 2 subjects had Basal cell carcinoma and Squamous cell carcinoma [d] Includes preferred terms of Squamous cell carcinoma, Squamous cell carcinoma of skin, and Bowen's disease One of the malignancies was fatal (hepatocellular carcinoma). Three cases of lymphoma were observed in the Phase 3 Safety Pool: 1 Hodgkin's lymphoma in Study IM011046 and 2 non-Hodgkin's lymphomas (1 B-cell lymphoma [follicular lymphoma] and 1 nodal marginal zone B-cell lymphoma) in the open-label, long-term extension study (IM011075). In addition, 1 case of Hodgkin's lymphoma was reported in a subject with erythrodermic psoriasis in a single-arm, open-label regional study in Japan (IM011066).[56] BMS concluded that a causal association of deucravacitinib with the reported cases of lymphoma has not been demonstrated and factors in each of the cases also suggest non-deucravacitinib related causes. While it is not possible to rule out an association, a causal link to deucravacitinib was not established in any of the reported cases. For the 2 cases of Hodgkin's lymphoma, while a highly immunosuppressive regimen in the transplant setting is associated with EBV-positive Hodgkin's lymphoma, the targeted immunomodulation conferred by deucravacitinib is intermittent and partial (approximately 50%) over a 24-hour period and not analogous to highly immunosuppressive regimens used in the transplant setting where outgrowth of EBV-positive B cell malignancies is observed. Marginal zone B cell lymphoma and follicular lymphoma are not commonly associated with immunosuppression. The subject who was reported to have follicular lymphoma had a heavy smoking history (20 cigarettes/day for over 36 years), which is a known risk factor for follicular lymphoma.[57,58] Among the subjects with solid malignancies, there was no preponderance of any one type and the majority of subjects had risk factors for malignancy, such as older age, previous melanoma, family history, smoking history, exposure to agents known to be associated with increased risk of cancer (eg, biologic therapy), and hepatitis C with cirrhosis (in the subject with hepatocellular carcinoma). Of the 14 subjects who experienced an NMSC in the Phase 3 Safety Pool, 9 had a medical history of NMSC. Other reported risk factors included actinic keratosis, older age, Fitzpatrick Skin Type 1 or 2, phototherapy with ultraviolet A light, and prior TNF inhibitor use. **Phase 2 Data** In the Phase 2 study in psoriasis (IM011011),[55] 1 malignant melanoma in situ (Grade 0) was diagnosed on skin biopsy of an atypical nevus in a subject who received deucravacitinib 3 mg QD.
Risk factors and risk groups	Patients with psoriasis have a slightly elevated baseline risk of malignancies, in particular lymphoproliferative diseases. Among patients with psoriasis, an increased risk of solid cancers appears to be related to alcohol use and cigarette smoking. In addition, exposure to PUVA radiation and immunosuppressants (including cyclosporin and possibly methotrexate) has been associated with squamous cell carcinoma in psoriasis patients. General risk factors for malignancy include increasing age, lifestyle factors (such as

Table 2.7.3.1-2: Important Potential Risk: Malignancies

Important Potential Risk: Malignancies	
	alcohol and tobacco use and obesity), family history of cancer, and certain environmental exposures.
Preventability	Measures to prevent specific malignancies (eg, smoking cessation, sun precautions) should be recommended as part of standard medical care.
Impact on the risk-benefit balance of the product	Malignancies can be associated with a fatal outcome. Based on the mechanism of action of deucravacitinib, it may affect host defenses against malignancies. Mechanistic studies to evaluate the role of TYK2 in malignancies are inconclusive. Based on the available clinical data and the relevant epidemiology for malignancy and specifically lymphoma, there does not appear to be a clear association with deucravacitinib exposure. The benefits of deucravacitinib outweigh the potential risk of malignancies.
Public health impact	The incidence of malignancies in clinical trials of deucravacitinib has been low. There is no public health impact outside of the treated patient population.
MedDRA terms	Malignant or unspecified tumours (SMQ)

Table 2.7.3.1-3: Important Potential Risk: MACE

Important Potential Risk: MACE	
Potential mechanisms	Based on the hypothesis that inflammatory cytokines contribute to CV events, blocking cytokines that are regulated by TYK2 (ie, IL-12 and IL-23) would not be expected to increase the risk of MACE. It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of MACE were observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in RA patients 50 years of age and older with at least one CV risk factor.
Evidence source and strength of evidence	Evidence for an increased background risk of MACE in patients with psoriasis is cited in the published literature. Although MACE were reported in subjects treated with deucravacitinib in clinical trials, available cumulative information does not indicate an increased risk of MACE in patients treated with deucravacitinib.
Characterization of risk	**Controlled Safety Pool** During Week 0-16, events were adjudicated as MACE in 2/842 subjects in the deucravacitinib group (0.8/100 p-y), 3/419 subjects in the placebo group (2.4/100 p-y), and 1/422 subjects in the apremilast group (0.8/100 p y). During Week 0-52, events were adjudicated as MACE in 3/1364 subjects for deucravacitinib (0.3/100 p-y), 3/666 subjects for placebo (1.2/100 p-y), and 2/422 subjects for apremilast (0.9/100 p-y). **Phase 3 Safety Pool** In the Phase 3 Safety Pool (Studies IM011046, IM011047, and IM011075), which included 1,519 subjects who received deucravacitinib with 3,261 p-y of exposure, 11 events were adjudicated as MACE (0.3/100 p-y). The events included 5 non-fatal myocardial infarctions, 4 non-fatal strokes, and 2 CV deaths. All events of MACE occurred in subjects with relevant medical/family/social history increasing MACE risk and/or concurrent inciting factors that predispose to MACE. The majority of the events were considered not related to deucravacitinib by the investigator.

