26 January 2023
EMA/68815/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sotyktu

International non-proprietary name: deucravacitinib

Procedure No. EMEA/H/C/005755/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AA	African American
ACR	American College of Rheumatology
AEs	adverse events
ANCOVA	analysis of covariance
APR	apremilast
AUC	area under the concentration time curve
AUC[INF]	area under the concentration time curve from time zero to infinity
BCRP	breast cancer resistance protein
BID	twice a day
BMI	body mass index
BMS	Bristol-Myers Squibb
BMS-986165	deucravacitinib (abbreviated as DEUC)
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
Cavg	average concentration
Cavg,ss	average concentration at steady state
CFB	change from baseline
CI	confidence interval
Cmax	maximum observed concentration
Cmaxss	maximum observed concentration at steady state
CMH	Cochran-Mantel-Haenszel
Cmin	minimum plasma drug concentration
COVID	coronavirus
CSR	clinical study report
CYP	cytochrome P-450
D/C	discontinuation
DDI	drug-drug interaction
DEUC	Deucravacitinib (BMS-986165)
DLQI	Dermatology Life Quality Index
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
Emax	maximum drug effect
E-R	exposure-response
ESRD	end stage renal disease
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first in human
FPFV	first patient first visit
GCP	Good Clinical Practice
IC50	concentration required for 50% inhibition
ICH	International Council on Harmonisation

IFN	interferon
IGRA	interferon gamma release assay
IL	interleukin
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
KM	Kaplan- Meier
LOCF	last observation carried forward
LPLV	last patient last visit
LTE	long-term extension
MAA	marketing authorisation application
mBOCF	modified baseline observation carried forward
MCID	Minimal Clinically Important Difference
MCS	mental component summary score
MMF	mycophenolate mofetil
NAS	new active substance
NRI	non-responder imputation
OCT	organic cation transporter
OLE	open-label extension
PAS	patient-reported outcome analysis set
PASI	Psoriasis Area and Severity Index
PBO	placebo
PCS	physical component summary score
PD	pharmacodynamics
PGA-F	Physician’s Global Assessment-Fingernail
PGI -C	Patient’s Global Impression of Change
PGI-S	Patient’s Global Impression of Severity
Pgp	P-glycoprotein
PK	pharmacokinetics
PO	orally
PPK	population pharmacokinetics
pp-PASI	palmoplantar PASI
pp-PGA	palmoplantar Psoriasis Area and Severity Index
PRO	patient reported outcomes
PSSD	Psoriasis Symptoms and Signs Diary
PSSD-24h	Psoriasis Symptoms and Signs Diary with a 24-hour recall period
PSSI	Psoriasis Scalp Severity Index
QD	once daily
QOD	every other day
QoL	quality of life
R	randomization
ROW	rest of world
SAP	statistical analysis plan

SCE	summary of clinical efficacy
SD	standard deviation
SE	standard error
SF-36	36-item Short Form Health Survey
sPGA	static Physician's Global Assessment
SQ	subcutaneous
ss-PGA	scalp-specific Physician's Global Assessment
TNF	tumour necrosis factor
TYK2	tyrosine kinase 2
UGT	uridine 5'-diphospho-glucuronosyl-transferase
UK	United Kingdom
US	United States
VAS	visual analog scale
W	week

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 6 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Sotyktu, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 September 2020.

The applicant applied for the following indication: Sotyktu is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0065/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0065/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request for consideration

1.5.1. New active substance status

The applicant requested the active substance deucravacitinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal

product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 April 2018	EMA/CHMP/SAWP/233865/2018	Blanca García-Ochoa Martín, Caroline Auriche

The Scientific advice pertained to the following non-clinical, and clinical aspects:

- Adequacy of the non-clinical data package to support a marketing authorisation application (MAA).
- Adequacy of the clinical pharmacology programme, including planned drug-drug interaction (DDI) studies, to support a MAA.
- The overall design of the phase 3 studies and, in particular, the study population, dosing approach, co-primary endpoints, secondary endpoints, comparator, statistical analysis, safety monitoring plan.
- Whether the Phase 3 studies are adequately designed to evaluate a) maintenance of effect, b) durability of response after cessation of therapy, and c) recapture rate after retreatment.
- Adequacy of the proposed efficacy and safety databases to support marketing authorisation.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Margareta Bego

The application was received by the EMA on	6 October 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 January 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	31 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 May 2022

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 July 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	21 July 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	15 November 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 November 2022
The CHMP agreed on a second list of outstanding issues to be sent to the applicant on	15 December 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 December 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 January 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sotyktu on	26 January 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	26 January 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Psoriasis is a chronic, non-communicable, painful, immunologically-mediated, disfiguring and disabling inflammatory skin disease with great negative impact on patients' quality of life (QoL). It is characterized by marked inflammation and thickening of the epidermis that result in thick, scaly plaques involving the skin. Psoriasis may be classified according to morphologic and clinical presentation: plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, generalized pustular and localized pustular psoriasis, and inverse or intertriginous psoriasis.

Plaque psoriasis is the most common form of the disease. Areas of the body that are frequently involved include the scalp, elbows, knees, buttocks, and genitalia. The extent of skin involved varies among affected individuals, and is a primary determinant of severity. In patients with plaque psoriasis, approximately 80% have mild to moderate disease, with 20% having moderate to severe disease. Nails of hands and feet are often involved. Nail psoriasis presents a spectrum of challenges to patients: pain associated with nail bed hyperkeratosis, functional deficits and cosmetic disfigurement.

Although psoriasis is rarely life-threatening, the psoriatic lesions are often on visible skin and unsightly. Patients experience shedding of scale and bleeding from their plaques as well as pain and itching. In addition to these common physical signs and symptoms, patients with moderate to severe psoriasis often experience feelings of self-consciousness and embarrassment, and as a result, may suffer depression, social isolation, and unemployment; all factors which contribute to a significant reduction in overall patient quality of life. For all of these reasons, the disease often requires chronic treatment, particularly for patients with moderate to severe disease.

Psoriatic arthritis occurs in 30% or more of patients with psoriasis and involves joint pain and destruction, and patients with psoriatic arthritis have reduced quality of life (QoL) and functional capacity compared with psoriasis patients or healthy controls.

2.1.2. Epidemiology

In most developed countries, prevalence of psoriasis is between 1.5 and 5% (WHO Global Report on Psoriasis, 2017). Psoriasis is uncommon before the age of 9 years, with a first peak of psoriasis generally occurring after the age of 20 with an increasing trend with age until around 60 years, after which the incidence is lower. Plaque psoriasis, the most common form of the disease affects approximately 80-90% of psoriasis patients. Plaque psoriasis often occurs together with nail psoriasis, the later has an estimated prevalence of 50% in plaque psoriasis patients.

2.1.3. Biologic features, aetiology and pathogenesis

Psoriasis is a prevalent chronic inflammatory disease. The inflammatory response is driven by T cells and mediated by multiple cytokines such as tumour necrosis factor and the interleukins IL-17 and IL-23.

Psoriasis pathogenesis is characterized by keratinocyte hyperplasia due to immunologic dysregulation. In particular, psoriasis is driven by a predominant TH17 immune response with elevated levels of cytokines including IL-17, IL-23, tumour necrosis factor-α, and IL-22, all of which are known to play important roles in psoriasis pathogenesis. The Janus kinase (JAK) and signal transducers and activators of transcription (STAT) pathway is required for molecular signalling in the TH17 axis, making JAK molecules an attractive target for psoriasis drug development.

Janus kinase (JAK) inhibitors block the intracellular signal pathway mediated by JAK and signal transducer and activator of transcription (STAT) proteins, thereby inhibiting gene transcription of pro-inflammatory cytokines.

There are 4 members of the JAK family—JAK1, JAK2, JAK3, and TYK2. Genome-wide association studies have linked the TYK2 gene to psoriasis susceptibility, and TYK2 gene impairment confers protection against the development of psoriasis and other autoimmune diseases. By examining mouse models deficient in TYK2 and selectively inhibiting TYK2 in mice and human cells, researchers have demonstrated that TYK2 activity is required for the signalling of IL-12, IL-23, and type I interferons. Therefore, blocking TYK2 activity inhibits the major downstream signalling effects of IL-12 and IL-23, ultimately interrupting many of the cellular processes that contribute to the formation of psoriatic lesions.

2.1.4. Clinical presentation, diagnosis

Clinically, plaque psoriasis is characterized by symmetrically distributed, well-defined, sharply demarcated, indurated, erythematous plaques that are covered by friable, dry, white-silvery scale. Areas of the body that are frequently involved include the scalp, elbows, knees, buttocks, and genitalia. The extent of skin involved varies among affected individuals, and is a primary determinant of severity. Psoriasis typically follows a chronic relapsing and remitting course around an individual's underlying baseline severity, with flare-ups occurring spontaneously or during times of illness, or psychological stress.

Although psoriasis is rarely life-threatening, the psoriatic lesions are often on visible skin and unsightly. Patients experience shedding of scale and bleeding from their plaques as well as pain and itching. In addition to these common physical signs and symptoms, patients with moderate to severe psoriasis often experience feelings of self-consciousness and embarrassment, and as a result, may suffer depression, social isolation, and unemployment; all factors which contribute to a significant reduction in overall patient quality of life. For all of these reasons, the disease often requires chronic treatment, particularly for patients with moderate to severe disease.

In addition to the physical and psychological impact of disease, psoriasis is associated with specific co-morbidities, including psoriatic arthritis (PsA), obesity, diabetes, cardiovascular disease, metabolic syndrome, and inflammatory bowel disease (IBD). It is estimated that between 6% and 42% of psoriasis patients develop PsA. Psoriasis has also been shown to be associated with a significantly increased risk of Crohn's disease (relative risk, 3.86, 95% confidence interval [CI] 2.23 to 6.67), which is especially pronounced among psoriatic patients with concomitant PsA (relative risk, 6.43, 95% CI 2.04 to 20.32). Psoriasis is also associated with an increased risk of occlusive vascular disease, including myocardial infarction (MI) and stroke. Multiple cardiovascular risk factors are associated with psoriasis (e.g., diabetes and obesity) and are more prevalent in severe disease, though psoriasis may also be an independent risk factor for MI. Several large epidemiologic studies have further demonstrated an association between the magnitude of cardiovascular risk and severity of psoriasis.

Malignancies of lymphoma, lung cancer, and non-melanoma skin cancer (NMSC) are known comorbidities of psoriasis as well. Published studies have shown that the risk for NMSC is increased in patients with long standing psoriasis.

2.1.5. Management

The traditional paradigms for the treatment of psoriasis recommend a stepwise approach to treatment starting with topical agents, followed by phototherapy, then systemic agents. More recently, the stepwise approach has been replaced by selection of treatment based on patient presentation, disease severity and patient-specific characteristics. Both professional and patient advocacy groups in the United States of America (USA), Europe, and Canada have issued guidelines on the treatment of psoriasis and more specifically the use of biologics for the treatment of psoriasis. Most commonly, a 2-tiered system is recommended, divided by patients who are candidates for localized therapy and should receive topical agents versus those who are candidates for systemic and/or phototherapy. Patients who are candidates for systemic and/or phototherapy include those who have moderate to severe disease based on the percentage of BSA involvement and/or plaque location with associated quality-of-life issues. For example, the presence of psoriasis on palms, soles, body folds, genitals, face, or nails may result in significant functional impairment. European recommendations generally introduce biologics after a contraindication, failure, or non-tolerance of phototherapy or conventional systemic agents.

Despite the availability of multiple therapeutic modalities, the treatment of chronic moderate to severe psoriasis remains challenging. Although various topical treatments (e.g., steroids, tar, anthralin [dithranol], calcipotriene, and tazarotene) are commonly used to treat milder cases of psoriasis, they are generally not suitable for treating more severe forms of the disease. Moreover, topical steroids can be associated with adverse events (AEs) such as skin atrophy, striae formation, suppression of the hypothalamic pituitary adrenal axis, and tachyphylaxis. Phototherapy (narrowband or broadband ultraviolet B [UVB] or the combination of psoralen [a photosensitizing drug] plus ultraviolet A light [PUVA]) is often effective and generally well tolerated, but inconvenient (2 to 3 treatments weekly) and sometimes unavailable due to the need for specialized equipment. Therefore, compliance and subsequently efficacy are rarely sustained over the long-term. Toxicities include sunburn, photo-aging, and increased risk of skin cancer, particularly with PUVA.

Conventional systemic therapies include MTX, acitretin, and cyclosporine. Although effective, each is associated with significant toxicities, particularly organ damage with long-term administration, and each agent has recommended limitations for long-term administration. Rotational therapy is employed to minimize these significant side effects, though no evidence exists that rotational strategies can lessen the risk of serious adverse events (SAE). The chronicity of psoriasis, the cumulative toxicities of these agents and the restrictions with their lifetime use often make these agents unsuitable as a long-term solution. Apremilast, an oral selective inhibitor of the enzyme phosphodiesterase 4, is also approved for the treatment of psoriasis in second line. Safety and tolerability concerns for Apremilast include diarrhoea, depression, weight decrease, and drug interactions.

A variety of biologic systemic therapies have been developed and approved for the treatment of psoriasis, including anti-tumour necrosis factor alpha (TNFα) agents (infliximab, adalimumab, etanercept), IL-12/23 antagonist (ustekinumab), IL-17A inhibitors (secukinumab, brodalumab and ixekizumab) and anti-IL 23 (risankizumab, guselkumab, tildrakizumab). These agents are generally well tolerated, and unlike conventional systemic agents, are not associated with cumulative toxicities that limit longer-term safety.

However, as immunomodulatory agents they have the potential to increase risk for infection and malignancy. Concerns for anti-IL-17 class agents also include Crohn's disease, neutropenia, and mucosal candida infections.

Historically, approved SC biologic agents have shown maximum response rates of 70% to 80% of subjects achieving ≥75% improvement in the Psoriasis Area and Severity Index (PASI) from baseline (PASI 75), which was considered a benchmark of efficacy. The most recently approved anti-IL-23 therapeutic agent risankizumab has demonstrated consistently higher PASI 75 responses than previous agents and as a class have reported PASI 90 response rates after 16 weeks of treatment of up to 81% and PASI 100 response rates up to 59%.

While conventional and systemic therapeutic modalities are available for the treatment of moderate to severe plaque psoriasis, most do not provide adequate efficacy to a majority of patients when assessed using clinically meaningful endpoints such as an Investigator's Global assessment (IGA) of cleared (0) or minimal (1), and PASI 90 and PASI 100. Moreover, multiple publications have noted that higher threshold PASI and IGA responses consistently correlate with better patient-reported outcomes across several treatment agents, supporting the concept that patients perceive incremental and meaningful benefit from these higher threshold responses. While the response rates of available treatments, including those for more stringent measures of efficacy, have increased over time, there is still substantial room for improving the proportion of patients that achieve clear skin. In addition, the currently available treatments have practical limitations due to tolerability, toxicity, safety risks, and/or issues with ease of use or convenience.

2.2. About the product

Deucravacitinib (abbreviated as DEUC; Bristol Myers Squibb [BMS]-986165) is a small molecule (molecular weight = 425.5 g/mol) that selectively inhibits the tyrosine kinase 2 (TYK2) enzyme. DEUC binds to the less conserved regulatory domain of TYK2, stabilizing an inhibitory interaction between the regulatory and the catalytic domains of the enzyme. Deucravacitinib is a selective TYK2 inhibitor (TYK2 belongs to the JAK family).

Deucravacitinib belong to the pharmacotherapeutic group: Immunosuppressants, selective immunosuppressant. The ATC code is L04AA56.

The following indication and posology are proposed for Sotyktu:

Indication:

- Sotyktu is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Posology (please see SmPC for full text):

- The recommended dose is 6 mg taken orally once daily.

  If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment discontinuation should be considered. The patient's response to treatment should be evaluated on a regular basis.

The Article 20 referral for JAK inhibitors used in chronic inflammatory disorders finalised on January 2023 (CHMP opinion) recommended measures to mimimise the risk of serious side effects with JAK inhibitors; compared with TNF-alpha inhibitors, JAK inhibitors used to treat chronic inflammatory disorders are linked to a higher risk of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy,

serious infections and all-cause mortality. Acknowledging the differences in mechanisms of action, and given the uncertainties with regards to the long-term safety profile, specific warnings for deucravacitinib were included in the SmPC (see section 2.6.).

2.3. Type of application and aspects on development

The application was submitted under the legal basis 8(3) of Directive 2001/83/EC which corresponds to a complete and independent application.

The development program for deucravacitinib in the treatment of moderate to severe plaque psoriasis was discussed with CHMP in a Scientific Advice procedure in April 2018 (see section 1.6. Scientific advice).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film coated tablets containing 6 mg of deucravacitinib as active substance.

Other ingredients are:

Tablet core: hypromellose acetate succinate, anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, colloidal hydrated silica, and magnesium stearate.

Film-coating: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, iron oxide red (E172), and iron oxide yellow (E172)

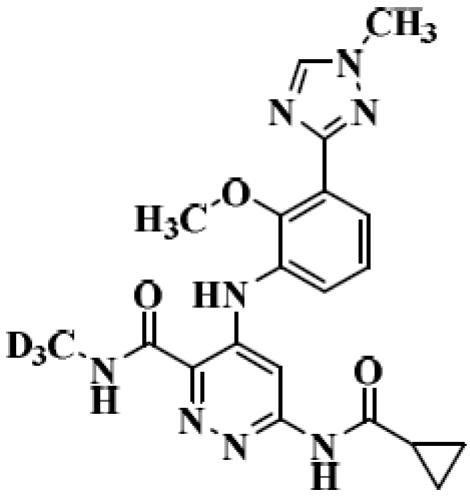
The product is available in polyvinyl chloride/polychlorotrifluoroethylene (PVC/PCTFE) clear blister with push through aluminium as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of deucravacitinib is 6-(cyclopropanecarbonylamido)-4-[2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)anilino]-N-(trideuteriomethyl)pyridazine-3-carboxamide corresponding to the molecular formula $C_{20}H_{19}D_3N_8O_3$. It has a relative molecular weight of 425.47 and the following structure:

Figure 1 Active substance structure



The chemical structure of active substance was elucidated by a combination of UV-Vis, FT-IR, ^{1}H and ^{13}C NMR, and MS. The solid-state properties of the active substance were measured by XRD.

The active substance is a non-hygroscopic white to yellow powder which may contain lumps. The active substance is classified as BCS Class 2 due to its limited solubility at a moderate to high pH. The solubility profile of the crystalline active substance in its free base shows high solubility in low pH systems (> 3 mg/mL at pH 1.05) and poor solubility at values above the pKa (0.009 mg/mL at pH 6.5).

The active substance has a non - chiral molecular structure.

Polymorphism has been observed for the active substance. Forms N-1 and N-2 are the solvent-free crystalline forms of free base deucravacitinib that have been isolated in laboratory studies. Two process-relevant neat crystal forms (N-1 and N-2) were identified during polymorph screening. The active substance manufacturing process has routinely produced the N-1 form. The crystallinity of the active substance is not critical for the bioavailability of the finished product since the active substance is completely dissolved in the spray solution as the first step of the finished product manufacture. Hence the absence of polymorphism control in the active substance specifications is considered justified.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site.

Deucravacitinib is synthesized in four main steps using 2 commercially available well defined starting materials (i.e. BMS-779036-01 and BMT-264558-01) with acceptable specifications and two custom-synthesized materials (i.e. BMT-166292-01 and BMT-224440-02).

Deucravacitinib has been routinely monitored for related substances, residual solvents and other

volatile impurities, elemental impurities, mutagenic and carcinogenic impurities. Batch

information and analytical data for the active substance batches investigated in toxicological, clinical, and stability studies.

The impurity profile of deucravacitinib relevant to the synthetic route was established from batches that were manufactured by the commercial process for the preparation of deucravacitinib. The structures of these related substances were provided. Related substances originate either from related substances in the starting materials or from the manufacturing process or a degradant observed during stability studies.

Residual solvents including benzene and 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide and other volatile impurities were monitored either in deucravacitinib or in the appropriate intermediate. The residual levels of each individual solvent/volatile impurity are consistently observed at low levels, well below permissible daily exposures (PDE) limits defined in ICH Q3C(R6), *Impurities: Guideline for Residual Solvents*, and do not pose a risk to patient safety or active substance quality.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been provided.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in closed, double, antistatic-treated, low-density polyethylene (LDPE) bags within a fiber board drum with a secure fitting lid which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description / appearance (visual), colour (visual), identification (IR-ATR, HPLC), assay (HPLC), impurities (HPLC), isotopologues (LCMS), inorganic impurities (ICP-MS), residual solvents, including benzene (GC) and 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide (LC-MS).

Water, reagents and solvents, mutagenic and carcinogenetic impurities, inorganic and elemental impurities, polymorphism, particle size distribution, and microbial testing were not included in the active substance specifications. Appropriate justification was provided and it was considered satisfactory.

The acceptance criteria proposed for all impurities in deucravacitinib are either based on qualified levels from nonclinical toxicological safety studies or at levels below or equal to the qualification threshold per ICH Q3A(R2), Guideline for Impurities in New Drug Substances. Details on the origin, fate and tolerance, and control strategy for each specified impurity were provided.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for purity, water content, and total volatiles testing has been presented.

Batch analysis data on 29 batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 30 months under long term

conditions (25ºC / 60% RH), for up to 12 months under intermediate conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, colour, assay, impurities/degradants, water content, form and identification. The analytical methods used were the same as for release and were stability indicating.

The test results showed little to no change for the active substance stored at long-term, intermediate, and accelerated conditions. Assay values showed some variability at the 24-month timepoint due to method variability but there was no apparent overall trend from initial through up to 30 months at long term conditions. The impurity levels of samples under long-term storage conditions remained essentially unchanged from the initial time point through the length of the study for all conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results demonstrated that the active substance is not sensitive to light.

Results on stress conditions (-20°C, 50°C, 40°C/75% RH exposed (open-bag)) were also provided on one batch. All tested parameters were within the specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored in low-density polyethylene without special storage conditions.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as a pink, round, biconvex, film-coated tablet of 8 mm diameter, printed with "BMS 895", and "6 mg" on one side in two lines, plain on the other side.

The quantitative and qualitative composition of the finished product is presented.

The finished product selected for commercialisation is a film-coated immediate release tablet formulation manufactured using an amorphous spray dried dispersion (SDD). The SDD, a finished product intermediate, enhances the solubility of the active substance across the physiological pH range enabling the performance of the finished product.

The pharmaceutical development was guided by ICH Q8, *Pharmaceutical Development* and followed recommendations in ICH Q9, *Quality Risk Management*. Quality risk assessments and experiments were performed to understand the compositional requirements for a robust formulation and the impact of manufacturing process parameters on the critical quality attributes (CQAs) of the SDD and the finished product quality target product (QTTP) profile. Prior knowledge and experience were also used to guide development work. The data obtained was used to establish the process parameter ranges and to define the control strategy for the commercial manufacture of deucravacitinib tablets. However, no design space was claimed.

The physicochemical characteristics of active substance were studied during the finished product development. Two process-relevant neat crystal forms (N-1 and N-2) were identified during polymorph screening. The active substance form and particle size has no impact on the SDD or the finished product because the active substance is completely dissolved in the spray solution as the first step in SDD manufacture.

Excipients commonly employed in SDD and tablet dosage forms were screened and active substance-excipient compatibility studies were conducted. The compatibility of deucravacitinib with the excipients is confirmed through the registrational stability study.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, with the exception of hydroxypropylmethylcellulose acetate succinate, which complies with NF and JP. The grade, substitution of hypromellose acetate succinate is stated. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

During pharmaceutical development three main different formulations were developed. To mitigate the gastric pH dependent absorption, a hydrochloride salt form of the active substance was used in Phase 1 and 2 clinical studies. Oral solution and capsule formulations of a hydrochloride salt form of the active substance were used in Phase 1 and Phase 2, respectively. The capsules required long-term storage under refrigerated conditions due to active substance disproportionation from the HCl salt to the free base form. To enable a desirable long-term storage of the finished product at room temperature while ensuring the desired *in-vivo* properties (drug absorption and to mitigate gastric pH dependency), a new formulation was considered for development to support Phase 3 studies. An amorphous SDD tablet formulation of deucravacitinib in its free base form was selected for Phase 3 and further selected for commercialisation. Initially, two tablet strengths were developed using the SDD approach. Phase 3 studies for treatment of psoriasis were supported with a 6 mg tablet strength, which was further selected to be the commercial strength. Relative bioavailability studies were performed to show bioequivalence between the oral solution, the capsules and the tablet formulations. In addition, a series of dissolution experiments were also conducted in addition to relative bioavailability study to support the formulation changes during development.

Physico-chemical properties and their impact on product performance were discussed. The active substance is classified as BCS Class 2 due to its limited solubility at a moderate to high pH. When formulated in the amorphous SDD based tablet, the active substance is more soluble across the physiological pH range.

A dissolution method has been developed for quality control (QC) during release and stability testing of the finished product (3 different dissolution methods were used in stability). The surfactant is used to avoid incomplete dissolution. The dissolution method has shown to provide the expected discriminative capabilities towards removal of disintegrant from the formulation, tablet hardness, hydroxypropylmethylcellulose acetate succinate grade polymer and its levels of acetyl and succinoyl functional groups, different levels of crystalline active substance. These factors were selected as having potential impact on tablet disintegration and dissolution of an immediate release tablet. No difference in profile was observable for tablets containing variations in lubricant level or containing variations in coating level.

The sequence of unit operations and equipment train utilised during development batches of SDD is similar to and/or representative of the commercial process. Manufacturing processes of commercial and development/clinical batches of deucravacitinib tablets consist of the same sequence of unit operations and equipment operating principles. A process risk assessment using Failure Mode and Effect Analysis was performed to identify the process risk factors of each unit operation that may potentially impact the finished product quality attributes. Prior knowledge and screening studies were used to inform the risk assessment. Through the process risk assessment, process parameters identified as potentially critical were further studied in design of experiments (DoE) using multivariate experimentation and statistical analysis, when possible, to determine the criticality of process parameters and to understand their impact on the drug product CQAs. Based on the development studies, proven acceptable ranges (PARs) for the process parameters and appropriate in-process controls (IPCs) were established for the commercial manufacturing process of the finished product. A PAR allows deliberate change in one parameter without changing the

others outside of their normal operating range or target. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. However, no design space was claimed. None of the process parameters were identified as Critical Process Parameters (CPP).

The primary packaging is polyvinyl chloride/polychlorotrifluoroethylene (PVC/PCTFE) clear blister with push through aluminum. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by two manufacturing sites:

The manufacturing process consists of 7 main steps: spray drying, blending, granulation by roller compaction, milling, blending, tablet compression, film-coating and laser printing. The process is considered to be a standard manufacturing process.

The manufacturing process consist in the manufacturing of SDD which involves the mixing of the active substance with hypromellose acetate succinate (H grade) to acetone and water to form a solution, to spray dry the solution to form the wet SDD and to bulk package SDD; the manufacture of the tablet which consists of mixing the SDD with the excipients (anhydrous lactose, microcrystalline cellulose, croscarmellose sodium (intragranular portion), and silicon dioxide, mill the pre-blend, add magnesium stearate (intragranular portion), roller compact the pre-blend, add croscarmellose sodium, add magnesium stearate (extra-granular portion), compress the final blend, coat the tablets and laser print the logo on the film-coated tablets and package the tablets.

A narrative description of the manufacturing process, process settings and IPCs were provided.

Control of critical steps and intermediate was discussed.

Process validation will be performed prior to commercial distribution. A validation protocol is provided in section 3.2.R. Validation results summary for the SDD manufacture was provided. Since the manufacturing process could be considered a standard process the absence of process validation data for the manufacturing steps after the SDD intermediate manufacture is considered acceptable. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description / appearance (visual), identification (UV, HPLC), uniformity of dosage units / content uniformity (Ph. Eur.), assay (HPLC), organic impurities (HPLC), performance tests /dissolution (Ph. Eur.), water content (KF), acetone (GC) and microbial limits (Ph. Eur.).

Tablet hardness, residual solvents, crystallinity, mutagenic and carcinogenetic impurities/ degradants and isotopic purity were not included in the finished product specifications. Appropriate justification was provided and it was considered satisfactory.

Impurities are controlled either with individual specifications or part of the individual unspecified impurities specification on the active substance. This is consistent with the ICH Q3B (R2) and ICH Q6A recommendations.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested as a Major Objection) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 4 commercial scale batches confirming the consistency of the manufacturing process.

Stability of the product

- Deucravacitinib spray-dried dispersion (SDD)

Stability data from 2 commercial scale batches of intermediate product stored for up to 12 months under long term conditions (5 ºC, and 25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches were manufactured by the commercial site and the batches were packaged in a representative commercial container closure system.

Samples were tested for description, assay, impurities/degradants. The analytical procedures used are stability indicating. No significant changes have been observed under long term and accelerated conditions.

One batch was tested in a photostability study according to the ICH Q1B Guideline. The photostability study indicates that the SDD does not need to be protected from light.

SDD was tested under stressed conditions. Stress data at -20°C and 50°C show little to no change.

The 12-month holding time without storage conditions proposed is acceptable.

- Deucravacitinib film-coated tablets, 6 mg packaged in PVC/Aclar blisters

Stability data were provided for three pilot scale batches of finished product stored under long term conditions for 36 months at 5°C, 25°C / 60% RH, 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. The batches were manufactured by a site involved in the manufacturing process development that is not the commercial site and the batches were packaged in a representative commercial container closure system.

A supportive stability study using two batches of the finished product manufactured with deucravacitinib SDD that was approximately 1 year old was performed to cover the potential storage of the SDD for 1 year prior to manufacture of tablets prior to placing on stability. Because of this, the study is considered an end-to-end

study where the study covers the age of SDD in addition to the age of the subsequently prepared tablets. The study was performed under long term conditions for 24 months at 5°C, 25°C / 60% RH, 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

Samples were tested for appearance, assay, impurity/degradants, water content (by Karl-Fischer titration), hardness, dissolution, microbial limit tests (USP) and microbial quality of pharmaceutical preparations (Ph. Eur.)

No significant changes have been observed under long term and accelerated conditions

One batch of the finished product was tested to the stress condition of -20°C, 50°C, seven freeze-thaw cycles (between -20°C and 40°C/75%RH for approximately 24 hours at each temperature) and photostability conditions according to the ICH Q1B Guideline.

The finished product exhibits an increasing trend in impurities after three months of storage at 50°C and should be protected from heat.

The photostability study indicates that the product does not need to be protected from light.

The freeze-thaw temperature cycling data support shipping through normal distribution channels.

Based on available stability data, the proposed shelf-life of 2 years without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

All excipients used in the manufacture of the finished product are non-animal derived materials, with the exception of lactose. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

One major objection has been raised during the procedure concerning the risk associated with the potential presence of nitrosamines. The applicant’s response was considered satisfactory.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

Deucravacitinib (BMS-986165) is a small molecule that selectively inhibits the tyrosine kinase 2 (TYK2) enzyme.

The non-clinical pharmacology of BMS-986165 was studied in vitro using biochemical, cellular assays, and whole blood, as well as in murine models of psoriasis, inflammatory bowel disease, and lupus. The in vitro assays evaluated the binding affinity and selectivity for TYK2 versus other kinases and pseudokinases, as well as the functional potency and selectivity against the action of interleukin (IL)-23, IL-12, and Type I interferons (IFNs) in human cellular and whole blood assays. BMS-986165 was evaluated for efficacy against the IL-23-induced acanthosis model of psoriasis in mice, murine anti-CD40 induced colitis, T-cell transfer colitis, and lupus nephritis in lupus-prone NZB/W mice. In vitro and in vivo nonclinical absorption, distribution, metabolism, and excretion (ADME) and pharmacokinetics (PK) of BMS-986165 were evaluated.

Safety pharmacology assessments (cardiovascular, central nervous system, and respiratory systems) were incorporated into select repeat-dose studies in rats and monkeys, and single-dose CV telemetry studies were conducted in rats, dogs, and monkeys, and were supplemented by in vitro safety pharmacology evaluations.

According to ICH M3(R2), the toxicology program for deucravacitinib consisted of investigations following oral administration in toxicology studies. These studies included single-dose studies in rats, dogs, and monkeys; repeat-dose studies ≤ 28 days in mice, ≤ 6 months in rats, and ≤ 9 months in monkeys; in vitro (bacterial reverse mutation, chromosomal aberration) and in vivo (micronucleus) genetic toxicity studies; in vitro phototoxicity study; fertility and pre- and postnatal development (PPND) (rat) and embryo-fetal development (EFD) (rat and rabbit) studies; juvenile study (rats); local tolerance (human skin and bovine cornea); local lymph node assays (LLNA) to evaluate risk of skin sensitization (mice); and carcinogenicity studies (Tg-rasH2 mice and Sprague-Dawley rats).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

BMS-986165 (deucravacitinib) is an oral, selective TYK2 inhibitor that acts by binding to the pseudokinase domain of TYK2. It prevents receptor-mediated activation of the adjacent catalytic domain, thereby inhibiting

the functional cellular responses to IL-23, IL-12 and Type I IFNs. Because the TYK2-dependent receptors (e.g., receptors for Type I IFNs, IL-10, IL-12, IL-22, IL-23) are distinct from those highly dependent on Janus kinase (JAK)1/JAK3 (e.g., receptors for IL-2, IL-7, IL-15, IL-6) or JAK2 (e.g., erythropoietin [EPO], thrombopoietin [TPO], granulocyte-macrophage colony-stimulating factor [GM-CSF]), BMS-986165 exhibits a highly differentiated profile from inhibitors of other JAK kinases. In human cellular and whole blood assays, BMS-986165 potently inhibited signaling, transcriptional and functional assays downstream of the receptors for IL-23, IL-12 and Type I IFNs with high selectivity compared to receptor-mediated pathways regulated by JAKs (JAK1, JAK2, and JAK3). In vitro addition of BMS-986165 to the blood from patients with lupus effectively inhibited the Type I IFN-driven gene signature.

In human whole blood assays, BMS-986165 exhibited a highly differentiated profile compared to JAK inhibitors tofacitinib, baricitinib, and upadacitinib. BMS-986165 was considerably more potent than tofacitinib, baricitinib, and upadacitinib in blocking signaling downstream of TYK2-dependent receptors IL-23 and IL-12 in human whole blood. In contrast, BMS-986165 was considerably less potent than tofacitinib, baricitinib, and upadacitinib in blocking signaling downstream of JAK1/JAK3-dependent receptors for IL-2 and IL-7, the JAK1/JAK2-dependent receptor for IL-6, and the JAK2-dependent receptor for TPO.

Concerning the three metabolites of BMS-986165: BMT-153261 exhibited a similar potency to that of BMS-986165, BMT-334616 has very weak pharmacological activity, and BMT-158170 is not pharmacologically active. Compared to TYK2-dependent responses in human whole blood, BMS-153261 and BMT-158170 were far less potent against JAK1/JAK3-dependent IL-2-induced STAT5 phosphorylation, similar to the profile of BMS-986165. Similar to BMS-986165, both BMT-153261 and BMT-158170 failed to inhibit JAK2-dependent TPO-induced STAT phosphorylation at concentrations as high as 10,000 nM.

The BMS-986165 pharmacologic activity was confirmed at all doses in several repeat-dose rat and monkey toxicology studies by decreasing phosphorylation of IFNα-induced STAT1 in blood CD3+ T lymphocytes, and/or involving a repression of select Type I IFN-inducible gene transcripts (e.g., IFIT1, IFIT3, OAS1, and MX1) in liver and/or blood. These data are consistent with in vitro results, in which BMS-986165 inhibited IFNα-induced phosphorylation of STAT with similar potency in rats, monkeys and human blood. Type I IFNs have been shown to both enhance B cell responses to antigen receptor ligation and lower the threshold for B cell induction, as well as induce the differentiation of monocytes into antigen-presenting dendritic cells to drive B and T cell responses. Furthermore, toxicity studies showed that some adverse effects on immune system and on skin could be due to a potential contribution from the activity against JAK1/3 at high BMS-986165 exposures achieved in nonclinical toxicology studies, since drug plasma levels in these studies approached or exceeded IC50 values in rat or monkey whole blood against JAK1/3-dependent IL-2-induced STAT5 phosphorylation.

Using IL-23-induced acanthosis in mice, analysis of skin biopsies showed BMS-986165 to be effective at blocking inflammatory cytokine expression, including IL-17A, IL-21, and subunits of IL-12 and IL-23.

2.5.2.2. Secondary pharmacodynamic studies

BMS-986165 and metabolites BMT-153261 and BMT-158170 were evaluated in vitro for potential to modulate ligand interactions against a panel of G-protein coupled receptors (GPCRs), transporters, ion channels, nuclear hormone receptors, and enzymes.

BMS-986165 activity was limited to inhibition of the opiate kappa receptor (free drug IC50 = 4.0 µg/mL) and PDE 4 enzyme (free drug IC50 = 0.9 µg/mL). All these IC50 values are significantly higher than the free

maximum concentration (Cmax) at the RHD, indicating low potential for undesirable effects in human subjects.

The 2 major human metabolites of BMS-986165, BMT-153261 and BMT-158170, did not exhibit noteworthy off-target activity in a panel of receptors, ion channels, transporters, or enzymes.

2.5.2.3. Safety pharmacology programme

The CV, CNS, and respiratory systems were evaluated as part of the repeat-dose GLP toxicity studies conducted with BMS-986165. In addition, a series of in vitro and/or in vivo single-dose safety pharmacology studies were conducted with BMS 986165, and to a lesser extent, its pharmacologically active metabolite, BMT-153261, and inactive metabolite, BMT-158170.

The CV effects were evaluated by assessing the effects on hERG currents and other cardiac ion channels, and by examining the effects of single doses of BMS 986165 on CV parameters in anesthetized rabbits (intravenous [IV] infusion) and oral telemetry studies in conscious rats, dogs, and monkeys.

BMS-986165 inhibited hERG currents by 43.9% at 10 µM (717× RHD free Cmax). These free concentrations are much higher than the free Cmax at the RHD, indicating low potential for undesirable cardiac ion channel effects in humans.

In addition, BMS 986165 was evaluated for potential functional effects on induced human pluripotent stem cell-derived cardiomyocytes, embryonic rat cardiomyocytes, isolated perfused rabbit hearts, and rat aortic smooth muscle preparations. BMS-986165 increased spontaneous beat rate and field potential duration in human cardiomyocytes at ≥ 10 µM and increased beat rate of rat cardiomyocytes at 30 µM (2,150× RHD free Cmax) with no effect on field potential duration. The non-GLP in vivo cardiovascular study in rabbits showed that BMS-986165 at 2 mg/kg IV induced a modest QT prolongation (Cmax 20 mg/mL; 443x/96× total/free RHD Cmax).

Concerning the heart rate, at high concentrations (>10 µM) there is an increased beating rate of multipotent stem cell-derived cardiomyocytes, of unclear origin since the drug is shown to block sodium, potassium and calcium currents at these high concentrations. Though, there is no effect on heart frequency of Langendorff isolated rabbit hearts up to the concentration of 30 µM. In monkeys, at 1 mg/kg (corresponding to the maximum concentration attained with an oral dose of 36 mg in human), there was an increase of ~30 bpm with no change in blood pressure. At 3 mg/kg, there was an increase of heart rate and contractility, contemporaneous to a decrease of blood pressure: the link between both effects are unknown. These findings suggest that deucravacitinib could have relaxing pre-contracted aortic rings, increasing of coronary flow, and decreasing the rabbit blood pressure, vaso-relaxing effects whose the origin is unknown. However, these hemodynamic effects had identifiable thresholds (NOELs) with exposure margins to the RHD. The safety margin on the GLP cardiovascular telemetry study in monkeys was low (NOEL = 0.65 mg/kg (Cmax 0.13 µg/mL; 3X RHD Cmax). Clinically, hemodynamic changes occurred in BMS-986165-treated subjects with psoriasis, however the changes were not clinically meaningful.

No independent safety pharmacology study was conducted to assess the potential CNS effects and potential respiratory effects of BMS-986165. However, in repeat-dose toxicity studies, in rat and monkey the safety pharmacology assessment of central nervous and respiratory system were included. No BMS-986165-related CNS or respiratory effects were noted. The results are consistent with very low brain-to-plasma concentration ratio.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies were not conducted.

2.5.3. Pharmacokinetics

Nonclinical PK, ADME, and DDI properties of BMS-986165 and its major circulating metabolites, BMT-153261 and BMT-158170, were characterized in a series of in vitro and/or in vivo PK studies in mice, rats, dogs, and monkeys.

Absorption

Oral absorption of BMS-986165 was rapid in animals (Tmax = 0.5 to 5 hours). Despite being a substrate for the intestinal efflux transporters, P-gp and BCRP, BMS-986165 has high absolute oral bioavailability in animals (87% to 100%) and humans (~ 99%), indicating it is well absorbed in animals and demonstrating near complete absorption in humans, which suggests that intestinal P-gp and/or BCRP do not limit its oral absorption. Following oral administration of deucravacitinib to mice, rats, rabbits, and monkeys there were no substantial sex differences, loss of exposure, or accumulation noted.

Distribution

Serum protein binding of BMS-986165 was moderate in humans (86.6%) and in mice, rats, and monkeys (ranged from 85.4% to 88.1%), and high in rabbit (97.1%). Similarly, serum protein binding of BMT-153261 (active metabolite) was moderate in humans (80.9%) and in mice, rats, and monkeys (ranged from 77.2% to 79.6%), and high in rabbit (94.1%).

The large steady-state volume of distribution following a single IV administration to mice, rats, dogs, and monkeys (2.8, 2.0, 2.3, and 2.0 L/kg respectively) indicates extravascular distribution. Similarly, steady-state volume of distribution (Vss) of BMS-986165 at 140 L, was greater than total body water (42 L) indicating extravascular distribution.