Table 2.7.3.1-3: Important Potential Risk: MACE

Important Potential Risk: MACE	
	Phase 2 Data In the Phase 2 study in psoriasis (IM011011),[55] there were no reports of MACE.
Risk factors and risk groups	The risk factors for the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, advanced age, male sex, obesity, and family history. Patients with psoriasis have been shown to be at increased risk for MACE compared with the general population.[59] Epidemiological studies have shown a higher prevalence of CV risk factors in psoriasis patients, including metabolic syndrome, smoking, obesity, hypertension, diabetes, insulin resistance, and dyslipidemia.[60] Additionally, literature suggests psoriasis may be an independent risk factor due to the high inflammatory burden of psoriatic disease.[61,62]
Preventability	Measures to prevent MACE (eg, control of modifiable CV risk factors) should be recommended as part of standard medical care.
Impact on the risk-benefit balance of the product	MACE can be associated with a fatal outcome. Based on the available clinical data and the relevant epidemiology for MACE, there does not appear to be an association with deucravacitinib exposure. The benefits of deucravacitinib outweigh the potential risk of MACE.
Public health impact	The incidence of MACE in clinical trials of deucravacitinib has been low. There is no public health impact outside of the treated patient population.
MedDRA terms	Myocardial infarction (Narrow) (SMQ); Central nervous system vascular disorders (Narrow) (SMQ); Cardiac disorders SOC (fatal), Vascular disorders SOC (fatal)

Table 2.7.3.1-4: Important Potential Risk: VTE (DVT/PE)

Important Potential Risk: VTE (DVT/PE)	
Potential mechanisms	The cytokines IL-12 and IL-23 have been implicated in thrombosis. IL-12 is important in animal models of thrombosis and loss of the related TH1 cells accelerates thrombus resolution.[63,64] In addition, inhibition of IL-23 or IL-17A is protective in a mouse model of psoriasis-related thrombosis.[65] These findings suggest that TYK2 inhibition by deucravacitinib, with consequent downstream inhibitory effects on IL-12 and IL-23, would not be predicted to be thrombogenic. It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of DVT and PE were observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in RA patients 50 years of age and older with at least one CV risk factor.
Evidence source and strength of evidence	Patients with psoriasis can have an increased risk for blood clots in veins due to their underlying condition and other risk factors. Although VTE were reported in subjects treated with deucravacitinib in clinical trials, available cumulative information does not indicate an increased risk of VTE in patients treated with deucravacitinib. The subjects who developed DVT/PE in clinical trials had recognized and well-established risk factors for thromboembolism.
Characterization of risk	**Controlled Safety Pool**

Table 2.7.3.1-4: Important Potential Risk: VTE (DVT/PE)

Important Potential Risk: VTE (DVT/PE)	
	During Week 0-16, there was 1 VTE, which was a DVT (non-serious) reported in a subject receiving deucravacitinib. During Week 0-52, there were 2 VTE in subjects receiving deucravacitinib. In addition to the event during Week 0-16, 1 subject experienced a PE (serious). There were no VTE reported with placebo or apremilast. **Phase 3 Safety Pool** Overall, in the Phase 3 Safety Pool (Studies IM011046, IM011047, and IM011075), which included 1,519 subjects who received deucravacitinib with 3,261 p-y of exposure, there were a total of 3 events of VTE (DVT/PE) with deucravacitinib, resulting in an IR of 0.1/100 p-y. In addition to the VTE in the Controlled Safety Pool, there was 1 DVT (non-serious) in the LTE study. All events of VTE occurred in subjects with relevant medical history, concomitant medication use, and/or concurrent inciting factors that predispose to VTE. • The subject who had a DVT during Week 0-16 was a current smoker using estrogen-containing oral contraceptives. The DVT was in the right radial vein, where the subject had had IV cannulation for administration of antibiotics. Thrombus formation in the radial vein may be observed following IV cannulation. The event resolved, and the subject discontinued the study for unspecified personal reasons. • The subject who had a PE had a concurrent aortic dissection and other risk factors that included, in addition to psoriasis, hypertension, obesity, and former smoker. Study treatment was temporarily interrupted. The subject subsequently enrolled into the LTE study, and continued in the study with no further VTE. • The subject who had a DVT in the LTE study was hospitalized with COVID-19 at the time of the DVT. COVID-19 has been associated with a high risk of VTE. This subject also had other risk factors that included, in addition to psoriasis, morbid obesity, hypertension, and former smoker. Study treatment was temporarily interrupted. The subject continued in the LTE study with no further VTE. All VTE were considered not related to study treatment by the investigator. **Phase 2 Data** In the Phase 2 study in psoriasis (IM011011),[55] there were no reports of VTE.
Risk factors and risk groups	An increased risk for VTE has been associated with a history of VTE, increasing age, immobility, obesity, smoking, hypertension, estrogen-containing oral contraceptives, COPD, infections (including COVID-19), and chronic inflammatory conditions, including psoriasis.[66,67,68,69,70]
Preventability	Measures to prevent VTE (eg, control of modifiable risk factors) should be recommended as part of standard medical care.
Impact on the risk-benefit balance of the product	VTE can be associated with a fatal outcome. Based on the available clinical data and the relevant epidemiology for VTE, there does not appear to be an association with deucravacitinib exposure. The benefits of deucravacitinib outweigh the potential risk of VTE.
Public health impact	The incidence of VTE in clinical trials of deucravacitinib has been low. There is no public health impact outside of the treated patient population.
MedDRA terms	PTs: Deep vein thrombosis, Pulmonary embolism

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information

Missing Information	Evidence Source
Population in need of further characterization: Use in pregnancy and lactation	No formal clinical studies have been conducted.
Long-term safety	There are limited data on the long-term safety of deucravacitinib.

2.8 Summary of the Safety Concerns

Safety concerns are summarized in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Important identified risks	None
Important potential risks	Serious infections
	Malignancies
	MACE
	VTE (DVT/PE)
Missing information	Use in pregnancy and lactation
	Long-term safety

3 PART III: PHARMACOVIGILANCE PLAN

The PV plan includes several integrated and complementary activities to proactively identify and characterize all safety concerns that have been identified or have potential to be associated with the use of deucravacitinib. The ongoing proactive activities involve a comprehensive approach to signal detection and assessment of all potential risks. The safety assessments included in the following sections are key elements that are part of a cohesive PV plan. The risk minimization plan is outlined in Section 5.

3.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities consist of adverse reaction reporting and signal detection.

3.2 Additional Pharmacovigilance Activities

A summary of ongoing and completed pharmacovigilance study protocols is provided in Annex 2.

Table 3.2-1: Post-Authorisation Safety Studies Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)	Due Date(s)
Long-term, observational cohort study of adults with plaque psoriasis, who are new users of deucravacitinib, non-TNFi (tumor necrosis factor inhibitor) biologics, TNFi biologics, or non-biologic systemic therapy in the real-world clinical setting (IM011194)	To evaluate the long-term safety of deucravacitinib in patients with psoriasis in the real-world setting.	Retrospective cohort study using EU/UK electronic medical records and/or patient registries	Psoriasis patients treated with deucravacitinib and other therapies for moderate/severe psoriasis	1. Submission of study protocol	Q2 2023
				2. Progress updates	PSUR
				3. Interim study report (1,000 p-y) submission	Q4 2026/ Q4 2028
				4. Final study report submission	Q4 2032
An open-label, multi-center extension study to characterize the long-term safety and efficacy of BMS-986165 in subjects with moderate-to-severe plaque psoriasis (IM011075)	To characterize the safety and tolerability of long-term use of deucravacitinib in subjects with moderate-to-severe plaque psoriasis	Extension of the Phase 3 clinical trials for patients with psoriasis to continue on deucravacitinib for an additional 240 weeks (plus 30 day safety follow-up visit)	Subjects originally determined to have moderate-to-severe plaque psoriasis who successfully completed the protocol-required treatment period in an applicable study of deucravacitinib	1. Study protocol finalization	05-Feb-2019
				2. Progress updates	PSUR
				3. Interim study report submission	Oct-2021
				4. Final study report submission	Dec-2026

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Long-term, observational cohort study of adults with plaque psoriasis, who are new users of deucravacitinib, non-TNFi (tumor necrosis factor inhibitor) biologics, TNFi biologics, or non-biologic systemic therapy in the real-world clinical setting (IM011194) Category 3 Planned	To evaluate the long-term safety of deucravacitinib in patients with psoriasis in the real-world setting.	Serious infections, Malignancies, MACE, VTE (DVT/PE), Long-term safety	1. Submission of study protocol 2. Progress updates 3. Interim report submission (1,000 p-y) 4. Final report submission	Q2 2023 PSUR Q4 2026/ Q4 2028 Q4 2032
Randomized, active-controlled clinical trial to evaluate the long-term safety of deucravacitinib in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy (IM0111130)[a] Category 3 Planned	To evaluate the long-term safety of deucravacitinib; the trial will be of sufficient size and duration to characterize safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.	Serious infections, Malignancies, MACE, VTE (DVT/PE), Long-term safety	1. Final protocol submission 2. Final report submission	Q4 2024 Dec 2029
Deucravacitinib pregnancy study: a retrospective observational study on the safety of deucravacitinib exposure in pregnant women and their offspring (IM011201)[a] Category 3 Planned	To assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to deucravacitinib during pregnancy compared to an unexposed control population.	Use in pregnancy	1. Final protocol submission 2. Progress updates 3. Final report submission	Q4 2024 PSUR Dec 2029

Table 3.3-1: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
An open-label, multi-center extension study to characterize the long-term safety and efficacy of BMS-986165 in subjects with moderate-to-severe plaque psoriasis (IM011075)[b] Category 3 Ongoing	To characterize the safety and tolerability of long-term use of deucravacitinib in subjects with moderate-to-severe plaque psoriasis.	Serious infections, Malignancies, MACE, VTE (DVT/PE), Long-term safety	1. Study protocol finalization	05-Feb-2019
			2. Progress updates	PSUR
			3. Final report submission	Dec-2026

[a] US FDA study commitment.

[b] Extension of the Phase 3 clinical studies IM011046 and IM011047.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no protocols planned for post-authorization efficacy studies.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimiation activities
Serious infections	**Routine risk communication:** SmPC (Sections 4.4 and 4.8); PL (Section 2) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Patients should be evaluated for TB infection prior to initiating treatment with deucravacitinib. **Other routine risk minimisation measures beyond the Product Label:** Restricted medical prescription
Malignancies	**Routine risk communication:** SmPC (Section 4.4); PL (Section 2) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Label:** Restricted medical prescription
MACE	**Routine risk communication:** SmPC (Section 4.4); PL (Section 2) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Label:** Restricted medical prescription
VTE (DVT/PE)	**Routine risk communication:** SmPC (Section 4.4); PL (Section 2) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Label:** Restricted medical prescription
Use in pregnancy and lactation	**Routine risk communication:** SmPC (Section 4.6); PL (Section 2)

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimiation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None **Other routine risk minimisation measures beyond the Product Label**: Restricted medical prescription
Long-term safety	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Label**: Restricted medical prescription

5.2 Additional Risk Minimisation Measures

Routine risk minimisation measures as described in Section 5.1 are sufficient to manage the safety concerns of the medicinal product. There are no additional risk minimisation measures.

5.3 Summary Table of Risk Minimisation Measures and Pharmacovigilance Activities

A summary of risk minimisation measures and pharmacovigilance activities is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Serious infections	**Routine risk minimisation measures:** SmPC (Sections 4.4 and 4.8); PL (Section 2)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (EU/UK medical records databases/patient registries [IM011194]) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Malignancies	**Routine risk minimisation measures:** SmPC (Section 4.4); PL (Section 2)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (EU/UK medical records databases/patient registries [IM011194]) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)
MACE	**Routine risk minimisation measures:** SmPC (Section 4.4); PL (Section 2)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (EU/UK Medical Records Databases and/or Patient Registries [IM011194]) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)
VTE (DVT/PE)	**Routine risk minimisation measures:** SmPC (Section 4.4); PL (Section 2)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (EU/UK Medical Records Databases and/or Patient Registries [IM011194]) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)
Use in pregnancy and lactation	**Routine risk minimisation measures:** SmPC (Section 4.6); PL (Section 2)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:**

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Pregnancy study (IM011201)
Long-term safety	**Routine risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** Non-interventional cohort study (EU/UK medical records databases/patient registries [IM011194]) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for SOTYKTU (deucravacitinib)

This is a summary of the RMP for SOTYKTU. The RMP details important risks of SOTYKTU and how more information will be obtained about SOTYKTU's risks and uncertainties (missing information).

SOTYKTU's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how SOTYKTU should be used.

This summary of the RMP for SOTYKTU should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SOTYKTU's RMP.

I. The medicine and what it is used for

SOTYKTU is not yet authorized for use. It is given by film-coated tablet for oral administration in a strength of 6 mg of deucravacitnib.

Further information about the evaluation of SOTYKTU’s benefits can be found in SOTYKTU’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of SOTYKTU, together with measures to minimise such risks and the proposed studies for learning more about SOTYKTU's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine’s legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of SOTYKTU is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of SOTYKTU are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SOTYKTU. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	None
Important potential risks	Serious infections
	Malignancies
	Major adverse cardiovascular events (MACE)
	Venous thromboembolic events (deep vein thrombosis and pulmonary embolism)
Missing information	Use in pregnancy and lactation
	Long-term safety