In Sprague-Dawley and pigmented Long-Evans rats, [14C]BMS-986165-derived radioactivity was rapidly absorbed and widely distributed. In a 14-day repeat dose tissue distribution study in male Sprague- Dawley rats, tissue distribution pattern and elimination of [14C]BMS-986165-derived radioactivity was generally similar to those in animals after a single dose, and no overt accumulation of radioactivity was observed in any tissue. There was a very low brain-to-plasma concentration ratio (0.03 to 0.04) for BMS-986165 in Sprague-Dawley rats 3 hours after a 10 mg/kg oral dose. The organs with highest concentrations of BMS-986165-derived radioactivity did not correspond to the target organs (lymphoid/immune, hematopoietic, and skin) identified in the repeat-dose toxicology studies. In pigmented rats, there was substantial, but reversible binding of [14C]BMS-986165-derived radioactivity to certain melanin-containing tissues, such as the eye uveal tract, but not in pigmented skin. In pregnant rats receiving [14C]BMS-986165 orally, radioactivity crossed into maternal placenta and amniotic sac, but was not measurable in the fetus following a single dose. In nursing rats receiving [14C]BMS-986165 orally, radioactivity was detected in rat milk from 0.5 through 48 hours post dose, with milk-to-plasma concentration ratios of 2.7 to 30 indicating that BMS-986165 and/or its metabolites distribute into rat milk.

Metabolism

In vitro and in vivo metabolism studies were conducted in various species to characterize the metabolism of BMS-986165. BMS-986165 undergoes primary metabolism in vivo via 4 distinct pathways: CYP1A2-mediated

N-demethylation at the triazole moiety to form BMT-153261, CES2-mediated cyclopropyl carboxamide hydrolysis to form BMT-158170, UGT1A9-mediated N-glucuronidation to form BMT-334616, and CYP2B6 and CYP2D6-mediated mono-oxidation at the deuterated methyl group to form M11. All of these 4 biotransformation pathways were present in every species, resulting in similar metabolite profiles in all species (humans, mice, rats, monkeys), although quantitative differences were observed. All metabolites present in humans were present in at least 1 of the nonclinical safety species, with every human metabolite being detected in rats, and there were no unique human metabolites. In humans, biotransformations mediated by CYP1A2, CES2, and UGT1A9 are the major metabolic pathways, with BMT-153261, BMT-158170, and BMT-334616 being the most abundant metabolites (18.5%, 9.02%, and 18.6% of the dose, respectively). Thus, BMS-986165 was the predominant drug-related component in circulation in all species tested, and 2 metabolites, BMT-158170 and BMT-153261, were the major circulating metabolites in humans (> 10% of total drug-related exposure at steady state).

Excretion

Excretion of BMS-986165, following a single oral dose of [14C]BMS-986165, was investigated in mice, rats (intact and BDC rats), BDC monkeys, and humans (mass balance studies). Excretion of [14C]BMS-986165-derived radioactivity is predominantly via fecal route in rats and monkeys, while renal excretion of radioactivity is a minor route. Radioactivity was evenly excreted in feces and urine in humans. Data from BDC animals suggest fecal excretion of unchanged drug included both biliary and intestinal excretion. Elimination profiles are closely similar among humans, rats and monkeys. For mice, fecal excretion dominated while metabolism and renal excretion were minor.

Based on the in vitro studies with cells expressing known transporters, P-gp and/or BCRP contribute to the renal excretion of BMS-986165 and it metabolites BMT-158170 and BMT-153261. Also MATE2-K may play a role in renal excretion of BMT-153261.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No acute effect occurred in the single dose toxicity studies in rats, dogs and monkeys.

2.5.4.2. Repeat dose toxicity

Several repeat-dose exploratory studies were conducted in mice (≤28 days), rats (≤2 weeks), and monkeys (≤5 days) to characterize dose-response, assess different oral vehicle formulations, and/or measure exposures to metabolites BMT 153261, BMT 158170, and BMT 334616. Pivotal repeat-dose GLP studies were conducted in CByB6F1 mice (≤28 days), Sprague-Dawley rats (≤6 months) and cynomolgus monkeys (≤9 months). No mortality in the repeat-dose toxicity studies were observed, except in 6-month rat toxicity study where 11 unscheduled deaths (1, 2, 1, and 7 at 0, 5, 15, and 50 mg/kg/day, respectively) occurred: the cause of death remained undetermined for five of these animals. These deaths were not considered BMS-986165-related for the following reasons: 1) similar total incidence in all dose groups, including control; 2) a lack of new or more severe microscopic findings in these early decedent rats compared to the findings in rats euthanized at scheduled necropsies; and 3) the lack of BMS-986165-related early deaths in the rat carcinogenicity study (see below). Moreover, the exposure margin (AUC) at 50 mg/kg/day is 247× recommended human dose [RHD].

The immune system, the hematopoietic system and the skin were considered main target organs with following main effects : 1) in rats, decreased lymphocyte counts and lymphoid cellularity in lymph nodes, decreased spleen and thymus size and weight correlating with decreased lymphoid cellularity of the thymus and spleen, and decreased TDAR to KLH (latter also seen in monkeys); 2) decreased RBC mass parameters and platelets in rats and monkeys and 3) varied clinical and microscopic skin changes in monkeys.

No specific mechanistic studies were conducted with BMS-986165, since the principal results (immunosuppression in both species and skin findings in monkeys) are consistent with the expected immunomodulatory activity of BMS-986165 against the inhibition of TYK2 and the biological role of TYK2 in mediating Type I IFN- and IL12/23-dependent immune responses. In rat and monkey toxicology studies, BMS-986165 inhibited IFNα-induced STAT1 phosphorylation in blood CD3+ T-cell lymphocytes, as well as repressed expression of Type I IFN-inducible transcripts (e.g., IFIT3, OAS1, or MX1) in blood and liver.

However, a potential contribution from the off-target activity against JAK1/3 at high BMS-986165 exposures achieved in the nonclinical toxicology studies cannot be excluded, since the drug plasma levels in these studies approached or exceeded the IC50 values in the rat or monkey whole blood against JAK1/3-dependent IL-2-induced STAT5 phosphorylation. As such, in view of the low RHD and systemic exposure in human subjects, the off-target inhibition of JAK1/3 potential in rats and monkeys at high drug exposures is not considered clinically relevant.

Immune System

In rats, dose-dependent minimally to moderately decreased lymphocyte counts (including total T, helper T, cytotoxic T, B, and NK cells) generally correlated with decreased spleen and thymus size and weights, decreased lymphoid cellularity in lymph nodes, thymus and splenic white pulp, and decreased TDAR to KLH-specific IgM and IgG responses. These changes were partially to fully reversible. Additionally, suppression of KLH-specific immune responses was also incomplete and was fully reversible during recovery in rats. In monkeys, suppression of KLH-specific IgM and IgG responses was noted at all doses.

However, BMS-986165-treated monkeys showed increase anti of-KLH IgM and IgG antibody responses, indicating partial inhibition only. The decreased TDAR to KLH was not accompanied by decreased lymphocyte counts or microscopic lymphoid depletion in the spleen, thymus or lymph nodes or diminished serum levels of IgG, IgM, or IgE. It is unclear why decreased blood and tissue lymphocyte counts were noted in rats, but not monkeys, since decreased TDAR to KLH responses were observed in both species. TYK2 is required for optimal signal transduction downstream of IL-12, IL-23, and Type I IFNs, and decreased TDAR to KLH is consistent with the partial contributions of Type I IFNs, IL-12 and IL-23 to these antigen-induced antibody responses. Importantly, in BMS-986165-treated rats and monkeys, antigen-induced antibody responses, while diminished, were still evident, and were either fully reversible (rats) or expected to be fully reversible (monkeys) based on the lack of microscopic effects in the lymphoid tissues, and reversible/transient biochemical nature of TYK2 inhibition by BMS-986165.

The relevance of the immune effect observed in animal was studied in the Phase 3 clinical trial of deucravacitinib in subjects with moderate-to-severe plaque psoriasis.

Hematopoietic System

Dose-dependent minimally to mildly decreased in RBC mass parameters (RBC counts, haemoglobin and haematocrit) as well as platelet counts was generally observed in rats and monkeys treated with BMS-986165. These changes were more prominent at higher doses and reversible. In addition, there was no gross or microscopic evidence of haemorrhage in any tissues. The exact mechanism for the decreased RBC mass

parameters and platelets is unclear, but may be multifactorial. While TYK2 phosphorylation has been reported following thrombopoietin (TPO) signaling, subsequent reports have not found an effect of TYK2 activity on thrombopoesis in humans or mice, and TYK2 does not seem to be essential in this pathway. However, to assess a potential contribution from the off-target activity of BMS-986165 against JAK2, a related family member of Janus kinases known to play an important role in erythropoiesis and thrombopoesis, BMS-986165 was evaluated in rat and monkey whole blood JAK2-dependent TPO-induced STAT3 and STAT5 phosphorylation assays. In both species, BMS-986165 was inactive at concentrations as high as 10 µM (4.3 µg/mL; highest tested concentration), suggesting that an off-target inhibition of JAK2 in vivo by BMS-986165 was unlikely to cause decreased RBC (via erythropoietin block) or platelet (via TPO block) counts in rats or monkeys.

In rat studies, a marked platelet decrease concurrent with marked decrease in the megakaryocytes number in the bone marrow in one rat indicates an effect on megakaryocyte development (and subsequent decreased platelet synthesis) in the most severely affected animal. The decreased RBC mass parameters were accompanied by secondary increases in mean cell volume and RBC distribution width, suggesting a regenerative response. In the 6-month rat study, decreased RBC mass parameters, platelets, and decreased bone marrow cellularity may suggest central effect on hematopoiesis of all (myeloid, erythroid, and megakaryocytic) cell lineages. However, decreases in food consumption, body weight and/or body-weight gains in rats may have also indirectly contributed to these hematology and bone marrow changes. In monkeys, decreased RBC mass parameters and platelets were seen without microscopic correlates. Platelet decreases were less likely due to peripheral demand, based on the lack of mean platelet volume (MPV) increases, which can indicate accelerated thrombopoesis in the bone marrow. In addition, there was no evidence of increased platelet consumption due to normal activation in situations like vasculitis or thrombosis. Decreased platelets have been reported to be associated with infections, which may potentially have been a contributing factor in individual animals in the 3-month and 9-month monkey studies, considering the skin findings and transient clinical observations of hunching, liquid feces, and increased body temperature.

The increase in eosinophil count in monkeys is not understood but considered non-adverse since no tissue infiltration is noted.

Skin

Various clinical skin changes (e.g., swelling, dryness, flaking, papule, redness, or scabbing) were noted throughout the body at all doses in the ≥ 3-month monkey studies. Microscopic correlates were noted in the epidermis (hyperkeratosis, erosion, crusts) and dermis (mixed cell infiltrates and inflammation) in the 9-month monkey study. Although no definitive microbial pathogens were confirmed as the causative or contributing agents, skin changes were considered likely infectious in etiology, as they generally improved after antibiotic treatments, and were present in the context of decreased TDAR to KLH, indicative of immunosuppression. The skin changes trended towards reversibility during recovery.

Although the mechanism responsible for the skin findings is unclear, the Applicant hypothesis is that a combined inhibition of several TYK2-dependent pathways by BMS-986165 may account for these changes. BMS-986165 is a potent inhibitor of several TYK2-dependent signaling pathways, including IL-10, IL-12, IL-22, and IL-23, as well as Types I and III IFNs. These pathways are involved in maintenance of innate and adaptive immune responses, including epithelial barrier immunity. For example, IL-23 is critical in the expansion and survival of Th17 cells, which secrete proinflammatory cytokines IL-17 and IL-22, which can be protective against infections by stimulating production of antimicrobial peptides (e.g., β-defensins, mucins, and S100 peptides) by epithelial keratinocytes; promoting epithelial proliferation, which helps to maintain

and restore epithelial barrier prior to and after infection; and inducing chemokines that foster the recruitment of neutrophils and induce other proinflammatory cytokines. The inhibition of Type III IFNλ may also contribute, since IFNLR1 is expressed preferentially in epithelia, and the antiviral effects of Type III IFN (e.g., IL-28 and IL-29) are most evident against pathogens targeting epithelia. It is important to note that, even though the skin findings appear consistent with the pharmacologic inhibition of TYK2, the potential contribution from the off-target activity against JAK1/3 at the high exposures achieved in the monkey studies cannot be excluded. Consistent with such a possibility, various skin lesions (e.g., scabs, discoloured and broken skin, red and dry skin, swelling in paws, etc.) associated with inflammation and infections resulting from immunosuppression were also reported in dogs treated with the approved JAK1/3 inhibitors baricitinib and upadacitinib, and in monkeys (e.g., skin scabs and bacterial infections) treated with the pan-JAK inhibitor tofacitinib. Importantly, the potential inhibition of JAK1/3 in rats and monkeys at such high drug exposures was not considered relevant at the much lower RHD and exposure in humans.

Heart

In the carcinogenicity study in rats, cardiomyopathies occurred in treated groups. In the 1-month repeat-dose oral toxicity study in monkeys, the subacute inflammation triggered characterized as an infiltration of the myocardium with inflammatory cells including lymphocytes, plasma cells, and macrophages, with a low number of granulocytes that in some instances was associated with rare degenerative cardiomyocytes. This finding was considered to be an exacerbation of a background finding, since minimal subacute inflammation was present in 1 female control animal each at the end-of-dose and post-dose necropsies. Furthermore, in the 6-month toxicity study in rats at doses ≤ 50 mg/kg/day (≤ 247× RHD AUC), there was no indication of BMS-986165-related cardiac findings. For instance, the incidence and severity of the cardiac cell inflammation during the dosing phase was mostly minimal to mild and comparable between the vehicle control and high-dose males and females, and there were no signs of cardiac toxicity, including cardiomyopathy. Similarly, in the rat carcinogenicity study at doses ≤ 15 mg/kg/day (≤ 51× RHD AUC), there was also no indication of BMS-986165-related cardiac findings. Cardiomyopathy, as a major cause of death in BMS-986165-treated preterminal decedent male rats was noted at a comparable or lower incidence than in the water and/or vehicle control groups during the carcinogenicity study.

Liver

In toxicity studies in rats, liver side effects were observed such as non-reversible decreased cholesterol and triglycerides, increased total bilirubin and increased aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase. In the carcinogenicity study in rats, a dose-independent increased minimal to mild iron-containing pigment in Kupffer cells of the liver at ≥ 3 mg/kg/day (at low dose) was also noted. In affected animals, the amount of brown pigment was minor, and the difference in severity was attributed to the number of affected Kupffer cells. This finding was considered non adverse, because it represented a minor exacerbation of the same background finding observed in control rats, and was not associated with any other microscopic findings, such as hepatocellular degeneration, necrosis, and/or inflammation. The 9-month toxicity study in monkeys showed that liver-related findings were limited to mostly minimal to mild increases in total bilirubin throughout the study in females at doses ≥ 3 mg/kg/day and males at 10/5 mg/kg/day and that the bilirubin changes were reversible after the 2-month recovery period. In the 6-month toxicity study in rats, minimal to mild BMS-986165-related increases, mostly in males, in ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin at doses ≥ 5 mg/kg/day were observed. These changes were considered non adverse due to the magnitude and lack of microscopic correlates. Similar to the finding in monkeys, the increased total bilirubin was considered likely related to the reversible inhibition of UGT1A1. The changes in the above clinical chemistry parameters at the no-observed-adverse-effect level (NOAEL) of 5

mg/kg/day (9× RHD AUC) are not considered to be clinically meaningful, because of the small magnitude of change, the lack of microscopic correlates in the liver, and acceptable safety margins relative to the RHD.

Kidneys

In toxicity studies in monkeys, decreased glomerular filtration rate (increased urea and creatinine) and decreased serum albumin were observed. However, no BMS-986165-related microscopic findings in the kidneys at any dose. In the 6-month toxicity study in rats, an obstructive uropathy was the cause of death of 1 male rat at 50 mg/kg/day. However, in the carcinogenicity study, no causal association were noted between BMS-986165 administrations for nearly 2 years. In the rat carcinogenicity study, chronic progressive nephropathy (CPN), common background finding in aging rats with little relevance to human risk assessment, was reported at a comparable incidence across all dose groups in the early decedents as major cause of death. These data demonstrate a lack of causal association with BMS-986165 administration.

Gut

In the 9-month toxicity study in monkeys, slight to severe liquid feces were observed at all doses: the etiology was unclear.

2.5.4.3. Genotoxicity

In vitro and in vivo genotoxicity studies showed that deucravacitinib as well as metabolites BMT-153261 and BMT-158170 do not present any genotoxic potential.

2.5.4.4. Carcinogenicity

The carcinogenic potential of BMS-986165 was evaluated in a 26-week oral study in CByB6F1-Tg(HRAS)2Jic hemizygous (Tg-rasH2 transgenic) mice, and a 2-year oral carcinogenicity study in Sprague-Dawley rats.

In the 6-months oral carcinogenicity study in rasH2 transgenic mice, all neoplastic findings were considered unrelated to treatment due to the absence of any dose relationship, lack of statistical significance, or very low magnitude of change. All non-neoplastic findings were considered unrelated to treatment due to the absence of any dose relationship or the very low magnitude of change and/or the findings represented background changes occasionally observed in CByB6F1-Tg (HRAS) 2Jic hemizygous mice. The NOAEL for carcinogenesis was considered to be the highest dose of 60 mg/kg/day, and the exposure ratio was estimated at 185, 27, and 11 for of BMS-986165, for metabolite BMT-153261 and metabolite BMT-158170, respectively. In addition, the comparison between the incidence of spontaneous hemangiosarcoma (skin, spleen, testes and abdominal cavity), bronchioalveolar adenoma and carcinoma, lymphoma, stomach sarcoma, skin papilloma, or harderian adenoma observed in the rasH2 carcinogenicity study and the incidence from Historical Control Data from 2017 to 2021 at the same testing facility with rasH2 transgenic indicated that the incidence the spontaneous neoplasms was less than or equal to the maximum incidence of testing facility historical control data. Moreover, the neoplastic findings were considered unrelated to BMS-986165 treatment due to the absence of dose-response relationship, lack of statistical significance, and/or low frequency of findings, which fall within the testing facility HCD in this strain of mouse.

In the 2-year oral carcinogenicity in CD rats, no BMS-986165-related neoplastic findings were noted. The most commonly observed spontaneous tumours were pituitary adenoma/carcinoma, adrenal gland pheochromocytoma, thyroid gland c-cell/follicular cell adenoma and mammary gland tumours (fibroadenoma/adenocarcinoma; only in females). Statistical analyses showed statistical significance for the

trend test for the following tumours: sebaceous cell adenoma in the skin for males, granulocytic leukemia, hepatocellular adenomas in the liver, and benign thymomas in thymus in females. Pairwise comparison tests performed for these tumours were all negative. In absence of a continuum (hyperplasia to tumour formation), and/or given low incidence of these tumours often considered as common in Sprague-Dawley rats, these increasing trends were considered incidental and not attributed to the administration of BMS-986165. Moreover, BMS-986165-related non-neoplastic microscopic findings were observed in the liver: increased incidence of minimal to mild brown pigment accumulation in the Kupffer cells in both sexes at all dose levels with no evidence of a dose relationship and not association with any other microscopic findings such as hepatocellular degeneration/necrosis and/or inflammation. Therefore, those findings were considered non adverse. The NOAEL was considered to be 15 mg/kg/day. The exposure ratio was estimated at 51, 6/2, and 12 for BMS-986165, metabolite BMT-153261, and metabolite BMT-158170, respectively. In conclusion, results showed deucravacitinib had no carcinogenic potential in 2-year rat study.

2.5.4.5. Reproductive and developmental toxicity

Potential deucravacitinib-related effects on fertility and early embryonic development were investigated in a dedicated study in female rats, and in the 6-month rat toxicity study wherein males were mated to naïve females after 57 daily doses with additional evaluation of sperm morphology and testes histopathology at necropsy. No effect on male and female fertility or on early embryonic development was identified at oral doses up to 50 mg/kg/day in these studies, corresponding to high rat-to-human exposure multiples for deucravacitinib based on either C_{max} or AUC levels (>160). Animals were also adequately exposed to metabolites BMT-153261 and BMT-158170 in these studies.

Pivotal embryo-foetal development toxicity studies were conducted in pregnant rats and rabbits dosed during the whole period of organogenesis at oral doses up to 75 mg/kg/day and 10 mg/kg/day, respectively. In both species, there were no significant deucravacitinib-related adverse effects on maternal animals or on embryo-fetal development (i.e. no embryolethal, foetotoxic or teratogenic effect). Safety margins calculated based on AUC levels were large in both species, i.e. 266 in rats and 91/20 in rabbits considering total/unbound exposure. In addition, additional toxicokinetic studies conducted in pregnant rats and rabbits showed adequate coverage for metabolites BMT-153261 and BMT-158170 at the NOAELs identified for embryo-foetal development.

In the pre- and post-natal development study performed in rats treated orally from implantation to weaning, a treatment-related decrease in the body weight of male and female pups was observed at the high dose level of 50 mg/kg/day during the preweaning period. During the postweaning period, body weight gain values of F1 offspring were comparable to the control group and the body weight of high dosed animals was not significantly affected from postnatal day (PND) 77 in males and PND38 in females. Otherwise, no treatment-related effects was noted on parameters evaluated in F1 offspring, including sexual maturation, neurobehavioural examinations, and reproductive performance. A safety margin of 19 can be derived for effects on postnatal development considering a NOAEL of 15 mg/kg/day derived based on treatment-related effect on preweaning body weights at 50 mg/kg/day. At 15 mg/kg, exposure ratios for metabolites BMT-153261 and BMT-158170 reached 0.4 and 9.4, respectively. Although the figure obtained for metabolite BMT-153261 is <1, it is noted that it was 3.3 at the high dose level. Toxicokinetic data generated from this study have shown pup exposure to the parent compound and both metabolites, in line with pharmacokinetic investigations showing lacteal excretion of drug-related metabolites with milk-to-plasma concentrations ratios ranging from 2.7 to 30.9 from 0.5 to 48 hours post-dose.

The current application is for the use of deucravacitinib in adult patients. Nevertheless a juvenile toxicity study was conducted in rats exposed for 10 weeks from PND21 at doses up to 50 mg/kg/day, with an additional 10-week recovery period. The main findings in juvenile animals were related to the pharmacological immunomodulatory activity of deucravacitinib, and reversible. These findings were in line with those reported in adult rat studies, and no new finding of concern was identified. There was also no treatment-related effect on the onset of puberty and reproductive performance.

2.5.4.6. Toxicokinetic data

Concerning toxicokinetical data in rat and mouse studies, BMS-986165 systemic exposures (AUC[0-24h]) increased generally greater than dose proportionally in the chronic toxicity and carcinogenicity studies. However, no sex differences, no noteworthy accumulation or loss of exposure were noted. Systemic exposures to metabolites BMT-153261 and BMT-158170 were only measured at the high dose in the 6-month toxicity study, thus the exposure ratio animal / human at NOAEL could not be calculated. In rat carcinogenicity study, systemic exposures to metabolites BMT-153261 and BMT-158170 were measured at mid and high dose: mean AUC(0-T) to the pharmacologically active metabolite BMT-153261 in males were greater (2.4 to 7.7×) than those in females and were approximately 0.02 to 0.03× and 0.004 to 0.008× (based on molar units), respectively, those of the parent. In addition, mean AUC(0-T) to the pharmacologically inactive metabolite BMT-158170 were approximately 0.04× and 0.07× those of the parent, with no substantial sex differences.

Concerning the chronic study in monkeys, mean BMS-986165 systemic exposures (AUC[0-24h]) increased slightly greater than dose proportionally across the dose range of 1 to 10/5 mg/kg/day, with no sex differences. No substantial accumulation was noted except in the 3-month toxicity study where BMS-986165 AUC(0-24h) values were greater (1.9x to 2.2x) than those following the first dose (dose from 0.75 to 5 mg/kg/day). In Week 39, mean systemic exposures to BMS-986165, BMT-153261, BMT-158170, and BMT-334616 were measured only at 10/5 mg/kg/day (based upon molar units for % calculations) and were 94.7%, 2.5%, 0.3%, and 2.6%, respectively, of mean total measured AUC(0-T).

Consistent with the guideline ICH M3(R2), exposures to the 2 human metabolites, BMT-158170 and BMT-153261, measured in several GLP-compliant toxicology studies at BMS-986165 doses which did not exceed the MTD, provide adequate AUC exposure multiples compared to the RHD.

2.5.4.7. Local Tolerance

In vitro and in vivo local tolerance studies showed that BMS-986165 was considered to be a non-sensitizer, nor a skin or ocular irritant.

2.5.4.8. Other toxicity studies

BMS-986165 absorbs light in the UV-B range and is distributed in some melanin-containing tissues such as uveal tract, but not to pigmented skin. No phototoxicity were noted in the Neutral Red Uptake Phototoxicity Assay in Balb/c 3T3 Mouse Fibroblasts at concentration from 0.56 to 31.7 mg/L so no additional study in vivo was conducted in accordance with ICH S10.

2.5.5. Ecotoxicity/environmental risk assessment

The screening for Persistence, Bioaccumulation, and Toxicity (PBT) showed that deucravacitinib was persistent and toxic but was not bio-accumulative. (see **Table 3** Summary of main study results)

A PEC_{SW} value by default was calculated and exceeded the Phase I action level of 0.01 µg/L, therefore a Phase II, Tier A was required.

The Koc values for adsorption-desorption were estimated in sludges from 209 to 328 L/kg, and in soils from 23,326 L/kg to 35,306 L/kg. Deucravacitinib is therefore strongly adsorbed on solids where it persists for a long time. In addition, it was poorly bound to the two sludges in the study (328 and 209 L/kg). The Koc values on sludges were lower than 10,000 L/kg, no test on terrestrial organisms was to be carried out.

The aerobic transformation in an aquatic sediment system is evaluated according to the OECD 308 protocol on 2 sediments. Deucravacitinib decreased from the aqueous phase (0.29 to 1.72% after 99 days) and increased at the same time in the aqueous phase (50.7 to 62.4% after 99 days) but no transformation products were detected at a value higher than 10%. After normalisation, the DT50 in the sediments were 211 and 330 days in the total system, and 424 and 676 days in sediments 1 and 2 respectively. Deucravacitinib is therefore persistent in sediment. Consequently, a test on sediment organisms (chironomids) was performed in Phase II Tier B.

Regarding the effects on aquatic organisms, an activated sludge respiration inhibition test was performed according to OECD 209. The no observed effect concentration (NOEC) for activated sludge microorganisms is 1000 mg/L. A growth inhibition test on the algae *Pseudokirchineriella subcapitata* was carried out according to OECD 201. The NOEC for the algae is 1.3 mg/L. A reproduction test on *Daphnia magna* was carried out according to OECD protocol 211. The NOEC for Daphnia is 9.8 mg/L for mortality and 3.1 mg/L for reproduction and growth. A test on fish *Pimephales promelas* was carried out according to the OECD 210 protocol. The NOEC for fish is 0.92 mg/L.

A refined PEC_{SW} was calculated from a refined Fpen. However, the refined Fpen calculation obtained by subtracting the metabolite fraction is not indicated in the guidance documents and is not considered acceptable. The guidance document EMEA/CHMP/4447/00 states that the Fpen can be refined by modelling water treatment plants (WTPs) using the SimpleTreat model described in the European Union Substance Evaluation System (EUSES). Moreover, the Question & Answer guidance document EMA/CHMP/SWP/44609/2016 also provides a formula to calculate the refined Fpen based on an estimate of product consumption. However, taking into account the worst case scenario and using non-refined PECsw from Phase I calculations, the PEC/PNEC ratios for surface and ground water are higher than those calculated by Applicant, but still far below the trigger value (see **Table 1** and **Table 2** below).

Table 1 Risk assessment with refined PECsw (from submitted ERA)

Environmental compartment	PEC	PNEC	PEC/PNEC	Trigger value	Conclusion
	µg/L	µg/L			
Surface water	0.023	92	2.5×10^{-4}	1	No risk
Groundwater	0.006	310	1.94×10^{-5}	1	no risk
Microorganism	0.023	100000	2.3×10^{-7}	0.1	no risk

Table 2 Risk assessment with non-refined PECsw (assessor's table)

Environmental compartment	PEC µg/L	PNEC µg/L	PEC/PNEC	Trigger value	Conclusion
Surface water	0.03	92	3.26×10^{-4}	1	no risk
Groundwater	0.0075	310	2.42×10^{-5}	1	no risk
Microorganism	0.03	100000	3×10^{-6}	0.1	no risk

Thus, even though the Applicant's approach is not considered acceptable, the revision of PEC/PNEC calculations will not change the outcome of risk assessment. Even with non-refined PEC values, triggers for further evaluation (Tier B) are not met.

Overall, the deucravacitinib was not readily biodegradable and various studies in aquatic systems showed that no risk to aquatic environment was identified.

Table 3 Summary of main study results

Substance (INN/Invented Name): Deucravacitinib			
CAS-number : 1609392-27-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 (Shake-Flask Method) OECD123 (Slow-Stir Method)	Log Pow for pH 7 = 2.44 log Pow for pH 4 and 9 = 2.33 and 2.39, respectively	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log Dow at pH 4, 7 and 9 was reported as 2.33, 2.44 and 2.39, respectively. Because the log Dow values at environmentally relevant pHs < 4.5.	not B Log Dow at environmentally relevant pHs < 3, a bioconcentration study was not conducted as part of a Phase II Tier B Assessment.
	BCF		B/not B
Persistence	DT_{50} or ready biodegradability OECD 301B	Does not achieve 60% CO2 evolution within a 10-day window of reaching 10% biodegradation	**P**
Toxicity	$NOEC_{surface\ water}$ $NOEC_{ground\ water}$ $NOEC_{microorganism}$	920µg/L 3100µg/L 1000000µg/L	**T** Toxic based on other evidence of chronic toxicity as indicated by its EU classification by BMS (EU Classification of Specific Target

			Organ Toxicity - Repeated Exposure Category 1; H372).
PBT-statement:	The compound is **not considered as PBT**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default calculation	0.03	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(Y/N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	**Sludge 1** Koc = 328 L/kg (2.52) **Sludge 2** Koc = 209 L/kg (2.32) **Soil 1** (pH 5.6) Koc = 25,181 L/kg (4.40) **Soil 2** (pH 6.8) Koc = 23,326 L/kg (4.37) **Soil 3** (pH 6.3) Koc = 35,306 L/kg (4.55)	McCall classification: classified as immobile in 3 soils and in 2 sludges as having medium mobility. As the Kocs in **sludge** < 10,000 L/kg (EMA), terrestrial testing was not conducted
Ready Biodegradability Test	OECD 301	Not readily biodegradable No Significant mineralization by day 28 (-0.10%)	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	<u>Sediment 1:</u> DT50*, water=14.0 DT50*, sediment=424 DT50*, total= 211 % shifting to sediment: 73.3% at day 4 and 50.7% at day 99 <u>Sediment 2:</u> DT50*, water=14.8 DT50*, sediment=676 DT50*, total= 330 % shifting to sediment: 72.9% at day 4 and decreased to 62.4% at day 99 *normalized to 12°C	>10% AR was observed in sediment at or after 14 days thus triggering a sediment toxicity assessment

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	ErC_{50} (72 hr)	> 5000	µg/L	P*seudokirchineriella subcapitata*

		NOEC	1300		
Daphnia sp. Reproduction Test	OECD 211	NOEC	3100	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	920	µg/L	*Pimephales promelas* Early Life Stage
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10/EC_{50}	1000	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	% lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT_{50} $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism	OECD218	NOEC	43* * Based on Initial Measured Sediment Concentrations (mg/kg sediment dry weight)	mg/kg	Species: *Chironomus Riparius*

2.5.6. Discussion on non-clinical aspects

Pharmacology

The non-clinical pharmacological properties of deucravacitinib have been adequately characterised. The studies provided showed that deucravacitinib binds to the pseudokinase domain of TYK2 to inhibit TYK2 activity. It prevents receptor-mediated activation of the adjacent catalytic domain, thereby inhibiting the functional cellular responses to IL-23, IL-12 and Type I IFNs. Deucravacitinib (BMS-986165) has three metabolites: BMT-153261 that exhibited a similar potency to that of BMS-986165, BMT-334616 that has a very weak pharmacological activity, and BMT-158170 that is not pharmacologically active.

BMS-986165 activity was limited to inhibition of the opiate kappa receptor (free drug IC50 = 4.0 µg/mL) and PDE 4 enzyme (free drug IC50 = 0.9 µg/mL). All the IC50 values are significantly higher than the free maximum concentration (Cmax) at the recommended human dose, indicating low potential for undesirable effects in human subjects.

Safety pharmacology studies were incorporated into the repeat-dose studies in rats and monkeys, and single-dose CV telemetry studies were conducted in rats, dogs, and monkeys. Deucravacitinib did not demonstrate meaningful effect on cardiovascular, neurological, or respiratory function in studies.

Pharmacokinetics

The pharmacokinetic profile of deucravacitinib was sufficiently characterized. Oral absorption of BMS-986165 was rapid in animals (Tmax = 0.5 to 5 hours). Serum protein binding of BMS-986165 was moderate in humans (86.6%) and in mice, rats, and monkeys (ranged from 85.4% to 88.1%), and high in rabbit (97.1%). BMS-986165 undergoes primary metabolism in vivo via 4 distinct pathways: CYP1A2-mediated N-demethylation at the triazole moiety to form BMT-153261, CES2-mediated cyclopropyl carboxamide hydrolysis to form BMT-158170, UGT1A9-mediated N-glucuronidation to form BMT-334616, and CYP2B6 and CYP2D6-mediated mono-oxidation at the deuterated methyl group to form M11. All of these 4 biotransformation pathways were present in every species, resulting in similar metabolite profiles in all species (humans, mice, rats, monkeys), although quantitative differences were observed. Excretion of [14C]BMS-986165-derived radioactivity is predominantly via fecal route in rats and monkeys, while renal excretion of radioactivity is a minor route. Radioactivity was evenly excreted in feces and urine in humans. Data from BDC animals suggest fecal excretion of unchanged drug included both biliary and intestinal excretion. Elimination profiles are closely similar among humans, rats and monkeys.

Toxicology

Pivotal repeat-dose GLP studies were conducted in CByB6F1 mice (≤28 days), Sprague-Dawley rats (≤6 months) and cynomolgus monkeys (≤9 months). No mortality in the repeat-dose toxicity studies were observed, except in the 6-month rat toxicity study where 11 unscheduled deaths occurred. For 5 of them, the cause of death was undetermined. At the CHMP request, further analysis on these deaths were conducted by the applicant. They were not considered BMS-986165-related as a similar total incidence was observed in all dose groups (including control); there was a lack of new or more severe microscopic findings in the early decedent rats compared to the findings in rats euthanized at scheduled necropsies; and there was a lack of BMS-986165-related early deaths in the rat carcinogenicity study. Moreover, the exposure margin (AUC) at 50 mg/kg/day is 247× the recommended human dose.

Some concerns were raised on adverse effects on heart, liver and kidneys which occurred during the toxicology studies in rats and monkeys. They have been discussed by the applicant, at the CHMP request, and ruled out due to the lack of imputability and of the statistically significant results. Nevertheless, the risks of MACE will be followed-up in the post marketing settings via pharmacovigilance activities.

Genotoxicities studies showed that deucravacitinib does not present any genotoxic potential. In the 6-months oral carcinogenicity study in rasH2 transgenic mice, all neoplastic findings were considered unrelated to treatment due to the absence of any dose relationship, lack of statistical significance, or very low magnitude of change. At the CHMP request, the applicant provided the comparisons of spontaneous neoplasms incidences in treated groups versus historical controls. The results indicated that the incidence the spontaneous neoplasms was less than or equal to the maximum incidence of testing facility historical control data. Moreover, the neoplastic findings were considered unrelated to BMS-986165 treatment due to the absence of dose-response relationship, lack of statistical significance, and/or low frequency of findings. Nevertheless, the risks of malignancies will be followed-up in the post marketing settings via pharmacovigilance activities.

The programme of reproductive and developmental toxicity studies was considered adequate. No effect on male and female fertility or on early embryonic development was identified at oral doses up to 50 mg/kg/day

in the studies, corresponding to high rat-to-human exposure multiples for deucravacitinib based on either Cmax or AUC levels (>160). There were no significant deucravacitinib-related adverse effects on maternal animals or on embryo-fetal development (i.e. no embryolethal, foetotoxic or teratogenic effect). Safety margins calculated based on AUC levels were large, i.e. 266 in rats and 91/20 in rabbits considering total/unbound exposure. In the pre- and post-natal development study performed in rats treated orally from implantation to weaning, a treatment-related decrease in the body weight of male and female pups was observed at the high dose level of 50 mg/kg/day during the preweaning period and reversed post-weaning with a safety margin of 19. Otherwise, no treatment-related effects were noted on parameters evaluated in F1 offspring, including sexual maturation, neurobehavioural examinations, and reproductive performance.

The current application is for the use of deucravacitinib in adult patients. Nevertheless a juvenile toxicity study was conducted in rats exposed for 10 weeks from PND21 at doses up to 50 mg/kg/day, with an additional 10-week recovery period. The main findings in juvenile animals were related to the pharmacological immunomodulatory activity of deucravacitinib, and reversible. These findings were in line with those reported in adult rat studies, and no new finding of concern was identified. There was also no treatment-related effect on the onset of puberty and reproductive performance.

In vitro and in vivo local tolerance studies showed that BMS-986165 was considered to be a non-sensitizer, nor a skin or ocular irritant.

ERA

Concerning the environmental risk assessment, the screening for Persistence, Bioaccumulation, and Toxicity (PBT) showed that deucravacitinib was persistent and toxic but was not bio-accumulative, thus deucravacitinib is not considered as a PBT substance. Deucravacitinib meets the criteria for being called toxic based on other evidence of chronic toxicity as indicated by its EU classification by BMS (EU Classification of Specific Target Organ Toxicity - Repeated Exposure Category 1; H372). Furthermore, deucravacitinib was not readily biodegradable and several studies in aquatic systems did not show a risk to aquatic environment.

In conclusion, no major issues were seen among the study results and concerning the non-clinical package.

2.5.7. Conclusion on the non-clinical aspects

The provided non-clinical package is considered sufficient to support the marketing authorisation application of deucravacitinib for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Identifier	Primary Study Objective	Study Design	Test Product(s); Dosage Regimen; Route of Administration	No. Subjects Treated	Study Population	Study Status; Type of Report
Safety/Pharmacokinetics/Pharmacodynamics						
IM011002	To assess the safety and tolerability of single and multiple oral doses of BMS-986165 in healthy subjects of any ethnic background (Parts A, B, C, D)	Phase 1, randomized, double- blind, placebo-controlled, SAD and MAD study to evaluate the safety, tolerability, PK, and PD of BMS-986165 in healthy subjects	Part A: DEUC or placebo ranging from 1 mg to 40 mg single dose/oral, liquid/Day 1 Part B: DEUC or placebo multiple ascending doses (with a range of 2 mg to 12 mg)/oral, liquid/BID every 12 hours for 12 days, and 12 mg every 24 hours for 12 days QD Part C: DEUC or placebo multiple ascending doses (with a range of 2 mg, 6 mg, and 12 mg)/oral, liquid/BID every 12 hours for 14 days, and 12 mg QD every 24 hours for 12 days Part D: DEUC 12 mg single dose/oral, liquid or capsule/Days 1, 8, 15 and 22.	140 subjects received study drug in all parts of the study. Part A: 40 randomized Part B: 60 randomized Part C: 32 randomized Part D: 8 dosed	Healthy males and females (Parts A, B and D), and healthy Japanese males and females (Part C).	Study Status: Completed Type of Report: Final CSR (Part A and Part B), CSR Addendum 01, CSR Addendum 02
IM011016	To assess the PK, metabolism, and routes and extent of elimination of a single oral dose of 24 mg [^{14}C] BMS-986165 containing approximately 100 µCi of total radioactivity in healthy male subjects	Phase 1, open-label, single oral dose PK study	[^{14}C]BMS-986165 24 mg single dose/oral, liquid/Day 1	6 treated	Healthy males	Study Status: Completed Type of Report: Final CSR

IM011048	To determine the effect of BMS-986165 plasma concentrations on the QTcF in healthy subjects	Phase 1, randomized, double-blind, positive-controlled, placebo-controlled, 4-period crossover study to investigate the electrocardiographic effects of BMS 986165	Single dose on Days 1, 6, 11, and 16 with each subject receiving 1 sequence of the 4 following treatments according to the randomization schedule: Placebo; DEUC 12 mg/oral, tablet; DEUC 36 mg/oral, tablet; Moxifloxacin 400 mg	40 treated	Healthy males and females	Study Status: Completed Type of Report: Final CSR (Part A and Part B)
Special populations						
IM011061	To assess the effect of renal impairment on the PK of BMS-986165 and BMT-153261	An open-label, single-dose study to evaluate the PK and safety of BMS-986165 in subjects with normal renal function and subjects with mild, moderate, and severe renal impairment and in subjects with ESRD on hemodialysis	5 renal function groups based on eGFR at screening (Groups A through E) Subjects in all groups are dosed with a single oral dose of DEUC 12 mg	44 treated	Males /females with mild, moderate, and severe renal impairment and in subjects with ESRD on hemodialysis	Study Status: Completed Type of Report: Final CSR, CSR Addendum 01, CSR Erratum 01
IM011062	To assess the effect of hepatic impairment on the PK of BMS-986165 and BMT-153261	An open-label, single-dose study to evaluate the PK and safety of BMS-986165 in subjects with normal hepatic function and subjects with mild, moderate and severe hepatic impairment	DEUC 12 mg single dose/oral, tablet, Day 1	32 treated	Males/ females with normal hepatic function and subjects with mild, moderate and severe hepatic impairment/	Study Status: Completed Type of Report: Final CSR
Drug-Drug Interactions (deucravacitinib as perpetrator)						

IM011015	To assess the effect of coadministration of multiple oral doses of BMS-986165 with rosuvastatin on the systemic exposure of rosuvastatin	Phase 1, open-label, single-sequence, drug-drug interaction study to assess the effect of coadministration of multiple doses of BMS-986165 on the systemic exposure of rosuvastatin	DEUC 12 mg single dose/oral/Days 1, 5-8, 10-12 Rosuvastatin 10 mg/oral/Day 9	20 treated	Healthy males and females	Study Status: Completed Type of Report: Final CSR
IM011025	To evaluate the PK of MTX when administered alone and in combination with BMS-986165.	Phase 1 open-label, single-sequence study to evaluate the effects of BMS-986165 on the PK and safety and tolerability of MTX	DEUC 12 mg QD/oral, capsule/7 days (Days 8 to 14) Methotrexate 7.5 mg single dose/oral/Days 1 and 12 Leucovorin 15 mg single dose/oral/Days 2 and 13	10 treated	Healthy males	Study Status: Completed Type of Report: Final CSR, CSR Addendum 01, CSR Erratum
IM011039	To assess the effect of BMS-986165 on the PK of NET and EE	Phase 1, open-label, 2-cycle, multiple-dose, single- sequence crossover study designed to assess drug-drug interactions between BMS-986165 and the oral contraceptive loestrin 1.5/30 (1.5 mg NET/30 µg EE)	Cycle 1: Loestrin 1.5/30 (1.5 mg NET and 30 mg EE) single dose/oral, tablet/Day 1 to Day 21 Cycle 2: Loestrin 1.5/30 (1.5 mg NET and 30 mg EE) single dose/oral, tablet/Day 1 to Day 21; DEUC 12 mg BID Day 8 to Day 21	24 treated	Healthy females/	Study Status: Completed Type of Report: Final CSR
IM011071	To evaluate the PK of a single dose of MMF when administered alone and in combination with steady-state BMS 986165 as measured by mycophenolic acid (MPA)	Phase 1, single center, open-label, single-sequence, three-treatment period study to assess if mycophenolate mofetil (MMF) PK is affected by BMS-986165 exposure	DEUC 12 mg QD/oral, tablet/Days 1-9 MMF 1000 mg QD/oral, capsule/Day 6 and Day 14	20 treated	Healthy males	Study Status: Completed Type of Report: Final CSR
Drug-Drug Interactions (deucravacitinib as a victim)						

IM011045	To evaluate the effect of single dose cyclosporine on multiple dose PK of BMS-986165 in healthy subjects	Phase 1, open-label, single-sequence study to investigate the effects of cyclosporine on the PK of BMS-986165 at steady-state	DEUC 6 mg QD/oral, capsule/Days 1-6 Cyclosporine 500 mg single dose/oral, capsule/Day 6	20 treated	Healthy males	Study Status: Completed Type of Report: Final CSR, CSR Addendum 01, CSR Erratum
IM011087	To evaluate the effect of CYP1A2 induction on PK of BMS-986165 by comparing the primary PK characteristics of BMS-986165 after a single-dose administration alone versus in combination with steady-state ritonavir	Phase 1, open-label, single-sequence study to investigate the effects of cytochrome P450 1A2 induction by ritonavir on the PK of BMS-986165	DEUC 12 mg single dose/oral, tablet/ Day 1, Day 5, and Day 15 Ritonavir 100 mg single dose/oral/Day 5 through Day 17	16 treated	Healthy males and females	Study Status: Completed Type of Report: Final CSR
IM011088	To compare the primary PK characteristics of BMS-986165 after a single-dose administration alone versus in combination with fluvoxamine (CYP1A2 inhibitor)	Phase 1, open-label, single-sequence study to investigate the effects of cytochrome P450 1A2 inhibition on the PK of BMS-986165	Single oral dose of DEUC 12 mg/oral, tablet/Day 1 and Day 8 Single oral dose of fluvoxamine 100 mg/Day 5 through Day 10	16 treated	Healthy males and females	Study Status: Completed Type of Report: Final CSR
IM011100	To evaluate the effect of OCT1 inhibition, by a single-dose of 50 mg pyrimethamine, on single-dose PK of BMS-986165	Phase 1, open-label, single-sequence, crossover study to investigate the effects of OCT1 inhibition utilizing pyrimethamine on the PK of BMS-986165	Single oral dose DEUC 6 mg/oral, tablet/Day 1 Coadministration of BMS 986165 6 mg oral, tablet and pyrimethamine 50 mg oral/Day 5	16 treated	Healthy males	Study Status: Completed Type of Report: Final CSR (Part A and Part B)

IM011101	To evaluate the effect of multiple doses of UGT1A9 inhibitor, diflunisal, on PK of a single 6 mg dose of BMS-986165 in healthy participants	Phase 1, open-label, single-sequence, crossover study to investigate the effects of UGT1A9 inhibitor diflunisal, at steady-state, on pharmacokinetics of a single dose of BMS-986165	Treatment period 1: DEUC 6 mg single dose/oral, tablet/Day 1 Treatment Period 2: Difunisal (500 mg BID) and DEUC 6 mg single dose/oral, tablet/Day 10	17 treated	Healthy males and females	Study Status: Completed Type of Report: Final CSR (Part A and Part B)
Biopharmaceutics						
IM011031	To assess the relative bioavailability, food effect, and gastric pH effect on the PK of BMS-986165	Phase 1, Randomized, Open-label, Single-dose, Crossover Study to Evaluate the Bioavailability of BMS-986165 Tablet Formulation Relative to BMS-986165 Capsule Formulation and the Effect of a High-fat/ High-calorie Meal and Increased Gastric pH on the Bioavailability of BMS-986165 Tablet Formulation in Healthy Subjects	Treatment A: single oral dose 12 mg DEUC capsule, fasted; Treatment B: single oral dose 12 mg DEUC tablet, fasted; Treatment C: single oral dose 12 mg DEUC tablet, fed; Treatment D single oral dose 12 mg DEUC tablet and 40 mg famotidine, fasted; Treatment E: single oral dose 3 mg DEUC capsule, fasted; Treatment F: single oral dose 3 mg DEUC tablet, fasted;	20 treated	Healthy males and females	Study Status: Completed Type of Report: Final CSR
IM011067	To assess the absolute oral bioavailability of BMS-986165 following single oral and IV administration of BMS-986165 and [$^{13}C_2$, $^{15}N_3$]-BMS-986165, to healthy male subjects	Phase 1, pen-label, non-randomized, single-period study with a single oral dose of BMS-986165 tablet and a single IV microdose of [$^{13}C_2$, $^{15}N_3$]-BMS-986165 solution	DEUC 12 mg single dose/oral, tablet/Day 1 [$^{13}C_2$, $^{15}N_3$]-BMS-9861650.1 mg (5mL) single dose/intravenous infusion, solution/Day 1 (1.75 hours after oral dose)	8 treated	Healthy male	Study Status: Completed Type of Report: Final CSR, CSR Addendum 01

IM011090	To evaluate the effect of sustained increase in gastric pH by repeated dosing of rabeprazole on Cmax and AUC of a single dose BMS-986165 12 mg	Phase 1, open-label, single-sequence study to investigate the effects of gastric acid suppression by rabeprazole on the PK of BMS-986165	DEUC 12 mg single dose/oral, tablet/Days 1 and 9 Rabeprazole 20 mg QD/oral/Days 5-11	21 treated	Healthy males and females	Study Status: Completed Type of Report: Final CSR
IM011119	To assess the effects of a high-fat/high-calorie meal on the primary PK parameters of BMS-986165 as a commercial 6-mg tablet in healthy subjects To assess the effects of increased gastric pH by famotidine on the primary PK parameters of BMS-986165 as a commercial 6 mg tablet in healthy subjects	Phase 1, open-label 3×3 Cross-over Study to Compare Effects of Famotidine Pretreatment and of Food on the Relative Bioavailability of Single Doses of BMS-986165 in Healthy Subjects	DEUC commercial formulation (6 mg) tablet Famotidine (marketed formulation) (10-mg, 20-mg, or 40-mg tablets)	18 treated	Healthy males and females	Study Status: Completed Type of Report: Final CSR
Studies in Subjects with moderate-to-severe plaque psoriasis						

IM011011 (Phase 2)	• To compare the proportion of subjects with moderate to severe psoriasis in experiencing a 75% improvement as measured by reduction in PASI score after 12 weeks of treatment between doses of BMS-986165 and placebo. • To assess the safety and tolerability of multiple oral doses of BMS-986165 in subjects with moderate to severe psoriasis.	12 week, randomized double-blind, placebo-controlled dose-ranging study 1:1:1:1:1:1:1 randomization to the DEUC (3 mg QOD, 3 mg QD, 3 mg BID, 6 mg BID, and 12 mg QD) and placebo groups	DEUC: 3 mg QOD 3 mg QD 3 mg BID 6 mg BID 12 mg QD Placebo QOD, QD, or BID PO	Total: 267 subjects treated DEUC 3 mg QOD (n = 44) 3 mg QD (n = 44) 3 mg BID (n = 45) 6 mg BID (n = 45) 12 mg QD (n = 44) Placebo (n = 45)	Subjects with moderate-to-severe plaque psoriasis	Study Status: Completed Type of Report: Final CSR, CSR Addendum
IM011046 (Phase 3)	To assess whether BMS-986165 is superior to placebo at Week 16 in the treatment of subjects with moderate -to -severe plaque psoriasis	52-week randomized, double-blind, placebo- and active comparator-controlled study 2:1:1 randomization to the DEUC, placebo, and apremilast groups	DEUC: 6 mg QD PO Placebo QD PO Apremilast: 30 mg BID PO (with initial titration per label)	Total: 665 subjects treated DEUC: 332 Placebo: 165 Apremilast: 168	Subjects with moderate-to-severe plaque psoriasis	Study Status: Completed Type of Report: Primary CSR
IM011047 (Phase 3)	To assess whether BMS-986165 is superior to placebo at Week 16 in the treatment of subjects with moderate -to -severe plaque psoriasis	52-week randomized, double-blind, placebo- and active comparator-controlled study 2:1:1 randomization to the DEUC, placebo, and apremilast groups	DEUC: 6 mg QD PO Placebo QD PO Apremilast: 30 mg BID PO (with initial titration per label)	Total: 1018 subjects treated DEUC: 510 Placebo: 254 Apremilast: 254	Subjects with moderate-to-severe plaque psoriasis	Study Status: Completed Type of Report: Primary CSR

IM011075 (Phase 3b)	To characterize the safety and tolerability of long-term use of BMS-986165 in subjects with moderate-to-severe plaque psoriasis	Open-label, study to evaluate the long-term safety and efficacy of DEUC	**DEUC:** 6 mg QD PO	Total: 1519 subjects treated with one dose of DEUC	Subjects with moderate-to-severe plaque psoriasis	Study Status: Ongoing Type of Report: Interim CSR
Study in subjects with active psoriatic arthritis						
IM011084 (Phase 2)	To assess the dose-response relationship of BMS 986165 (6 or 12 mg once daily [QD]) at Week 16 in the treatment of subjects with active PsA	16-week (Part A) randomized, double-blind, placebo-controlled study 1:1:1 randomization to the DEUC (6 mg QD or 12 mg QD) and placebo groups Part B: optional 36 weeks of double-blind treatment with ustekinumab, DEUC, or ustekinumab + DEUC after completing Part A	**DEUC:** 6 mg QD PO 12 mg QD PO **Placebo:** QD PO	Total: 203 subjects treated DEUC 6 mg QD: 70 DEUC 12 mg QD: 67 Placebo: 66	Subjects with active psoriatic arthritis	Study Status: Ongoing (Part B) Type of Report: Primary CSR of Part A (Week 16), CSR Erratum of Part A (Week 16)

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacological program for deucravacitinib encompasses 21 completed clinical studies as well as one ongoing Phase 3b study (IM011075) and one ongoing Phase 2 Study IM011084. Overall, the following 18 Phase 1 studies have been conducted:

- One first-in-human single ascending / multiple ascending dose (SAD/MAD) study investigating deucravacitinib in healthy Japanese and non-Japanese volunteers (IM011002)
- Four biopharmaceutical PK studies investigating relative bioequivalence between formulations, food effect or pH effect (IM011002, IM011031, IM011090, and IM011119)
- One mass balance and metabolism study (IM011016)
- One absolute bioavailability study (IM011067)
- In total, 11 PK studies investigating intrinsic factors (IM011061, IM011062) and extrinsic factors (IM011015, IM011025, IM011039, IM011045, IM011071, IM011087, IM011088, IM011100, and IM011101)
- One safety study evaluating the electrocardiographic effect of deucravacitinib (IM011048)

Moreover, deucravacitinib was investigated in adult patients with psoriasis in the Phase 2 study IM011011 and in the two pivotal Phase 3 studies IM011046 and IM011047.

Deucravacitinib has two major circulating metabolites, BMT-153261 and BMT-158170. The major metabolites were measured in healthy subjects and subjects with psoriasis. BMT-153261 is an active metabolite with comparable in vitro potency and selectivity as the parent compound, and BMT-158170 is pharmacologically inactive (< 0.3% of DEUC activity).

A population PK analysis of deucravacitinib and its main active metabolite BMT-153261 was conducted (Population PK report v1.0, date 30 June 2021). Furthermore, exposure-response (E-R) analyses for efficacy and safety endpoints have been performed using data obtained in the Phase 2 study IM011011 and the two pivotal Phase 3 studies IM011046 and IM011047 based on population PK model-predicted PK parameters of deucravacitinib and BMT-153261 (Report "Exposure-response analyses of deucravacitinib in subjects with moderate to severe psoriasis", date 14 July 2021).

Methods

Bioanalysis

Throughout the clinical development, several bioanalytical methods were developed to quantify, DEUC only (DCN 930096221, DCN 930105411, DCN 930115607), DEUC and its main active metabolite BMT 153261 (DCN 930132477, DCN 9301524, DCN 930154085), other major metabolites BMT-158170 (DCN 930132513, DCN 930152474, DCN 930141442), BMT-334616 (DCN 930151196), and minor metabolite BMT-409408 (DCN930140230) in human K2EDTA plasma, or in urine for DEUC and its metabolites (DCN 930095799, DCN 930115623, DCN 930138482, DCN 930152165), or feces homogenate for BMT-409408 (DCN 930145148). Short and long-term stability of the analytes in biological matrix were tested.

Pharmacokinetic analyses

PK data were analyzed using non-compartmental analysis (NCA) and population PK modelling.

Population pharmacokinetic modelling and simulation were performed. The PKs of deucravacitinib and its major active metabolite BMT-153261 were investigated in healthy volunteers and patients with moderate to severe psoriasis, using modelling and simulation techniques (Population PK report v1.0, date 30 June 2021). For each compound a population PK model was developed using the nonlinear-mixed effects modelling approach with NONMEM software (Version 7.4.3; ICON, Hanover, MD, US) in order to characterise and predict the PK of deucravacitinib and BMT-153261, obtain exposure metrics for E-R analyses of efficacy and safety, and finally to support dose selection.

Statistical analysis

Generally, standard summary statistics (e.g. mean, median, standard deviation [SD], and coefficient of variation [CV]) have been generated. For comparison, in most cases the 90 % confidence intervals (CI) were calculated in case of equivalence testing. In addition, in case significance levels were used, the significance level in most trials was 5%. SAS® software, version 9.4 or higher (SAS Institute, Cary, NC, USA) was used for randomization, statistical analysis the reporting of PK data.

Absorption

Deucravacitinib is a weak base, classified as a BCS II drug substance due to limited solubility of the crystalline form at higher pH values. The amorphous form (present in the tablet formulation intended for the market) exhibits better solubility across the physiological pH range.

In vitro evaluation of permeability in non-cellular PAMPA assay, as well as in the Caco-2 and MDCK cells indicates high permeability of deucravacitinib.

In vitro assays also suggest deucravacitinib is a substrate of P-gp and BCRP efflux transporters. However, the influence of intestinal P-gp or BCRP on the oral absorption of deucravacitinib is not expected to be clinically relevant due to high deucravacitinib permeability. This was confirmed in vivo given the very high absolute bioavailability (99%) and in a DDI study with strong P-gp and BCRP inhibitor cyclosporine.

Following single dose of DEUC as a film-coated tablet formulation in healthy volunteers, absorption was reasonably rapid with Cmax approximately achieved at Tmax of 2-3 h for doses up to 36 mg. At 6 mg geometric mean Cmax was 36.5 ng/mL and AUCinf 372 ng.h/mL.

Following multiple dose of 6 mg DEUC as capsule formulation in healthy volunteers (Study **IM011045**), at steady state geometric mean Cmax was 41.7 ng/mL and AUCtau 359 ng.h/mL.

Following multiple dose of DEUC dose of 6 mg QD as film coated tablet in patients, based on the PPK analysis predicted geometric mean Cmax was 45.1 ng/mL and Cavg of 19.7 ng/mL.

Absolute bioavailability

The absolute bioavailability of Deucravacitinib has been investigated in study **IM011067** and estimated at 99%.

Relative bioavailability/ Bioequivalence

Throughout the clinical development, three formulations were used, an oral solution (0.1 or 10 mg/mL) a capsule (one strength of 3 mg), and a film-coated tablet (strength of 3, 6 and 12 mg).

The commercial formulation of 6 mg strength is the same as the tablet formulation used in the pivotal Phase 3 studies (**IM011046** and **IM011047**), differing only in the film-coat (pink Opadry II for the commercial formulation vs pale pink to off-white Opadry II) and laser printing.

Two relative bioavailability (rBA) studies were performed to bridge the PK between formulations (Study **IM011002** and **IM011031**) and in vitro dissolution study to compare performance of the clinical tablet vs the commercial formulation at pH 6.3.

Results from the rBA Study **IM011002** between the oral solution and capsule formulations, indicated that both formulations perform similarly with only AUCinf geometric mean ratio included in the 90 % CI of 0.8-1.25. Geometric mean Cmax was slightly decreased by 10% with the capsule formulation.

Results from the rBA Study **IM011031** between the capsule and film-coated tablet formulations at the two tested strengths of 3 mg and 12 mg, indicated that both formulations can be considered bioequivalent with both geometric mean ratios of Cmax and AUCinf in the 90 % CI of 0.8-1.25.

Influence of food

The effect of a standardized high fat meal on Deucravacitinib PK was investigated in healthy subjects using the capsule formulation (Study **IM011002-Part D**), the film-coated tablet formulation (Study **IM011031**) and the Phase 3 formulations, without laser printing (Study **IM011119**).

In Study **IM011119**, the effect of a high fat meal on Deucravacitinib PK was investigated in 18 healthy volunteers who were administered a single oral dose of 6 mg Deucravacitinib (film-coated tablet) in the fasted and the fed states. PK results indicated that administration of a high fat meal decreased geometric mean Cmax by 23.9%, median Tmax was delayed by 1h and AUC0-inf slightly decreased by 10.7%.

Influence of gastric modifier

The effect of acidic reducing agents (famotidine) on Deucravacitinib PK was investigated in the three clinical studies **IM011002 –Part D** (as capsule) and **IM011031** (as film-coated tablet) and **IM011119** (as film-coated tablet commercial formulation). In addition, the effect of gastric acid suppression by rabeprazole (30 mg) on DEUC PK was also investigated in study **IM011090**.

In Study **IM011031**, the effect of famotidine administration on Deucravacitinib PK was investigated in 19 healthy volunteers who were administered a single oral dose of 12 mg Deucravacitinib (film-coated tablet) with or without famotidine. PK results indicated that when DEUC is administrated with famotidine, geometric mean Cmax was 16.1% lower, median Tmax was unchanged and AUC0-inf slightly decreased by 6.2%.

In Study **IM011119**, the effect of famotidine administration on Deucravacitinib PK was investigated in 18 healthy volunteers who were administered a single oral dose of 6 mg Deucravacitinib (film-coated tablet) with or without famotidine. PK results indicated that when DEUC is administrated with famotidine geometric mean Cmax and AUC0-inf of DEUC were similar to those observed without famotidine.

Distribution

DEUC has a moderate 81.6 % protein binding, mainly on HSA, a B/P near 1 from the ADME study **IM011016** and 1.26 following in vitro investigations and is extensively distributed in tissue with Vz estimated at 140 L.

Based on in vitro investigations, plasma protein binding of BMS-153261 was moderate and not concentration dependent, with mean value 83.1%.

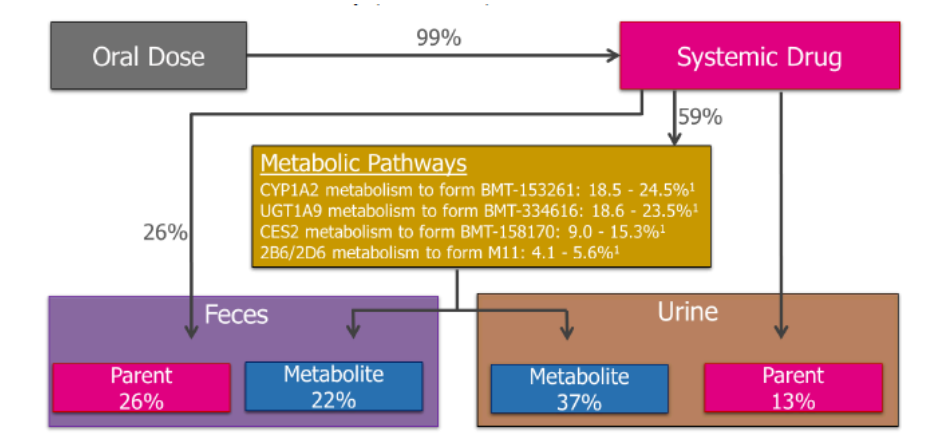
Based on in vitro investigations human serum protein binding for BMT-158170 was 83.8%.

Elimination

Across clinical studies in healthy volunteers, after single dose of DEUC as film coated tablet mean half-life at a 6 mg dose was approximately 10h (9.88h). In healthy volunteers, CL/F was estimated at 16.1 L/h.

Based on the mass balance study (**Figure 2**), DEUC is extensively metabolised, with 59% of orally administered ^{14}C-DEUC dose eliminated as metabolites in urine (37%) and feces (22%). Unchanged DEUC accounted for 13% and 26% of the dose in urine and feces respectively.

Figure 2 Mass balance model for DEUC following oral administration based on human ADME (IM011016) and absolute bioavailability (IM011067) studies



[1] Lower value is recovery as primary metabolite in C14 ADME study and upper bound indicates maximal contribution considering potential secondary metabolism

- Mass balance

The excretion and biotransformation of a ^{14}C-radiolabeled Deucravacitinib oral dose was investigated in 6 healthy subjects in Study **IM011067**

The total recovery of radioactivity in this mass balance study was high (near 100%) and is considered adequate. Approximately 51.9 % and 52.5 % of the radioactive dose was recovered in feces and urine respectively, unchanged DEUC was found at 26 % in feces and 13 % in urine.

The geometric mean of CLR was 1.87 L/h (approximately 11.6% of total clearance of 16.1 L/h) was somewhat higher than the estimated value of renal filtration (fu*GFR=1.3 L/h) suggesting that there might be a contribution of active renal secretion.

- Metabolism

Metabolite profiling was performed and up to 13 metabolites were identified. DEUC accounted for 43% of the total radioactivity in plasma and three main metabolites were identified BMT-153261, BMT-158170 and BMT-334616 which accounted for 11 %, 24 % and 7.0% respectively. Approximately 95.6 % and 92.4% of the recovered radioactivity in urine and feces respectively was identified.

Based on in vitro investigations four primary pathways are involved in DEUC's biotransformation. CYP1A2 is involved in the formation of the major active metabolite BMT-153261, CES2 is involved in the formation of major metabolite BMT 158170, UGT1A9 in the formation of the glucuronide metabolite BMT-334616 and CYP 2B6/2D6 is involved in the formation of metabolite M11.

- Pharmacokinetic of metabolites

PK of DEUC's main metabolites BMT-153261, BMT-158170 and BMT-334616 were investigated thoroughly across the nonclinical (Studies NCPK) and clinical development program in studies **IM011002**, **IM011100** and **IM011101** (for the three), **IM011045**, **IM011046**, **IM011047**, **IM011048**, **IM011061**, **IM011062**, **IM011071**, **IM011084**, **IM011087**, **IM011088**, **IM011090** (for BMT-153261 and BMT-158170), **IM011011**, **IM011025**, **IM011031**, **IM011039**, **IM011045** and **IM011119** (only for BMT-1532261).

BMT-153261

Based on in vitro investigations, BMT-153261 was found as active as DEUC (similar potency) and is expected to contribute to 18% of the total pharmacological activity.

BMT-153261 has a protein binding of 80.9% (mainly to HSA) and is a substrate of P-gp and BCRP.

At a 6 mg single dose of DEUC (as tablet) geometric mean Cmax was 5.02 ng/mL, AUCinf was 118.84 ng.h/mL, median Tmax at 6 h and half-life estimated 13.6 h.

BMT-158170

Based on in vitro investigations, BMT-151870 was found inactive (376-fold less active than DEUC). BMT-158170 has a protein binding of 83.8%.

At a 6 mg single dose of DEUC, BMT-158170 geometric mean Cmax was 7.9 ng/mL, AUCinf was 132.4 ng.h/mL, median Tmax at 4 h and half-life estimated at 12.9 h (Study IM011101).

BMT-334616

BMT-334616 is the glucuronide metabolite of DEUC and is therefore expected biologically inactive.

At a 6 mg single dose of DEUC, BMT-334616 geometric mean Cmax was 6.36 ng/mL, AUCinf was 73.4 ng.h/mL, median Tmax at 3 h and half-life estimated at 11.8 h (Study IM011101).

Dose proportionality and time dependencies

DEUC dose proportionality is demonstrated between 3 to 36 mg. Across all the available clinical studies in healthy volunteers, DEUC show no or minimal accumulation with accumulation less than 1.4. Steady-state is reached by Day 5.

Intra- and inter-individual variability

Based on Phase 1 studies with rich sampling, intra-individual variability in AUC and Cmax was low (6 to 20%). Inter-individual variability in AUC and Cmax was as well low (17 to 32%).

Pharmacokinetics in target population

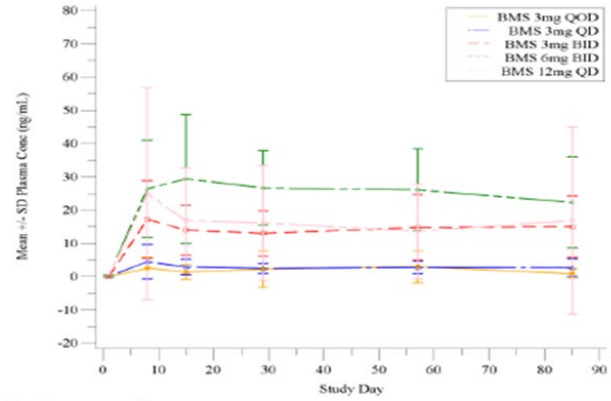
The PKs of deucravacitinib and its active metabolite BMT-153261 in patients with moderate to severe psoriasis was evaluated using one Phase 2 study IM011011 and two Phase 3 studies IM011046 and IM011047. The collected data were sparse and undertaken at steady-state (essentially C_{trough} concentrations).

- Phase 2 study IM011011:

No NCA calculations could be found. Plasma concentrations for deucravacitinib and its active metabolite BMT-153261 were analysed through graphical illustrations (**Figure 3**) and summary statistics (**Table 4**). Mean plasma concentrations of deucravacitinib appeared to be at steady-state at Day 8. Comparing the 3 mg BID and 6 mg BID, a 1.6-fold increase in Day 8 geometric mean C_{trough} was noted. In the 3 mg QD and 12 mg QD, a 5-fold higher geometric mean C_{trough} on Day 8 was noted. The geometric mean C_{trough} values for 3 mg BID and 12 mg QD were relatively constant over time.

In the dose groups having higher PASI-75 response rates (≥ 66.7%; 3 mg BID, 6 mg BID, and 12 mg QD), median observed C_{trough} of BMS-986165 were above the IC50 of the compound in cellular assays. The C_{trough} in the 3 mg QOD and 3 mg QD groups were lower than the IC50 value.

Figure 3 Study IM011011 mean (±) SD deucravacitinib C_{trough} by day (upper left), and at 0.5, 1, 4, and 6 h post-dose (upper right), and BMT-153261 C_{trough} over time (days) by treatment arm on linear scale



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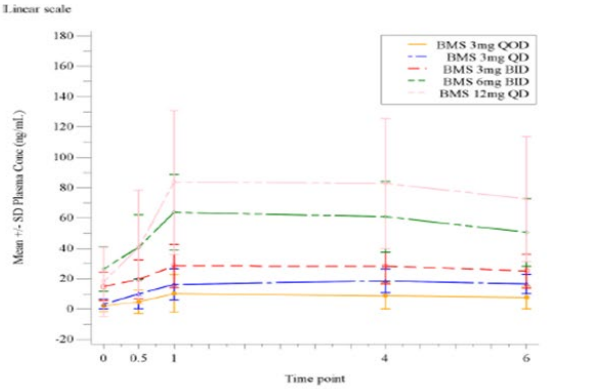

0=Predose, 0.5 = 0.5 Hour post dose, 1 = 1 Hour post dose, 4 = 4 Hour post dose, 6 = 6 Hour post dose
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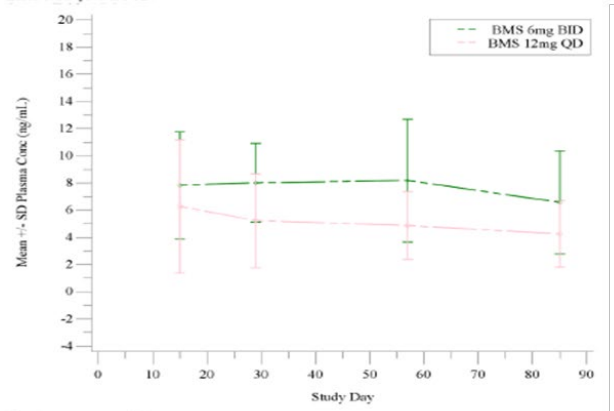


Error bar represents SD.

Table 4 Study IM01101 summary statistics of observed deucravacitinib C_{trough} (ng/mL) by study day.

Study Day	BMS 3mg QOD (N=44)	BMS 3mg QD (N=44)	BMS 3mg BID (N=45)	BMS 6mg BID (N=45)	BMS 12mg QD (N=44)
DAY 1 (Baseline)					
N	44	44	44	44	44
MEAN	0.071	0.050	0.069	0.108	0.070
STANDARD DEVIATION	0.1186	0	0.1236	0.3814	0.1351
MEDIAN	0.050	0.050	0.050	0.050	0.050
MINIMUM, MAXIMUM	0.05 , 0.83	0.05 , 0.05	0.05 , 0.87	0.05 , 2.58	0.05 , 0.95
Q1, Q3	0.050, 0.050	0.050, 0.050	0.050, 0.050	0.050, 0.050	0.050, 0.050
GEOMETRIC MEAN	0.056	0.050	0.053	0.055	0.053
%CV	165.9915	0	180.1081	354.8017	191.9700
DAY 8					
N	43	43	42	44	44
MEAN	2.570	4.555	17.192	26.435	24.947
STANDARD DEVIATION	3.2343	5.2421	11.6079	14.5732	31.8395
MEDIAN	1.280	2.600	15.550	22.750	9.905
MINIMUM, MAXIMUM	0.05 , 13.80	0.05 , 23.70	0.66 , 66.10	1.41 , 72.90	1.20 , 144.00
Q1, Q3	0.630, 3.070	1.550, 4.850	9.470, 21.600	17.200, 33.650	7.165, 29.000
GEOMETRIC MEAN	1.279	2.772	13.685	22.150	13.857
%CV	125.8271	115.0809	67.5200	55.1288	127.6297
DAY 15					
N	42	41	42	41	44
MEAN	1.397	2.962	14.010	29.406	16.894
STANDARD DEVIATION	2.1721	2.3461	7.4711	19.3730	15.9430
MEDIAN	0.828	2.540	13.500	27.200	10.200
MINIMUM, MAXIMUM	0.05 , 13.50	0.05 , 12.90	0.05 , 31.80	1.66 , 114.00	0.05 , 67.70
Q1, Q3	0.270, 1.690	1.580, 3.780	8.280, 18.500	16.600, 38.200	6.565, 20.200
GEOMETRIC MEAN	0.661	2.236	10.910	23.676	10.921
%CV	155.4997	79.2035	53.3280	65.8820	94.3730
DAY 29					
N	36	41	42	36	41
MEAN	2.285	2.519	13.045	26.664	16.195
STANDARD DEVIATION	5.5661	1.5083	6.7613	11.2613	17.2474
MEDIAN	0.500	2.250	11.900	26.800	10.000
MINIMUM, MAXIMUM	0.05 , 29.80	0.59 , 7.21	0.05 , 30.70	8.31 , 49.20	1.02 , 89.70
Q1, Q3	0.172, 1.915	1.570, 3.070	7.910, 17.900	15.000, 36.450	6.720, 17.200
GEOMETRIC MEAN	0.552	2.102	10.372	24.127	10.937
%CV	243.5976	59.8750	51.8299	42.2339	106.4972
DAY 57					
N	33	35	42	39	41
MEAN	3.017	2.812	14.820	26.095	13.657
STANDARD DEVIATION	4.8154	1.9219	9.7864	12.3010	14.2788
MEDIAN	1.200	2.790	12.550	25.100	9.340
MINIMUM, MAXIMUM	0.05 , 20.50	0.05 , 8.85	0.05 , 45.20	2.78 , 56.50	0.05 , 89.40
Q1, Q3	0.236, 2.840	1.280, 3.610	7.910, 19.000	16.500, 34.200	6.230, 15.400
GEOMETRIC MEAN	0.914	1.780	10.110	22.657	9.177
%CV	159.6119	68.3485	66.0330	47.1398	104.5563
DAY 85					
N	39	39	38	37	38
MEAN	1.013	2.739	15.052	22.334	16.907
STANDARD DEVIATION	1.3932	2.6729	9.1788	13.6814	28.2222
MEDIAN	0.634	2.140	14.150	22.000	9.340
MINIMUM, MAXIMUM	0.05 , 5.73	0.05 , 14.10	0.13 , 36.40	0.05 , 55.80	0.23 , 151.00
Q1, Q3	0.055, 1.140	0.566, 4.030	9.180, 19.000	12.700, 32.800	6.020, 15.500
GEOMETRIC MEAN	0.403	1.213	10.737	12.567	8.726
%CV	137.4614	97.5693	60.9813	61.2578	166.9305

Values below LLOQ (0.0500 ng/mL) were set to 0.0500 ng/mL

- Phase 3 studies IM011046 and IM011047:

All plasma concentration data obtained in this study were analysed by population PK modelling (Population PK report v1.0, date 30 June 2021).

According to the Applicant, PK assessment was not part of the primary and secondary objectives in the study. The PK endpoint to summarize C_{trough} of deucravacitinib, as planned according to the statistical analysis plan, was not included in the final analysis. Instead, a by-subject listing of deucravacitinib concentration was provided in Appendix 8.1 of the final CSRs.

- Population PK modelling and simulation (Population PK report v1.0, date 30 June 2021):

PK data from 10 Phase 1 studies (IM011031, IM011067, IM011045, IM011071, IM011090, IM011119, IM011002, IM011061, IM011062, and IM011048), one Phase 2 study (IM011011) and two pivotal Phase 3 studies (IM011046 and IM011047) were integrated in the population PK analyses. Sparse and extensive PK samples were used. Oral PK data after administration of an oral solution, capsules and a tablet formulation

were analysed along with intravenous (IV) data of deucravacitinib and [$13C^2$, $15N^3$]- deucravacitinib. Model development was performed sequentially (structural model, random effect, residual error model, and covariate model), each separately for deucravacitinib and BMT-153261. A metabolisation conversion fraction, as obtained from in vitro and C_{14} ADME studies, from deucravacitinib to BMT-153261 was used as input parameter in the BMT-153261 model. To evaluate the potential influence of covariates on the PK of deucravacitinib, age, body weight, sex, race, region, renal function (eGFR), hepatic function (Assessed by NCI Criteria), food (fed vs fasted), formulation (capsule, oral liquid, and tablet), smoking status, healthy vs psoriasis patient, and disease characteristics (baseline PASI, disease duration, and naïve vs previous biologic use), were investigated. For BMT-153261 the covariates age, body weight, sex, race, renal function, hepatic function, and healthy vs psoriasis patient were investigated. The Bayesian information criterion [BIC] was used for selection of structural models and for assessment of covariates. Goodness-of-fit (GOF) plots as well as precision and plausibility of parameter estimates were used to assess the adequacy of the models. Simulations were performed using the final models and the predictive performance of the final PK models was evaluated by prediction-corrected visual predictive checks (pcVPC).

Deucravacitinib population PK model: Overall, 1388 participants (76 % were patients with psoriasis) who received at least one dose of deucravacitinib and had at least one quantifiable post-dose deucravacitinib plasma concentration were included in the population PK analysis for deucravacitinib. Of the 23194 deucravacitinib PK observations, 18781 (89.5%) were included in the analysis.

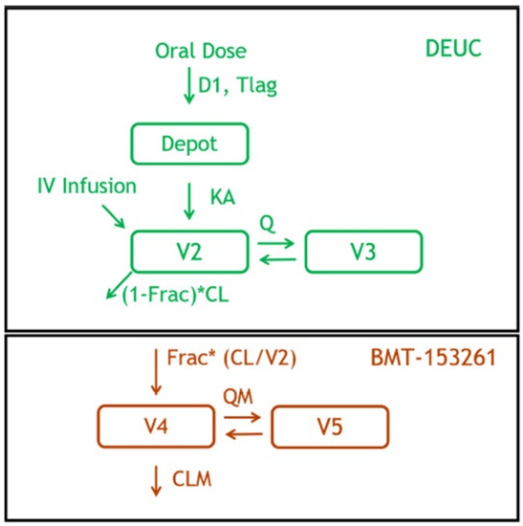
The final PK model for deucravacitinib was a 2-compartment model with sequential zero-and first-order absorptions with a lag time and linear clearance (**Figure 4**). Logistic-transformed F1 was modelled through a dose-dependent Emax function. IIV was found on CL, V2, KA and F1. A separate IIV on CL for patients with psoriasis was estimated. Combined residual error models for the Phase 2 and Phase 3 studies were chosen. Body weight, age, baseline eGFR, sex, and subject type (healthy vs. patients) were identified as covariates on clearance. Body weight, subject type (healthy vs. patients), sex, and disease duration on volume of distribution (V2), and food and formulation on the absorption rate constant kA. In order to reduce the high estimated RSE in this model, a systematic re-investigation of residual error models for deucravacitinib and BMT-153261 was conducted. A new final model for deucravacitinib with more complex residual error models (Model "final-res2.2") was selected. Based on this model, the covariate selection was re-runs using BIC and LRT criteria, both resulting in a model containing the same covariates; all previous covariates remained but "population effect on V2" was excluded from the model. However, since this model is more complex while results remain overall similar, the previous model is considered final. The parameter estimates are listed in **Table 5**.

BMT-153261 population PK model: Overall, 1152 (98.8%) participants were included in the population PK analysis for BMT-153261. In total, 79.8 % (n=919 from IM011011, IM011046, and IM011047) were patients with psoriasis. Participants treated with deucravacitinib at low dose levels (≤ 3 mg) did not have any BMT-153261 data collected. Of the 18672 BTM-153261 PK observations, 13503 (80.2%) were included in the analysis.

The final population PK model for BMT-153261 (**Figure 4**) was a two-compartment model with linear elimination, fixed parent to metabolite conversion fraction of 0.22, IIV on clearance (CLM) and volume of distribution of the central compartment (V4), separate residual error models for Phase 1 participants (healthy volunteers) and patients with psoriasis. Combined residual error models for the Phase 2 and Phase 3 studies were chosen, where the additive errors were fixed to 0.5 ng/mL. Age, hepatic impairment, eGFR, and race (Asian and Others vs. White) were identified as covariates on CLM. Age, hepatic impairment, race (Asian and

Others vs. White), and subject type on V4, and body weight on CLM and V4. The parameter estimates are listed in **Table 6**.

Figure 4 Final population PK model structure for BMT-153261 linked to the final population PK model for deucravacitinib



PK parameters for parent drug: CL = clearance of DEUC; D1 = absorption duration; Frac = fraction of DEUC dose metabolized into BMT-153261; KA = absorption rate constant; Q = inter-compartmental clearance; Tlag = absorption lag time; V2 = central volume of distribution of DEUC; V3 = peripheral volume of distribution of DEUC.
PK parameters for metabolite BMT-153261: CLM = clearance of BMT-153261; QM = peripheral clearance of BMT-153261; ; V4 = central volume of distribution of BMT-153261; V5 = peripheral volume of distribution of BMT-153261; Cpt = compartment.
Note: The model of BMT-153261 was developed sequentially after the parent PK model. The parent PK model was first developed and the individual EBE parameters were used to drive the parent part of the model in the metabolite model as shown above.