II.B Summary of important risks

Important potential risks

Serious Infections	
Evidence for linking the risk to the medicine	Deucravacitinib has the potential to increase the risk of serious infections, based on its mechanism of action of selective TYK2 inhibition. Although serious infections have been reported in patients treated with deucravacitinib in clinical trials, available cumulative information does not suggest an increased risk of serious infection in patients treated with deucravacitinib.
Risk factors and risk groups	Psoriasis has been shown to increase the risk of serious infection. Other risk factors for the development of serious infection include clinically significant metabolic and endocrine disorders such as diabetes, obesity, thyroid disorders, cardiovascular disorders, and renal and hepatic disorders; advanced age; and the concomitant use of corticosteroids and other immunosuppressants.
Risk minimisation measures	Routine risk minimisation measures: SmPC (Sections 4.4 and 4.8); PL (Section 2); restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional cohort study (EU/UK medical records databases/patient registries [IM011194]) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075) See section II.C of this summary for an overview of the post-authorisation development plan.
Malignancies	
Evidence for linking the risk to the medicine	As with any modulator of the immune system, there is a theoretical risk of increased malignancy with deucravacitinib. Although malignancies have been reported in patients treated with deucravacitinib in clinical trials, available cumulative information does not suggest an increased risk of malignancy in patients treated with deucravacitinib.
Risk factors and risk groups	Patients with psoriasis have a slightly elevated baseline risk of malignancies, in particular lymphoproliferative diseases. Among patients with psoriasis, an increased risk of solid cancers appears to be related to alcohol use and cigarette smoking. In addition, exposure to PUVA radiation and immunosuppressants (including cyclosporin and possibly methotrexate) has been associated with squamous cell carcinoma in psoriasis patients. General risk factors for malignancy include increasing age, lifestyle factors (such as alcohol and tobacco use and obesity), family history of cancer, and certain environmental exposures.
Risk minimisation measures	Routine risk minimisation measures: SmPC (Section 4.4); PL (Section 2); restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

Important potential risks

	Non-interventional cohort study (EU/UK medical records databases/patient registries [IM011194]) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075) See section II.C of this summary for an overview of the post-authorisation development plan.
MACE	
Evidence for linking the risk to the medicine	Evidence for an increased background risk of MACE in patients with psoriasis is cited in the published literature. Although MACE were reported in patients treated with deucravacitinib in clinical trials, available cumulative information does not indicate an increased risk of MACE in patients treated with deucravacitinib. It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of MACE were observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in RA patients 50 years of age and older with at least one CV risk factor.
Risk factors and risk groups	The risk factors for the development of CV disease are well known and include hypertension, hypercholesterolemia, diabetes, smoking, advanced age, male sex, obesity, and family history. Patients with psoriasis have been shown to be at increased risk for MACE compared with the general population. Epidemiological studies have shown a higher prevalence of CV risk factors in psoriasis patients, including metabolic syndrome, smoking, obesity, hypertension, diabetes, insulin resistance, and dyslipidemia. Additionally, literature suggests psoriasis may be an independent risk factor due to the high inflammatory burden of psoriatic disease.
Risk minimisation measures	Routine risk minimisation measures: SmPC (Section 4.4); PL (Section 2); restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional cohort study (EU/UK medical records databases/patient registries [IM011194]) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075)See section II.C of this summary for an overview of the post-authorisation development plan.
VTE (DVT/PE)	
Evidence for linking the risk to the medicine	Patients with psoriasis can have an increased risk for blood clots in veins due to their underlying condition and other risk factors. Available cumulative information does not indicate an increased risk of VTE in patients treated with deucravacitinib. Patients who developed DVT/PE in clinical trials had

Important potential risks

	recognized and well-established risk factors for thromboembolism. It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of JAK inhibition. Higher rates of DVT and PE were observed in patients treated with a JAK inhibitor compared to those treated with TNF blockers in RA patients 50 years of age and older with at least one CV risk factor.
Risk factors and risk groups	An increased risk for VTE has been associated with a history of VTE, increasing age, immobility, obesity, smoking, hypertension, estrogen-containing oral contraceptives, COPD, infections (including COVID-19), and chronic inflammatory conditions, including psoriasis.
Risk minimisation measures	Routine risk minimisation measures: SmPC (Section 4.4); PL (Section 2); restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional cohort study (EU/UK medical records databases/patient registries [IM011194]) Long-term safety randomized clinical trial (IM0111130) Clinical trial long-term extension (IM011075) See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information

Use in Pregnancy and Lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC (Section 4.6); PL (Section 2); restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Pregnancy study (IM011201) See section II.C of this summary for an overview of the post-authorisation development plan.
Long-term Safety	
Risk minimisation measures	Routine risk minimisation measures: Restricted medical prescription
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional cohort study (EU/UK medical records databases/patient registries [IM011194]) Long-term safety clinical trial (IM0111130) Clinical trial long-term extension (IM011075) See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation.

II.C.2 Other studies in post-authorisation development plan

Category 3 on-going and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
Long-term, observational cohort study of adults with plaque psoriasis, who are new users of deucravacitinib, non-TNFi (tumor necrosis factor inhibitor) biologics, TNFi biologics, or non-biologic systemic therapy in the real-world clinical setting (IM011194)	To evaluate the long-term safety of deucravacitinib in patients with psoriasis in the real-world setting.
Randomized, active-controlled clinical trial to evaluate the long-term safety of deucravacitinib in patients with moderate to severe plaque psoriasis (IM0111130)	To evaluate the long-term safety of deucravacitinib; the trial will be of sufficient size and duration to characterize safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.
Deucravacitinib pregnancy study: a retrospective observational study on the safety of deucravacitinib exposure in pregnant women and their offspring (IM011201)	To assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to deucravacitinib during pregnancy compared to an unexposed control population.
An open-label, multi-center extension study to characterize the long-term safety and efficacy of BMS-986165 in subjects with moderate-to-severe plaque psoriasis (IM011075)	To characterize the safety and tolerability of long-term use of deucravacitinib in subjects with moderate-to-severe plaque psoriasis.

APPENDIX 1: REFERENCES

6 page(s) excluding cover page

APPENDIX 1: REFERENCES

1 Bell LM, Sedlack R, Beard CM, et al. Incidence of psoriasis in Rochester, Minn, 1980-1983.Arch Dermatol. 1991; 127:1184–7.

2 Donker GA, Foets M, Spreeuwenberg P, et al. Management of psoriasis in general practice now more in agreement with the guidelines of the Dutch College of General Practitioners (NHG). Ned Tijdschr Geneeskd. 1998; 142:1379–83.

3 Huerta C, Rivero E, Garcia Rodriguez LA. Incidence and risk factors for psoriasis in the general population. Arch Dermatol. 2007; 143:1559-65.

4 Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013; 133(2):377-85.

5 Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. J Am Acad Dermatol. 2014; 70(3):512-6.

6 World Health Organization. Global Report on psoriasis. WHO. 2016.

7 Stern RS, Nijsten T, Feldman SR, et al. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Investig Dermatol Symp Proc. 2004; 9:136–9.

8 Gelfand JM, Weinstein R, Porter SB,et al. Prevalence and treatment of psoriasis in the United Kingdom - a population-based study. Arch Dermatol. 2005; 141:1537–41.