Table 5 Parameter estimates of the final population PK model for deucravacitinib

Parameter (Units)[a]	Symbol	Parameter Estimate	Standard Error	RSE%	Median [95% CI[b]]
Fixed Effects					
CL (L/h)	θ_1	10.7	0.36	3.36	10.7 [9.42, 11.3]
V2 (L)	θ_2	104	4.01	3.86	104 [90.9, 111]
V3 (L)	θ_3	42.5	1.89	4.45	42.1 [37.8, 46.4]
Q (L/h)	θ_4	3.15	0.233	7.41	3.12 [2.64, 3.59]
KA (1//h)	θ_5	2.35	0.164	6.98	2.41 [2.09, 2.86]
Logit of F1	θ_6	2.53	0.444	17.5	2.47 [1.53, 3.87]
ED50 on F1 (mg)	θ_7	0.713	0.141	19.8	0.698 [0.488, 0.997]
Tlag (h)	θ_8	0.112	0.0254	22.6	0.115 [0.0591, 0.216]
D1 (h)	θ_9	0.573	0.0464	8.11	0.571 [0.373, 0.674]
CLBBWT: Baseline BW on CL	θ_{14}	0.502	0.0573	11.4	0.493 [0.387, 0.599]
CLAGE: Age on CL	θ_{16}	-0.154	0.0323	21	-0.154 [-0.223, -0.0858]
CLBGFRM: Baseline eGFR on CL	θ_{17}	0.124	0.0321	25.9	0.126 [0.065, 0.192]
CLPOP: Subject Type on CL	θ_{18}	0.153	0.0262	17.1	0.149 [0.0969, 0.203]
CLSEXN: Sex on CL (Female vs Male)	θ_{19}	-0.177	0.0236	13.3	-0.179 [-0.226, -0.137]
V2BBWT: Baseline BW on V2	θ_{15}	0.859	0.0463	5.39	0.863 [0.766, 0.959]
V2POP: Subject Type on V2	θ_{23}	-0.0758	0.0234	30.8	-0.0762 [-0.127, -0.0324]
V2SEXN: Sex on V2 (Female vs Male)	θ_{24}	-0.119	0.0182	15.3	-0.118 [-0.151, -0.0805]
V2DISDUR	θ_{25}	-0.0471	0.0135	28.7	-0.0467 [-0.0723, -0.0237]
KAFED: Food on KA (High-fat Meal vs Fasted)	θ_{20}	-1.46	0.15	10.3	-1.44 [-1.81,-1.2,]
KAFORMN1: Formulation on KA (Tablet vs Solution)	θ_{21}	0.858	0.107	12.5	0.858 [0.368, 1.24]
KAFORMN2: Formulation on KA (Tablet vs Capsule)	θ_{22}	0.337	0.126	37.5	0.353 [0.0833, 0.616]
IIV					
CL	ω^2_{CL}	0.0762	0.00847	11.1	0.0755 [0.0601, 0.095]
CL-V2	$\omega_{CL,\omega V2}$	0.0291	0.00575	19.8	0.0279 [0.0174, 0.0409]
V2	ω^2_{V2}	0.0225	0.00487	21.7	0.0211 [0.0116, 0.0319]
KA	ω^2_{KA}	1.4	0.13	9.29	1.43 [1.19, 1.84]
LF	ω^2_{LF}	1.68	0.645	38.4	1.66 [0.466, 3.94]
CL-PsO	$\omega^2_{CL\text{-}PSO}$	0.152	0.00886	5.83	0.152 [0.135, 0.17]
Residual Error					
Proportional Error (Phase 1) (%)	θ_{10}	0.269	0.00867	3.22	0.268 [0.25, 0.286]
Additive Error (Phase 1) (ng/mL)	θ_{11}	0.291	0.0435	14.9	0.286 [0.189, 0.38]
Proportional Error (Phases 2 and 3) (%)	θ_{12}	0.492	0.00776	1.58	0.49 [0.472, 0.507]
Additive Error (Phases 2 and 3) (ng/mL)	θ_{13}	0.158	0.0469	29.7	0.155 [0.0254, 0.406]

Notes: Condition number is 343.8
Abbreviations: BW = body weight; CI = confidence interval; CL = clearance of DEUC; D1 = zero order absorption time; ED50 = DEUC dose to achieve half maximal F1; eGFR = estimated glomerular filtration rate; F1 = bioavailability of DEUC; IIV = interindividual variability; KA = absorption rate constant; LF = logit transformation of F1; Q = intercompartmental clearance of DEUC; PsO = psoriasis; RSE = relative standard error; Tlag = absorption lag time; V2 = central volume of distribution of DEUC; V3 = peripheral volume of distribution of DEUC.

[a] Eta shrinkage (%): 49.6, 53.4, 16.6, 51.6, and 18.5 for ω^2CL, ω^2V2, ω^2KA, ω^2LF, and $\omega^2CL\text{-}PSO$.

[b] CIs are from bootstrap with 83.7% successful runs.

Table 6 Parameter estimates of the final population PK model for BMT-153261

Parameter (Units)[a]	Symbol	Parameter Estimate	Standard Error	Standard Error (RSE%)	Median [95% CI[b]]
Fixed Effects					
CLM (L/h)	θ_1	9.6	0.136	1.42	9.6 [9.33, 9.89]
QM (L/h)	θ_2	16.4	0.469	2.87	16.4 [15.4, 17.3]
V4 (L)	θ_3	14.1	0.9	6.37	14.1 [12.6, 16]
V5 (L)	θ_4	54.3	0.762	1.4	54.3 [52.8, 55.7]
Fraction Conversion (Parent to Metabolite)	θ_5	0.22 FIX	-	-	-
CLMAGE: AGE on CLM	θ_{10}	0.228	0.0367	16.1	0.227 [0.162, 0.296]
CLMHEPAN: HEPAN on CLM	θ_{11}	0.228	0.039	17.1	0.231 [0.15, 0.31]
CLMBBWT: BBWT on CLM	θ_{12}	0.786	0.0466	5.93	0.789 [0.696, 0.877]
CLMBGFRM: BGFRM on CLM	θ_{13}	0.275	0.035	12.7	0.276 [0.209, 0.343]
CLMRACE1: RACE1 on CLM	θ_{14}	0.16	0.0426	26.6	0.16 [0.0782, 0.24]
CLMRACE2: RACE2 on CLM	θ_{15}	-0.0368	0.0465	126	-0.0383 [-0.125, 0.0547]
V4BBWT: BBWT on V4	θ_{16}	0.993	0.0656	6.61	0.992 [0.862, 1.11]
V4AGE: AGE on V4	θ_{17}	0.585	0.114	19.5	0.579 [0.388, 0.794]
V4POP: Subject Type on V4	θ_{18}	0.365	0.0895	24.5	0.366 [0.186, 0.527]
V4RACE1: RACE on V4	θ_{19}	0.479	0.142	29.6	0.486 [0.214, 0.742]
V4RACE2: RACE on V4	θ_{20}	-0.285	0.131	45.9	-0.276 [-0.518, -0.0215]
V4HEPAN: HEPAN on V4	θ_{21}	0.599	0.12	20.1	0.597 [0.366, 0.824]
IIV					
CLM	ω^2_{CLM}	0.139	0.00682	4.91	0.139 [0.127, 0.154]
V4	ω^2_{V4}	0.704	0.0562	7.98	0.706 [0.607, 0.823]
Residual Error					
Proportional Error (Phase 1) (%)	θ_6	0.185	0.00262	1.42	0.185 [0.18, 0.19]
Additive Error (Phase 1) (ng/mL)	θ_7	0.5	-	-	-
Proportional Error (Phases 2 and 3) (%)	θ_8	0.343	0.00407	1.19	0.343 [0.336, 0.351]
Additive Error (Phases 2 and 3) (ng/mL)	θ_9	0.5 FIX	-	-	-

Active Metabolite/script/PPK-Diagnostics-BMT153261-all.html

Notes: Condition number is 11.69.
Abbreviations: BBWT = baseline body weight; BGFRM = baseline eGFR by MDRD method; CLM = BMT-153261 clearance; Fraction = DEUC to the active metabolite BMT-153261 conversion fraction; HEPAN = hepatic impairment groups; IIV = Inter-individual variability; QM = inter-compartmental clearance of BMT-153261; RSE = relative standard error; V4 = central volume of distribution of BMT-153261; V5 = peripheral volume of distribution of BMT-153261.

[a] Eta shrinkage (%): 8.786 and 29.32 for $\omega^2 CLM$, $\omega^2 V4$.

[b] CIs are from sampling importance resampling (SIR).

Special populations

- Renal impairment

A formal open-label, single-dose dedicated PK study (IM011061) was performed in participants with mild, moderate, and severe impaired renal function and participants with end-stage renal disease on haemodialysis compared to matched-control healthy volunteers to investigate safety and the effect of different degrees of

renal impairment on the PK of deucravacitinib and its major circulating metabolites (BMT-153261 and BMT-158170). Deucravacitinib was administrated on day 1 as a single oral 12 mg dose (tablet formulation) to 32 participants with varying degrees of renal impairment (each group n=8) and 12 participants matching control (similar age and BMI) with normal renal function. Participants in the end-stage renal disease requiring haemodialysis (ESRDH) were dosed before dialysis in Period 1 and after dialysis in Period 2. Washout between periods was defined as ≥ 16 days between dosing.

Renal function was categorized using the Modification of Diet in Renal Disease (MDRD) equation to measure estimated glomerular filtration rate (eGFR) (mL/min): normal renal function for eGFR ≥ 90 mL/min, mild renal impairment for eGFR ≥ 60 - < 90 mL/min, moderate renal impairment for eGFR ≥ 30 - < 60 mL/min, and severe renal impairment for eGFR < 30 mL/min. ESRDH was defined as eGFR < 15 mL/min. Blood PK samples and urine PK samples, for analysis of deucravacitinib and its two major circulating metabolites BMT-153261 and BMT-158170, were collected frequently on Days 1 through 9 (up to 192 h post-dose) and Days 1 through 6, respectively.

Plasma concentration-time profiles of deucravacitinib and the main PK parameters of total and unbound deucravacitinib by renal function group are presented in **Figure 5** and **Table 7**. A summary of the statistical analysis (ANOVA) of the main PK parameters (total and unbound) for deucravacitinib, BMT-153261 are provided in **Table 8** and **Table 9**.

Figure 5 Plot of mean (+SD) deucravacitinib plasma concentrations versus time by renal function group (semi log)

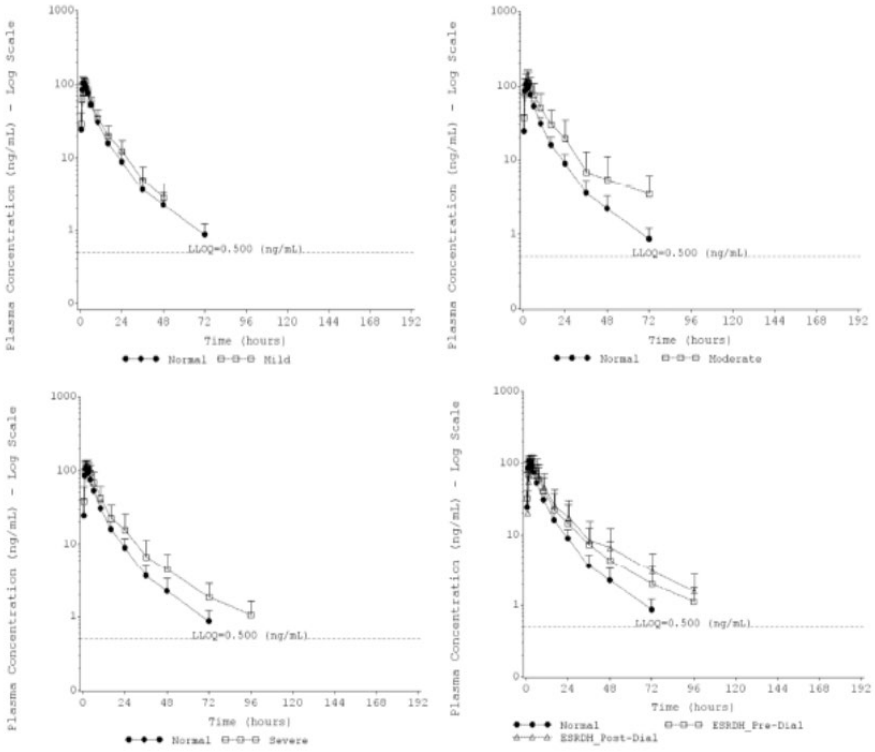


Table 7 Summary of main PK parameters of deucravacitinib for by rental impairment group

PK Parameter (unit)	Statistics	Normal (N=15)	Mild (N=6)	Moderate (N=7)	Severe (N=8)	ESRDH_Pre-Dial (N=8)	ESRDH_Post-Dial (N=8)
Unbound Cmax (ng/mL)	n	15	6	7	8	8	8
	Mean	11.6	12.1	13.8	11.9	14.6	13.2
	SD	2.52	2.70	4.01	2.19	3.62	2.69
	%CV	21.7	22.4	29.0	18.5	24.8	20.3
Unbound Cmax (ng/mL)	Median	12.1	13.1	13.7	12.1	13.5	14.1
	Min - Max	6.19 - 14.8	8.21 - 14.8	9.13 - 21.2	8.33 - 14.5	10.4 - 21.9	9.23 - 17.2
	Geometric Mean	11.3	11.8	13.4	11.7	14.2	13.0
Unbound AUC(0-T) (hr*ng/mL)	n	15	6	7	8	8	8
	Mean	108	111	175	141	170	165
	SD	30.9	26.9	94.7	57.8	89.0	73.1
	%CV	28.6	24.1	54.0	41.0	52.4	44.4
	Median	105	118	146	145	163	160
	Min - Max	58.0 - 162	77.6 - 140	81.4 - 372	69.8 - 222	84.9 - 365	81.9 - 300
	Geometric Mean	104	109	158	130	153	151
Unbound AUC(INF) (hr*ng/mL)	n	15	6	7	8	7	8
	Mean	111	114	178	143	183	167
	SD	32.3	27.8	94.4	58.4	90.3	72.8
	%CV	29.1	24.5	53.0	40.8	49.3	43.6
	Median	107	120	149	147	177	163
	Min - Max	59.0 - 164	79.7 - 143	82.2 - 374	70.7 - 224	87.3 - 367	82.8 - 302
	Geometric Mean	106	111	161	132	167	154
Tmax (hr)	n	15	6	7	8	8	8
	Mean	2.08	2.09	2.64	1.88	1.95	2.69
	Median	2.02	2.27	2.50	1.76	2.25	2.50
	Min - Max	1.08 - 3.00	1.00 - 3.00	1.50 - 6.00	1.00 - 3.00	0.500 - 2.57	1.50 - 4.00
T-HALF (hr)	n	15	6	7	8	7	8
	Mean	17.1	9.54	12.3	19.6	19.0	22.2
	SD	10.4	1.91	3.93	9.67	7.03	14.7
	%CV	60.5	20.0	32.0	49.3	37.1	66.1
T-HALF (hr)	Median	15.2	9.25	12.5	15.7	17.3	16.8
	Min - Max	5.93 - 37.9	7.14 - 12.4	6.54 - 18.2	8.77 - 39.2	14.4 - 34.5	8.60 - 51.7
	Geometric Mean	14.5	9.39	11.7	17.8	18.2	18.7
CLT/F (L/hr)	n	15	6	7	8	7	8
	Mean	12.3	12.5	8.82	10.4	10.5	9.91
	SD	3.20	2.59	3.69	5.22	5.08	4.48
	%CV	26.1	20.8	41.8	50.1	48.6	45.2
	Median	12.6	12.3	8.94	8.59	8.83	8.35
	Min - Max	7.70 - 20.5	9.09 - 16.5	3.33 - 14.7	5.93 - 20.5	4.62 - 17.8	4.02 - 16.6
	Geometric Mean	11.9	12.2	8.07	9.43	9.48	9.00
Fu	n	15	6	7	8	8	8
	Mean	0.106	0.114	0.109	0.105	0.134	0.116
	SD	0.013	0.013	0.008	0.020	0.017	0.016
	%CV	12.0	11.7	7.6	18.8	13.0	13.7
	Median	0.114	0.115	0.109	0.105	0.133	0.120
	Min - Max	0.084 - 0.122	0.093 - 0.128	0.098 - 0.121	0.084 - 0.144	0.109 - 0.168	0.088 - 0.135
	Geometric Mean	0.106	0.113	0.108	0.104	0.133	0.115

Table 8 ANOVA of primary PK parameters for deucravacitinib

Analyte	Comparison (Test/Reference)	PK Parameter (unit)	Test n	Test Geometric LS Mean	Reference* n	Reference* Geometric LS Mean	Geometric LS Mean Ratio(Test/Ref) Estimate	90% CI
BMS-986165	Mild vs. Normal	Cmax (ng/mL)	6	105	15	107	0.977	(0.810, 1.180)
		AUC(0-T) (h*ng/mL)	6	961	15	983	0.978	(0.716, 1.340)
		AUC(INF) (h*ng/mL)	6	981	15	1007	0.974	(0.714, 1.330)
	Moderate vs. Normal	Cmax (ng/mL)	7	123	15	107	1.150	(0.966, 1.380)
		AUC(0-T) (h*ng/mL)	7	1461	15	983	1.490	(1.110, 2.000)
		AUC(INF) (h*ng/mL)	7	1487	15	1007	1.480	(1.100, 1.980)
	Severe vs. Normal	Cmax (ng/mL)	8	113	15	107	1.050	(0.888, 1.250)
		AUC(0-T) (h*ng/mL)	8	1253	15	983	1.270	(0.960, 1.690)
		AUC(INF) (h*ng/mL)	8	1273	15	1007	1.260	(0.953, 1.670)
	ESRDH vs. Normal	Cmax (ng/mL)	8	113	15	107	1.050	(0.888, 1.250)
		AUC(0-T) (h*ng/mL)	8	1310	15	983	1.330	(1.000, 1.770)
		AUC(INF) (h*ng/mL)	8	1333	15	1007	1.320	(0.999, 1.750)

Table 9 ANOVA of primary PK parameters for BMT-153261

Analyte	Comparison (Test/Reference)	PK Parameter (unit)	Test n	Test Geometric LS Mean	Reference* n	Reference* Geometric LS Mean	Geometric LS Mean Ratio(Test/Ref) Estimate	90% CI
BMT-153261	Mild vs. Normal	Cmax (ng/mL)	6	8.79	15	8.65	1.020	(0.702, 1.470)
		AUC(0-T) (h*ng/mL)	6	224	15	208	1.070	(0.736, 1.560)
		AUC(INF) (h*ng/mL)	6	251	15	231	1.090	(0.763, 1.550)
	Moderate vs. Normal	Cmax (ng/mL)	7	8.01	15	8.65	0.925	(0.652, 1.310)
		AUC(0-T) (h*ng/mL)	7	271	15	208	1.300	(0.910, 1.860)
		AUC(INF) (h*ng/mL)	7	293	15	231	1.270	(0.905, 1.770)
	Severe vs. Normal	Cmax (ng/mL)	8	11.6	15	8.65	1.340	(0.956, 1.860)
		AUC(0-T) (h*ng/mL)	8	396	15	208	1.900	(1.350, 2.670)
		AUC(INF) (h*ng/mL)	8	426	15	231	1.840	(1.340, 2.540)
	ESRDH vs. Normal	Cmax (ng/mL)	8	9.78	15	8.65	1.130	(0.809, 1.580)
		AUC(0-T) (h*ng/mL)	8	275	15	208	1.320	(0.939, 1.860)
		AUC(INF) (h*ng/mL)	8	300	15	231	1.300	(0.942, 1.790)

Results from the population PK modelling and simulation (Population PK report v1.0, date 30 June 2021):

Renal impairment was identified as a statistically significant covariate on both, deucravacitinib and BMT-153261 clearance. Simulations for a 6 mg QD dosing were conducted using empirical Bayesian estimates (EBE) individual PK parameters from participants in Phase 3 studies IM011046 and IM011047, and phase 1 study IM011061. Overall, 584 participants in the deucravacitinib dataset had a normal renal function, while 465 had mild, 39 moderate, and 8 severe renal impairment. Another 8 had end-stage renal disease. In the BMT-153261 dataset 497 participants had a normal renal function, while 414 had mild, 36 moderate, and each 8 severe renal impairment and end-stage renal disease. Based on these findings, deucravacitinib and BMT-153261 $C_{max,ss}$, $C_{avg,ss}$ were comparable in patients with mild renal impairment to those with normal renal function. Deucravacitinib $C_{max,ss}$ and $C_{avg,ss}$ were higher in moderate (25.1% and 39.1%) and severe (31.9% and 27.2%) renal impaired patients, as well as in patients with end-stage renal disease (32.9% and 42.9%).

BMT-153261 C_{max} and C_{avgss} were higher in moderate (24.3% and 36.8%), severe (83.6% and 106%) renal impaired patients and patients with end-stage renal disease (45% and 59.9%).

- Hepatic impairment

An open-label, parallel group, single-dose formal dedicated PK study (IM011062) was performed in participants with mild, moderate and severe impaired hepatic function compared to matched-control healthy volunteers (each group n=8) to investigate safety and the effect of hepatic impairment on the PK of deucravacitinib and its metabolites BMT-153261 and BMT-158170 after administration of a single oral 12 mg dose of deucravacitinib (tablet formulation) on day 1. Hepatic function was categorized using the recommended Child-Pugh classification. Blood PK samples for analysis of deucravacitinib and its metabolites BMT-153261 and BMT-158170, were collected on Days 1 through 9 (up to 192 h post-dose).

Plasma concentration-time profiles of deucravacitinib by hepatic impairment group are presented in **Figure 6**. A summary of the statistical analysis (ANOVA) of the main PK parameters (total and unbound) for deucravacitinib and BMT-153261 are provided in **Table 10** and **Table 11**.

Figure 6 Plot of Mean (+SD) deucravacitinib plasma concentrations versus time by hepatic function group

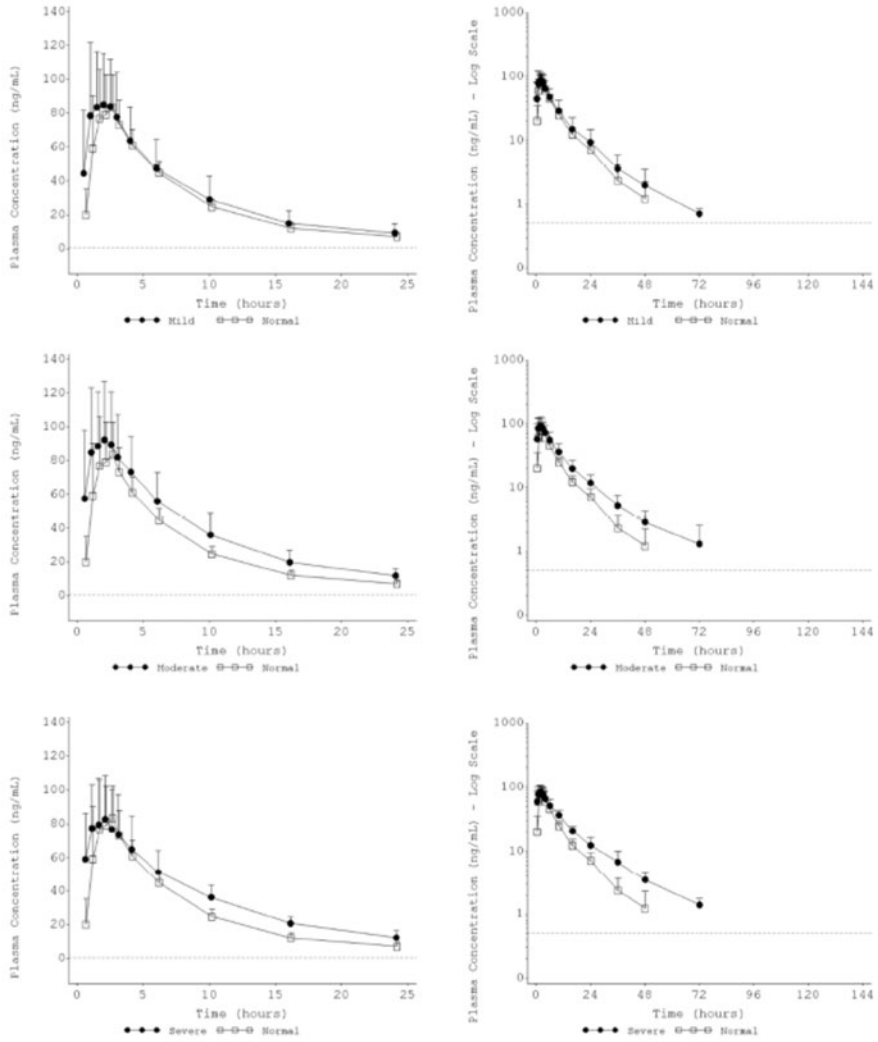


Table 10 Statistical analysis (ANOVA) of primary PK parameters and hepatic function for deucravacitinib

Comparison (Test/ Reference)	PK parameter	Test		Reference[a]		Geo LS Mean Ratio (Test/Ref)	
		n	Geo LS mean	n	Geo LS mean	Estimate	90% CI
Mild vs Normal	Cmax (ng/mL)	8	86.9	8	83.6	1.04	(0.797, 1.36)
	AUC(0-T) (h·ng/mL)	8	817	8	738	1.11	(0.858, 1.43)
	AUC(INF) (h·ng/mL)	8	828	8	752	1.1	(0.854, 1.42)
	Unbound Cmax (ng/mL)	8	10	8	9.4	1.07	(0.853, 1.33)
	Unbound AUC(0-T) (h·ng/mL)	8	94.1	8	82.9	1.14	(0.894, 1.44)
	Unbound AUC(INF) (h·ng/mL)	8	95.4	8	84.5	1.13	(0.888, 1.43)
Moderate vs Normal	Cmax (ng/mL)	8	92.3	8	83.6	1.1	(0.846, 1.44)
	AUC(0-T) (h·ng/mL)	8	1040	8	738	1.4	(1.09, 1.81)
	AUC(INF) (h·ng/mL)	8	1060	8	752	1.4	(1.09, 1.81)
	Unbound Cmax (ng/mL)	8	11.8	8	9.4	1.26	(1.01, 1.57)
	Unbound AUC(0-T) (h·ng/mL)	8	133	8	82.9	1.6	(1.26, 2.03)
	Unbound AUC(INF) (h·ng/mL)	8	135	8	84.5	1.6	(1.26, 2.03)
Severe vs Normal	Cmax (ng/mL)	8	84.1	8	83.6	1.01	(0.771, 1.31)
	AUC(0-T) (h·ng/mL)	8	1060	8	738	1.43	(1.11, 1.85)
	AUC(INF) (h·ng/mL)	8	1080	8	752	1.43	(1.11, 1.85)
	Unbound Cmax (ng/mL)	8	15.3	8	9.4	1.62	(1.3, 2.03)
	Unbound AUC(0-T) (h·ng/mL)	8	191	8	82.9	2.31	(1.82, 2.93)
	Unbound AUC(INF) (h·ng/mL)	8	196	8	84.5	2.31	(1.82, 2.94)

Table 11 Statistical analysis (ANOVA) of primary PK parameters and hepatic function for BMT-153261

Comparison (Test/ Reference)	PK parameter	Test		Reference[a]		Geo LS Mean Ratio (Test/Ref)	
		n	Geo LS mean	n	Geo LS mean	Estimate	90% CI
Mild vs Normal	Cmax (ng/mL)	8	5.67	8	7.51	0.755	(0.442, 1.29)
	AUC(0-T) (h·ng/mL)	8	129	8	159	0.808	(0.456, 1.43)
	AUC(INF) (h·ng/mL)	6	170	8	174	0.972	(0.679, 1.39)
	Unbound Cmax (ng/mL)	8	0.72	8	0.937	0.769	(0.457, 1.29)
	Unbound AUC(0-T) (h·ng/mL)	8	16.3	8	19.9	0.823	(0.468, 1.45)
	Unbound AUC(INF) (h·ng/mL)	6	22	8	21.8	1.01	(0.714, 1.43)
Moderate vs Normal	Cmax (ng/mL)	8	3.06	8	7.51	0.407	(0.238, 0.696)
	AUC(0-T) (h·ng/mL)	8	75.4	8	159	0.473	(0.267, 0.837)
	AUC(INF) (h·ng/mL)	6	140	8	174	0.803	(0.561, 1.15)
	Unbound Cmax (ng/mL)	8	0.435	8	0.937	0.465	(0.276 ,0.782)
	Unbound AUC(0-T) (h·ng/mL)	8	10.7	8	19.9	0.54	(0.307, 0.948)
	Unbound AUC(INF) (h·ng/mL)	6	19.1	8	21.8	0.876	(0.619, 1.24)
Severe vs Normal	Cmax (ng/mL)	6	1.6	8	7.51	0.213	(0.119, 0.38)
	AUC(0-T) (h·ng/mL)	6	37.6	8	159	0.236	(0.127, 0.437)
	AUC(INF) (h·ng/mL)	1[b]	87	8	174	0.499	(0.247, 1.01)
	Unbound Cmax (ng/mL)	6	0.221	8	0.937	0.236	(0.135, 0.414)
	Unbound AUC(0-T) (h·ng/mL)	6	5.2	8	19.9	0.262	(0.142, 0.481)
	Unbound AUC(INF) (h·ng/mL)	1[b]	12.5	8	21.8	0.576	(0.291, 1.14)

Results from the population PK modelling and simulation (Population PK report v1.0, date 30 June 2021):

Hepatic function, as assessed by NCI classification, was not a statistically significantly covariate on the PK of deucravacitinib or BMT-153261. Nonetheless, simulations for a 6 mg QD dosing were conducted using EBE individual PK parameters from participants in Phase 3 studies IM011046 and IM011047, and phase 1 study IM011062 (results not presented here). Overall, 956 participants in the deucravacitinib dataset had a normal hepatic function, while 125 had mild, 8 moderate, and 3 severe hepatic impairment. For the assessment of hepatic impairment on the PK of BMT-153261 overall 833 participants with normal hepatic function, 107 with mild, 9 with moderate, and one participant with severe hepatic impairment were included in the analysis.

In addition, model-predicted exposures for deucravacitinib and BMT-153261, after administration of 6 mg deucravacitinib QD, with only participants from study IM011062 were used to simulate the effect of hepatic impairment, as assessed by Child Pugh classification, on C_{max} and C_{avg}. Results reveal that in the mild hepatic impairment group the maximum change in exposure for both compounds was <15%. In the moderate hepatic impairment group, C_{max} and C_{avg} for deucravacitinib increased by around 33.5 and 41%, while C_{max} and C_{avg} for BMT-153261 decreased by 41.5 and 36% respectively. In the severe hepatic impairment group, C_{max} and C_{avg} for deucravacitinib increased by around 32 and 46%, while C_{max} and C_{avg} for BMT-153261 decreased by 62 and 53% respectively.

- Gender

Results from the population PK modelling and simulation (Population PK report v1.0, date 30 June 2021):

Among the overall 1388 patients included in the dataset for deucravacitinib, both sexes were represented with less female (n= 444; 32 %) than male (n = 944; 68 %). Results suggest sex as a significant covariate

on clearance and volume of distribution of the central compartment (V2) of deucravacitinib indicating female patients might tend to have higher deucravacitinib $C_{max,ss}$ (31.6%) and $C_{avg,ss}$ (28.7%) and 18 % higher BMT-153261 $C_{max,ss}$ and $C_{avg,ss}$ compared to male patients.

- Race / Ethnicity

A formal PK study investigating the effect of the ethnicity on the PK of DEUC has been performed as part of Study **IM011002 Part B** (healthy non-Japanese) and **Part C** (healthy Japanese). Results of this study indicated that body weight adjusted AUCtau are similar between the two populations, the PK of DEUC is expected similar.

Results from the population PK modelling and simulation (Population PK report v1.0, date 30 June 2021):

Among the overall 1388 participants included in the dataset for deucravacitinib, a majority of patients n= 1149 (82.8 %) were White Caucasian, n= 61 (4.4 %) were Black or African American, n= 153 (11 %) were Asian, n=74 (5.3 %) were Japanese, and 25 (1.1 %) were other races or not classified.

Race was not identified as a significant covariate for deucravacitinib, but according to the Applicant was statically significantly on clearance and volume of distribution for BMT-153261 (RACE1 = Asian vs. White, and RACE2 = Black / Others vs. White). Model-based predicted exposures (simulating 6 mg QD in patients with psoriasis) from the population PK models suggest that deucravacitinib and BMT-153261 exposures might be comparable (< 20 % difference) across Asians and White patients with psoriasis (deucravacitinib $C_{max,ss}$ about +13.2 %, $C_{avg,ss}$ about +13.9 in Asian).

Ethnicity was not evaluated as a covariate in the model. However, model-based exposures (using the population PK model) for 6 mg QD were generated in Japanese (n=50, 4.7 %) and non-Japanese participants (n=1010, 95.3 %) from the Phase 2/3 studies as well as Korean, overall suggesting deucravacitinib and BMT-153261 exposures were comparable between Asian Ethnicities.

- Body weight

Results from the population PK modelling and simulation (Population PK report v1.0, date 30 June 2021):

Among the 1388 participants included in the population PK analysis of deucravacitinib, mean body weight was 87.1 kg (median = 85.5 kg, min = 36 kg, max = 180 kg). Out of the 1060 patients with psoriasis, mean body weight was 89.7 kg (median = 88.2 kg, min = 36 kg, max = 180 kg).

Baseline body weight was included as a continuous covariate in the population PK analysis and was found to be a significant covariate for deucravacitinib clearance and volume of distribution of the central compartment (V2) and BMT-153261 clearance and volume of distribution of the central compartment (V4). Model-based predicted exposure after administration of 6 mg QD by body weight group were generated for patients from Phase 3 studies IM011076 and IM011047 (36 to 60 kg n=52 and 51, 60 to 90 kg n=388 and 386, and 90 to 180 kg n=398 and 387 for deucravacitinib and BMT-153261, respectively). Based on the results using the population PK model, patients with psoriasis receiving 6 mg QD deucravacitinib with body weight above 90 kg might have a lower deucravacitinib $C_{max,ss}$ (24.8%) and $C_{avg,ss}$ (19.3%) and lower BMT-153261 $C_{max,ss}$ (24.4%) and $C_{avg,ss}$ (22.5%), compared to the reference body weight group weighing 60 to 90 kg. Patients with a body weight below 60 kg might have a higher deucravacitinib $C_{max,ss}$ (36.4%) and $C_{avg,ss}$ (24.2%) and BMT-153261 $C_{max,ss}$ (44%) and $C_{avg,ss}$ (36.9%).

- Elderly

No formal dedicated study investigating the effect of age on the PK of deucravacitinib and its metabolite BMT-153261 PKs has been performed.

Results from the population PK modelling and simulation (Population PK report v1.0, date 30 June 2021):

Out of the 1388 participants included in the population PK analysis of deucravacitinib, mean age was 43.3 years (median = 43 years, min = 18 years, max = 84 years). Out of the 1060 patients with psoriasis, mean age was 46 years (median = 45 years, min = 18 years, max = 84 years). Overall, 13 patients (out of 1387; 0.94 %) were aged 75 – 84 years and none 85 years or older. In total, 87 (6.3 %) were aged 65 – 74 years of age. The number of older patients per age range (age range: 65-74, 75-84, and 85+) in the population pharmacokinetic dataset is provided in **Table 12**.

Table 12 Number of Older Subjects per Age Range Included in the Population Pharmacokinetics Datasets

PK Trials	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
IM011011	17 /221	0 /221	0 /221
IM011046	20 /331	6 /331	0 /331
IM011047	46 /507	7 /507	0 /507
IM011061	4 /44	0 /44	0 /44
Total	**87 /1387**	**13 /1387**	**0 /1387**

Note: No subjects ages 65 years and above were enrolled in studies IM011002, IM011031, IM011045, IM011048, IM011062, IM011067, IM011071, IM011090, IM011119
Note: In Study IM011011, one subject without PK record was excluded from this table for not having any PK records but was included in PPK report

Age was identified as a significant covariate on clearance of deucravacitinib and BMT-153261. Results of the population PK model suggest an increase in age from 40 to 65 years might be associated with a 12 % decrease in deucravacitinib clearance and a decrease in age to 18 years might be associated with about 9 % increase in clearance. Patients aged 65-74 years are expected to have higher mean $C_{avg,ss}$ (31%), and patients aged 75-84 years higher mean $C_{max,ss}$ (33%) and $C_{avg,ss}$ (53%).

- Children

No PK data are available. The safety and efficacy of deucravacitinib in children and adolescents below the age of 18 years have not yet been established.

- Disease status

Results from the population PK modelling and simulation (Population PK report v1.0, date 30 June 2021):

The effects of disease state (i.e. participant type: Phase 1 volunteers versus patients with psoriasis) and baseline disease (baseline PASI) were evaluated as covariates in the population PK model and identified as a significant covariate on clearance of deucravacitinib. Based on the results of the population PK model, clearance was 18 % higher in healthy volunteers relative to patients with psoriasis, suggesting that deucravacitinib and BMT-153261 $C_{max,ss}$ and $C_{avg,ss}$ were generally comparable (≤ 20%) between healthy volunteers and patients.

Baseline PASI was not identified as a significant covariate on deucravacitinib in the final population PK model. Nonetheless, model-predicted $C_{max,ss}$ and $C_{avg,ss}$ using the population PK models were generated for PASI score groups of 12 to 15.3, 15.3 to 18.9, 18.9 to 24.3, and 24.3 to 58.8, suggesting baseline PASI change might have a small effect on deucravacitinib and BMT-153261 exposures.

- Smoking status

Results from the population PK modelling and simulation (Population PK report v1.0, date 30 June 2021):

Smoking status was not identified as a significant covariate for deucravacitinib PK parameters. However, model-predicted exposures for smokers and non-smokers, receiving 6 mg deucravacitinib QD, were generated using the population PK model. These results suggest that deucravacitinib and BMT-153261$C_{max,ss}$ and $C_{avg,ss}$ were generally comparable (≤ 20%) between patients who were smokers and non-smokers.

Pharmacokinetic interaction studies

In vitro

▪ *Potential for interactions related to DEUC metabolism: DEUC as a victim drug*

BMS-986165 was extensively metabolized in vivo in humans. The primary biotransformation pathways were cytochrome P450 (CYP) 1A2-mediated N-demethylation at the triazole moiety to form BMT-153261, carboxylesterase (CES) 2-mediated cyclopropyl carboxamide hydrolysis to form BMT-158170, uridine-diphosphoglucuronosyl transferase (UGT) 1A9-mediated N-glucuronidation to form BMT-334616, and CYP2B6 and CYP2D6-mediated mono-oxidation at the deuterated methyl group to form M11 (see previous part on metabolism).

▪ *Potential for interactions related to enzymes (CYPs, UGTs and CES): DEUC, BMT-153261 and BMT-158170 as inhibitors*

The **Table 13** presents results from in vitro studies on the ability of DEUC and its two metabolites BMT-153261 and BMT-158170 to inhibit the main CYPs, UGTs and CES2:

Table 13 Summary of Finding of In Vitro Evaluations of Deucravacitinib, BMT-153261, and BMT-158170 as Inhibitors of Drug Metabolizing Enzymes

Enzyme	IC50 (μM)[a,b]		
	DEUC	BMT-153261	BMT-158170
CYP1A2	> 40 (> 40)	> 40 (> 40)	> 40 (> 40)
CYP2B6	> 40 (> 40)	6.6 ± 0.6 (8.6 ± 0.3)	> 40 (> 40)
CYP2C8	> 40 (> 40)	37.5 ± 2.1 (> 40)	> 40 (> 40)
CYP2C9	> 40 (> 40)	22.1 ± 1.7 (38.0 ± 1.6)	> 40 (> 40)
CYP2C19	> 40 (> 40)	32.3 ± 4.5 (> 40)	> 40 (> 40)
CYP2D6	> 40 (> 40)	> 40 (> 40)	> 40 (> 40)
CYP3A4 (Midazolam 1'-hydroxylation)	> 40 (> 40)	16.0 ± 3.0 (16.6 ± 1.3)	> 40 (> 40)
CYP3A4 (Testosterone 6β-hydroxylation)	> 40 (> 40)	11.3 ± 1.4 (11.1 ± 1.2)	> 40 (> 40)
UGT1A1	2.0 (r)	2.0 (r)	> 20 (r)
UGT1A1	12.6 (HLM)	14.7 (HLM)	ND
UGT1A4	> 30 (HLM)	> 30 (HLM)	ND
UGT1A6	> 30 (HLM)	> 30 (HLM)	ND
UGT1A9	> 30 (HLM)	> 30 (HLM)	ND
UGT2B7	> 30 (HLM)	> 30 (HLM)	ND

[a] Values in parenthesis represent IC50 values corresponding to time-dependent inhibition (after 30-minutes of preincubation).

[b] Predicted R-values can be found in Table 7.2.4-1 of Pharmacokinetics Written Summary[65]

Abbreviation: r = recommend enzyme; IC50 = concentration at which 50% inhibition observed; ND = not determined

▪ *Potential for interactions related to CYP1A2, 2B6 and CYP3A4: DEUC, BMT-153261 and BMT-158170 as inducers*

The **Table 14**, **Table 15** and **Table 16** presents study setup and results from in vitro induction studies:

Table 14 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes (Induction in Sandwich-cultured Transporter Certified™ Human Hepatocytes)

Test Article:	BMS-986165
Location in Dossier:	4.2.2.6
Study No./ Document Control No:	NCPK518/ 930135474
Method:	Transporter certified cryopreserved human hepatocytes from 3 donors were cultured in sandwich configuration to maximize the function of drug transporters and cytochrome P450 enzymes (CYP). Cultures were treated with varying concentrations of BMS-986165. Omeprazole (50 µM), phenobarbital (1000 µM), and Rifampicin (10 µM) were included as positive controls for CYP1A2, CYP2B6, and CYP3A4, respectively. Flumazenil (25 µM) was included as a negative positive control.
Incubation time:	72 hours
Concentrations:	0.019, 0.052, 0.14, 0.38, 1.0, 2.7, 7.4 and 20 µM
Assay:	To measure induction, gene expression of all the targets was quantified by using TaqMan®. Additionally, enzyme activity of the target CYP was determined to confirm the results of the gene expression analysis.

BMS-986165 (µM)	mRNA and Enzyme Activity Changes in 3 Hepatocyte Donors (Fold Over DMSO Control)					
	CYP1A2		CYP2B6		CYP3A4	
	mRNA	Enzyme Activity[a]	mRNA	Enzyme Activity[b]	mRNA	Enzyme Activity[c]
0.019	0.90, 1.12, 1.92	0.74, 0.72, 0.77	0.54, 0.77, 2.81	0.59, 0.52, 0.67	0.17, 0.29, 1.65	0.31, 0.28, 0.38
0.052	1.17, 0.97, 0.87	0.84, 0.76, 0.82	0.44, 0.44, 0.58	0.46, 0.44, 0.76	0.13, 0.30, 0.30	0.25, 0.25, 0.42
0.14	0.92, 1.28, 1.99	0.64, 0.70, 0.81	0.47, 0.68, 1.21	0.47, 0.44, 0.76	0.15, 0.30, 0.62	0.25, 0.24, 0.41
0.38	0.95, 1.32, 0.54	0.71, 0.76, 0.84	0.55, 0.76, 0.42	0.51, 0.47, 0.79	0.24, 0.42, 0.20	0.29, 0.29, 0.44
1	1.05, 1.19, 1.16	0.68, 0.81, 0.89	0.48, 0.71, 0.68	0.54, 0.53, 0.89	0.23, 0.35, 0.01	0.32, 0.33, 0.50
2.7	1.22, 1.16, 1.14	0.75, 0.76, 0.82	0.60, 0.73, 0.89	0.62, 0.60, 1.08	0.27, 0.30, 0.27	0.35, 0.34, 0.53
7.4	1.37, 1.43, 1.85	0.76, 0.72, 0.84	0.87, 0.97, 1.74	0.79, 0.80, 1.36	0.63, 0.64, 0.46	0.53, 0.49, 0.66
20	1.78, 1.86, 1.83	0.86, 0.79, 0.85	1.59, 1.95, 2.08	1.33, 1.31, 1.66	2.61, 1.72, 1.02	1.15, 0.99, 0.81

Additional Information: NA: not applicable. CYP: cytochrome P450. mRNA: messenger ribonucleic acid.
No mRNA or enzyme activity response is >= 20% of the positive control response for all three donors and at every concentration tested.

Table 15 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes (Induction of Cytochrome P450 in Human Hepatocytes) (continued)

Test Article:	BMT-153261
Location in Dossier:	4.2.2.6
Study No./ Document Control No:	NCPK383/ 930115915
Method:	Primary human hepatocytes from 3 donors were exposed to BMT-153261 (0.31 to 40 µM) for a total of 2 days. CYP1A2, CYP2B6, and CYP3A4 mRNA levels were determined. Omeprazole (60 µM), phenobarbital (1000 µM), and Rifampicin (10 µM) were included as positive controls for CYP1A2, CYP2B6, and CYP3A4, respectively.
Incubation time:	48 hours
Concentrations:	0.31, 0.63, 1.25, 2.5, 5.0, 10, 20, and 40 µM
Assay:	Real-time reverse transcription-polymerase chain reaction assay to measure CYP1A2, CYP2B6, and CYP3A4 mRNA. The cytotoxic effect of the test substance at a given concentration is assessed by comparing the alamar blue signal of DMSO-treated cells with compound-treated cells.

Isozyme	EC50 (µM)	Emax.conc (fold induction)
CYP1A2 mRNA	> 40, > 40, and > 40	0.7, 0.3, and 0.4
CYP2B6 mRNA	> 40, > 40, and > 40	1.4, 1.6, and 1.4
CYP3A4 mRNA	> 40, > 40, and > 40	1.8, 1.0, and 1.0

Additional Information: NA: not applicable. CYP: cytochrome P450. EC50: effective concentration at which half of the maximal response is observed. Emax = maximal effect that can be achieved with BMT-153261, as estimated using a 4-parameter logistic regression model. E.max.conc = effect observed at maximal (the highest) tested concentration of BMT-153261 that is not affected by cytotoxicity or compound precipitation in the assay buffer (40 µM). The values represent mean results where BMT-153261was tested with each of the 3 donors in duplicate (N = 2) and the result were generated for each of the duplicate samples. In primary human hepatocytes from 2 donors, BMT-153261 did not demonstrate cytotoxic effects at any of the tested concentrations.

Table 16 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes (Induction of Cytochrome P450 in Human Hepatocytes) (continued)

Test Article:	BMT-158170
Location in Dossier:	4.2.2.6
Study No./ Document Control No:	NCPK382/ 930115920
Method:	Primary human hepatocytes from 3 donors were exposed to BMT-158170 (0.31 to 40 µM) for a total of 2 days. CYP1A2, CYP2B6, and CYP3A4 mRNA levels were determined. Omeprazole (60 µM), phenobarbital (1000 µM), and Rifampicin (10 µM) were included as positive controls for CYP1A2, CYP2B6, and CYP3A4, respectively.
Incubation time:	48 hours
Concentrations:	0.31, 0.63, 1.25, 2.5, 5.0, 10, 20, and 40 µM
Assay:	Real-time reverse transcription-polymerase chain reaction assay to measure CYP1A2, CYP2B6, and CYP3A4 mRNA. The cytotoxic effect of the test substance at a given concentration is assessed by comparing the alamar blue signal of DMSO-treated cells with compound-treated cells.

Isozyme	EC50 (µM)	Emax.conc (fold induction)
CYP1A2 mRNA	≥ 10.9, > 40, and > 40	5.4, 4.2, and 4.1
CYP2B6 mRNA	> 40, > 40, and > 40	1.2, 1.1, and 1.1
CYP3A4 mRNA	> 40, > 40, and > 40	1.5, 1.1, and 1.3

Additional Information: NA: not applicable. CYP: cytochrome P450. EC50: effective concentration at which half of the maximal response is observed. Emax = maximal effect that can be achieved with BMT-158170, as estimated using a 4-parameter logistic regression model. E.max.conc = effect observed at maximal (the highest) tested concentration of BMT-158170 that is not affected by cytotoxicity or compound precipitation in the assay buffer (40 µM). The values represent mean results where BMT-158170 was tested with each of the 3 donors in duplicate (N = 2) and the result were generated for each of the duplicate samples. In primary human hepatocytes from 2 donors, BMT-158170 did not demonstrate cytotoxic effects at any of the tested concentrations.

▪ *Potential for interactions related to transporters (P-gp-BCRP, OCTs, OATP1B1, OATP1B3, NTCP, OAT1, OAT2, and OAT3, OCT2, MATE1, and MATE2-K): DEUC, BMT-153261 and BMT-158170 as substrate*

The **Table 17** presents results from in vitro studies on the ability of DEUC and its two metabolites BMT-153261 and BMT-158170 to be substrates of the main efflux and uptake transporters:

Table 17 Summary of Finding of In Vitro Evaluations of Deucravacitinib, BMT-153261, and BMT-158170 as Substrates of Transporters

Transporter	Substrate		
	DEUC	BMT-153261	BMT-158170
P-gp	Yes	Yes	Yes
BCRP	Yes	Yes	Yes
OATPs	No	No	No
NTCP	No	No	No
OAT1	No	No	ND
OAT2	No	No	No
OAT3	No	No	ND
OCT1	Yes	Yes	No
OCT2	No	No	ND
MATE1	No	No	ND
MATE2-K	No	Yes	ND

Abbreviations: ND = not determined

▪ Potential for interactions related to transporters (P-gp-BCRP, OCTs, OATP1B1, OATP1B3, NTCP, OAT1, OAT2, and OAT3, OCT2, MATE1, and MATE2-K): DEUC, BMT-153261 and BMT-158170 as inhibitors

The **Table 18** presents results from in vitro studies on the ability of DEUC and its two metabolites BMT-153261 and BMT-158170 to be inhibit the main efflux and uptake transporters:

Table 18 Summary of Finding of In Vitro Evaluations of BMS-986165, BMT-153261, and BMT153170 as Inhibitors of Drug Metabolizing Enzymes and Transporters

Enzyme/Transporter	IC50 (μM)[a]		
	BMS-986165	BMT-153261	BMT-158170
Digoxin transport (P-gp)	37.2 ± 8.1	> 50.0	> 50
BCRP	0.31 ± 0.22	8.9 ± 4.5	38.5 ± 9.3
OATP1B1	6.1 ± 1.0	5.0 ± 0.8	> 50
OATP1B3	1.1 ± 0.4	1.0 ± 0.2	> 50
NTCP	> 50	> 50	> 50
BSEP	17.0 ± 2.1	23.9 ± 4.2	> 50
MRP2	> 50	15.7 ± 2.9	> 50
OAT1	16.8 ± 2.7	32.4 ± 5.7	> 50
OAT3	17.2 ± 0.9	11.4 ± 1.3	15.8 ± 1.8
OCT1	4.7 ± 0.6	0.6 ± 0.1	19.9 ± 2.4
OCT2	24.7 ± 5.0	40.9 ± 9.4	> 50
MATE1	6.7 ± 1.6	2.9 ± 0.5	16.0 ± 1.6
MATE2-K	3.33	0.12	3.08

Source: NCPK156[21], NCPK213[28], NCPK382[32], NCPK383[33], NCPK409[78], NCPK441[73], NCPK457[74], and NCPK590[79].

Abbreviations: BSEP = bile salt export pump; CYP = cytochrome P450; HLM = human liver microsomes; IC50 = concentration at which 50% inhibition observed; MATE = multidrug and toxin extrusion protein; MRP = multiple drug-resistance protein; NTCP = Na+-taurocholate-cotransporting peptide; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; OCT = organic cation transporter; r = recombinant; UGT = uridine 5'-diphospho-glucuronosyltransferase; ND = not determined.

[a] Values in parenthesis represent IC50 values corresponding to time-dependent inhibition (after 30-minutes of preincubation).

In vivo

Based on in vitro data, thirteen clinical studies were performed to evaluate potential for interactions with deucravacitinib in vivo. Nine studies assessed deucravacitinib as a victim, the remaining four studies evaluated deucravacitinib as a perpetrator.

- *DEUC as a perpetrator: Effect of DEUC PK of co-administered drugs*

The effect of DEUC as a perpetrator on the exposures of concomitant medications like rosuvastatin, methotrexate, mycophenolate mofetil (MMF) or oral contraceptives (norethindrone acetate and ethinyl estradiol) was evaluated.

IM011015 (rosuvastatin, BCRP/OATP1B1/1B3 substrate)

In vitro studies suggested a potential of deucravacitinib to inhibit BCRP and OATP1B3 transporters in vivo. A clinical DDI study was performed with rosuvastatin as a dual BCRP/OATP sensitive substrate. Multiple dose administration of deucravacitinib did not affect significantly plasma exposure (Cmax and AUC) of rosuvastatin.

IM011025 (methotrexate, concomitant medication)

Deucravacitinib dosed to steady-state did not have effect on plasma exposure (Cmax and AUC) of concomitantly administered methotrexate and two medicinal products can be co-administered without the need for a dose modification.

IM011039 (oral contraceptive, concomitant medication)

Concomitant administration of deucravacitinib with oral contraceptive containing norethindrone (1.5 mg) and ethinyl estradiol (30 µg) did not have significant effect on PK of either component. Deucravacitinib can be administered with oral contraceptives in women of childbearing potential without the need for a dose modification.

IM011071 (mycophenolate mofetil, concomitant medication)

Effect of single dose MMF on steady state deucravacitinib and vice versa, the effect of steady-state deucravacitinib on single dose MMF were evaluated. Co-administration of steady-state deucravacitinib resulted in a mild increase of 8% in MPA Cmax, while AUC was not affected. This increase was driven by a single subject and is not deemed clinically meaningful. Plasma exposure of deucravacitinib and its metabolites was not influenced by co-administration of MMF.

- *DEUC as a victim: Effect of co-administered drugs on the PK of DEUC*

The effect of cyclosporine (dual P-gp/BCRP inhibitor), fluvoxamine (CYP1A2 inhibitor), ritonavir (CYP1A2 inducer), diflunisal (UGT 1A9 inhibitor), pyrimethamine (OCT1 inhibitor), or gastric pH modulating agents like famotidine or rabeprazole, on DEUC exposure (as a victim) has been also evaluated in healthy subjects.

IM011045 (cyclosporine, a P-gp and BCRP inhibitor)

Co-administration of cyclosporine (a P-gp and BCRP inhibitor) did not significantly affect Cmax of deucravacitinib and its metabolites. AUC of deucravacitinib and BMT-153261 was only modestly increased (29% and 21%, respectively), while there was no significant effect on AUC of BMT-158170. This is in line with deucravacitinib showing high permeability and confirms that P-gp and BCRP do not play a major role in deucravacitinib elimination.

Deucravacitinib can be administered with P-gp/BCRP inhibitors without the need for a dose modification.

IM011087 (ritonavir, CYP1A2 inducer, P-gp inhibitor)

Formation of active metabolite BMT-153261 from deucravacitinib is mediated by CYP1A2. Therefore, a study with ritonavir (a CYP1A2 inducer) was conducted to evaluate its effect on deucravacitinib and its metabolites PK. However, ritonavir acts also as a transporter inhibitor (such as P-gp). Evaluation of the overall CYP1A2 induction/P-gp inhibition (Day15/Day 1 comparison) and separate induction (Day15/Day5) and inhibition effects (Day5/Day1) was covered by the study design.

Ritonavir 100 mg QD administered to steady-state (overall induction and inhibition) had no effect on exposures of deucravacitinib and BMT-158170. Exposures of active metabolite BMT-153261 modestly increased; Cmax by 49% and AUC by 33%.

Following single 100 mg dose of ritonavir (P-gp inhibition effects) there was also no significant effect on exposures of deucravacitinib and BMT-158170. Exposures of BMT-153261 modestly increased; Cmax by 30% and AUC by 32%.

Co-administration of multiple doses of ritonavir 100 mg QD versus a single 100 mg dose (CYP1A2 induction effect) showed no significant changes in the exposures of deucravacitinib and its metabolites. A lower dose of ritonavir was used in this study, to avoid triggering other inductive and inhibitory processes that may confound interpretation of results and not provide a clear guidance on the role of CYP1A2 induction on DEUC exposures. To further substantiate findings from Study IM011087, the effect of smoking, which is another moderate CYP1A2 inducer like ritonavir, was evaluated by population pharmacokinetic (PPK) analysis. Heavy smokers (≥20 cigarettes a day) had 21% lower deucravacitinib geometric mean Cavg,ss compared to non-smokers/past smokers, while exposure to metabolite BMT-153261 which is formed via CYP1A2 was slightly higher (13%).

IM011088 (fluvoxamine, strong CYP1A2 inhibitor)

Co-administration of deucravacitinib with fluvoxamine resulted in no significant changes in Cmax and a modest increase in AUC (57%). Similar results were observed for the inactive metabolite BMT-158170; no changes in Cmax with a modest increase in AUC (45%). In contrast, there was a significant decrease in the exposure to the active metabolite BMT-153261; Cmax and AUC decreased approximately 94%. This also confirms that formation of BMT-153261 is primarily mediated by CYP1A2.

Since deucravacitinib exposure (AUC) increased by 57% and BMT-153261 exposure decreased by 94%, calculation of the exposure to total active moieties was made by adjusting for molecular weight (the potency is considered to be equal for parent and active metabolite). The calculation shows that exposure (AUC) to total active moieties increased approximately by 22% with co-administration of a strong CYP1A2 inhibitor. Large decrease in the exposure to active metabolite was compensated by the modest increase in the exposure to the parent. No clinically meaningful effect on deucravacitinib efficacy or safety is expected.

IM011100 (pyrimethamine, OCT1 inhibitor)

Co-administration of a single pyrimethamine dose did not have effect on the plasma exposure of deucravacitinib and its metabolites. No changes were observed in renal clearance of deucravacitinib and BMT-153261. The amount of BMT-158170 excreted in urine was decreased by 60%, however with no changes in plasma exposure.

IM011101 (diflunisal, UGT1A9 inhibitor)

Co-administration of steady-state diflunisal (UGT1A9 inhibitor) did not have effect on deucravacitinib Cmax, while it resulted in approximately 19% increase in AUC. The exposure of active metabolite BMT-153261 increased 23% based on Cmax, and 75% and 50% based on AUC0-t and AUCinf, respectively.

The increase in exposure to inactive metabolite BMT-158170 was the highest; Cmax increased around 2-fold, while AUC0-t and AUCinf increased 4.4- and 3.8-fold. There was a decrease in the exposure of glucuronide metabolite BMT-334616, as expected; 55% decrease in Cmax and 31% decrease in AUC. All these changes were not deemed clinically relevant by the applicant.

Concomitant administration with gastric acid reducing agents DDI study results for concomitant administration with famotidine and rabeprazole are described above.

- *Exposure relevant for safety evaluation*

DEUC and BMT-153261 steady state exposures predicted by the final PPK models in PsO subjects at a 6 mg QD dosing regimen were not considered reliable due to Pop PK model deficiencies. Steady state exposure measures were re-generated using revised Model "final-res2.2-V2POP" and compared with those from the original final model reported in the population PK report. No major differences in exposures were noted.

Steady-state PK parameters from study IM011045 after 6mg QD capsule administration are shown in the **Table 19** below:

Table 19 Pharmacokinetic Parameters for BMS-986165 and Metabolites

		BMS-986165 (N=18)		BMT-153261 (N=18)		BMT-158170 (N=18)	
Parameter	Statistic	Day 5	Day 6	Day 5	Day 6	Day 5	Day 6
Cmax (ng/mL)	Geo Mean	41.7	48.2	7.04	8.05	13.4	12.4
	%CV	27.7	22.7	27.7	22.9	32.5	26.7
Tmax (h)	Median	2.50	2.50	4.00	6.00	2.50	4.00
	Min, Max	1.00, 4.00	2.00, 8.00	2.50, 6.00	2.50, 8.07	1.50, 4.00	2.50, 8.03
AUC(TAU) (h*ng/mL)	Geo Mean	359	463	110	133	138	158
	%CV	29.4	27.0	25.8	23.6	33.6	30.5
MR(Cmax)	Geo Mean			0.175	0.173	0.383	0.307
	%CV			32.5	33.6	25.0	20.8
MR(AUC(TAU))	Geo Mean			0.317	0.297	0.459	0.406
	%CV			31.7	32.6	23.4	21.3

Days 1-5: BMS-986165 6 mg QD; Day 6: BMS-986165 6 mg coadministered with cyclosporine 500 mg
CV = coefficient of variation; Max = maximum; Min = minimum; n = number of evaluable samples; N = number of participants included in the analysis population

The maximal increases in DEUC exposure noted with various intrinsic and extrinsic factors was ~57% increase in AUC[INF] in the fluvoxamine DDI (IM011088) and a 60% higher unbound AUC[INF] in moderate HI subjects. The maximal increases in BMT-153261 exposure noted with various intrinsic and extrinsic factors was a ~81% increase in AUC[INF] in severe RI subjects. These exposure changes were within the 2-fold (100%), and according to the applicant are not expected to meaningfully impact clinical safety of DEUC.

Consequently, no dose adjustment is recommended in patients with mild, moderate, or severe RI, in patients with mild or moderate HI, in combination with concomitant medications, or based on other intrinsic or extrinsic factors. The unbound exposure (AUC[INF]) of DEUC in severe HI subjects is higher (131%) relative to normal subjects and DEUC is not recommended for subjects with severe HI.

2.6.2.2. Pharmacodynamics

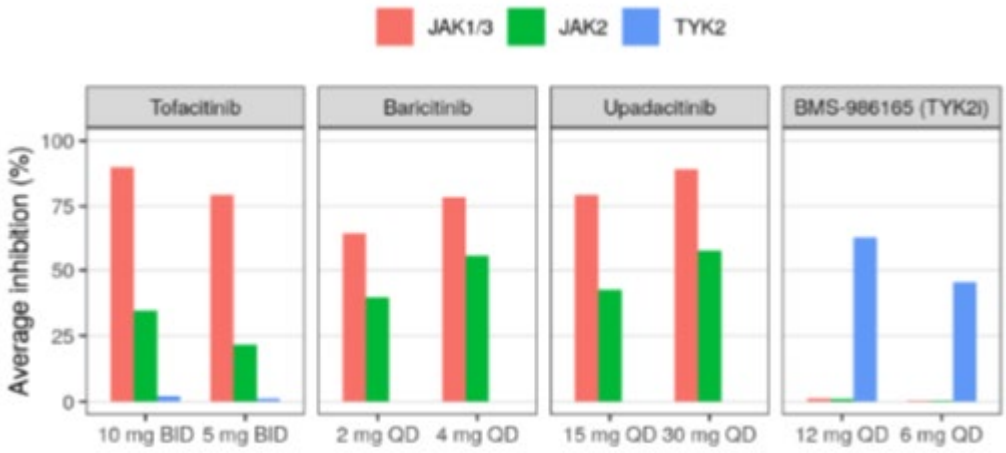
Mechanism of action

DEUC (BMS-986165) is a selective inhibitor of TYK2 and also inhibits IL-23, IL-12 and Type I interferon in cellular assays in vitro.

Deucravacitinib had an IC50 of 0.2 nM and a KD of 0.02 nM for the interaction with TYK2 pseudokinase compared to an IC50 = 0.95 nM and a KD of 0.33 nM for the pseudokinase domain of JAK1.

In silico analysis was conducted to integrate plasma drug exposure measures and compare the predicted TYK2, JAK1/3, and JAK2 inhibition profiles of DEUC versus those of the JAK inhibitors baricitinib, tofacitinib, and upadacitinib at clinically relevant doses and exposures. The results showed a specific affinity of DEUC on TYK2 signalling.

Figure 7 Plots of Simulated Daily Average Percent Inhibition of Pathways, JAK1/3, JAK2, and TYK2 for Deucravacitinib, Baricitinib, Tofacitinib, and Upadacitinib



Several in vitro models using human cell lines or primary cells (T lymphocytes, monocytes, B lymphocytes) were used to assess the effects of DEUC on TYK2 signalling and also on other JAKs. The parameters measured were the phosphorylation of STATs (JAK-activated transcription factors) and the transcriptional activity of STATs.

In a model using human PBMCs and measurement of STAT transcription factor phosphorylation, DEUC showed a very good activity on TYK2 signalling and no or little effect on JAK1/JAK3 (IL-2) signalling. Other studies measuring STAT factor phosphorylation in whole blood showed that DEUC had little effect on JAK1/JAK3-mediated IL-2 and IL-7 signalling. The IC50s found were 1946 (IL-2) and 1960 nM (IL-7).

The **Table 20** below using the kit225 cell line (IL-2-dependent human T cell line) shows that DEUC has negligible activity on IL-2 signalling via JAK1/JAK3 with an IC50 = 1886 nM.

Table 20 Cellular Potency of BMS-986165 and Its Metabolites, BMT-153261 and BMT-158170, against Functional Responses in Human Kit225 T cells

Stimulus	Kinase Dependency	BMS-986165 IC50 (nM)	BMT-153261 IC50 (nM)	BMT-158170 IC50 (nM)
IFNα	TYK2/JAK1	5	15	3,190
IL-23	TYK2/JAK2	8	14	3,720
IL-2	JAK1/JAK3	1,886	4,560	> 12,500

Abbreviations: IFNα, interferon alpha; IC50, concentration required for 50% inhibition; IL-2, interleukin-2; IL-23, interleukin-23; JAK, Janus kinase; TYK2, tyrosine kinase 2.

DEUC inhibited also IL-6 (JAK1/JAK2) signalling with an IC50 approximately 1 log higher (IC50 = 423 to 1179 nM) than the JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) with IC50s between 7.8 and 245 nM. The endpoints measured were STAT3 or STAT5 phosphorylation.

Besides, deucravacitinib significantly inhibited IL-10 signalling (TYK1/JAK2; STAT3 phosphorylation) measured in B lymphocytes (IC50 = 28 nM), T lymphocytes (IC50 = 77 nM) and monocytes (IC50 = 169 nM)

Primary and Secondary pharmacology

Several studies were conducted:

The Phase 1 FIH study IM011002 was a randomized, double-blind, placebo-controlled, single- (Part A), multiple- (Part B, Part C, Part D) ascending dose study to assess the safety, tolerability, PK, pharmacodynamics, and target engagement of DEUC in 140 healthy subjects following oral administration of a solution formulation.

The primary focus of this biomarker analysis was evaluation of DEUC PD parameters to estimate the level of target engagement in this pathway, which included IFNalpha mediated STAT5 phosphorylation and IL-12/ IL-18 induced IFN gamma production as secondary endpoints.

DEUC showed an inhibition of TYK2 mediated pathways and via ex-vivo inhibition in two assays and in IFNalpha-mediated gene transcription and Interferon-responsive genes (IRG) induction was inhibited.

Ex vivo whole blood assays in healthy subjects showed dose- and concentration-dependent inhibition of two TYK2 dependent pathways by deucravacitinib: IFNalpha-mediated phosphorylation of STAT5 and inhibition of IL-12+IL-18-mediated IFNgamma production, in both SAD and MAD part of the study. In vivo, deucravacitinib inhibited interferon regulated gene expression in a dose-dependent manner.

In the Phase 2 study (IM011011), the objectives of this exploratory biomarker study were to assess the effect of DEUC on transcriptome profiles of skin biopsy and circulating whole blood in psoriasis patients.

Decreases in epidermal thickness were seen with doses ≥3 mg QD. By Day 85, improvements in epidermal hyperplasia (H&E; K16), T-cell counts (CD3), and myeloid cell counts (CD11c) were seen in lesional skin among DEUC–treated patients (doses ≥3 mg QD). Ki67, a marker of cell proliferation, decreased from baseline in lesional skin following DEUC treatment.

A trend towards normalization of IL-17A expression in the skin was observed at the highest doses (3 mg BID, 6 mg BID, and 12 mg QD) over time compared to no changes in the samples from placebo-treated subjects. In addition, expression of genes downstream of IL-23 and IL-17-mediated signal transduction, i.e., defensin beta 4, IL22, S100A8, and S100A9, were also reduced in a dose and time-dependent manner.

Overall, DEUC treatment led to suppression of the IL- 23/Th17 pathway and keratinocyte activation, as well as reduction in Type I IFN-response genes in the skin of patients with moderate to severe psoriasis.

In Phase 3 studies (IM011046 and 047), median levels of IL-17A, IL-19 and β defensin were reduced by 48-50%, 72%, and 81-84%, respectively. In Phase 2 and Phase 3 studies, biomarkers of JAK1 or JAK3 inhibition, NK cell and lymphocyte counts, were not meaningfully changed by DEUC. Further, biomarkers of JAK2 inhibition, haemoglobin or platelet counts, were not changed by DEUC. Cholesterol, a biomarker of JAK mediated IL-6-pathway inhibition, was also not changed by DEUC. DEUC reduced levels of serum biomarkers of IL-23/TH17 pathway which were associated with psoriasis disease activity.

Study IM011084 (Part A) was a Phase 2 study of DEUC in psoriatic arthritis of 16 weeks (completed, double-blind, and placebo-controlled). The Part B of 36 weeks is still ongoing.

In this study, serum protein biomarkers related to the TYK2 signalling pathway, skin, and joint damage were measured by different immunoassays. The Pharmacodynamics objectives were to assess the effect of DEUC

on inflammatory damage up to Week 52 and on inflammation and immune mediated disease activity up to Week 52.

Change from baseline in soluble markers and immune cell counts were observed. DEUC reduced PsO associated gene expression in psoriatic skin, including reductions in IL-23 pathway and type I IFN pathway genes.

Serum biomarker results showed suppression of IL-23/IL-17 pathway activation, and reduction of skin and joint-related biomarkers by DEUC. No decrease in NK cell counts or mean haemoglobin levels were observed after DEUC treatments, in contrast with observations after treatment with JAK1-3 inhibitors.

Study IM011048 Thorough QT/ QTc study (TQT)

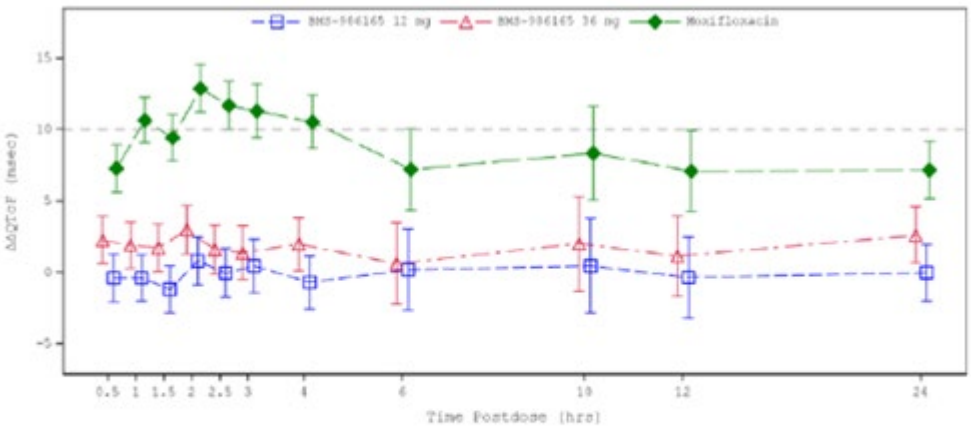
This was a randomized, double-blind, positive-controlled, placebo-controlled, 4-period crossover study to investigate the electrocardiographic effects of DEUC (12 or 36 mg) in 40 healthy male and female subjects, with moxifloxacin (400 mg) as the positive control.

The primary objective of this study was to determine the effect of BMS-986165 plasma concentrations on the QT interval corrected for heart rate (HR) using Fridericia's method (QTcF) in healthy subjects.

Subjects received a single oral dose of either placebo, DEUC 12 mg, DEUC 36 mg or moxifloxacin 400 mg on Days 1, 6, 11, and 16. Blood PK samples for analysis of DEUC and its metabolites (BMT-153261 and BMT-158170) were collected on Days 1 through 20. DEUC, at the studied doses of 12 mg and 36 mg, did not have a clinically relevant effect on relevant ECG parameters, including QTc interval and a QT interval with Fridericia's correction effect (ΔΔQTcF) exceeding 10 msec can be excluded at DEUC plasma concentrations of at least 500 ng/mL.

The plot of ΔΔQTcF across time for deucravacitinib (12 mg and 36 mg) and moxifloxacin is presented in the **Figure 8** below.

Figure 8 Plot of Placebo-corrected Change from Baseline QTcF (ΔΔQTcF) across Time Points (QT/QTc Set)



Source: Appendix 16.1.14 (Figure 14.2.1.2.3 of the Cardiac Safety Report)

LS mean and 90% confidence interval based on a linear mixed-effects model: ΔQTcF = Period + Sequence + Time + Treatment + Time • Treatment + Baseline QTcF. An unstructured covariance structure was used to specify the repeated measures (time for subjects within period). Baseline was defined as the mean of the 4 predose values on Days 1, 6, 11, and 16 in each corresponding treatment period. The gray dotted line indicated the threshold of 10 (msec).

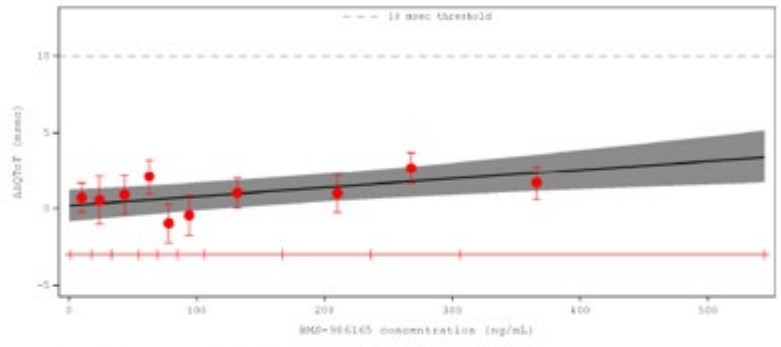
In the DEUC concentration ΔΔQTcF analysis, the QT effect (ΔΔQTcF) of DEUC was predicted to 0.7 msec (90% CI: -0.21 to 1.68) and 2.1 msec (90% CI: 0.91 to 3.19) at the geometric mean Cmax of the 12 mg

and 36 mg doses, respectively (92 and 313 ng/mL), which encompasses a range of potentially therapeutic and supratherapeutic doses.

The estimated population slope of the moxifloxacin concentration-ΔΔQTcF relationship was 0.0045 msec per ng/mL (90% CI: 0.0034 to 0.0055) with an intercept of 4.0 msec (90% CI: 2.32 to 5.64) (**Figure 9** and **Figure 10** below). Both the slope of the relationship and the intercept were statistically significant at the 0.1 level. Assay sensitivity was demonstrated by the QT effect of moxifloxacin with a statistically significant slope of the concentration-ΔΔQTc relationship and the lower bound of the 2-sided 90% CI of the predicted effect at the observed geometric Cmax above 5 msec.

No AEs or other safety findings were related to changes in ECG parameters during the study.

Figure 9 Plot of Model-Predicted ΔΔQTcF (Mean and 90% CI) and Observed ΔΔQTcF (Mean and 90% CI) across Deciles of Plasma Concentrations for Deucravacitinib (PK/QTc Set)

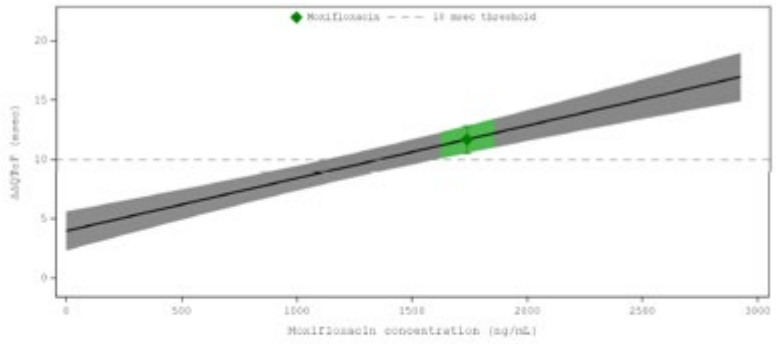


Source: IM011048 CSR, Figure 11.3-1[33]

CI= confidence interval; PK = pharmacokinetic

Note: Prediction was based on the model ΔΔQTcF=0.19 + [Concentrations of DEUC • 0.0059]. The red filled circles with vertical bars denote the observed mean ΔΔQTcF with 90% CI displayed at the median plasma concentration within each decile for DEUC. The solid black line with gray shaded area denotes the model-predicted mean ΔΔQTcF with 90% CI. The horizontal red line with notches shows the range of concentrations divided into deciles for DEUC. The distance between each decile represents the point at which 10% of the data is present; the first notch to second notch denotes the first 10% of the data, the second notch to third notch denotes the 10-20% of the data and so on.

Figure 10 Plot of Predicted ΔΔQTcF Interval at Geometric Mean Peak Moxibloxacin Concentrations (PK/QTc Set)



Source: IM011048 CSR, Figure 11.3-2[33]

CI = confidence interval; Cmax = maximum concentration; PK = pharmacokinetic

Note: Prediction was based on the model ΔΔQTcF=3.98 + Concentrations of moxifloxacin • 0.0045. The solid black line with gray shaded area denotes the model-predicted mean (90% CI) ΔΔQTcF. The green diamonds with shaded bands denote the estimated mean (90% CI) ΔΔQTcF at the geometric mean (90% CI) Cmax of moxifloxacin.

Relationship between plasma concentration and response

- Exposure-response (E-R) analysis (*Report: "Exposure-response analyses of deucravacitinib in subjects with moderate to severe psoriasis", Report Date: 14 July 2021)*

Moderate to severe psoriasis was defined as Psoriasis Area and Severity Index (PASI) ≥ 12, body surface area (BSA) involvement ≥ 10 %, and static Physician Global Assessment (sPGA) ≥ 3. The co-primary endpoints in the two Phase 3 studies were PASI 75 response and sPGA 0 or 1 (0/1) response at Week 16. (Excising sPGA response categories are sPGA of >1, 0 or 1 (0/1), and 0 [defined as clear skin]).

Exposure-response analyses for efficacy and safety were performed using data from the Phase 2 study IM011011 and Phase 3 studies IM011046 and IM011047 in patients with moderate to severe psoriasis.

- *Phase 2 study IM011011:* With the primary objectives: (i) Compare the proportion of patients experiencing a 75 % improvement as measured by reduction in PASI-75 score after 12 weeks of treatment between 5 doses of deucravacitinib and placebo. (ii) Assess the safety and tolerability of multiple oral doses of deucravacitinib. Planned sample size: 252 total, 42 per dose arm.
- *Phase 3 study IM011046 and IM011047:* With the primary objectives: Assess whether deucravacitinib is superior to placebo at Week 16, as measured by sPGA 0/1 and PASI 75 response. Planned sample size: 600 and 1000, respectively.

The E-R analyses of efficacy characterized the relationship of deucravacitinib and its major active metabolite, BMT-153261, exposure to the time course of the: (i) PASI score from baseline of 50%, 75%, 90%, and 100% (PASI 50/75/90/100) response, and (ii) sPGA 0 or 1 (0/1) response. The sPGA response categories were sPGA of >1, 0 or 1 (0/1), and 0 (defined as clear skin).

The E-R analyses of safety evaluated the potential association of drug exposure and the following selected safety endpoints of interest: overall infections and infestations, major adverse cardiovascular events (MACE), extended MACE, serious infections, herpes zoster infection, malignancies, and creatine phosphokinase (CK) grade 3 and above (Gr3+).

Overall, 1524 (99.7 %) and 1522 (99.6 %) patients were included in the PASI and sPGA analyses, and 1524 (99.7 %) in the safety analyses. In total, 838 patients received deucravacitinib 6 mg QD.

For efficacy analyses data up to 12 weeks (Phase 2 study) and 52 weeks (Phase 3 studies) were used. Placebo treated patients in Phase 3 studies were included up to week 16 and excluded from the analyses after week 16, although they were subsequently treated with deucravacitinib. For the Phase 3 Study IM011047, data from patients initially randomized to deucravacitinib treatment were included up to 24 weeks as some of the deucravacitinib treated patients switched treatment due to a randomized withdrawal design at Week 24.

For safety analyses, data from the placebo controlled parts of the studies (12 weeks for the Phase 2 study and 16 weeks for the Phase 3 studies) were used. The graphical exploratory analysis was also performed for up to Week 52 (Phase 3 studies deucravacitinib treated).

Model developments were performed sequentially first using only Phase 2 studies identifying the base model (functional form, i.e. a linear, log-linear, or Emax functions and best descriptor, i.e. $C_{min,ss}$, $C_{max,ss}$, $C_{avg,ss}$ for deucravacitinib, BMT-153261, or composite [deucravacitinib+BMT-153261]). Afterwards, all data (Phase 2 and 3) were included in the development process for covariate analyses (full and final model). BIC (limit of 2) was used for model selection.

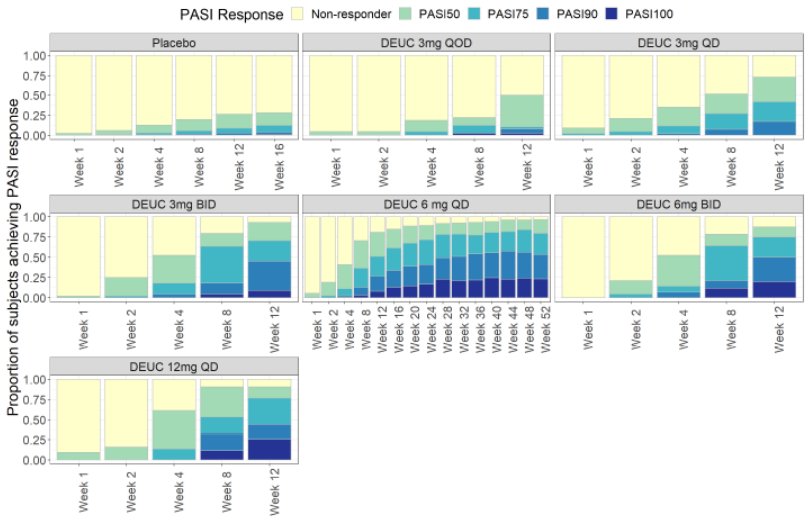
For efficacy analyses, the final model was used to predict a range of deucravacitinib exposures of $C_{avg,ss}$ from 0-100 ng/mL at week 16 or 24. For safety analyses, deucravacitinib exposure range of $C_{min,ss}$ from 0-60 ng/mL) at week 16 was generated.

Exposure measures ($C_{min,ss}$, $C_{max,ss}$, and $C_{avg,ss}$) were derived from the individual EBE of the PK parameters for each patient, obtained from the final population PK models, using the concentration time profile after 25 daily doses (> 16 maximum predicted half-life). Exposure for deucravacitinib, BMT-153261 and the composite exposure (total circulating active species) were generated, but BMT-153261 and composite exposure are missing for the 3 mg QD, BID, and QOD dosing regimens. The Exposure-response analyses were re-run using an updated PK model for deucravacitinib with more complex residual error models (Model "final-res2.2"), but results remain similar compared to the previous model. Thus, results are presented using the previous PK and exposure-response models.

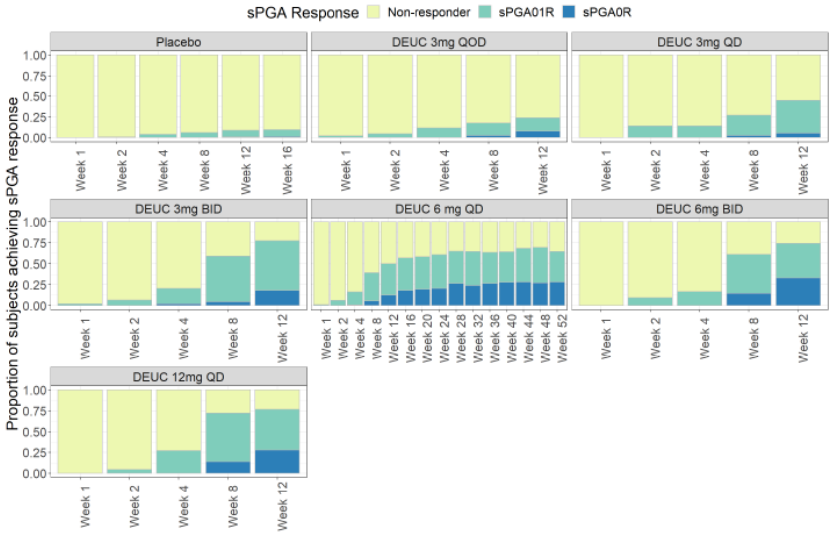
E-R for efficacy:

A summary of the observed proportion of responders for PASI and sPGA response by treatment and week are provided in **Figure 11**.