9 Kurd SK, Gelfand JM. The prevalence of previously diagnosed andundiagnosed psoriasis in US adults: results from NHANES 2003-2004. [Erratum appears in J Am Acad Dermatol. 2009;61(3):507]. JAmAcad Dermatol. 2009; 60:218–24.

10 Farber E, Nall M. Epidemiology: Natural History and Genetics. New York: Marcel Dekker. 1998.

11 Brandrup F, Green A. The prevalence of psoriasis in Denmark. Acta Derm Venereol. 1981; 61:344–6.

12 Kavli G, Forde OH, Arnesen E, et al. Psoriasis: familial predisposition and environmental factors. Br Med J (Clin Res Ed). 1985; 291:999–1000.

[13] Bo K, Thoresen M, Dalgard F. Smokers report more psoriasis, but no atopic dermatitis or hand eczema: results from a Norwegian population survey among adults. Dermatology. 2008; 216:40–5.

[14] Naldi L. Epidemiology of psoriasis. Current Drug Targets - Inflammation & Allergy. 2004; 3:121–8.

[15] Wolkenstein P, Revuz J, Roujeau JC,et al. Psoriasis in France and associated risk factors: results of a case-control study based on a large community survey. Dermatology. 2009; 218:103–9.

[16] Armstrong AW. Psoriasis. JAMA dermatology. 2017; 153(9):956-956.

[17] Icen M, Crowson CS, McEvoy MT, et al. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. J Am Acad Dermatol. 2009; 60:394–401.

[18] Kamiya K, Kishimoto M, Sugai J, et al. Risk Factors for the Development of Psoriasis. Int J Mol Sci. 2019; 20(18):4347.

[19] Trembath RC, Clough RL, Rosbotham JL, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. Hum Mol Genet. 1997; 6:813–820.

[20] Burden AD, Javed S, Bailey M, et al. Genetics of psoriasis: Paternal inheritance and a locus on chromosome 6p. J Invest Dermatol. 1998; 110:958–960.

[21] Sagoo GS, Tazi-Ahnini R, Barker JW, et al. Meta-analysis of genome-wide studies of psoriasis susceptibility reveals linkage to chromosomes 6p21 and 4q28-q31 in Caucasian and Chinese Hans population. J Invest Dermatol. 2004; 122:1401–1405.

[22] Nair RP, Stuart PE, Nistor I, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet. 2006; 78:827–851.

[23] Chen L, Tsai TF. HLA-Cw6 and psoriasis. Br J Dermatol. 2018; 178:854–862.

[24] Kawada A, Tezuka T, Nakamizo Y, et al. A survey of psoriasis patients in Japan from 1982 to 2001. J Dermatol Sci. 2003; 31:59–64.

[25] Takahashi H, Nakamura K, Kaneko F, et al. Japanese Society for Psoriasis Research. Analysis of psoriasis patients registered with the Japanese Society for Psoriasis Research from 2002–2008. J Dermatol. 2011; 38:1125–1129.

[26] Ito T, Takahashi H, Kawada A, et al. Japanese Society for Psoriasis Research. Epidemiological survey from 2009 to 2012 of psoriatic patients in Japanese Society for Psoriasis Research. J Dermatol. 2018; 45:293–301.

[27] Love TJ, Qureshi AA, Karlson EW, et al. Prevalence of the metabolic syndrome in psoriasis: Results from the national health and nutrition examination survey, 2003–2006. Arch Dermatol. 2011; 147:419–424.

[28] Langan SM, Seminara NM, Shin DB, et al. Prevalence of metabolic syndrome in patients with psoriasis: A population-based study in the United Kingdom. J Invest Dermatol. 2012; 132:556–562.

[29] Coto-Segura P, Eiris-Salvado N, Gonzalez-Lara L, et al. Psoriasis, psoriatic arthritis and type 2 diabetes mellitus: A systematic review and meta-analysis. Br J Dermatol. 2013; 169:783-793.

[30] Takahashi H, Takahashi I, Honma M, et al. Prevalence of metabolic syndrome in Japanese psoriasis patients. J Dermatol Sci. 2010; 57:143-144.

[31] Takahashi H, Iizuka H. Psoriasis and metabolic syndrome. J Dermatol. 2012; 39:212–218.

[32] Bremmer S, Van Voorhees AS, Hsu S, et al. Obesity and psoriasis: From the medical board of the national psoriasis foundation. J Am Cad Dermatol. 2010; 63:1058–1069.

[33] Jensen P, Skov L. Psoriasis and obesity. Dermatology. 2016; 232:633-639.

[34] Neimann AL, Shin DB, Wang X, et al. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol. 2006; 55:829–835.

[35] Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol. 2005; 141:1527–1534.

[36] Mallbris L, Granath F, Hamsten A, et al. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol. 2006; 54:614–621.

[37] Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: A systematic review and meta-analysis of observational studies. J Hypertens. 2013; 31:433–442.

[38] Binus AM, Han J, Qamar AA, et al. Associated comorbidities in psoriasis and inflammatory bowel disease. J Eur Acad Dermatol Venereol. 2012; 26:644-50.

[39] Abuabara K, Azfar RS, Shin DB, et al. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol. 2010; 163(3):586-92

[40] Rhee TM, Lee JH, Choi EK, et al. Increased Risk of Atrial Fibrillation and Thromboembolism in Patients with Severe Psoriasis: a Nationwide Population-based Study. Sci Rep. 2017; 7(1):9973.

[41] Chiesa Fuxench ZC, Shin DB, Ogdie Beatty A, et al. The Risk of Cancer in Patients With Psoriasis: A Population-Based Cohort Study in the Health Improvement Network. JAMA Dermatol. 2016; 152(3):282–90.

[42] Pouplard CBE, Horreau C, Barnetche T, et al. Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies. J Eur Acad Dermatol Venereol. 2013; 27(suppl3):36–46.

[43] Vaengebjerg S, Skov L, Egeberg A, et al. Prevalence, Incidence, and Risk of Cancer in Patients With Psoriasis and Psoriatic Arthritis: A Systematic Review and Meta-analysis. JAMA Dermatol. 2020; 156(4):421-429.

[44] Takeshita J, Shin DB, Ogdie A, et al. Risk of Serious Infection, Opportunistic Infection, and Herpes Zoster among Patients with Psoriasis in the United Kingdom. Journal of Investigative Dermatology. 2018; 138:1726-1735.

[45] Henseler T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol. 1995; 32:982-6

[46] Christophers E. Comorbidities in psoriasis. Clin Dermatol. 2007; 25:529-34.

[47] Naldi L, Mercury SR. Epidemiology of comorbidities in psoriasis. Dermatol Ther. 2010; 23:114-8.