Figure 11 Proportion of responders – PASI (upper plots), sPGA (lower plots)



Abbreviations: BID = twice daily; DEUC = deucravacitinib; PASI 50/75/90/100 = 50/75/90/100% reduction in baseline PASI; QD = once daily; QOD = every other day.



Abbreviations: BID = twice daily; DEUC = deucravacitinib; sPGA01R = sPGA responder counts if 0 or 1; sPGA0R = sPGA responder counts if 0; QD = once daily; QOD = every other day.

The time course of PASI 50/75/90/100 responses were best characterized by a longitudinal ordered categorical logistic regression model with the temporal response described by a sigmoid model, and the E-R relationship by a hyperbolic (Emax) model with deucravacitinib $C_{avg,ss}$ as the measure of exposure. Covariates identified were sex and previous biologic use on Bmax, body weight on Emax, age, baseline PASI score, and smoking status on ET_{50}. Parameter estimates of the final model are listed in

Table 21 and the predicted probability of PASI 75 response by Cavg is shown in **Figure 12**.

The time course of sPGA responses were characterized by a longitudinal ordered categorical logistic regression model with the temporal response described by a sigmoid model, and the E-R relationship by a hyperbolic (Emax) model with deucravacitinib $C_{avg,ss}$ as the measure of exposure. Covariates identified were body weight on Bmax and ET_{50}, and region on Emax. Parameter estimates from the final longitudinal sPGA E-

R model are provided in **Table 22** and the predicted E-R curves for sPGA 0/1 response at Weeks 16 and 24 are shown in **Figure 13**.

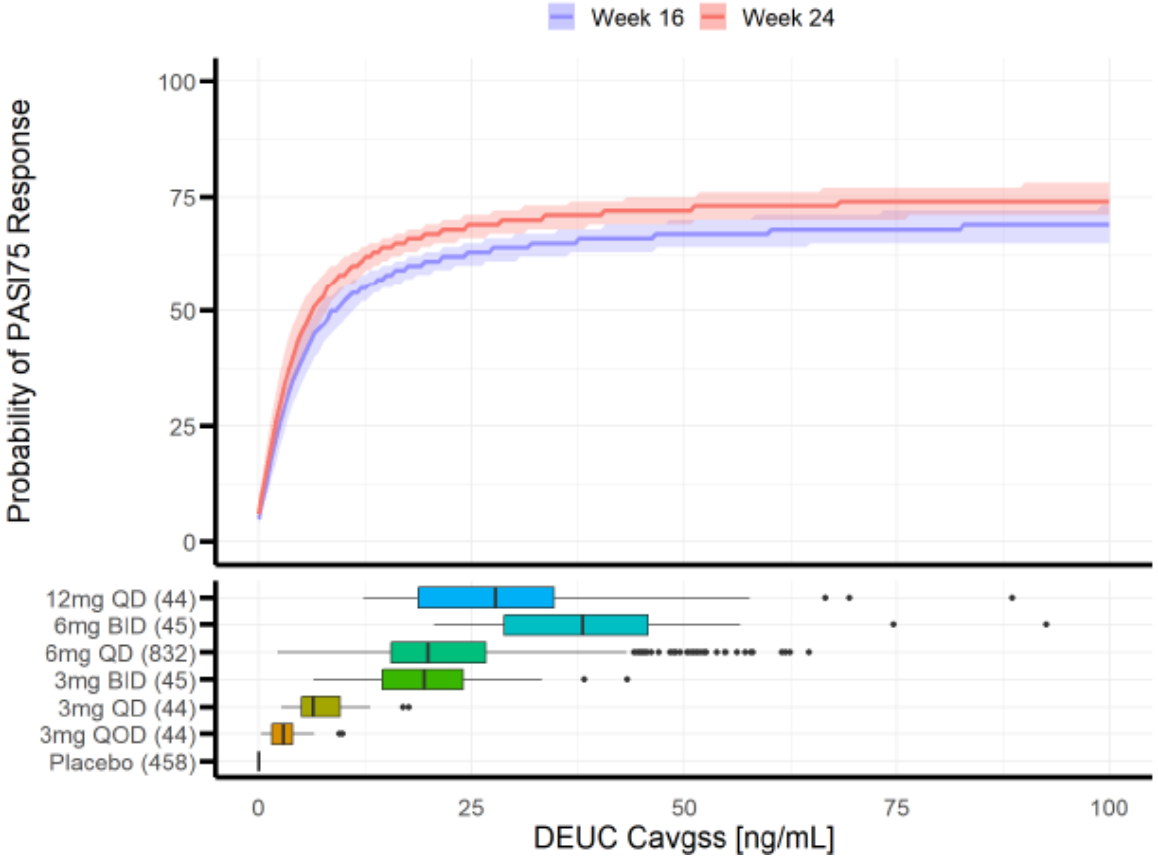
Table 21 Parameter estimates of the final E-R model - PASI

Parameter	Symbol	Parameter Estimate	Standard Error	RSE (%)	Median [95% CI]
B10: Baseline log-odds of placebo PASI 50 response	θ_1	-3.4	0.118	3.5	-3.41 [-3.65, -3.19]
B2: Difference in log-odds between PASI 50 and PASI 75	θ_2	2.56	0.0729	2.8	2.56 [2.43, 2.72]
B3: Difference in log-odds between PASI 75 and PASI 90	θ_3	2.57	0.0788	3.1	2.57 [2.43, 2.73]
B4: Difference in log-odds between PASI 90 and PASI 100	θ_4	2.92	0.126	4.3	2.93 [2.72, 3.19]
Emax: Maximal DEUC effect in log-odds	θ_5	14	1.21	8.6	14 [11.8, 16.1]
Ln(EC50): exposure achieving half of the maximal effect on log-odds [ng/mL] at log scale	θ_6	1.05	0.24	22.9	1.05 [0.477, 1.53]
GAM: Hill coefficient on DEUC effect	θ_7	1 FIX	-	-	1 [1, 1]
Bmax: Maximum log-odds of placebo PASI 50 response	θ_8	-1.59	1.11	70.1	-1.55 [-3.58, 0.555]
ln(ET50): Time achieving half of the maximal effect on log-odds [days] at log scale	θ_9	3.93	0.0777	2	3.93 [3.78, 4.08]
DELT (1/s): Steepness parameter on sigmoidal time term	θ_{10}	1 FIX	-	-	1 [1, 1]
Scaling factor for placebo IIV	θ_{11}	8.05	1.11	13.8	8.01 [6.24, 10.4]
Scaling factor for DEUC IIV	θ_{12}	4.3	0.191	4.4	4.3 [3.94, 4.67]
Biologic use on Bmax	θ_{13}	-1.05	0.289	27.5	-1.07 [-1.6, -0.514]
Female vs male on Bmax	θ_{14}	1.06	0.322	30.5	1.07 [0.492, 1.69]
Body Weight on Emax	θ_{15}	-0.0517	0.00835	16.2	-0.0525 [-0.0681, -0.0364]
Age on ET50	θ_{16}	0.0071	0.00249	35.1	0.00701 [0.0028, 0.0116]
Baseline PASI on ET50	θ_{17}	-0.0178	0.00508	28.5	-0.0172 [-0.0283, -0.00787]
Current smoker on ET50	θ_{18}	-0.195	0.0922	47.3	-0.193 [-0.383, -0.0266]
Previous smoker on ET50	θ_{19}	-0.364	0.115	31.6	-0.366 [-0.563, -0.141]
Missing smoking status on ET50	θ_{20}	-0.366	0.0894	24.5	-0.354 [-0.524, -0.182]
IIV on baseline log-odds of placebo PASI 50 response	ω_1^2	1 FIX	-	-	1 [1, 1]

Notes: Median and 95% CI were derived from bootstrap analysis. Condition number is 466.9.

Abbreviations: Bmax = maximal placebo effect; CI = confidence interval; DEUC = deucravacitinib; EC50 = concentration corresponding to half of the maximal drug effect; Emax = maximal drug effect; ET50 = time to achieve half of the maximal drug effect; IIV = inter-individual variability; PASI = Psoriasis Area and Severity Index; PASI 50/75/90/100 = reductions in PASI score from baseline of 50%, 75%, 90%, and 100%, respectively; RSE = relative standard error

Figure 12 Predicted median (90 % PI) probability of PASI 75 response versus $C_{avg,ss}$ by visit



Notes: Solid curve on upper panel gives the median PASI 75 probability for Week 16 or 24 with a ribbon showing the corresponding 90% prediction interval. The boxplots at the bottom represent the exposure range achieved by each dosing regimen

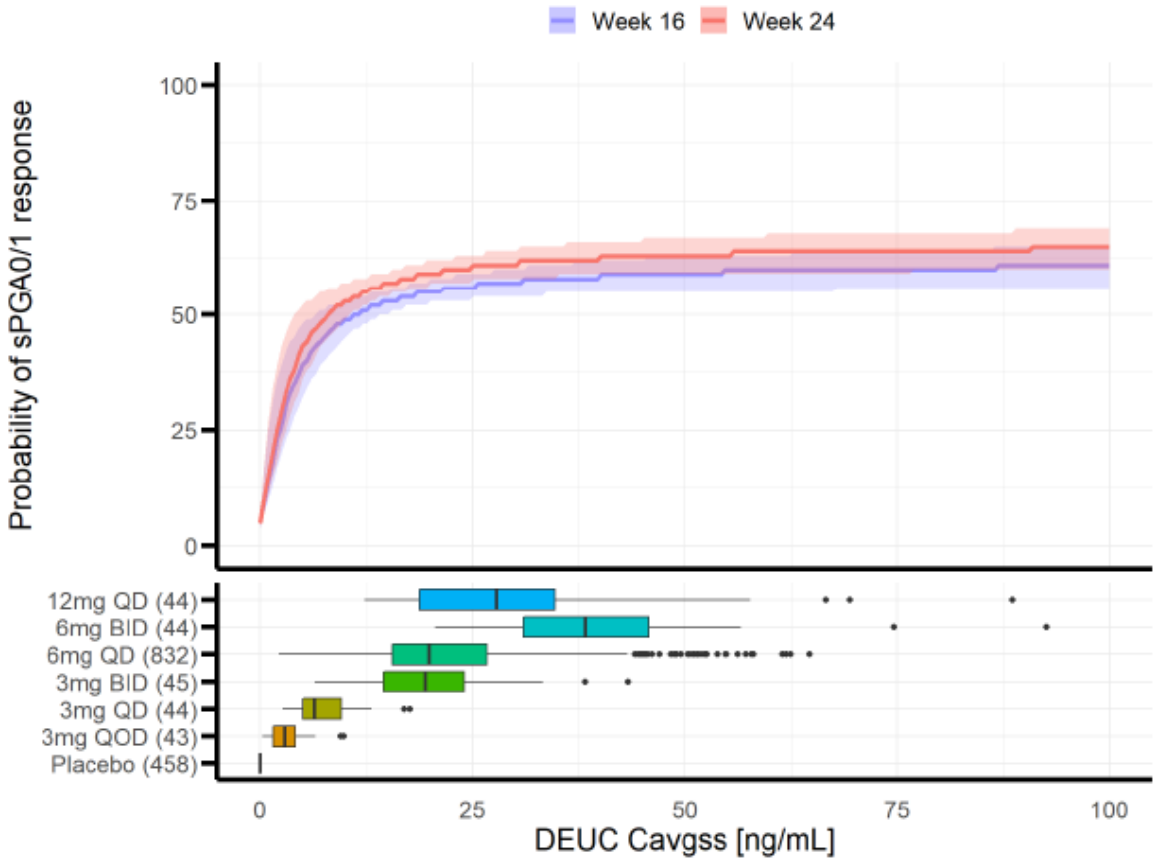
Table 22 Parameter estimates of the final E-R model - sPGA

Parameter	Symbol	Parameter Estimate	Standard Error	RSE (%)	Median [95% CI]
B10: Baseline log-odds of placebo sPGA response	θ_1	-4.54	0.192	4.2	-4.55 [-4.94, -4.2]
B2: Difference in log-odds between sPGA0 and sPGA1	θ_2	3.85	0.119	3.1	3.84 [3.61, 4.11]
Emax: Maximal DEUC effect in log-odds	θ_5	13.7	0.882	6.4	13.9 [12.1, 15.5]
Ln(EC50): exposure achieving half of the maximal effect on log-odds [ng/mL]	θ_6	0.565	0.416	73.6	0.581 [-0.838, 1.2]
GAM: Hill coefficient on DEUC effect	θ_7	1 FIX	-	-	1 [1, 1]
Bmax: Maximum log-odds of placebo sPGA response	θ_8	-4.77	0.791	16.6	-4.84 [-6.38, -3.41]
Ln(ET50): Time achieving half of the maximal effect on log-odds [days]	θ_9	3.56	0.104	2.9	3.56 [3.34, 3.76]
DELT (1/s): Steepness parameter on sigmoidal time term	θ_{10}	1 FIX	-	-	1 [1, 1]
THETA(11): Scaling factor for placebo IIV	θ_{13}	10.3	1.01	9.8	10.4 [8.29, 12.4]
THETA(12): Scaling factor for DEUC IIV	θ_{14}	3.9	0.217	5.6	3.87 [3.48, 4.32]
WT on BMAX	θ_{15}	-0.0316	0.009	28.5	-0.0326 [-0.0518, -0.015]
REGION (US vs EU) on Emax	θ_{16}	-2.05	0.408	19.9	-2.07 [-2.9, -1.31]
REGION (ROW vs EU) on Emax	θ_{17}	-0.483	0.37	76.6	-0.497 [-1.16, 0.21]
WT on ET50	θ_{18}	0.00605	0.00253	41.8	0.00587 [0.000105, 0.011]
IIV on baseline log-odds of placebo sPGA response	ω_1^2	1 FIX	-	-	1 [1, 1]

Notes: The 95% CI is derived from bootstrap analysis. The condition number is 315.3.

Abbreviations: Bmax = maximal placebo effect; CI = confidence interval; DEUC = deucravacitinib; EC50 = concentration corresponding to half of the maximal drug effect; Emax = maximal drug effect; ET50 = time achieving half of the maximal effect; EU = European Union; IIV = inter-individual variability; ROW = rest of the world; sPGA = Static Physician's Global Assessment; US = United States.

Figure 13 Predicted median (90 % PI) probability of sPGA 0/1 response versus $C_{avg,ss}$ by visit



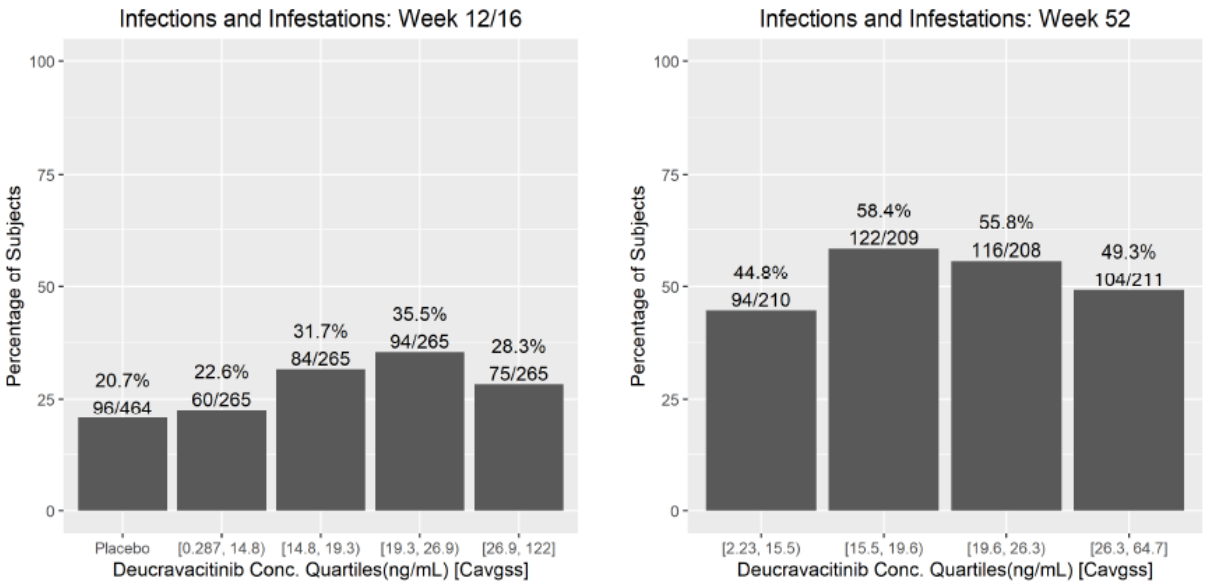
Notes: Solid curve on upper panel gives the median sPGA01 probability for Week 16 or 24 with a ribbon showing the corresponding 90% prediction interval. The boxplots at the bottom represent the exposure range achieved by each dosing regimen

E-R for safety:

Overall, there were 4 (0.3 %) MACE, 5 (0.3 %) extended MACE, 8 (0.5 %) serious infections, 64 (4.2 %) CK Grade 2+, 24 (1.6 %) CK Grade 3+ events, 2 (0.1 % malignancies, 409 (26.8%) total infection events up to and including Week 16 (n =245 (29.2%) out of the 838 patients in the deucravacitinib 6 mg QD treatment).

An E-R relationship was observed between deucravacitinib or BMT-153261 exposure and the occurrence of infections/infestations at Week 12/16, whereas the E-R trend at Week 52 was not as clear (**Figure 14).**

Figure 14 Percentage of infections/infestations by deucravacitinib $C_{avg,ss}$



Note:
Week 12/16 plots include AE events for patients originally randomized to deucravacitinib treatment or placebo in Phase 2/3 studies for the period during which the patient did not switch treatment. The events occurring after the patients switch treatment are not accounted in this analysis.
Week 52 plots include AE events only from patients originally randomized to deucravacitinib treatment in Phase 3 studies for the period during which the patient do not switch treatment. The events for placebo subjects or the events occurring after the subjects switch treatment are not accounted in this analysis.

The probability of infection and infestation at Week 12/16 was characterized by a logistic regression model, in which the E-R relationship was described by a hyperbolic (Emax) model with deucravacitinib $C_{min,ss}$ as the measure of exposure. Covariates identified were previous biologics use and baseline BSA on Emax, and age on placebo effect. Parameters estimates for the final model are presented in **Table 23** and predicted probabilities of infections and infestations by $C_{min,ss}$ are shown in **Figure 15**.

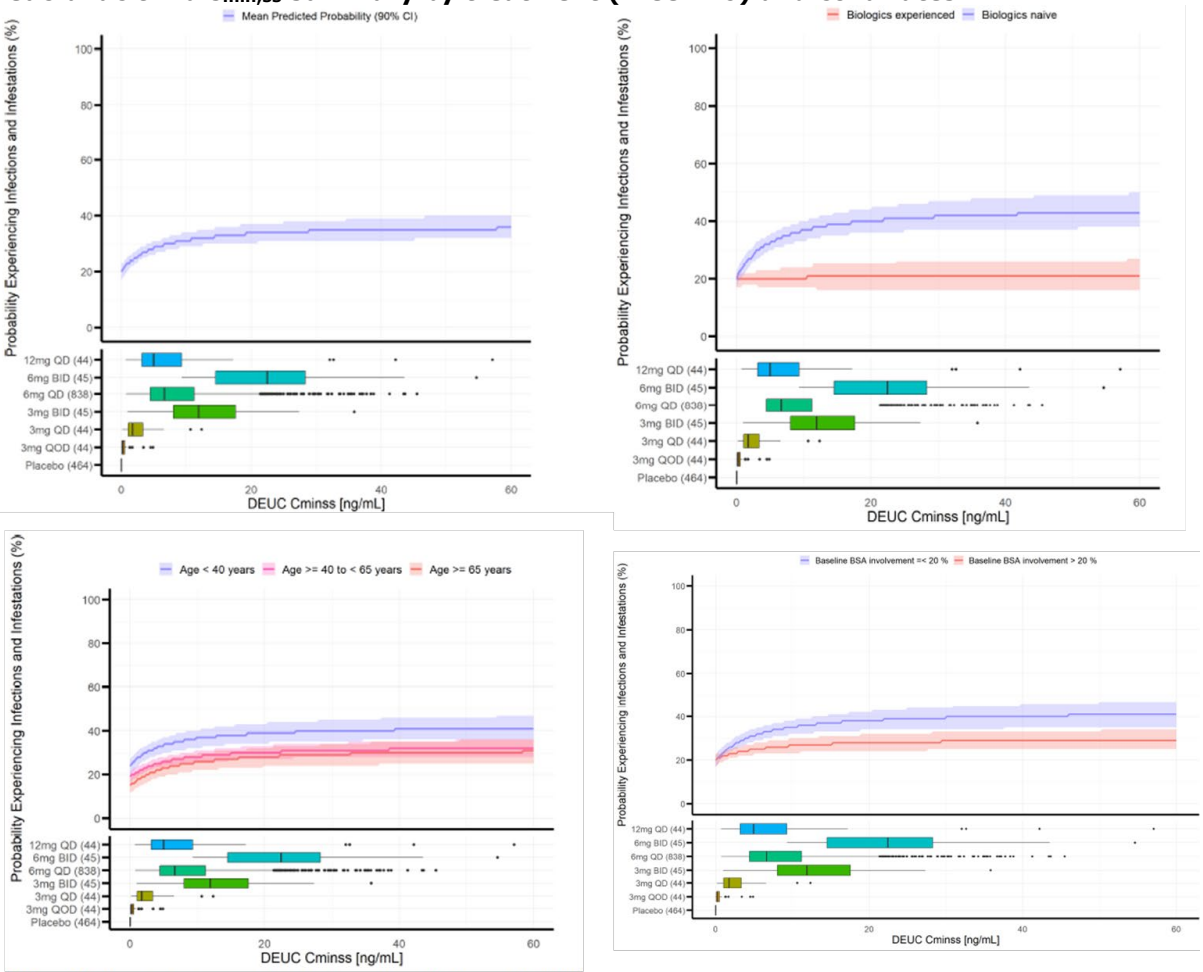
Table 23 Parameter estimates of the final exposures-safety model for infections/infestations

Parameter	Symbol	Parameter Estimate	Standard Error	RSE (%)	Median [95% CI]
RPCB: Placebo effect	θ_1	-1.4	0.108	7.7	-1.3 [-1.55, -1.1]
Emax: Maximal DEUC response on log-odds scale	θ_2	1.31	0.237	18	1.33 [0.902, 1.94]
ln(EC50): exposure achieving half of the maximal response on log-odds scale [ng/mL]	θ_3	1.36	0.429	31.6	1.37 [0.542, 2.24]
GAM: Hill coefficient on DEUC effect	θ_4	1 FIX	-	-	1 [1, 1]
Effect of previous biologic use on maximal DEUC response	θ_7	-1.08	0.258	-23.8	-1.1 [-1.78, -0.604]
Effect of baseline BSA involvement on maximal DEUC response	θ_8	-0.0256	0.009	35.2	-0.0265 [-0.0513, -0.0108]
Effect of age on placebo effect	θ_9	-0.0145	0.004	30.5	-0.0145 [-0.0249, -0.00573]

Notes: The 95% CI is derived from bootstrap analysis. The condition number is 22.12.

Abbreviations: BSA = body surface area; CI = confidence interval; DEUC = deucravacitinib; EC50 = concentration corresponding to half of the maximal drug effect; Emax = maximal drug effect; RSE = relative standard error.

Figure 15 Model-predicted median (90% PI) probability of infections/infestations vs $C_{min,ss}$ and deucravacitinib $C_{min,ss}$ summary by treatment (Week 16) and covariates



Notes: Solid curve on upper panel gives the median infections probablilty for with a ribbon showing the corresponding 90% prediction interval.

Abbreviations: BID = twice daily; Cminss = minimum concentration during a dosing interval; DEUC = deucravacitinib; QD = once daily; QOD = every other day; mg = milligram.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Population PK modelling

The PKs of deucravacitinib and its major active metabolite BMT-153261 were investigated in healthy volunteers and patients with moderate to severe psoriasis, using modelling and simulation techniques. For each compound a population PK model was developed in order to characterise and predict the PK of deucravacitinib and BMT-153261, obtain exposure metrics for E-R analyses of efficacy and safety, and finally to support dose selection. PK data from healthy volunteers and patients with psoriasis (from Phase 1, 2 and 3 studies across a broad dose range of deucravacitinib) were used for the analyses. The Bayesian information criterion (BIC) was used for selection of structural models and for assessment of covariates and a sensitivity analysis was performed using the likelihood ratio test (LRT). Overall, the modelling strategy and used data

are considered acceptable. The descriptive and predictive performance of the developed population PK models were investigated using commonly used methods.

For deucravacitinib: the PK of deucravacitinib was described by a two-compartment model with sequential zero-and first-order absorptions with a lag time and linear clearance (CL). In general, the population typical values were precisely estimated (low RSE% <20%, except for Tlag where RSE was 22.4%). However, several covariate effects were poorly estimated: CLCr as covariate on CL/F, subject type on V2, formulation on Ka, with RSE of 25.9, 30.8 and 37.5%. Importantly, the proportional error in patients, estimated at 49.2 %, is considered high. In addition, eta shrinkages with values of 51.6 % (ω^2LF), and 53.5 % (ω^2V2) are considered high. Mean model-based oral bioavailability after administration of 12 mg was estimated at 87.4 % (95% CI's: 77.4%, 91.8%) and therewith lower than the value of 99 % obtained from the absolute bioavailability study (IM011067) in healthy volunteers. The applicant provided a discussion on possible reasons for these differences (i.e. heterogeneous study population in Phase 3 studies, use of Emax function on the absorption process, and correlation to estimation of CL). Overall, as CL/F appears to be well estimated as evidenced by the good agreement between observed and predicted trough, the adequate capture of plasma concentration profiles, the impact of such difference on model estimated exposures is not expected to be clinically meaningful. Moreover, both values are higher than 85 %, thus overall indicating near complete drug absorption. The geometric mean terminal half-life of deucravacitinib in patients with PsO was determined by population PK analysis at 16.2 h, thus modestly higher (14%) than the predicted half-life in healthy volunteers (i.e. 14 h).

For BMT-153261: the PK of the active metabolite BMT-153261 was developed separately but linked to the deucravacitinib PK via the metabolite conversion fraction of 0.22. The Applicant explained that this fraction was based on in vitro and C_{14} ADME studies that indicated approximately 18.5%-24.5% of deucravacitinib dose is converted to BMT-153261. A number of covariates were identified to be statistically significant. But several covariate effects were poorly estimated (e.g. covariate relationship of race2 on clearance RSE = 126), and as for the deucravacitinib model, the proportional residual error in patients, is deemed high estimated at 34.3 %. The Applicant explained that for BMT-153261 population PK modelling, samples with a time after previous dose greater than 72 h were excluded for model stability.

At the CHMP request, the applicant refined and updated the PK models. With the updated model, the number of model parameters increased by five (plus the fixed Tmax parameter), compared to the previous model, but the model performance was comparable with the previous model and exposures remained similar.

Therefore, the initial model is considered final, although the population PK models show some deficiencies, the overall results and predictive performance is considered sufficient to provide supporting information on the expected PK behaviour, exposures, as well as exposure-response for efficacy and safety.

Special populations

Renal impairment:

A "full-range" renal impairment (RI) study **(IM011061)** was performed to evaluate the PK and safety of deucravacitinib in subjects with mild, moderate, severe RI and in subjects with ESRD on hemodialysis compared to matched healthy volunteers. A single dose of 12 mg was administered which is higher than the clinically recommended dose. Due to linear PK, the study results are also considered applicable to the lower recommended dose.

Initially, subjects were classified according to the BSA-normalized GFR (ml/min/1.73 m^2). Since renal elimination capacity is related to absolute GFR (ml/min), the applicant was asked to perform a recalculation

and present study results per absolute GFR, in accordance with the EMA guideline (EMA/CHMP/83874/2014). The Applicant provided the requested analyses. The study measured concentrations of deucravacitinib and its two major metabolites: active BMT-153261 and inactive BMT-158170. Fraction unbound was also measured for active moieties. A modest increase in fraction unbound was observed only in ESRD group dosed pre-dialysis for both deucravacitinib and BMT-153261.

Results (based on either absolute or BSA normalized GFR classification) show that RI did not have a significant impact on Cmax for both active compounds, except for BMT-153261 in the severe renal impairment group in which subjects displayed a moderate increase (34%) in Cmax compared to normo-renal subjects. AUC generally increased with increasing degree of renal impairment: up to 1.48-fold for deucravacitinib (in the moderate RI group) and up to 1.84-fold for BMT-153261 (in the severe RI group). According to the exposure-safety analysis, a 2-fold increase in deucravacitinib or BMT-153261 exposure would not lead to clinically meaningful changes in safety and the applicant proposes no dose adjustment in any degree of renal impairment, including patients on dialysis. Taking these elements into account, the proposed dosing recommendations is considered acceptable. However, doctors and prescribers have to be clearly informed about the systemic overexposure on deucravacitinib and BMT-153261 in renally impaired patients. These information are detailed in sections 4.2 and 5.2 of the SmPC. In addition, only a limited amount of deucravacitinib was extracted via dialysis (< 6%), this is adequately reflected in the SmPC sections 4.9 and 5.2.

For the inactive metabolite BMT-158170, Cmax and AUC both increased with increasing degree of renal impairment up to 1.65-fold and 4.16-fold, respectively in ESRD subjects. Since this metabolite is not pharmacologically active, not genotoxic and has no DDI liabilities at these exposures, it is not considered that it would have an impact on safety.

The trends in model predicted total deucravacitinib and BMT-153261 exposures were generally similar to observed trends.

Hepatic impairment:

A "full-range" hepatic impairment (HI) study was performed to evaluate the PK and safety of deucravacitinib in subjects with mild, moderate and severe HI (using Child-Pugh classification) compared to matched healthy volunteers. A single dose of 12 mg was administered which is higher than the clinically recommended dose. Due to linear PK, the study results are also considered applicable to the lower recommended dose.

The study measured concentrations of deucravacitinib and its two major metabolites: active BMT-153261 and inactive BMT-158170. Fraction unbound was also measured for active moieties. Linear regression analysis was performed to explore the relationship between clinical laboratory parameters contributing to Child-Pugh scores (bilirubin, prothrombin time and albumin) and PK parameters of deucravacitinib and BMT-153261.

Results show that hepatic impairment did not have a significant impact on Cmax of total deucravacitinib. AUC was higher in subjects with moderate and severe hepatic impairment (up to 1.43-fold). Increases in unbound deucravacitinib concentrations were similar to increases in total concentrations for mild and moderate HI groups. Unbound Cmax and AUCinf in subjects with severe HI were 1.62- and 2.31- fold higher compared to matched subjects with normal hepatic function. Linear regression analysis indicated that deucravacitinib AUC correlated with increasing Child-Pugh score. Some correlation was also found between Child-Pugh score individual components (albumin, bilirubin, prothrombin time) and deucravacitinib exposure.

The exposure of the active metabolite BMT-153261 decreased with increasing degree of HI, likely due to lowering of metabolic capacity via CYP1A2 in HI; Cmax decreased up to 79% and AUC up to 76% in subjects

with severe HI. Increases in unbound BMT-153261 concentrations were similar to increases in total concentrations for all HI groups. Linear regression analysis indicated that BMT-153261 Cmax and AUC correlated with increasing Child-Pugh score. Some correlation was also found between Child-Pugh score individual components (albumin, bilirubin, prothrombin time) and BMT-153261 exposure.

Since parent exposure is increased and active metabolite exposure decreased in subjects with HI, an analysis of PK parameters of the total circulating active moieties was performed. Based on this analysis, no loss of efficacy is expected despite the substantial decrease in exposure of the active metabolite, as the contribution of the active metabolite to the total activity is minor (~18%). For patients with mild and moderated hepatic impairment no dose adjustment is proposed. However, prescribers and doctors have to be informed of the systemic overexposure on deucravacitinib exposure (+40 and 60% for total and unbound fraction) in patients with moderate hepatic impairment and this is reflected in section 5.2 of the SmPC. As deucravacitinib unbound AUCinf was increased more than 2-fold in subjects with severe HI the use in those patients is not recommended, these information are included in sections 4.2 and 5.2 of the SmPC.

The exposure of the inactive metabolite BMT-158170 was only modestly decreased, probably due to its formation via CES2 enzyme which is available in the extrahepatic tissues, such as blood cells and kidney.

The trends in model predicted total deucravacitinib and BMT-153261 exposures were generally similar to observed trends.

Gender:

Gender was identified as a statistically significant covariate on clearance and volume of distribution for deucravacitinib. As such, the exposure ($C_{max,ss}$ and $C_{avg,ss}$) is expected to be roughly 30 % higher in females compared to males. Exposure increase up to 2-fold (100 %) appear to be safe, therefore, no dose adjustments are warranted based on gender. However, the observed increase in exposure has to be communicated to the prescribers and is detailed in the SmPC (section 5.2).

Race / Ethnicity:

Race was not a statistically significant covariate in the population PK model for deucravacitinib, but on BMT-153261. Based on the presented simulations, exposure of deucravacitinib ($C_{max,ss}$ and $C_{avg,ss}$) seem to be about up to 14% between White, Asian, Blacks and others. For BMT-153261, exposures are similar between these subpopulations. Furthermore, model-predicted expected exposures were compared between Japanese and Non-Japanese, and Korean, other Asian and non-Asian patients receiving 6 mg deucravacitinib QD. Results reveal similarity between these populations. Exposure increase up to 2-fold (100 %) appear to be safe. Therefore, no dose adjustments is proposed for patients of different ethnicities/races.

Body weight:

Body weight was a statistically significant covariate on clearance and volume of distribution of the central compartments of deucravacitinib and BMT-153261. In the model, typical body weight of 80 kg was assumed. The systemic exposure for deucravacitinib is expected to increase in patients with lower body weight (<60kg) and decrease in patients with higher body weight (>90kg). The increase in exposure of deucravacitinib ($C_{max,ss}$) and BMT-153261 ($C_{max,ss}$ and $C_{avg,ss}$) for patients with a lower body weight exceeds 25 %. Nevertheless, exposure increase up to 2-fold (100 %) appear to be safe. Therefore, no dose adjustment is proposed based on body weight. However, the observed change in exposure has to be communicated to the prescribers and is detailed in the SmPC (section 5.2).

Elderly

As requested by CHMP, the table detailing the number of older patients per age ranges (age 65-74, 75-84, and 85+) and per PK studies was provided.

Age was a statistically significant covariate on clearance of deucravacitinib and BMT-153261. This results in an increase of mean $C_{avg,ss}$ (31%) in patients aged 65-74 years [n= 87 of 1387 (6.3 %)] and an increase of $C_{max,ss}$ (33%) and $C_{avg,ss}$ (53%) in patients aged 75-84 years [n= 13 of 1387 (0.94 %)]. Exposure increase up to 2-fold (100 %) appear to be safe. Therefore, no dose adjustment is proposed based on these two subgroups of age. However, section 5.2 of the SmPC was updated to clearly reflect the expected systemic overexposure in elderly patients, and mention that exposure in subjects ≥85 years of age are not available. In addition, section 4.2 of the SmPC was updated to mention that clinical experience in patients ≥ 75 years is very limited and deucravacitinib should be used with caution in this group of patients.

However, it is noted that acceptance of up to 2-fold increased exposure in some groups of patients is not generally appreciated from the PK point of view. The fact that only one dose / strength as a film-coated tablet was selected to be investigated in pivotal trials is not ideal. It was missed to further investigate whether some patients could benefit from dose adjustments and the current drug formulation also does not allow any. With the proposed ”one-fits-all” dosing of 6 mg QD, some patients will be exposed to unnecessarily higher concentrations, much higher than needed to achieve levels that are efficacious, while other individuals could be at risk of under-dosing (e.g. patients with higher body weight). Nonetheless, these risks appear to be covered by the flat exposure-response relationships for efficacy and safety.

Pharmacokinetic drug-drug interactions

Deucravacitinib undergoes a metabolism through two main enzymes CYP1A2 and CES2 leading to two main metabolites, BMT-153261 and BMT-158170, respectively. These major circulating metabolites represent more than 10% of total drug-related exposure at steady state in humans. Other minor pathways involved CYP2B6, CYP2D6, UGT1A9 and, in a lesser extent, CYP3A4.

Based on in vitro data, 13 dedicated in vivo DDI studies were conducted to assess the magnitude of the potential interactions with deucravacitinib in the clinical setting.

The effect of deucravacitinib (as perpetrator) on exposures of concomitant medications like rosuvastatin, methotrexate, mycophenolate mofetil (MMF) or oral contraceptives (norethindrone acetate and ethinyl estradiol) was assessed. Results show that clinically relevant interaction are not expected.

The effect of cyclosporine (dual P-gp/BCRP inhibitor), fluvoxamine (CYP1A2 inhibitor), ritonavir (CYP1A2 inducer), diflunisal (UGT 1A9 inhibitor), pyrimethamine (OCT1 inhibitor), or gastric pH modulating agents like famotidine or rabeprazole, on deucravacitinib exposure (as a victim) were also evaluated. Clinically relevant interaction were ruled out.

The applicant provided a comprehensive evaluation of a potential for DDIs with deucravacitinib. In summary, based on the results from *in vitro* and *in vivo* studies, the potential for deucravacitinib to cause clinically significant interactions with other concomitant medication is low. Deucravacitinib is eliminated via multiple different pathways and it was shown that blocking any of those pathways does not result in clinically meaningful changes in its exposure. In the opposite direction, deucravacitinib was not shown to have effect on exposures of BCRP and OATP1B3 substrates, as well as other concomitant medication (methotrexate, mycophenolate mofetil and oral contraceptives). This is appropriately reflected in section 4.5 of the SmPC.

Pharmacodynamics

Mechanism of action

Deucravacitinib showed an IC50 of 0.2 nM and a KD of 0.02 nM for the interaction with TYK2 pseudokinase compared to an IC50 = 0.95 nM and a KD of 0.33 nM for the pseudokinase domain of JAK1.

Deucravacitinib selectively inhibits the TYK2 pathway (average daily inhibition of 50-71%) at doses up to 12 mg QD with a higher inhibition of TYK2 at 12 mg QD compared to 6 mg QD. This should have been explored for the selection of dose in the Phase 2 study but in place of 6 mg QD, 3 mg BID was tested.

Deucravacitinib did not meaningfully inhibit JAK1/3 and JAK2 pathways at doses up to 12 mg QD. In contrast, upadacitinib, baricitinib and tofacitinib inhibited the JAK1/3 and JAK2 pathways as expected, but did not meaningfully inhibit the TYK2 pathway at clinically relevant doses.

These data are considered convincing for a selective inhibition of TYK2 by deucravacitinib. Deucravacitinib mechanism of action is detailed in section 5.1 of the SmPC.

Primary pharmacology

The pharmacodynamic analyses from skin biopsies and whole blood of healthy and psoriatic subjects showed that deucravacitinib treatment led to suppression of the IL- 23/Th17 pathway and keratinocyte activation, as well as reduction in Type I IFN-response genes in the skin of patients with moderate to severe psoriasis with an effect increasing from 3 mg QD to 6 mg BID. The dose of 12 mg BID did not lead to higher effects of deucravacitinib compared to 6 mg BID.

The effect of deucravacitinib on transcriptome profiles of skin biopsy and circulating whole blood in participants enrolled in Study IM011-011 were assessed with beta-defensin, IL-17A and IL-19 chosen as biomarkers of primary interest as they have shown correlation with PASI and BSA scores. Therefore IL-19 and beta-defensin are acceptable biomarkers of psoriasis disease as downstream markers of IL-23 activity through the Th17 cell activation. Treatment with deucravacitinib reduced levels of IL-19, IL-17A and beta-defensin. However, IL-17 expressed at lower levels than IL-19, changes correlated with the therapeutic response were difficult to capture, limited to the lower limits of quantification. Therefore IL-17 could not be accepted as a biomarker for deucravacitinib.

Overall, PD data provided from biomarkers of psoriasis disease corroborate a TYK2 inhibition by deucravacitinib with doses ≥ 3 mg QD even if this Phase 2 study had some limitations (e.g. gene expression may not necessarily reflect the levels of protein expression in the skin. Besides only a relatively small number of skin biopsy samples were available for evaluation). Due to the relatively short study duration (12 weeks), long-term effects of deucravacitinib treatment were not studied.

Secondary Pharmacodynamic

The TQT study IM011048 fulfilled the requirements of central tendency to conclude that deucravacitinib meets the ICH E14 criteria of a negative TQT study since the upper limits of one sided 2-sided 95% CI for deucravacitinib–placebo difference in QT_{cF} prolongation at all postdose time points were below 10 msec. Deucravacitinib at supratherapeutic doses of 12 mg and 36 mg did not cause clinically meaningful prolongation of QT interval, and did not have an effect on other relevant ECG parameters. Sensitivity of the assay was demonstrated by the QT prolongation observed with moxifloxacin as a positive control. Moreover, the results of the categorical analysis of QTcF interval data from Study IM011048, performed per the ICH E14 guidance, support the assertion that IM011048 was a negative TQT study.

Although no pharmacodynamics interaction was performed, a potential one was suspected between deucravacitinib and ethinylestradiol. During the study IM011039 with deucravacitinib and EE/norethindrone, an increase in hepatic transaminases (ALT and AST) was reported in 6 subjects. An additional discussion by the Applicant on the lack of meaningful changes from baseline in ALT and AST in Phase 3 studies in subjects with psoriasis (IM011046 and IM011047) which included women of child-bearing potential on oral contraceptives, allow to consider that no further action is presently needed however this should be closely monitored as part of the forthcoming PSURs.