[48] Gelfand JM, Troxel AB, Lewis JD, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol. 2007; 143:1493-9.

[49] Ogdie A, Gelfand JM. Identification of risk factors for psoriatic arthritis: scientific opportunity meets clinical need. Arch Dermatol. 2010; 146:785-788.

[50] Krueger G, Koo J, Lebwohl M, et al. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patientmembership survey. Arch Dermatol. 2001; 137:280-4.

[51] Esposito M, Saraceno R, Giunta A, et al. An Italian study on psoriasis and depression. Dermatology. 2006; 212:123-7.

[52] Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. Br J Dermatol. 1998; 139:846-50.

[53] Campolmi E, Zanieri F, Santosuosso U, et al. The importance of stressful family events in psoriatic patients: a retrospective study. J Eur Acad Dermatol Venereol. 2012; 26:1236-9.

[54] Investigator's Brochure v.7.0 for BMS-986165. Bristol-Myers Squibb Company; 2020. Document Control No. 930090873.

[55] Final Clinical Study Report for IM011011. A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Phase 2 Study to Evaluate the Clinical Efficacy and Safety of BMS-986165 in Subjects with Moderate to Severe Psoriasis. Bristol-Myers Squibb Company; 2018. Document Control No. 930129274.

[56] Module 2.5 Clinical Overview. Bristol-Myers Squibb Company; 2021. Document Control No. 930172314.

[57] Taborelli M, Montella M, Libra M, et al. The dose-response relationship between tobacco smoking and the risk of lymphomas: a case-control study. BMC Cancer. 2017; 17(1):421.

[58] Morton LM, Hartge P, Holford TR, et al. Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (interlymph). Cancer Epidemiol Biomarkers Prev. 2005; 14(4):925-33.

[59] Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc. 2013 Apr 4;2(2):e000062.

[60] Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, Jullien D, Aractingi S, Aubin F, Joly P, Le Maître M, Ortonne JP, Paul C, Richard MA. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol. 2013 Aug;27 Suppl 3:12-29.

[61] Hu SC, Lan CE. Psoriasis and cardiovascular comorbidities: Focusing on severe vascular events, cardiovascular risk factors and implications for treatment. Int J Mol Sci. 2017 Oct 21;18(10):2211.

[62] Egeberg A, Skov L, Joshi AA, Mallbris L, Gislason GH, Wu JJ, Rodante J, Lerman JB, Ahlman MA, Gelfand JM, Mehta NN. The relationship between duration of psoriasis, vascular inflammation, and cardiovascular events. J Am Acad Dermatol. 2017 Oct;77(4):650-656.e3.

[63] Schönfelder, T., Brandt, M., Kossmann, S. et al. Lack of T-bet reduces monocytic interleukin-12 formation and accelerates thrombus

resolution in deep vein thrombosis. Sci Rep 8, 3013 (2018). https://doi.org/10.1038/s41598-018-21273-5

64 Luther N, Shahneh F, Brähler M, Krebs F, Jäckel S, Subramaniam S, Stanger C, Schönfelder T, Kleis-Fischer B, Reinhardt C, Probst HC, Wenzel P, Schäfer K, Becker C. Innate Effector-Memory T-Cell Activation Regulates Post-Thrombotic Vein Wall Inflammation and Thrombus Resolution. Circ Res. 2016 Dec 9;119(12):1286-1295. doi: 10.1161/CIRCRESAHA.116.309301. Epub 2016 Oct 5. PMID: 27707800.

65 Li Y, Golden JB, Camhi MI, Zhang X, Fritz Y, Diaconu D, Ivanco TL, Simon DI, Kikly K, McCormick TS, Wang Y, Ward NL. Protection from Psoriasis-Related Thrombosis after Inhibition of IL-23 or IL-17A. J Invest Dermatol. 2018 Feb;138(2):310-315. doi: 10.1016/j.jid.2017.09.021. Epub 2017 Sep 23. PMID: 28951241; PMCID: PMC6693345.

66 Gregson J, Kaptoge S, Bolton T, et al. Cardiovascular risk factors associated with venous thromboembolism. JAMA Cardiol 2019;4:163-73.

67 Zöller B, Li X, Sundquist J, Sundquist K. Autoimmune diseases and venous thromboembolism: a review of the literature. Am J Cardiovasc Dis 2012;2:171-83.

68 Keenan CR, White RH. The effects of race/ethnicity and sex on the risk of venous thromboembolism. Curr Opin Pulm Med 2007;13:377-83.

69 Hillary T, Clijmans J, Vermeire S, et al. Venous thrombotic events in psoriasis patients: a systematic review with meta-analysis. Ann Med 2021;53:1074-81.

70 Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. Int J Gynaecol Obstet. 2018 Jun;141(3):287-294.

APPENDIX 2: NONCLINICAL TOXICOLOGY SUMMARY

6 page(s) excluding cover page

APPENDIX 2: NONCLINICAL TOXICOLOGY SUMMARY

A comprehensive battery of nonclinical studies, including in vitro and in vivo genetic toxicology and safety pharmacology assessments, in vitro phototoxicity, local tolerance, embryo-fetal development (EFD) in rats and rabbits, male and female fertility and early embryonic development in rats, pre-and post-natal development (PPND) in rats, developmental study in juvenile rats, carcinogenicity studies in rasH2 transgenic mice and rats; and single- and/or repeat-dose (≤ 9 months) oral toxicity studies in mice, rats, dogs, and/or monkeys, were completed to assess the toxicologic profile of BMS-986165. All pivotal studies were conducted in compliance with GLP regulations and according with the ICH guidelines. Safety pharmacology assessments (cardiovascular [CV], neurologic, and respiratory systems) were incorporated in select toxicity studies in rats and monkeys, and single-dose CV telemetry studies were conducted in conscious rats, dogs, and monkeys. The rat and cynomolgus monkey were selected as the main species for the toxicologic evaluation, as they are the standard models for toxicity assessments with large historical databases; demonstrated comparable potency against TYK2 inhibition in whole blood of rats and monkeys compared to humans, and also in ex vivo pharmacodynamic (PD) activity assays as part of the toxicology studies, and comparable metabolism to human. Doses that generated high systemic exposures were used to ensure a comprehensive evaluation of the toxicity profile of BMS-986165 and to support its safe use in human subjects. Based on the studies conducted, the dose ranges used, and the observed effects, the nonclinical toxicity profile of BMS-986165 was well characterized in the selected animal species. Systemic exposure multiples between animal species used in toxicity studies and human subjects were calculated relative to recommended human dose (RHD) of 6 mg once daily (mean steady-state Cmax 0.0451 µg/mL and AUC[0-24h] 0.473 µg•h/mL) in subjects with moderate-to-severe psoriasis. The two major human metabolites, BMT-158170 and BMT-153261, are nongenotoxic, have favorable pharmacologic profile with no noteworthy off-target effects at clinically relevant exposure, and were quantified in the toxicity studies at plasma levels, which provide adequate exposure multiples to human exposure at the RHD. The totality of the toxicity assessments demonstrate that BMS-986165, at doses associated with robust PD effects, has a favorable dose-related safety profile in both rodents and monkeys, and toxicological findings, which are either fully reversible or trending toward recovery, clinically monitorable and manageable. A summary of the principal BMS-986165-related findings is presented below.

Safety Pharmacology

In vitro and in vivo safety pharmacology evaluation of the cardiovascular system, and in vivo safety pharmacology evaluation of the central nervous and respiratory systems were conducted within pivotal repeat-dose toxicity studies and/or dedicated single-dose safety pharmacology studies. There were no BMS-986165-related CNS or respiratory effects in animals. BMS-986165 did not exhibit off-target activity in a panel of receptors, ion channels, transporters or enzymes[1] and did not inhibit cardiac hERG/IKr potassium, SCN5A sodium or L-type calcium channel currents[2] at clinically relevant concentrations. Transiently decreased blood pressure and increased heart rate were seen in anesthetized rabbits[3], and conscious telemetered dogs[4] and monkeys[5,6]

(most sensitive species). In telemetered monkeys[6], no hemodynamic effects were noted at a dose of 0.65 mg/kg (3× RHD), and transiently increased heart rate was noted at 1 mg/kg (6× RHD C_{max}). However, these hemodynamic effects had identifiable thresholds with high exposure margins in dogs and rabbits; were transient/reversible; were absent in the repeat-dose (≤ 9 months)[7][8][9] toxicity studies in monkeys at higher doses (≤ 10/5 mg/kg/day; 49× RHD C_{max}) or in telemetered rats; and were not associated with any macroscopic or microscopic findings in the monkey CV system. Overall, the totality of nonclinical data indicate that BMS-986165 has low potential for CV, CNS and respiratory effects or other off-target effects at the RHD.

Single-Dose Toxicity Studies

Overall, BMS-986165 was well tolerated at high exposures and up to the highest oral single doses of 75, 100, and 30 mg/kg in rats[10], dogs[11], and monkeys[12], respectively.

Repeat-Dose Toxicity Studies

In repeat dose oral toxicity studies in rats, BMS-986165 was tolerated at all doses (≤ 75 mg/kg/day for 1 month[13]; ≤ 15 mg/kg/day for 3 months[14]; and ≤ 50 mg/kg/day for 6 months[15] [247× RHD AUC]). In the 6-month study, consistent with pharmacologic immunomodulation, the primary findings at ≥ 5 mg/kg/day (≥ 9× RHD AUC) were decreased blood lymphocytes, decreased lymphoid cellularity in lymph nodes and spleen, and/or suppression of T-cell-dependent antibody (IgM and IgG) response (TDAR) to keyhole limpet hemocyanin (KLH) immunization. Additional findings considered adverse at ≥ 15 mg/kg/day (≥ 42× RHD AUC) included decreased mean body weights and body weight gains, decreased red blood cell (RBC) mass parameters, reticulocytes, platelets, and bone marrow cellularity. All BMS-986165-related changes were reversible except for the decreased food consumption body weights and spleen weights, and nonadverse increased incidence of macrophage aggregation in the lung. Based on the absence of adverse findings, the no-observed-adverse-effect-level (NOAEL) was considered to be 5 mg/kg/day (9× RHD AUC).

In repeat-dose (≤ 3 months)[7,8] oral toxicity studies in monkeys, BMS-986165 was tolerated at all doses (≤ 5 mg/kg/day). In the 9-month monkey toxicity study with a 2-month recovery[9], the high dose of 10 mg/kg/day was reduced to 5 mg/kg/day (denoted as 10/5 mg/kg/day) due to poor clinical tolerability. The main findings at all doses (≥ 1 mg/kg/day, ≥ 7× RHD AUC) included generally dose-dependent skin changes (swollen, dry, lesion, flaking, papule, red, white, scab) located throughout the body. Most monkeys did not require any veterinary treatments for the skin observations; others were treated with Vaseline, antibiotics, topical chlorhexidine, and/or Epsom salts. The skin findings generally improved clinically after start of the veterinary treatments. Additional findings at all doses included transient gastrointestinal effects (eg, diarrhea/loose feces), dose-dependent decreased RBC mass parameters, and suppression of TDAR to KLH, and at ≥ 3 mg/kg/day (≥ 33× RHD AUC) transiently decreased activity, hunched posture, pale gums, and increased body temperature, with decreased platelets and occult blood in urine at 10/5 mg/kg/day (65× RHD AUC). Following the 2-month recovery, all BMS-986165-related findings were partially or fully reversible. The NOAEL was not identified due to adverse skin findings at all doses (≥ 1 mg/kg/day; ≥ 7× RHD AUC).

Genotoxicity

BMS-986165 was not genotoxic in any pivotal mutagenicity[16] or clastogenicity[17] studies. In addition, in a definitive in vivo micronucleus test as part of the 1-month toxicity study in rats[13], BMS-986165 was not genotoxic at doses up to 75 mg/kg/day (343× RHD C_{max}).

Carcinogenicity

BMS-986165 was not carcinogenic in a 6-month study in rasH2 mice at doses up to 60 mg/kg/day (185× RHD AUC) or a 2-year study in rats at doses up to 15 mg/kg/day (51× RHD AUC).

Reproductive and Developmental Toxicity

In the pivotal EFD studies in rats at doses up to 75 mg/kg/day (266× RHD AUC)[18] and rabbits at doses up to 10 mg/kg/day (total/free-fraction 91×/20× RHD AUC, respectively)[19], there was no evidence of teratogenicity or effects on embryo-fetal development. BMS-986165 had no effects on male rat reproductive parameters (mating, fertility, and sperm morphology), or early embryonic development of litters sired by BMS-986165-treated males up to the highest dose of 50 mg/kg/day (247× RHD AUC) conducted as part of the 6-month toxicity study[15]. In a female rat fertility study[20], there were no BMS-986165-related effects on mating and fertility parameters up to 50 mg/kg/day, and the maternal and reproductive NOAEL were considered to be 50 mg/kg/day (171× RHD AUC). In a PPND study in rats[21], BMS-986165 dosed to pregnant/lactating dams at doses up to 50 mg/kg/day was well tolerated with no maternal toxicity. BMS-986165 was associated with transient adverse effects on pup body weight in the preweaning period at 50 mg/kg/day, which recovered postweaning. Based on these results, the maternal NOAEL was 50 mg/kg/day (110× RHD AUC) and the developmental NOAEL was 15 mg/kg/day (19× RHD AUC).