Inflammatory cytokines are up-regulated in psoriasis patients and could induce suppression of CYP metabolizing enzymes. When patients improve upon treatment and their cytokine levels normalize, CYP activity could also restore leading to an increase in metabolism of concomitantly administered medication. In the EMA scientific advice there was a recommendation to investigate such modulation of CYP activity during Phase 3 trials. The applicant provided a systematic evaluation of deucravacitinib potential to modulate CYP activity via downregulation of cytokines. The assessment indicated a minimal potential. In summary, the conclusion is based on the following arguments: psoriasis patients show lower systemic inflammation and lower levels of proinflammatory cytokines compared to other autoimmune diseases (such as rheumatoid arthritis); mechanism of action of deucravacitinib is via TYK2 inhibition and it is not expected to cause CYP450 activity modulation; no changes in deucravacitinib PK were observed with time that would indicate a change in drug metabolizing enzyme activity.

Exposure-Response (E-R) analysis

The relationship between deucravacitinib exposure and key measures of efficacy (PASI and sPGA response) and selected safety endpoints in Phase 2/3 studies were characterized by E-R analyses. The Applicant performed an Exposure-Response analysis based on the average concentration of deucravacitinib at steady state (Cavgss) for predicting PASI 75 and s-PGA response, regardless of QD or BID dosing to finally select the dose of 6 mg QD.

The E-R modelling described E-R relationship by a hyperbolic (Emax) model with PASI 75 and sPGA 0/1 responses achieving a plateau with increase in exposure. Model predicted probability of PASI 75 and sPGA 0/1 at Week 16 for 6 mg QD dose was close to maximal response.

Model-based results reveal that exposure-response relationships for efficacy and safety measures are relatively flat for Cavg,ss and Cmin,ss, respectively. The probability of infections and infestations with increasing exposure seem to approach a limit from approximately 20 ng/mL Cmin,ss and onwards. Thus an increase in exposure doesn't seem to be associated with a remarkable change in safety (doses up to 12 mg QD or 6 mg BID). The results and totality of data indicates that a deucravacitinib dose of 6 mg QD is optimal in patients across all subpopulations.

As requested by the CHMP, the effect of gender, race / ethnicity and body weight were reassessed using model-based predictions from the updated population PK models. The Applicant provided a discussion and concluded that flat dose of 6 mg QD is recommended in all patients regardless of gender, race/ethnicity and body weight (see discussion above).

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of deucravacitinib has been sufficiently characterized in healthy volunteers and in the target population with moderate to severe psoriasis based on formal phase 1 and 2 studies. The provided

population PK analyses showed some misspecifications, but overall, was deemed sufficient to support PK characterisation and exposure-response information by the CHMP.

Overall, the recommended 6 mg QD dosing is acceptable from a PK perspective. A flat dosing across all patients, including some specific groups (i.e. renal impairment, moderate hepatic impairment, elderly, and underweighted) can be proposed, as the observed and expected increase in exposure is less than 2-fold (100 %). This decision is supported by the flat exposure-response relationships for efficacy and safety and findings that a 2-fold increase in systemic exposure is not expected to lead to meaningful changes in the safety profile. In addition, clear information regarding the magnitude of systemic overexposure in some patient populations is adequately reflected in the SmpC.

Regarding drug-drug interaction, the Applicant performed a complete drug-drug interaction development and the overall assessment of DDI data show that deucravacitinib can be co-administered with other medicinal products without dose recommendation.

The mode of action of deucravacitinib as a selective inhibitor of TYK2 is considered demonstrated with little effect on other JAK family kinases.

No major safety issues have been identified following the assessment of the TQT study.

Appropriate information relevant for the prescribers and patients has been included in the SmPC and package leaflet accordingly. The dossier is considered approvable from a clinical pharmacology perspective.

2.6.5. Clinical efficacy

The clinical development program for DEUC in psoriasis includes 4 clinical efficacy studies:

- 1 completed dose-finding, placebo-controlled, 12-week Phase 2 study IM011011,
- 2 completed pivotal, double-blind, placebo- and active-controlled 52-week, Phase 3 studies, IM011046 and IM011047,
- 1 ongoing Phase 3 open-label, long-term extension (LTE) study, IM011075.

Table 24 Phase 2 and Phase 3 Clinical Studies of Deucravacitinib in Psoriasis and Psoriatic Arthritis Included in the Summary of Clinical Efficacy

Study Information	Population	Design	Efficacy Endpoints	Test Drugs and Dose	No. of Subjects
Placebo-Controlled Phase 2 Studies					
IM011011 (Phase 2) FPFV: 15-Nov-2016; LPLV for the Final CSR: 16-Nov-2017 67 sites in EU, North America (Canada and US), Australia, Mexico, and Japan Completed	Subjects with moderate-to-severe plaque psoriasis	12 week, randomized double-blind, placebo- controlled dose-ranging study 1:1:1:1:1:1 randomization to DEUC (3 mg QOD, 3 mg QD, 3 mg BID, 6 mg BID, or 12 mg QD) or placebo	**For DEUC compared with Placebo** Primary: PASI 75 at Week 12 Key Secondary and Additional: PASI 50, PASI 75, PASI 90, and PASI 100 over 12 weeks sPGA 0/1 at Week 12 Improvement in PRO over 12 weeks: DLQI 0/1	DEUC: 3 mg QOD 3 mg QD 3 mg BID 6 mg BID 12 mg QD **Placebo** QOD, QD, or BID PO	267 subjects randomized and treated: **DEUC** 3 mg QOD (44) 3 mg QD (44) 3 mg BID (45) 6 mg BID (45) 12 mg QD (44) **Placebo** (45)

Study Information	Population	Design	Efficacy Endpoints	Test Drugs and Dose	No. of Subjects
Placebo- and Active-Controlled Phase 3 Studies					
IM011046 (Phase 3) FPFV: 07-Aug-2018; LPLV for the Primary CSR: 02-Sep-2020 154 sites in US, China, Japan, EU (Germany, Poland, Spain, UK), and ROW (Canada, Russia, South Korea, and Taiwan) Completed	Subjects with moderate-to-severe plaque psoriasis who were candidates for systemic or phototherapy; males and females ≥ 18 years of age; PASI ≥ 12, sPGA ≥ 3, BSA ≥ 10%	52-week randomized, double-blind, placebo- and active comparator-controlled study 2:1:1 randomization to the DEUC, placebo, and apremilast groups Subjects randomized to placebo were to be switched to DEUC at Week 16; subjects randomized to apremilast were switched to DEUC if they did not achieve PASI 50 at Week 24	**Co-Primary:** sPGA 0/1 and PASI 75 at Week 16 for DEUC compared with Placebo **Key Secondary:** DEUC compared with Placebo PASI 90, ss-PGA 0/1, sPGA 0, PASI 100, PSSD Symptom Score 0, DLQI, and PGA-F 0/1 at Week 16 DEUC compared with Apremilast sPGA 0/1, PASI 75, and PASI 90 at Week 16, Week 24, and at both Week 52 and 24; ss-PGA 0/1, sPGA 0, CFB in PSSD symptom score, and PSSD symptom score 0 at Week 16	DEUC: 6 mg QD PO Placebo QD PO Apremilast: 30 mg BID PO (with initial titration per label)	666 randomized subjects: 332 (DEUC), 166 (placebo), and 168 (apremilast) Completed the Week 16 placebo-controlled period: 307 (DEUC), 145 (placebo), and 145 (apremilast)
IM011047 (Phase 3) FPFV: 26-Jul-2018; LPLV for the Primary CSR: 30-Nov-2020 191 sites in US, EU (Czech Republic, Finland, France, Germany, Hungary, Italy, Poland, Spain, Sweden, and UK) and ROW (Australia, Canada, Israel, New Zealand, and Puerto Rico)	Subjects with moderate-to-severe plaque psoriasis who were candidates for systemic or phototherapy; males and females ≥ 18 years of age; PASI ≥ 12, sPGA ≥ 3, BSA ≥ 10%	52-week randomized, double-blind, placebo- and active comparator-controlled study 2:1:1 randomization to the DEUC, placebo, and apremilast groups Subjects randomized to placebo were to be switched to DEUC at Week 16. Randomized Treatment Withdrawal Phase: At Week 24, subjects initially randomized to DEUC 6 QD who were PASI 75 responders were switched (1:1) to DEUC 6 QD or placebo. Once first predefined relapse occurred (≥ 50% loss of Week 24 PASI improvement from	**Co-Primary:** sPGA 0/1 and PASI 75 at Week 16 for DEUC compared with Placebo **Key Secondary:** DEUC compared with Placebo PASI 90, ss-PGA 0/1, sPGA 0, PASI 100, PSSD Symptom Score 0, DLQI, and PGA-F 0/1 at Week 16; time to relapse through Week 52 DEUC compared with Apremilast sPGA 0/1, PASI 75, and PASI 90 at Week 16 and at Week 24; ss-PGA 0/1, sPGA 0, CFB in PSSD symptom score, and PSSD Symptom Score 0 at Week 16	DEUC: 6 mg QD PO Placebo QD PO Apremilast: 30 mg BID PO (with initial titration per label)	1020 randomized subjects: 511 (DEUC), 255 (placebo), and 254 (apremilast) Completed the Week 16 placebo-controlled period: 456 (DEUC), 212 (placebo, and 217 (apremilast)

Study Information	Population	Design	Efficacy Endpoints	Test Drugs and Dose	No. of Subjects
Completed		baseline), subjects were to be switched to DEUC 6 mg QD (through Week 52). At Week 24, subjects initially randomized to apremilast who were responders (≥ PASI 75) were switched to placebo. Once first predefined relapse occurred (≥ 50% loss of Week 24 PASI improvement from baseline), subjects were to be switched to DEUC 6 mg QD (Week 24 -52). Subjects initially randomized to DEUC or apremilast who did not achieve PASI 75 at Week 24, remained on DEUC or were switched to DEUC at Week 24, respectively			
Long-Term Extension Phase 3 Study					
IM011075 (Phase 3b) FPFV: 12-Aug-2019; Data Cutoff for the Interim CSR: 15-Jun-2021 264 sites in US, EU, and ROW Ongoing	Subjects with moderate-to-severe plaque psoriasis who completed IM011046 or IM011047 (parent studies)[a]	Open-label, single-arm study to evaluate the long-term safety and efficacy of DEUC	**For DEUC** Secondary (provided in this SCE): sPGA 0/1 and PASI 75	DEUC: 6 mg QD PO	1221 subjects treated

Abbreviations: BID - twice a day; BMS - Bristol Myers Squibb; BSA - body surface area; CSR - Clinical Study Report; DLQI - Dermatology Life Quality Index; DEUC (deucravacitinib) - BMS - 986165; EU - European Union; FPFV - first patient first visit; LPLV - last patient last visit; PASI - Psoriasis Area and Severity Index; PGA-F - Physician's Global Assessment-Fingernail; PO - orally; PRO - patient reported outcomes; PSSD - Psoriasis Symptoms and Signs Diary; QD - once daily; QOD - every other day; ROW - rest of world; SCE - summary of clinical efficacy; sPGA - static Physician's Global Assessment; ss-PGA - scalp-specific Physician's Global Assessment; UK - United Kingdom

Note that a Primary Clinical Study Report (CSR) is the same as a Final CSR.

Source: IM011046 Primary CSR,[5] IM011047 Primary CSR,[6] IM011075 Interim CSR,[7] IM011011 Final CSR,[4] and IM011084 Part A Primary CSR[8]

2.6.5.1. Dose response study

The clinical development program contributing to dose selection included a **first-in-human study** that studied a 40-fold dose range (1-40 mg QD) of DEUC in healthy volunteers (IM011002) followed by a phase 2 study (study IM011011). In Phase 1 clinical development, PK and target engagement data from the single and multiple ascending dose portions of the first in human (FIH) study were leveraged to develop a direct effect (Emax [maximum drug effect]) model to characterize the concentration-response relationship. Subsequently this PK/PD characterization enabled a selection of Phase 2 dosing regimens to efficiently investigate the benefit-risk of DEUC.

Study IM011011:

This was a 12-week, multi-centre, randomised double-blind, placebo-controlled, parallel-group multiple oral dose study in subjects with moderate to severe psoriasis. Subjects were randomly assigned 1:1:1:1:1:1 to one of six treatment groups to receive DEUC:

- 3 mg every other day (Q2D);
- 3 mg every day (QD);
- 3 mg twice daily (BID);
- 6 mg BID;
- 12mg (QD)
- or placebo.

A total of 268 subjects were randomized to the 6 treatment groups. The subjects could have received any topical and systemic treatment but at distance of DEUC initiation. The subjects could be also naïve to any therapeutic agent targeted to IL-12, IL-17, or IL-23 (ustekinumab, secukinumab, or ixekizumab) within 6 months of first administration of DEUC or had a lack of response to ustekinumab, secukinumab, or ixekizumab (any therapeutic agent targeted to IL-12, IL-17, or IL-23) at approved doses after at least 3 months of therapy.

The PASI-75 response rates on Day 85, week 12 (primary endpoint) were 9.1%, 38.6%, 68.9%, 66.7%, and 75.0% in the DEUC 3 mg QOD, 3 mg QD, 3 mg BID, 6 mg BID, and the 12 mg QD treatment groups, respectively, compared to 6.7% in the placebo group (see table)

The proportion of subjects who achieved PASI-75 on week 12 (Day 85) was statistically significantly higher than placebo in each of the active treatment groups (nominal p-values: 0.0003 for DEUC 3 mg QD and <0.0001 for DEUC 3 mg BID, DEUC 6 mg BID, and DEUC 12 mg QD).

In terms of PASI 75 at week 12, which is the primary endpoint, DEUC 12 mg QD showed the highest efficacy.

Table 25 Response Rates of Efficacy Endpoints on Day 85 (Week 12)

Response at Week 12	Placebo N=45	BMS 3 mg QOD N=44	BMS 3 mg QD N=44	BMS 3 mg BID N=45	BMS 6 mg BID N=45	BMS 12 mg QD N=44
Response rate: number of subjects <n/N> (%)						
PASI-50	14/45 (31.1)	19/44 (43.2)	30/44 (68.2)	41/45 (91.1)	35/45 (77.8)	39/44 (88.6)
PASI-75	3/45 (6.7)	4/44 (9.1)	17/44 (38.6)	31/45 (68.9)	30/45 (66.7)	33/44 (75.0)
PASI-90	1/45 (2.2)	3/44 (6.8)	7/44 (15.9)	20/45 (44.4)	20/45 (44.4)	19/44 (43.2)
PASI-100	0/45 (0)	1/44 (2.3)	0/44	4/45 (8.9)	8/45 (17.8)	11/44 (25.0)
sPGA 0/1	3/45 (6.7)	9/44 (20.5)	17/44 (38.6)	34/45 (75.6)	29/45 (64.4)	33/44 (75.0)
sPGA 0	0/45 (0)	3/44 (6.8)	2/44 (4.5)	8/45 (17.8)	13/45 (28.9)	12/44 (27.3)
DLQI 0/1	2/34 (5.9)	7/.38 (18.4)	7/41 (17.1)	19/43 (44.2)	27/40 (67.5)	28/43 (65.1)

Source: Table 7.2.1-1, Table 7.3.1-1, Table 7.3.2.1-1, Table 7.3.2.2-1, Table 7.3.3-1; Table S7.1.1.11, Table S7.1.1.8
Abbreviations: BID = twice daily; DLQI = Dermatology Quality Life Index; n = number of responders; N = total number of subjects in a treatment group; PASI = Psoriasis Area and Severity Index; PASI-50 = 50% reduction in PASI; PASI-90 = 90% reduction in PASI; PASI-100 = 100% reduction in PASI; QOD = every other day; QD = once daily; sPGA = Static Physician's Global Assessment

The selection of the 6 mg QD dose of DEUC for the Phase 3 program was based on the efficacy and safety results from the Phase 2 dose-ranging study along with E-R modelling of these results. For the E-R modelling results, refer to 2.6.2.2. Pharmacodynamics section.

2.6.5.2. Main studies

The 2 pivotal Phase 3 studies of DEUC for moderate-to-severe plaque psoriasis are controlled Phase 3 clinical studies named **IM011046 and IM011047**.

They were of similar design (identical up to Week 24), with the same comparators; both studies had 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, and Apremilast-controlled through Week 24, and were of 52 weeks in treatment duration. In both studies, eligible subjects were randomized 2:1:1 to receive DEUC 6 mg orally QD, placebo, or Apremilast 30 mg twice daily (BID). Subjects were stratified by geographic region, previous biologic use, and body weight.

IM011046: A Multi-Centre, 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

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

Methods

Figure 16 IM011046 Study Design

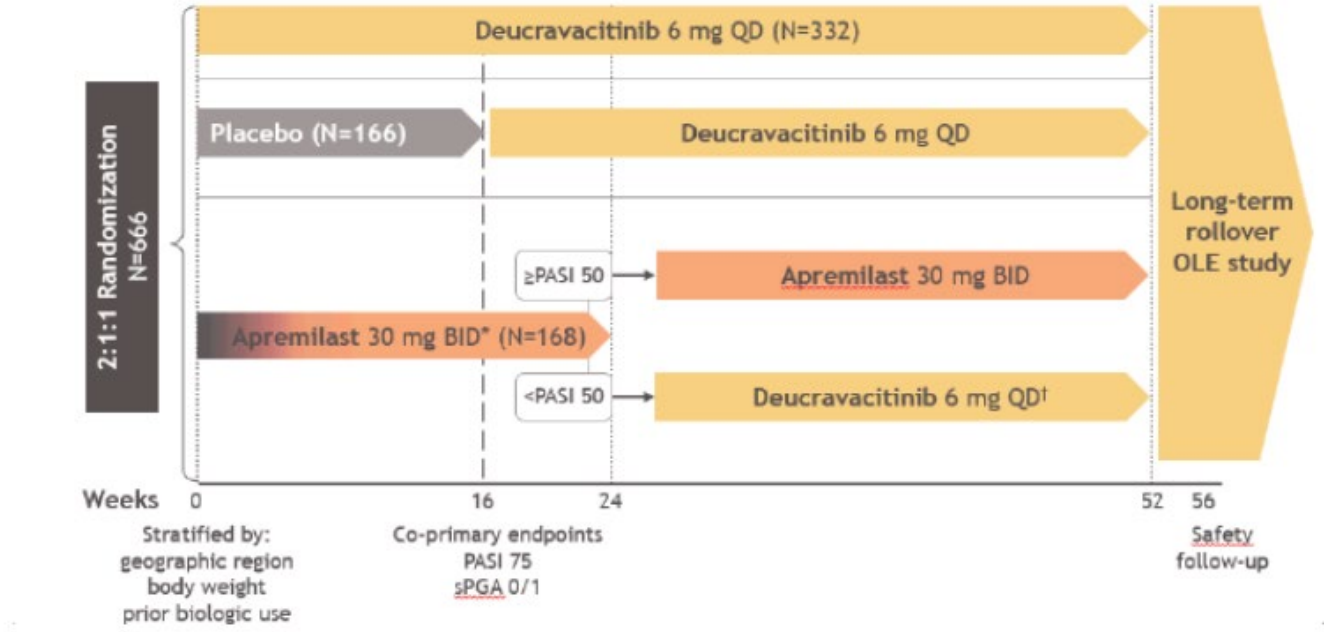
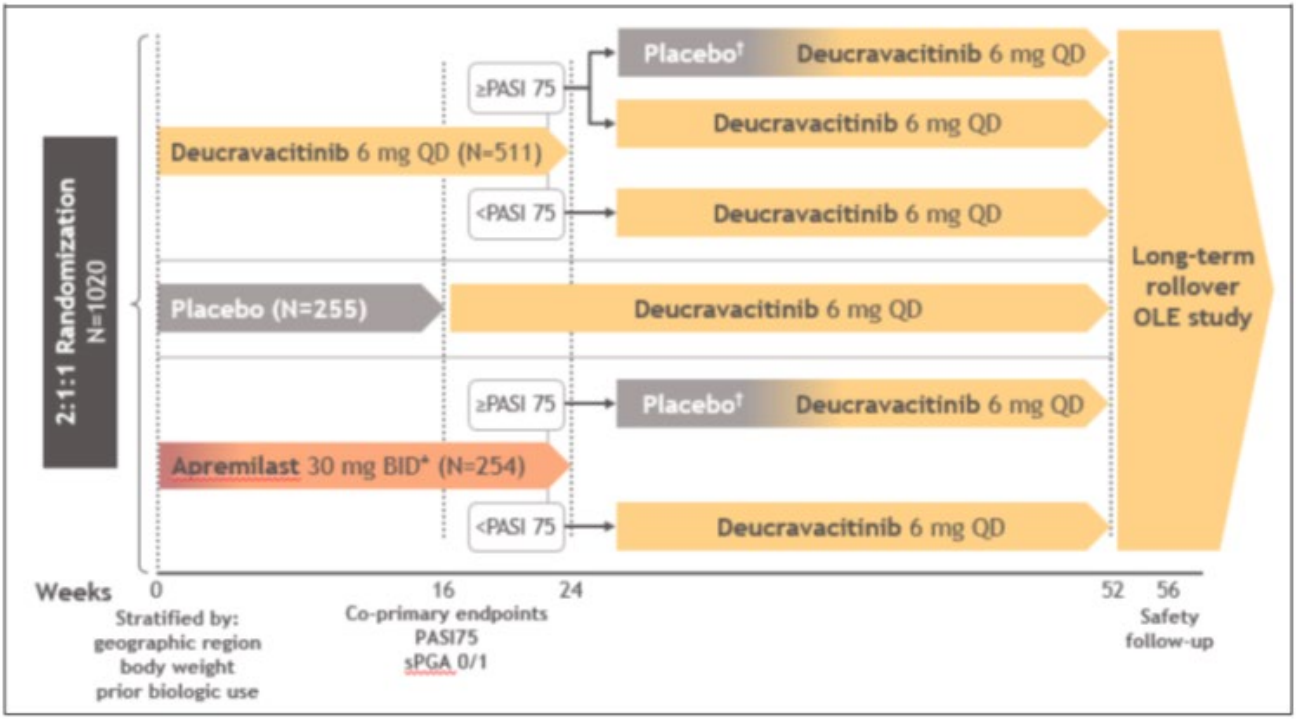


Figure 17 IM011047 Study Design



*Upon relapse (at least a 50% loss of Week 24 PASI percent improvement from baseline), subjects were switched to BMS-986165 6 mg QD.
†Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
Abbreviations: Abbreviations: BID = twice daily; OLE - open label extension; PASI = Psoriasis Area and Severity Index; QD = once daily

- **Study Participants**

IM011046 and IM011047 had identical entry criteria. Both studies enrolled adult subjects with moderate-to-severe plaque psoriasis (defined as PASI ≥ 12, sPGA score ≥ 3, and body surface area [BSA] involvement ≥ 10%) and were required to be candidates for phototherapy or systemic therapy for their psoriasis.

Main inclusion criteria

- Age ≥ 18 years at screening visit
- Men and women diagnosed with stable plaque psoriasis for 6 months or more. Stable psoriasis was defined as no morphology changes or significant flares of disease activity in the opinion of the investigator
- Have an involved BSA ≥ 10% and
- Have a PASI score ≥ 12 and
- Have a sPGA score of ≥ 3 at Screening Visit and Day 1
- Deemed by the investigator to be a candidate for phototherapy or systemic therapy.

Main exclusion criteria

- Had non plaque psoriasis (i.e., guttate, inverse, pustular, erythrodermic, or drug-induced psoriasis) at Screening or Day 1
- Prior exposure to investigational product (i.e., DEUC or Apremilast)
- Use of any restricted medication as specified or any drug considered likely to interfere with the safe conduct of the study
- Known chronic or relevant acute bacterial, fungal, or viral infection infections including active tuberculosis, HIV, herpes zoster or viral hepatitis or any evidence of or test positive for these infections
- Any significant/uncontrolled neuropsychiatric illness judged as clinically significant by the investigator during Screening or at Day 1 or any lifetime history of suicidal ideation, suicidal behavior, or suicidal attempts
- Surgery within 12 months, documented or suspected malignancy, history allergy/hypersensitivity, pregnancy or planned pregnancy
- Use of biologics not respecting washout period: e.g., ustekinumab, secukinumab, tildrakizumab, ixekizumab, or guselkumab) within 6 months of Day 1, etanercept, adalimumab, infliximab, certolizumab) within 2 months of Day 1, alemtuzumab, abatacept, or visilizumab within 3 months of Day 1, rituximab within 6 months of Day 1
- Use of systemic non biologic psoriasis medications and/or any systemic immunosuppressants (including, but not limited to, methotrexate, azathioprine, cyclosporine, JAK inhibitors) within 4 weeks prior to Day 1.

- **Treatments**

DEUC, Apremilast and matching placebo were administered as film-coated tablets:

• DEUC 6 mg QD (or BMS-986165) from Day 1 to week 52

• Placebo from Day 1 to week 16

• Apremilast titrated to 30 mg BID, administered from Day 1 to week 52 as follows:

  o Day 1: 10 mg tablet in the morning

  o Day 2: 10 mg tablet in the morning and evening

  o Day 3: 10 mg tablet in the morning and 20 mg tablet in the evening

  o Day 4: 20 mg tablet in the morning and the evening

  o Day 5: 20 mg tablet in the morning and 30 mg tablet in the evening

  o Day 6 and thereafter: 30 mg tablet in the morning and the evening.

Dummy tablets (placebo to the DEUC 6 mg tablet, placebo to Apremilast 30 mg tablet BID, and placebo to Apremilast 10 mg, 20 mg, and 30 mg during titration) were administered to the subjects to maintain blinding.

Apremilast was titrated over 5 days to a maintenance dose of 30 mg BID. To maintain the blind between subjects receiving Apremilast and DEUC during the titration period, active Apremilast and matching Apremilast placebo tablets were provided.

Rescue treatment: at Week 24, a subject who has an sPGA or ss-PGA ≥3 may be treated with restricted topicals or shampoos, respectively, at the investigator's discretion. These treatments may be only initiated at Week 24, and not at subsequent time points.

- **Objectives**

The primary objective was to assess whether DEUC was superior to placebo at Week 16 in the treatment of subjects with moderate-to-severe plaque psoriasis.

Both studies had similar secondary objectives. Key secondary objectives were: a) to evaluate whether DEUC is superior to placebo at week 16 in endpoints other than sPG 0/1 and PASI 75; b) to evaluate whether DEUC is superior to apremilast at week 16, week 24 and week 52; c) to evaluate efficacy in nail, scalp and palmoplantar psoriasis compared to placebo and to apremilast; d) to assess patient reported outcomes (most important being PSSD Symptom Score and DLQI score); e) to evaluate the maintenance and durability of response through week 52 in subjects who were initially randomised to DEUC and in study IM011047 also to assess rebound and recapture rates.

- **Outcomes/endpoints**

Co-Primary endpoints at week 16

- sPGA 0/1 response (score of 0 or 1): proportion of subjects achieving sPGA score of 0 (clear) or 1 (almost clear), with at least a 2-point reduction from baseline at Week 16.
- PASI 75 response: proportion of subjects achieving at least a 75% reduction from baseline in the PASI score at Week 16.

Key secondary endpoints

Study IM011046	
Comparisons to Placebo (α = 0.025)	**Comparisons to Apremilast (α = 0.025)**
1. PASI 90 at Week 16	1. sPGA 0/1 at Week 16
2. ss-PGA 0/1 at Week 16	2. PASI 75 at Week 16
3. sPGA 0 at Week 16	3. PASI 90 at Week 16
4. PASI 100 at Week 16	4. sPGA 0/1 at Week 24
5. PSSD Symptom Score of 0 at Week 16	5. PASI 75 at Week 24
6.* DLQI 0/1 at Week 16	6. PASI 90 at Week 24
7. PGA-F 0/1 at Week 16	7. Change from baseline in PSSD Symptom Score at Week 16
	8. ss-PGA 0/1 at Week 16
	9. sPGA 0/1 at Week 52 and at Week 24
	10. PASI 75 at Week 52 and at Week 24

Study IM011046	
Comparisons to Placebo (α = 0.025)	**Comparisons to Apremilast (α = 0.025)**
	11. PASI 90 at Week 52 and at Week 24
	12. sPGA 0 at Week 16
	13. PSSD Symptom Score of 0 at Week 16
Study IM011047	
Comparisons to Placebo (α = 0.025)	**Comparisons to Apremilast (α = 0.025)**
1. PASI 90 at Week 16	1. sPGA 0/1 at Week 16
2. ss-PGA 0/1 at Week 16	2. PASI 75 at Week 16
3. sPGA 0 at Week 16	3. PASI 90 at Week 16
4. PASI 100 at Week 16	4. sPGA 0/1 at Week 24
5. PSSD Symptom Score of 0 at Week 16	5. PASI 75 at Week 24
6.* DLQI 0/1 at Week 16	6. PASI 90 at Week 24
7.* *Time-to-relapse until Week 52 for Week 24 DEUC PASI 75 responders*	7. Change from baseline in PSSD Symptom Score at Week 16
8. PGA-F 0/1 at Week 16	8. ss-PGA 0/1 at Week 16
	9. sPGA 0 at Week 16
	10. PSSD Symptom Score of 0 at Week 16

- **Sample size**

Sample size considerations were based on providing exposure in sufficient numbers of subjects for the DEUC 6 mg QD arm. A total sample size of 600 / 1000 subjects (respectively IM011046 and IM011047) randomized in a blinded fashion in a 2:1:1 ratio to DEUC 6 mg QD, Apremilast 30 mg BID, and placebo respectively aimed at providing adequate power to compare DEUC 6 mg QD with placebo for each co-primary efficacy endpoint (proportion of subjects with sPGA 0/1 and PASI 75 at Week 16). DEUC 6 mg QD response rates were estimated from the Phase 2 BMS Study IM011011. Response rates for placebo were estimated from published rates for placebo and Apremilast (USPI dated 06/2017). Assuming a 2-sided chi-square test with α = 0.05 and expected response rates of 60% and 10% for DEUC and placebo, respectively, this study had >99% power to test superiority of DEUC to placebo for each of the co-primary efficacy endpoints.

Assuming a 2-sided chi-square test with an α = 0.025 and expected response rates of 60% and 35% for DEUC and Apremilast, respectively, studies had > 99% power to test the superiority of DEUC to Apremilast for each of the co-primary efficacy endpoints.

- **Randomisation and Blinding (masking)**

Before the study was initiated, each user (at investigative sites) received log-in information and directions on how to access the interactive response technology (IRT) system.

The randomization list was generated by the IRT vendor using a permuted block design within each stratum combination level.

The randomization in both studies was stratified by geographic region (U.S., Japan [body weight stratum not applied in Japan], China [body weight stratum not applied in China], and Rest of World), previous biologic use (for psoriasis, psoriatic arthritis or other inflammatory diseases only; yes/no), and body weight (≥90 kg and <90 kg).

At Week 16, subjects who received placebo were switched to DEUC 6 mg QD; during the switch, treatment blinding was maintained.

At Week 24, subjects who were originally randomized to Apremilast 30 mg BID who did not achieve PASI 50 in study IM011046 and PASI 75 response in study 047 were switched to DEUC 6 mg QD. Moreover in IM011047, subjects who were originally randomized to DEUC who did not achieve PASI 75 were switched to DEUC 6 mg QD or placebo. During the switches, treatment blinding was maintained.

In order to avoid the possibility of unblinding investigators in evaluation of efficacy and safety assessments, PASI scores at Week 24 were masked in the ERT system (eResearch Technology Inc.) to site staff and study team.

- **Statistical methods**

A stratified Cochran-Mantel-Haenszel (CMH) test was used to compare the sPGA 0/1 and PASI 75 response rates at Week 16 between DEUC 6 mg QD and placebo using the stratification factors from IRT.

The definitions for Populations for Analyses were used in the summary and analysis of study data:

- Enrolled population: All subjects who sign informed consent.
- Full Analysis Set (FAS): All subjects who were randomized. Following the intent-to-treat (ITT) principle, subjects were analysed according to the treatment group assigned at randomization.

  The FAS was the primary efficacy analysis population.
- Per Protocol Set (PPS): A subset of the FAS who are compliant with study treatment and who do not have any relevant protocol deviations that may impact the co-primary efficacy endpoint assessments. The PPS was analysed according to the treatment assigned at randomization. The PPS was a supportive efficacy analysis population and only the co-primary endpoints were analysed using this set.
- As-treated population: All randomized subjects who take at least one dose of study treatment. Subjects were analysed according to treatment received.
- Biomarker population: All randomized subjects who take at least one dose of study treatment and have at least one post-treatment biomarker measurement. Subjects were analysed according to the treatment actually received.
- Pharmacokinetic (PK) population: All randomized subjects who take at least one dose of DEUC and have any available concentration data. The bioanalytical lab received the true randomization file and analysed only the plasma samples from the subjects who received DEUC drug. Subjects were analysed according to the treatment received.

Adjustment for Multiplicity

The study hypothesis to be tested was to assess if the odds of achieving both sPGA 0/1 response and PASI 75 response at Week 16 in subjects receiving DEUC 6 mg QD are statistically greater than subjects receiving placebo. Each co-primary endpoint was tested at a 2-sided Type 1 error = 0.05. Both endpoints need to demonstrate statistical significance to result in a successful study.

- sPGA 0/1 at Week 16: H01: OR = 1 versus H11: OR ≠ 1
- PASI 75 at Week 16: H02: OR = 1 versus H12: OR ≠ 1

Statistical analysis of the key secondary endpoints were performed only if both co-primary endpoint are significant. The primary family of co-primary endpoints were the serial gatekeeper for proceeding with testing of the key secondary family of endpoints.

In order to control for Type I error rate inflation within the secondary family of key secondary endpoints, separate testing branches with a 2-sided Type 1 error = 0.025 was used for comparisons of DEUC 6 mg QD compared to placebo and DEUC 6 mg QD compared to Apremilast. A hierarchical testing method within each testing branch was implemented for the key secondary endpoints. Alpha-controlled testing may only proceed to the next key secondary endpoint within each testing branch if the null hypothesis is rejected at Type 1 error = 0.025. If an endpoint failed at any step, then all subsequent comparisons in that testing branch was considered descriptive.

No interim analysis was performed for both studies.

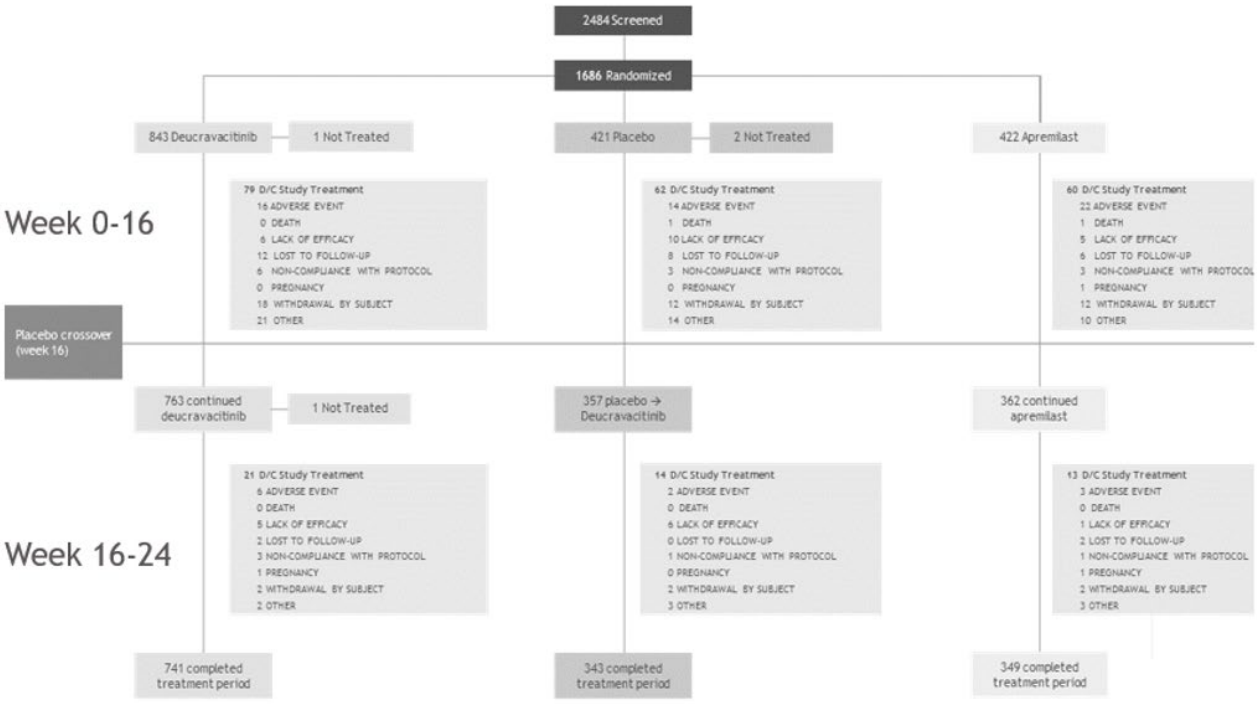
Sensitivity analyses

As a method to assess the sensitivity of the primary imputation method for the co-primary endpoints, further imputation methods were used to impute Week 16 data in subjects who discontinued treatment or study prior to Week 16 or had missing Week 16 endpoint data for any reason: Last Observation Carried Forward (LOCF); LOCF and NRI; Tipping Point Analysis and Multiple Imputation.

Results

- **Participant flow**

Figure 18 Consolidated Standards of Reporting Trials Diagram for Week 0 – 24 (Pooled IM011046 and IM011047)

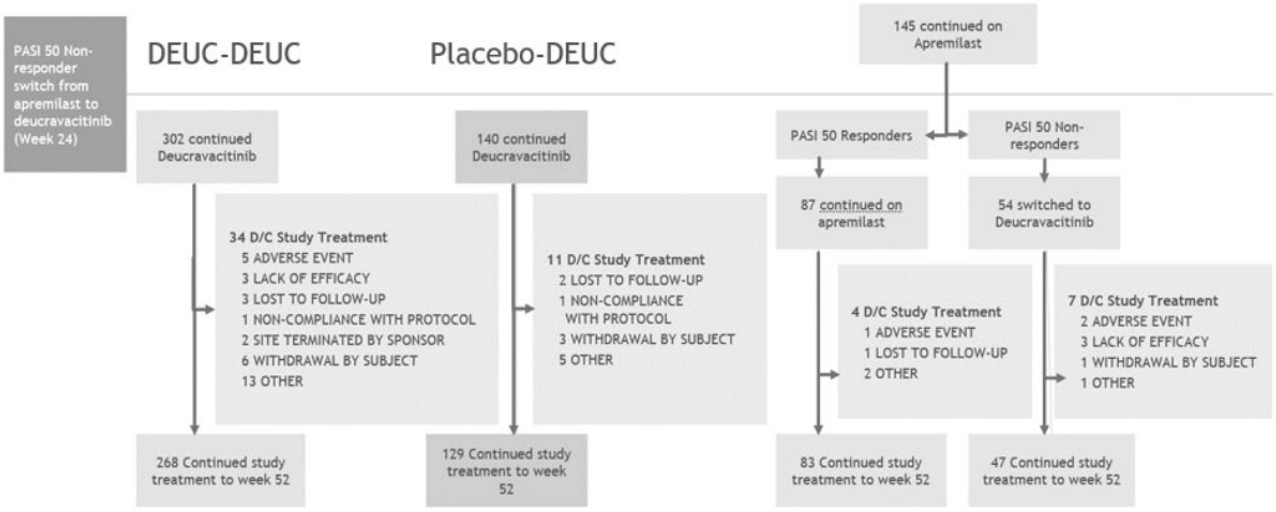


In IM011047, there was 1 death in the DEUC group in the Week 0-16 period. On Day 13 (9 days after the last dose of study therapy), the subject (75-year-old female) died due to severe cardiac failure, the event was considered as not related to study drug.

Abbreviation: D/C - discontinuation

Source: Table S.1.1, Table S.1.2, and Table S.1.3 in Appendix 3

Figure 19 Consolidated Standards of Reporting Trials Diagram for Week 24 -52 (IM011046)



Abbreviations: D/C - discontinuation; PASI 50 - 50% or greater improvement in Psoriasis Area and Severity Index score from baseline.

Source: Table S.2.3.1 (End of Treatment Status), Table S.2.3.4 (W24 through W52), Table S.2.3.5 (W0 through W52), Table S.2.3.7 (End of Treatment Status Week 24-52), Table S.2.4 (End of Study Subject Status) in the IM011046 Primary CSR[5]

Figure 20 Consolidated Standards of Reporting Trials Diagram for Week 24 -52 (IM011047)

Abbreviations: D/C - discontinuation; PASI 75 -75% or greater improvement in Psoriasis Area and Severity Index score from baseline.

Source: Table S.2.3.6 (End of Treatment Status Week 16-24), Table S.2.3.7 (End of Treatment Status Week 24-52), Table S.2.3.1 (End of Treatment Status), Table S.2.4 (End of Study Subject Status)

In study IM011046, out of the 665 subjects who were randomized and received treatment, the majority completed the placebo-controlled period (92.5% in the DEUC, 87.9% in the placebo, and 86.3% in the apremilast treatment group). The proportion of subjects who discontinued treatment during the placebo-controlled period was lowest in the DEUC treatment group (7.5%) compared with the placebo (12.1%), and apremilast (13.7%) treatment groups. The most common reasons for discontinuation during placebo controlled period were AEs.

A total of 79.1% (527/666) participants completed treatment through Week 52 (80.7% from DEUC, 77.7% from placebo and 77.4% from apremilast group). Lack of efficacy was not noted to be a clinically significant reason for discontinuations (11 subjects overall, 1.7%).

Overall 80.3% subjects completed the study, of which 77.6% rolled over to the long-term extension study (IM011075). The most common reasons for not completing the study overall were: withdrawal by subject, AEs, and lost to follow up.

In study IM011047, the majority of 1018 randomized and treated subjects completed the placebo-controlled period including 456 (89.4%) in the DEUC, 212 (83.5%) in the placebo, and 217 (85.4%) in the apremilast treatment groups. The proportion of subjects who discontinued treatment during the placebo-controlled period was lowest in the DEUC treatment group (10.6%) compared with the placebo (16.5%), and apremilast (14.6%) treatment groups. Most common reasons for not completing placebo controlled period were AEs, other reasons and withdrawal by subject.

A total of 73.4% (749/1020) participants completed treatment through Week 52 (77.5% from DEUC, 71% from placebo and 67.7% from apremilast group).

Overall, 4.3% of subject discontinued treatment due to lack of efficacy, with somewhat lower proportion in DEUC group compared to placebo and apremilast groups (3.3% vs 5.1% and 5.5%, respectively).

Overall, 73.6% of subjects completed the study, with the lowest proportion of subjects who did not complete the study in original DEUC group. Withdrawal by subject was the most common reason for not completing the study (overall 12.5%, with 10.4% in DEUC, 16.9% in placebo and 12.6% in apremilast group).

- **Recruitment**

Dates defining the periods of recruitment and follow-up.

IM011046	IM011047
Study Initiation Date: 07-Aug-2018 Last patient last visit: 02-Sep-2020 Clinical database lock: 15-Oct-2020	Study Initiation Date: 26-Jul-2018 Last patient last visit: 30-Nov-2020 Clinical database lock: 22-Dec-2020

- **Conduct of the study**

Both study protocols were amended regarding the hierarchical testing order of key secondary endpoints, two separate hierarchies have been provided, one for US submission and one for ex-US submission.

IM011046: There were no potential serious breaches of GCP.

Site 0092 was initially put on a screening hold on 13-Nov-2018 following non-compliance issues raised during the first interim monitoring visit (IMV), the site did not improve to an acceptable level and was closed on 17-

Sep-2019 for non-compliance. The 2 subjects enrolled at this site were discontinued, despite the option to transfer the subjects to another local site. The primary analysis of co-primary endpoints included data of those patients, the additional analysis of the co-primary endpoints excluded their study data and showed no impact on interpretation of results.

Major deviations to the protocol IM011046

	DEUC 6 mg N=332	Placebo N=166	Apremilast N=168	Total N=666
Total subjects with a deviation	**26 (7.8)**	**15 (9.0)**	**8 (4.8)**	**49 (7.4)**
Non respect of inclusion criteria	0	2 (1.2)	0	2 (0.4)
Prohibited medication	5 (1.5)	4 (2.4)	0	9 (1.4)
No postbaseline PASI or sPGA	2 (0.6)	0	2 (1.2)	4 (0.6)
Randomised but not dosed	0	1 (0.6)	0	1 (0.2)
Non-compliance with treatment	18 (5.4)	11 (6.6)	6 (3.6)	35 (5.3)
Wrong treatment	1 (0.3)	0	1 (0.6)	2 (0.3)

IM011047: Two GCP deviations were reported as potential serious breaches (PSB), of those, one was a BMS reportable serious breach (1). One event was self-reported by a site (2).

1) There was a failure in the IRT system controls to manage study treatment assignment, which caused subjects to not be systematically placed on DEUC when subjects assigned placebo in the randomized withdrawal and maintenance period of the study experienced a relapse after Week 24.

A failure of the IRT system did not allow this to occur, which resulted in 106/1020 (10.4%) subjects not being switched to DEUC after experiencing a protocol defined relapse.

2) UK site 0145 reported a PSB to the MHRA in November 2019 due to a third party (research nurses) that was not appropriately mentioned within the Clinical Trial Agreement and did not have appropriate indemnification. Study participants were not made aware within the informed consent form that the third party would have access to the patient data. This third party applied across multiple trials from different commercial sponsors at the site (i.e. not specific to the IM011047 trial). It had no impact on the data integrity or the patient safety in the trial.

Major deviations to the protocol IM011047

	DEUC 6 mg N=511	Placebo N=255	Apremilast N=254	Total N=1020
Total subjects with a deviation	**30 (5.9)**	**17 (6.7)**	**11 (4.3)**	**58 (5.7)**
Prohibited medication	11 (2.2)	3 (1.2)	1 (0.4)	15 (1.5)
No postbaseline PASI or sPGA	6 (1.2)	7 (2.7)	1 (0.4)	14 (1.4)
Randomised but not dosed	1 (0.2)	1 (0.4)	0	2 (0.2)
Non-compliance with treatment	13 (2.5)	6 (2.4)	8 (3.1)	27 (2.6)
Wrong treatment	0	1 (0.4)	1 (0.4)	2 (0.2)

In total, 49 (7.4%) subjects in IM011046 and 58 (5.7%) subjects in IM011047 had relevant protocol deviations (RPD), respectively, during the placebo-controlled period (week 0-16). Most common RPD was non-compliant with treatment and use of prohibited medication. These RPDs did not impact the

interpretability of the study results or conclusions derived from the data (based on supportive/sensitivity analyses).

- **Baseline data**

Across the 2 Phase 3 studies, the majority of subjects were white (approximately 87%) and male (approximately 67%), with a mean age of approximately 47 years with approximately 10% of subjects being ≥ 65 years of age. The overall proportions of female subjects and male subjects were similar, but the distribution by sex varied slightly across the treatment groups. Within each study the distribution of race was similar among the treatment groups; however, due to the different geographic footprints of the 2 studies there was a greater proportion of Asian race in IM011046 (total 18.2%) compared with IM011047 (total 4.3%).

Overall, the mean body weight and mean body mass index (BMI) were similar across the treatment groups in each study.

In the pooled analyses of IM011046 and IM011047, the subjects were summarized by the following geographic regions: 737 (43.7%) subjects were from the EU (Czech Republic, Finland, France, Germany, Hungary, Poland, Spain, Sweden, and United Kingdom), 540 (32.0%) subjects were from the US, and 409 (24.3%) subjects were from ROW (Australia, Canada, China, Israel, Japan, New Zealand, Puerto Rico, Russia, South Korea, and Taiwan).

Table 26 Baseline Demographics and Physical Measurements (IM011046, IM011047, and Pooled) - As Randomized

	IM011046			IM011047			Pooled IM011046 and IM011047			
	DEUC (N = 332)	Placebo (N = 166)	APR (N = 168)	DEUC (N = 511)	Placebo (N = 255)	APR (N = 254)	DEUC (N=843)	Placebo (N=421)	APR (N=422)	Total (N = 1686)
Age (years)										
Mean	45.9	47.9	44.7	46.9	47.3	46.4	46.5	47.5	45.7	46.6
Median	45	48	43	46	47	46	46	47	45	46
Min, Max	18, 80	19, 81	20, 77	18, 84	18, 83	18, 79	18, 84	18, 83	18, 79	18, 84
< 65, n (%)	306 (92.2)	141 (84.9)	158 (94.0)	457 (89.4)	229 (89.8)	226 (89.0)	763 (90.5)	370 (87.9)	384 (91.0)	1517 (90.0)
≥ 65, n (%)	26 (7.8)	25 (15.1)	10 (6.0)	54 (10.6)	26 (10.2)	28 (11.0)	80 (9.5)	51 (12.1)	38 (9.0)	169 (10.0)
≥ 75, n (%)	6 (1.8)	3 (1.8)	1 (0.6)	7 (1.4)	3 (1.2)	3 (1.2)	13 (1.5)	6 (1.4)	4 (0.9)	23 (1.4)
Sex, n (%)										
Male	230 (69.3)	113 (68.1)	110 (65.5)	336 (65.8)	181 (71.0)	157 (61.8)	566 (67.1)	294 (69.8)	267 (63.3)	1127 (66.8)
Female	102 (30.7)	53 (31.9)	58 (34.5)	175 (34.2)	74 (29.0)	97 (38.2)	277 (32.9)	127 (30.2)	155 (36.7)	559 (33.2)
Race, n (%)										
White	267 (80.4)	128 (77.1)	139 (82.7)	474 (92.8)	232 (91.0)	229 (90.2)	741 (87.9)	360 (85.5)	368 (87.2)	1469 (87.1)
Black/AA	2 (0.6)	3 (1.8)	1 (0.6)	8 (1.6)	9 (3.5)	9 (3.5)	10 (1.2)	12 (2.9)	10 (2.4)	32 (1.9)
Asian	59 (17.8)	34 (20.5)	28 (16.7)	24 (4.7)	8 (3.1)	12 (4.7)	83 (9.8)	42 (10.0)	40 (9.5)	165 (9.8)
Other	4 (1.2)	1 (0.6)	0	5 (1.0)	6 (2.4)	4 (1.6)	9 (1.1)	7 (1.7)	4 (0.9)	20 (1.2)

	IM011046			IM011047			Pooled IM011046 and IM011047			
	DEUC (N = 332)	Placebo (N = 166)	APR (N = 168)	DEUC (N = 511)	Placebo (N = 255)	APR (N = 254)	DEUC (N=843)	Placebo (N=421)	APR (N=422)	Total (N = 1686)
Baseline Weight (kg)										
Mean	87.90	89.13	87.52	92.26	91.53	93.47	90.55	90.58	91.10	90.69
Median	85.4	85.8	86.0	90.7	91.2	90.9	89.0	88.6	89.1	89.0
Min, Max	36.0, 173.0	46.3, 181.6	45.5, 187.3	40.0, 180.0	48.3, 160.0	49.7, 173.3	36.0, 180.0	46.3, 181.6	45.5, 187.3	36.0, 187.3
Baseline BMI (kg/m^2)										
Mean	29.77	30.24	29.64	31.00	30.39	31.56	30.52	30.33	30.80	30.54
Median	28.8	28.7	28.5	30.2	29.5	30.4	29.7	29.4	29.7	29.6
Min, Max	15.0, 68.6	17.3, 61.3	18.7, 59.3	16.9, 61.6	17.9, 55.3	17.0, 58.8	15.0, 68.6	17.3, 61.3	17.0, 59.3	15.0, 68.6

Abbreviations: AA - African American; APR - apremilast; BMI - Body Mass Index, DEUC - deucravacitinib; BSA - body surface area; CSR - clinical study report
Source: Table 5.3.1-1 and Appendix 3.1 in the IM011046 Primary CSR; Table 5.3.1-1 and Appendix 3.1 in the IM011047 Primary CSR; Table S.3.1 (demographics and physical measurements) in Appendix 3 of the SCE

Across the 2 Phase 3 studies, the mean (median) duration of disease was approximately 19 (16) years, with a mean age at disease onset of approximately 29 years. In IM011046, the median duration of disease was slightly lower in the DEUC and placebo treatment groups (approximately 13 and 15 years, respectively) compared with IM011047 (approximately 17 and 18 years, respectively).

Most subjects (approximately 80%) in the Phase 3 studies had a sPGA score of 3 (moderate disease), and approximately 20% of subjects had a sPGA score of 4 (severe disease). The mean PASI score in each treatment group was approximately 21 and approximately 43% of subjects had a PASI score > 20, indicative of severe disease. Mean BSA involvement in each treatment group was approximately 26% and approximately 50% of subjects had BSA involvement > 20%, another measure of severe disease.

Most subjects (approximately 87%) had active scalp psoriasis; approximately 42% of subjects had active fingernail psoriasis, and approximately 16% of subjects had active palmoplantar psoriasis as assessed by the investigator at the week 0 visit. Approximately 18% of patients had a history of psoriatic arthritis.

Table 27 Baseline Disease Characteristics (IM011046, IM011047, and Pooled) - As Randomized

	IM011046			IM011047			Pooled IM011046 and IM011047			
	DEUC (N=332)	Placebo (N=166)	APR (N=168)	DEUC (N=511)	Placebo (N=255)	APR (N=254)	DEUC (N=843)	Placebo (N=421)	APR (N=422)	Total (N=1686)
Age at Disease Onset (years)										
Mean	29.6	31.5	27.8	28.2	28.4	28.4	28.8	29.6	28.1	28.8
Median	27	30	26	26	26	25	26	28	26	26
Duration of Disease, n (%)										
Mean	17.10	17.30	17.74	19.56	19.93	18.94	18.59	18.89	18.46	18.63
Median	13.4	14.7	16.3	17.6	18.2	16.0	16.2	16.5	16.3	16.3

	IM011046			IM011047			Pooled IM011046 and IM011047			
	DEUC (N=332)	**Placebo (N=166)**	**APR (N=168)**	**DEUC (N=511)**	**Placebo (N=255)**	**APR (N=254)**	**DEUC (N=843)**	**Placebo (N=421)**	**APR (N=422)**	**Total (N=1686)**
sPGA Score, n (%)										
2[a]	0	1 (0.6)	0	0	0	0	0	1 (0.2)	0	1 (0.1)
3	257 (77.4)	128 (77.1)	139 (82.7)	408 (79.8)	217 (85.1)	196 (77.2)	665 (78.9)	345 (81.9)	335 (79.4)	1345 (79.8)
4	75 (22.6)	37 (22.3)	29 (17.3)	103 (20.2)	38 (14.9)	58 (22.8)	178 (21.1)	75 (17.8)	87 (20.6)	340 (20.2)
PASI Score										
Mean	21.76	20.67	21.43	20.73	21.09	21.63	21.14	20.92	21.55	21.19
Median	19.5	17.8	19.1	18.5	18.2	19.2	18.9	18.0	19.2	18.7
> 20	155 (46.7)	64 (38.6)	70 (41.7)	213 (41.7)	103 (40.4)	111 (43.7)	368 (43.7)	167 (39.7)	181 (42.9)	716 (42.5)
BSA Involvement										
Mean	26.6	25.3	26.6	26.3	25.3	28.3	26.4	25.3	27.6	26.4
Median	21	18	20	20	20	22	21	20	21	20
10-20	162 (48.8)	94 (56.6)	87 (51.8)	259 (50.7)	132 (51.8)	113 (44.5)	421 (49.9)	226 (53.7)	200 (47.4)	847 (50.2)
> 20	170 (51.2)	72 (43.4)	81 (48.2)	252 (49.3)	123 (48.2)	141 (55.5)	422 (50.1)	195 (46.3)	222 (52.6)	839 (49.8)
Psoriasis Location, n (%)										
Scalp	288 (86.7)	152 (91.6)	152 (90.5)	434 (84.9)	221 (86.7)	223 (87.8)	722 (85.6)	373 (88.6)	375 (88.9)	1470 (87.2)
Fingernail	125 (37.7)	70 (42.2)	60 (35.7)	226 (44.2)	111 (43.5)	117 (46.1)	351 (41.6)	181 (43.0)	177 (41.9)	709 (42.1)
Palmoplantar	40 (12.0)	21 (12.7)	31 (18.5)	84 (16.4)	43 (16.9)	57 (22.4)	124 (14.7)	64 (15.2)	88 (20.9)	276 (16.4)

[a] 1 subject in IM011046 had an sPGA score of 2 and a PASI score < 12; these were relevant protocol deviations. This subject was randomized and not treated.

Abbreviations: APR - apremilast; BSA - body surface area; CSR - clinical study report; DEUC - deucravacitinib; PASI - Psoriasis Area and Severity Index; sPGA - static Physician's Global Assessment

Source: Table 5.3.2-1 in the IM011046 Primary CSR, Table 5.3.2-1 in the IM011047 Primary CSR, and Table S.3.2 in Appendix 3

Across the 2 Phase 3 studies, 42.4% of subjects were naïve to any systemic therapy for psoriasis including biologics and 57.6% of subjects had received some type of prior systemic treatment (including biologic and/or non-biologic systemic treatment for psoriasis or psoriatic arthritis). There were 34.8% of subjects who had received a prior biologic systemic treatment. Of the subjects who had received a prior biologic systemic treatment, 16.1% received a TNF inhibitor, 16.6% received an IL-17 inhibitor, 4.9% received an IL-12/23 inhibitor, and 4.4% received an IL-23 inhibitor. There were 40% of subjects who had received prior phototherapy.

Table 28 Prior Psoriasis-Related Treatment (IM011046, IM011047, and Pooled) - As Randomized

	Number (%) of Subjects									
	IM011046			IM011047			Pooled IM011046 and IM011047			
	DEUC (N=332)	Placebo (N=166)	APR (N=168)	DEUC (N=511)	Placebo (N=255)	APR (N=254)	DEUC (N=843)	Placebo (N=421)	APR (N=422)	Total (N=1686)
Naive to Prior Systemic Treatment[a]	132 (39.8)	57 (34.3)	59 (35.1)	237 (46.4)	116 (45.5)	114 (44.9)	369 (43.8)	173 (41.1)	173 (41.0)	715 (42.4)
Prior Systemic Treatment Use	200 (60.2)	109 (65.7)	109 (64.9)	274 (53.6)	139 (54.5)	140 (55.1)	474 (56.2)	248 (58.9)	249 (59.0)	971 (57.6)
Prior Systemic Biologic Use[b]	130 (39.2)	63 (38.0)	66 (39.3)	165 (32.3)	83 (32.5)	79 (31.1)	295 (35.0)	146 (34.7)	145 (34.4)	586 (34.8)
Prior Phototherapy Use	118 (35.5)	57 (34.3)	64 (38.1)	228 (44.6)	105 (41.2)	102 (40.2)	346 (41.0)	162 (38.5)	166 (39.3)	674 (40.0)

[a]Prior systemic treatment use includes subjects who had ever received biologic and/or non-biologic (systemic conventional) therapies for psoriasis, psoriatic arthritis, and other inflammatory diseases.

[b]Prior biologic treatment use includes subjects who had ever received a biologic. Subjects could have also received a non-biologic.

Abbreviations: APR - apremilast; DEUC- deucravacitinib; CSR - clinical study report

Source: Table 5.3.2-1 in the IM011046 Primary CSR, Table 5.3.2-1 in the IM011047 Primary CSR, and Table S.3.2 (disease characteristics pooled) in Appendix 3

In IM011046, a greater proportion of subjects had prior systemic biologic use compared with IM011047; in IM011047, a greater proportion of subjects were naïve to prior systemic treatment compared with IM011046, which may be attributed to regional distribution of the IM011046 and IM011047 study populations.

- **Outcomes and estimation**

Pooled results

At week 16, statistical significance was achieved for the DEUC group compared with placebo and Apremilast for the co-primary endpoints (sPGA 0/1 and PASI 75) and for all the key secondary endpoints in the statistical hierarchy including scalp localisation of psoriasis. It is of note that versus apremilast, fingernail and palmoplantar psoriasis scores (PGA-F 0/1 and pp-PGA) were not statistically significant at week 16 (p=0.1601 and p=0.4329 respectively).

At week 24, nominal significance was also achieved versus Apremilast with increase in co-primary endpoints for DEUC only.

Different Patient-reported Outcomes (PRO) and Health-related Quality of Life Measures were assessed such as PSSD Symptom and Sign scores and DLQI. Statistically significant differences in favour of DEUC versus placebo were observed for improvement for these scores in both pivotal studies.

Nominal significant difference between DEUC and Apremilast were also observed at week 16 which was maintained at Week 24.

Table 29 Summary of Selected Efficacy Endpoints from the Controlled Phase 3 Studies (IM011046 and IM011047)

	IM011046			IM011047			Pooled IM011046 and IM011047		
	DEUC	**Placebo (p-value)**	**Apremilast (p-value)**	**DEUC**	**Placebo (p-value)**	**Apremilast (p-value)**	**DEUC**	**Placebo (p-value)**	**Apremilast (p-value)**
sPGA									
sPGA 0/1 at Week 16	53.6%	7.2% **(< 0.0001)**	32.1% **(< 0.0001)**	49.5%	8.6% **(< 0.0001)**	33.9% **(< 0.0001)**	51.1%	8.1% *(< 0.0001)*	33.2% *(< 0.0001)*
sPGA 0 at Week 16	17.5%	0.6% **(< 0.0001)**	4.8% **(< 0.0001)**	15.7%	1.2% **(< 0.0001)**	6.3% **(0.0002)**	16.4%	1.0% *(< 0.0001)*	5.7% *(< 0.0001)*
sPGA 0/1 at Week 24	58.7%	--	31.0% **(< 0.0001)**	49.8%	--	29.5% **(< 0.0001)**	53.3%	--	30.1% *(< 0.0001)*
sPGA 0 at Week 24	20.2%	--	10.1% *(0.0044)*	17.1%	--	7.9% *(0.0004)*	18.3%	--	8.8% *(< 0.0001)*
sPGA 0/1 at Week 52 and 24	45.5%	--	22.2% **(< 0.0001)**	--	--	--	--	--	--
PASI									
PASI 75 at Week 16	58.4%	12.7% **(< 0.0001)**	35.1% **(< 0.0001)**	53.0%	9.4% **(< 0.0001)**	39.8% **(0.0004)**	55.2%	10.7% *(< 0.0001)*	37.9% *(< 0.0001)*
PASI 90 at Week 16	35.5%	4.2% **(< 0.0001)**	19.6% **(0.0002)**	27.0%	2.7% **(< 0.0001)**	18.1% **(0.0046)**	30.4%	3.3% *(< 0.0001)*	18.7% *(< 0.0001)*
PASI 100 at Week 16	14.2%	0.6% **(< 0.0001)**	3.0% *(< 0.0001)*	10.2%	1.2% **(< 0.0001)**	4.3% *(0.0051)*	11.7%	1.0% *(< 0.0001)*	3.8% *(< 0.0001)*
PASI 75 at Week 24	69.3%	--	38.1% **(< 0.0001)**	58.7%	--	37.8% **(< 0.0001)**	62.9%	--	37.9% *(< 0.0001)*
PASI 90 at Week 24	42.2%	--	22.0% **(< 0.0001)**	32.5%	--	19.7% **(0.0001)**	36.4%	--	20.6% *(< 0.0001)*
PASI 100 at Week 24	17.5%	--	6.5% *(0.0007)*	13.1%	--	6.7% *(0.0066)*	14.8%	--	6.6% *(< 0.0001)*
PASI 75 at Week 52 and 24	56.3%	--	30.5% **(< 0.0001)**	--	--	--	--	--	--
PASI 90 at Week 52 and 24	31.0%	--	15.6% **(0.0002)**	--	--	--	--	--	--
Scalp, Fingernail, and Palmoplantar Psoriasis									
ss-PGA 0/1 at Week 16	70.3%	17.4% **(< 0.0001)**	39.1% **(< 0.0001)**	59.7%	17.3% **(< 0.0001)**	36.7% **(< 0.0001)**	64.0%	17.3% *(< 0.0001)*	37.7% *(< 0.0001)*

	IM011046			IM011047			Pooled IM011046 and IM011047		
	DEUC	**Placebo (p-value)**	**Apremilast (p-value)**	**DEUC**	**Placebo (p-value)**	**Apremilast (p-value)**	**DEUC**	**Placebo (p-value)**	**Apremilast (p-value)**
PSSI 90 at Week 16	57.9%	11.6% (< 0.0001)	26.4% *(< 0.0001)*	45.6%	9.8% *(< 0.0001)*	25.9% *(< 0.0001)*	50.6%	10.5% *(< 0.0001)*	26.1% *(< 0.0001)*
PGA-F 0/1 at Week 16	20.9%	8.8% (0.1049)	35.3% (0.5493)	20.3%	7.9% (0.0621)	27.7% (0.3891)	20.5%	8.3% *(0.0272)*	29.7% (0.1601)
pp-PGA 0/1 at Week 16	55.6%	0 [a]	42.9% (0.1244)	46.2%	23.5% (0.0594)	40.0% (0.7529)	49.1%	16.0% *(0.0052)*	41.2% (0.4329)
Patient-Reported Outcomes									
PSSD Symptom Score of 0 at Week 16	7.9%	0.7% **(0.0013)**	4.4% (0.1702)	7.5%	1.3% **(0.0005)**	4.3% (0.0928)	7.7%	1.0% *(< 0.0001)*	4.4% *(0.0321)*
CFB in PSSD Symptom Score at Week 16[b]	-26.7	-3.6 *(< 0.0001)*	-17.8 **(< 0.0001)**	-28.3	-4.7 *(< 0.0001)*	-21.1 **(< 0.0001)**	-27.2	-3.8 *(< 0.0001)*	-19.3 *(< 0.0001)*
DLQI 0/1 at Week 16	41.0%	10.6% **(< 0.0001)**	28.6% *(0.0088)*	37.6%	9.8% **(< 0.0001)**	23.1% *(< 0.0001)*	38.9%	10.1% *(< 0.0001)*	25.2% *(< 0.0001)*

[a] The p value could not be calculated because there were 0 responders in the placebo group. The difference from placebo was 41.5 (95% CI: 6.8, 76.1).

[b] Adjusted mean

p-values were obtained using a stratified Cochran-Mantel-Haenszel test.

p-values are DEUC compared with placebo and DEUC compared with apremilast.

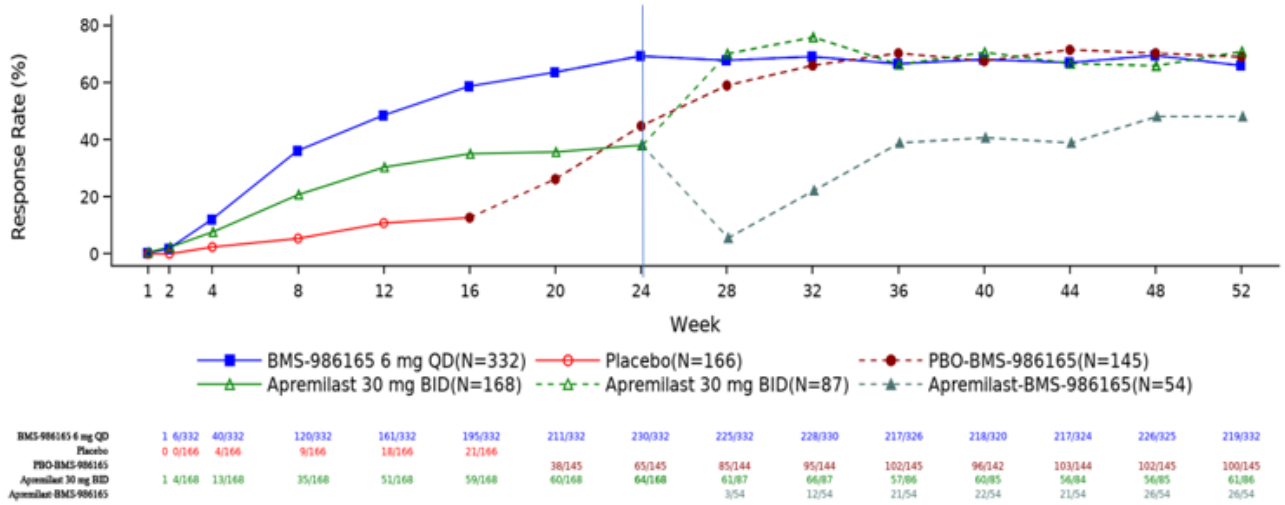
Statistically significant p-values are designated using boldface type and nominally significant p-values are designated using italicized type

Efficacy over Time (IM011046 and IM011047)

Efficacy at Week 52 was assessed in both studies.

In **IM011046**, among subjects who were randomized to DEUC on Day 1 and achieved a PASI 75 response at Week 24, 81.3% (n=187/230) maintained a PASI 75 response and 77.4% (n=151/195) maintained a sPGA0/1 response, at week 52.

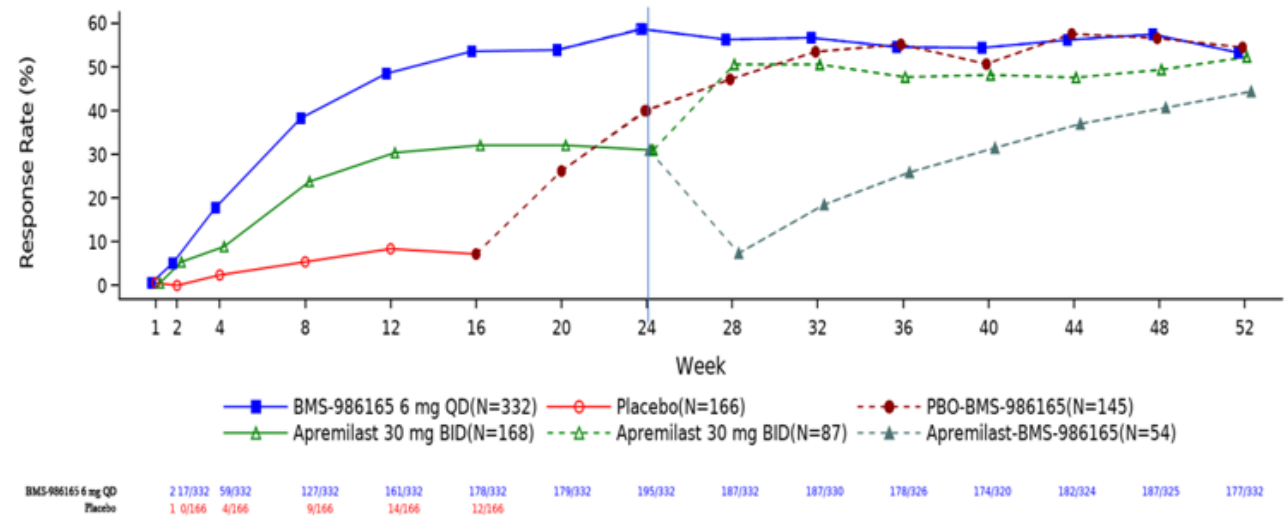
Figure 21 PASI 75 Response: Week 1 Through Week 52 - NRI (IM011046)



BMS-986165 6 mg QD	1 6/332	40/332	120/332	161/332	195/332	211/332	230/332	225/332	228/330	217/326	218/320	217/324	226/325	219/332
Placebo	0 0/166	4/166	9/166	18/166	21/166									
PBO-BMS-986165						38/145	65/145	85/144	95/144	102/145	96/142	103/144	102/145	100/145
Apremilast 30 mg BID	1 4/168	13/168	35/168	51/168	59/168	60/168	64/168	61/87	66/87	57/86	60/85	56/84	56/85	61/86
Apremilast-BMS-986165								3/54	12/54	21/54	22/54	21/54	26/54	26/54

The green closed triangles represent PASI 50 non-responders in the apremilast group at Week 24 who were switched to DEUC, and the green open triangles represent the PASI 50 responders in the apremilast group at Week 24 who continued on apremilast.

Figure 22 sPGA 0/1 Response: Week 1 Through Week 52 - NRI (IM011046)



BMS-986165 6 mg QD	2 17/332	59/332	127/332	161/332	178/332	179/332	195/332	187/332	187/330	178/326	174/320	182/324	187/325	177/332
Placebo	1 0/166	4/166	9/166	14/166	12/166									
PBO-BMS-986165						38/145	58/145	68/144	77/144	80/145	72/142	83/144	82/145	79/145
Apremilast 30 mg BID	1 9/168	15/168	40/168	51/168	54/168	54/168	52/168	44/87	44/87	41/86	41/85	40/84	42/85	45/86
Apremilast-BMS-986165								4/54	10/54	14/54	17/54	20/54	22/54	24/54

The green closed triangles represent PASI 50 non-responders in the apremilast group at Week 24 who were switched to DEUC, and the green open triangles represent the PASI 50 responders in the apremilast group at Week 24 who continued on apremilast.

Results of sPGA 0/1 and PASI 75 responses are presented at weeks 16, 24 and 52 in the **Table 30** and **Table 31** below for Study IM011046 and IM011047.

Table 30 Study IM011046 – Response rate at Week 16, 24 and 52 - FAS

%Responders	**DEUC N=332**		**Placebo N=166**		**Apremilast N=168**			
At week 16	sPGA 0/1	PASI 75	sPGA 0/1	PASI 75	sPGA 0/1		PASI 75	
	53.6%	58.4%	7.2%	12.7%	32.1%		35.1%	
At week 24	**DEUC N=332**		**Pbo-DEUC N=145**		**Apremilast If ⩾ PASI 50 N=168**		**Apre-DEUC If < PASI 50**	
	58.7%	69.3%	39.3%	44.1%	31.0%	38.1%	-	-
At week 52	N=332		N=145		N=86		N=54	
	52.7%	65.1%	53.8%	68.3%	51.2%	69.8%	42.6%	46.3%

From S.5.22.11 and S.5.22.12, study IM011046

Table 31 Study IM011047 - Response rate at Week 16, 24 and 52 - FAS

%Responders	**DEUC**						**Apremilast**			
	sPGA 0/1		PASI 75				sPGA 0/1		PASI 75	
At week 16	N=511		N=511				N=168		N=254	
	49.5%		53.0%				33.9%		39.8%	
	If ⩾ PASI 75				**If < PASI 75**		**If ⩾ PASI 75**		**If < PASI 75**	
	DEUC-Pbo Pbo-DEUC if relapse		**DEUC-DEUC**		**DEUC-DEUC**		**Apr-Pbo Pbo-DEUC if relapse**		**Apr-DEUC**	
At week 24	N=150	N=150	N=148	N=148	N=136	N=136	N=97	N=97	N=111	N=111
	79.3%	100%	79.7%	98.0%	10.3%	0	71.1%	97.9%	4.5%	0
At week 52	N=150	N=150	N=148	N=148	N=143	N=143	N=97	N=97	N=111	N=111
	23.3%	31.3%	63.5%	80.4%	22.4%	31.5%	17.5%	26.8%	27.0%	42.3%

From S.5.22.11 and S.5.22.12, study IM011047 - The placebo arm is not shown.

Given the randomized maintenance and withdrawal design of the study, maintenance and durability were assessed in **IM011047**. Subjects initially randomized to the DEUC group on Day 1, who had achieved a PASI 75 response at Week 24, were re-randomized 1:1 to either continue DEUC treatment (maintenance group) or to be withdrawn from DEUC treatment and treated with placebo (withdrawal group). Durability of response (loss of response or relapse) after drug withdrawal was assessed given the randomized withdrawal design.

Among subjects who were randomized to DEUC on Day 1 and achieved PASI 75 response at Week 24, 80.4% (119/148) of subjects re-randomized to DEUC had a PASI 75 response at Week 52 compared with 31.3% (47/150) of subjects who were re-randomized to placebo.

Among subjects who were randomized to DEUC on Day 1 and achieved sPGA 0/1 response at Week 24, 70.3% (83/118) of subjects re-randomized to DEUC had a sPGA 0/1 response at Week 52 compared with 23.5% (28/119) of subjects who were re-randomized to placebo.

Durability of Response from week 24 through Week 52 (IM011047 only)

The durability of DEUC effects in terms of co-primary endpoints was assessed as the time to loss of effect defined as the time to the first loss of PASI 75 and sPGA 0/1 response after re-randomization at Week 24 among subjects who were PASI 75 responders at Week 24.

Among subjects re-randomized from DEUC to placebo at Week 24, the loss of sPGA 0/1 response and PASI 75 response occurred as early as the first assessment, approximately 4 weeks after withdrawal of therapy.

The median time to loss of sPGA 0/1 response was 57 days (approximately 8 weeks) and the median time to loss of PASI 75 response was 85 days (approximately 12 weeks).

The time to relapse was a key secondary efficacy endpoint, where relapse was defined as a loss of 50% or more of the Week 24 PASI response among subjects who had a PASI 75 response in the DEUC group and were re-randomized at Week 24. The median time to relapse could not be estimated in either the DEUC or the placebo group because less than 50% of the subjects relapsed through Week 52 that is, among subjects re-randomized to placebo, the median time to relapse was > 196 days (6.5 months approximately).

Rebound

A retrospective post-hoc review was conducted and no subjects rebounded (had worsening psoriasis over baseline [measured as a PASI score >125% over the baseline PASI score] or had new pustular, erythrodermic or more inflammatory psoriasis occurring within 2 months [60 days] of stopping therapy) in any treatment group.

Recapture

There were only 150 subjects re-randomized to placebo at week 24, and due to IRT issues, 68 patients had not been switched to DEUC after experiencing relapse during withdrawal period. Due to this, no information on recapture of efficacy after retreatment could be obtained and no conclusion on continuous vs on demand treatment could be made. However, an analysis was performed on subjects who experienced a relapse on placebo in the withdrawal group and subsequently received DEUC treatment in the LTE study. Among these subjects (N = 54), 42 (77.8%) achieved PASI 75 by Week 16 and 48 (88.9%) achieved PASI 75 by Week 24 of the LTE study; 42 (77.8%) subjects achieved sPGA 0/1 by Week 16 and 40 (74.1%) subjects achieved sPGA 0/1 by Week 24 of the LTE study.

- **Ancillary analyses**

The efficacy of DEUC in subgroups was evaluated using the co-primary endpoints of PASI 75 and sPGA 0/1 response at Week 16. The subgroups analysed included demographic factors (i.e., sex, race, age, weight, BMI, geographic region), baseline disease characteristics (i.e., baseline PASI, sPGA, and BSA), and prior psoriasis therapy (i.e., phototherapy, conventional systemic therapy, and biologic therapy).

Based on the forest plot for the comparison of DEUC vs placebo, DEUC was superior to placebo across each subgroup factor regardless of baseline disease activity and prior systemic therapy.

Based on the forest plot for the comparison of DEUC and Apremilast, DEUC was superior to Apremilast across multiple subgroup factors where there were sufficient numbers of subjects across the treatment groups for a meaningful comparison.

However, some differences in effect size are noted in subgroup of patients from USA and patients with body weight ≥90 kg.

In study IM011046,

- Response rates of sPGA 0/1 at week 16 in patients with body weight <90 kg vs ≥90 kg were in DEUC group 62% (95%CI 55.3-68.7) vs 40.9% (95%CI 32.5-49.3), respectively.
- Response rates of PASI 75 at week 16 in patients with body weight <90 kg vs ≥90 kg were in DEUC group 64.5% (95%CI 57.9-71.1) vs 49.2% (95%CI 40.7-57.8), respectively. Response rates in

patients with body weight ≥90 kg were almost entirely outside of CI bounds for co-primary analyses (sPGA 0/1 53.6 and 95%CI 48.3, 59.0; PASI 75 58.4 and 95%CI 53.1, 63.7).

Also, some inconsistencies in effect size are observed in subgroups according to geographic region.

- Response rates of sPGA 0/1 at week 16 in ROW vs USA in DEUC group were 56.7% (95%CI 49.6-63.8) and 42.2% (95%CI 32.9-51.5), respectively.
- Response rates of PASI 75 at week 16 in ROW vs USA in DEUC group were 63.1% (95%CI 56.2-70.0) and 44% (95%CI 34.7-53.4), respectively.

Small number of included patients in Japan is acknowledged, however response rates of sPGA 0/1 and PASI 75 at week 16 in DEUC group were also higher compared to USA, i.e. 75% and 78.1% vs 42.2% and 44% in USA, respectively.

Similar differences are noted also in study IM011047.

- Response rates of sPGA 0/1 at week 16 in patients with body weight <90 kg vs ≥90 kg were in DEUC group 60.2% (95%CI 54.0-66.3) vs 40.0% (95%CI 34.2-45.8), respectively.
- Response rates of PASI 75 at week 16 in patients with body weight <90 kg vs ≥90 kg were in DEUC group 59.8% (95%CI 53.6-65.9) vs 47% (95%CI 41.1-53.0), respectively.

Response rates in patients with body weight ≥90 kg were lower than CI bounds for co-primary analyses (sPGA 0/1 49.5% and 95%CI 45.2-53.8; PASI 75 53% and 95%CI 48.7-57.4) with some overlap between CIs for PASI 75 response rate.

Similar results are also seen in subgroup analyses performed using pooled data:

- Response rates of sPGA 0/1 at week 16 in patients with body weight <90 kg vs ≥90 kg were in DEUC group 61.0% vs 40.3%, respectively.
- Response rates of PASI 75 at week 16 in patients with body weight <90 kg vs ≥90 kg were in DEUC group 61.9% vs 47.8%, respectively.

These results were discussed in the context of the results from the population pharmacokinetic (PPK) and E-R analysis. Increasing DEUC dose and consequently exposure, is not expected to meaningfully increase PASI 75 or sPGA0/1 response rates in any of these body weight subgroups.

- **Summary of main efficacy results**

The following **Table 32** and **Table 33** summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32 Summary of Efficacy for trial IM011046

Title: 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		
Study identifier	IM011046	
Design	52-week, multi-center, randomized, double-blind, double dummy, placebo and active comparator controlled Phase 3 study	
	Duration of main phase: Duration of Run-in phase:	52 weeks not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Superiority of DEUC 6 mg QD to placebo and superiority of DEUC 6 mg QD to apremilast.		
Treatments groups	DEUC 6mg QD		Deucravacitinib 6 mg QD for 52 weeks 332 randomized subjects
	Apremilast 30mg BID		Apremilast 30 mg BID for 24 weeks At Week 24, subjects who achieved Psoriasis Area and Severity Index (PASI 50) continued on apremilast until Week 52 At Week 24, subjects who did not achieve PASI 50 were switched to DEUC 6 mg QD until Week 52 168 randomized subjects
	Placebo		Placebo for 16 weeks. At Week 16, subjects were switched to DEUC 6 mg QD 166 randomized subjects
Endpoints and definitions	Co-Primary endpoint	sPGA 0/1 at Week 16	Proportion of subjects who achieved an sPGA score of 0 or 1 at Week 16 in subjects with ≥ 2-point improvement from baseline (DEUC vs placebo)
		PASI 75 at Week 16	Proportion of subjects with ≥ 75% improvement from baseline in PASI score at Week 16 (DEUC vs placebo)

	Key Secondary endpoint	sPGA 0/1 at Week 16	Proportion of subjects who achieved sPGA 0/1 at Week 16 in subjects with ≥ 2-point improvement from baseline (vs apremilast)
		PASI 75 at Week 16	Proportion of subjects with ≥ 75% improvement from baseline in PASI score at Week 16 (vs apremilast)
		PASI 90 at Week 16	Proportion of subjects with ≥ 90% improvement from baseline in the PASI score at Week 16 (vs placebo and vs apremilast)
		ss-PGA 0/1 at Week 16	Proportion of subjects who achieved ss-PGA 0/1 in subjects with ≥ 2-point improvement from baseline and a baseline ss-PGA ≥ 3 at Week 16 (vs placebo and vs apremilast)
		sPGA 0 at Week 16	Proportion of subjects who achieved sPGA score of 0 at Week 16 (vs placebo and vs apremilast)
		PASI