Juvenile Toxicity

In a 10-week oral development toxicity study in juvenile rats with a 10-week postdose recovery period[22], BMS-986165 was clinically well tolerated when dosed daily from post-natal day (PND) 21 through PND 90 at doses ≤ 50 mg/kg/day. Most findings, including effects on lymphocytes, spleen, and suppression of TDAR to KLH, were consistent with immunomodulatory activity, were reversible, and considered nonadverse. Notably, the changes in this study were previously observed in adults rats at a similar magnitude, indicating that juvenile rats are not more sensitive nor demonstrate unique toxicity relative to findings in mature rats. Based on the absence of adverse findings, the NOAEL in juvenile rats was considered to be 50 mg/kg/day (125× RHD AUC).

Local Tolerance

BMS-986165 was not a skin sensitizer in mouse lymph node assays[23,24]. BMS-98165 was not a human skin irritant[25], or ocular irritant[26] in in vitro assays.

Phototoxicity

BMS-986165 was not cytotoxic or phototoxic in an in vitro 3T3 mouse fibroblast assay.[27]

REFERENCES

[1] BMS-986165: In vitro receptor, ion channel, transporter binding and enzyme interaction assessment (Study DT15044). Bristol-Myers Squibb Company; 2015. Document Control No. 930088978.

[2] BMS-986165: Effects on cardiac ion channels (Study DT14174). Bristol-Myers Squibb Company; 2015. Document Control No. 930088188.

[3] BMS-986165: Electrophysiological effects in anesthetized rabbits (Study DT13168). Bristol-Myers Squibb Company; 2015. Document Control No. 930088763.

[4] BMS-986165: Single-dose oral exploratory cardiovascular telemetry study in dogs (Study DT14075). Bristol-Myers Squibb Company; 2015. Document Control No. 930088760.

[5] BMS-986165: Single-dose exploratory cardiovascular telemetry study in cynomolgus monkeys (Study DT14097). Bristol-Myers Squibb Company; 2015. Document Control No. 930088757.

[6] BMS-986165: Single-dose oral cardiovascular telemetry study in monkeys (Study DT14128). Bristol-Myers Squibb Company; 2015. Document Control No. 930088889.

[7] BMS-986165: One-month oral toxicity study in monkeys with a two-week recovery (Study DN15003); Final Report and Amendment 1. Bristol-Myers Squibb Company; 2015. Document Control No. 930088708.

[8] BMS-986165: Three-month oral toxicity study in monkeys with a one-month post-dose recovery (Study DN15057). Bristol-Myers Squibb Company; 2016. Document Control No. 930102908.

[9] BMS-986165: Nine-month oral toxicity study in monkeys with a two-month post-dose recovery (Study DN16021); Final Report and Amendments 01, 02 and 03. Bristol-Myers Squibb Company; 2017. Document Control No. 930116004.

[10] BMS-986165: Single-dose oral exploratory toxicokinetic and tolerability study in rats (Study DM14059). Bristol-Myers Squibb Company; 2015. Document Control No. 930088674.

[11] BMT-143848: Single-dose oral exploratory toxicokinetic and tolerability study in dogs (Study DT14068). Bristol-Myers Squibb Company; 2015. Document Control No. 930088753.

[12] BMT-143848: Single-dose oral exploratory toxicokinetic and tolerability study in monkeys (Study DT14084). Bristol-Myers Squibb Company; 2015. Document Control No. 930088804.

[13] BMS-986165: One-month oral toxicity study in rats with a 2-week recovery (Study DN15002). Bristol-Myers Squibb Company; 2015. Document Control No. 930088705.

[14] BMS-986165: Three-month oral toxicity study in rats with a one-month post-dose recovery (Study DN15056). Bristol-Myers Squibb Company; 2016. Document Control No. 930104133.

[15] BMS-986165: Six-month oral toxicity study in rats with a two-month post-dose recovery (Study DN16020). Bristol-Myers Squibb Company; 2017. Document Control No. 930115166.

[16] BMS-986165: Ames reverse mutation study in *Salmonella typhimurium* and *Escherichia coli* (Study DN15012). Bristol-Myers Squibb Company; 2015. Document Control No. 930088702.

[17] BMS-986165: Cytogenetics study in Chinese hamster ovary cells (Study DN15016). Bristol-Myers Squibb Company; 2015. Document Control No. 930088711.

[18] BMS-986165: Oral study of embryo-fetal development in rats (Study DN16073). Bristol-Myers Squibb Company; 2016. Document Control No. 930106044.

[19] BMS-986165: Oral study of embryo-fetal development in rabbits (Study DN16057). Bristol-Myers Squibb Company; 2016. Document Control No. 930107383.

[20] BMS-986165: Oral study of fertility and early embryonic development in female rats (Study DN16234); Final Report and Amendment 1. Bristol Myers Squibb Company; 2018. Document Control No. 930115619.

[21] BMS-986165: Oral Study of pre - and postnatal development in rats (Study DN18002). Bristol- Myers Squibb Company; 2018. Document Control No. 930134746.

[22] BMS-986165: Ten-week oral developmental toxicity study in juvenile rats with a ten-week post-dose recovery period (Study DN18003); Final Report and Amendments 1, 2 and 3. Bristol- Myers Squibb Company; 2019. Document Control No. 930137808.

[23] Assessment of contact hypersensitivity to BMS-986165-01 in the mouse (Reduced Local Lymph Node Assay) (Study 507939). Bristol-Myers Squibb Company; 2015. Document Control No. 930120053.

[24] BMS-986165-01: Local lymph node assay in the mouse - individual method (Study DO17092). Bristol-Myers Squibb Company; 2018. Document Control No. 930125451.

[25] BMS-986165-01: Determination of skin irritation using the EpiDerm reconstructed human EpiDermal model and skin corrosion potential using the Corrositex assay (Study DO17152). Bristol-Myers Squibb Company; 2018. Document Control No. 930133085.

[26] BMS-986165-01: The bovine corneal opacity and permeability (BCOP) assay (Study DO17144). Bristol-Myers Squibb Company; 2018. Document Control No. 930133204.

[27] BMS-986165: Neutral red uptake phototoxicity assay in Balb/c 3T3 mouse fibroblasts (Study DN15001). Bristol-Myers Squibb Company; 2015. Document Control No. 930088710.

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

There are no product specific adverse drug reaction follow-up forms for deucravacitinib.

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable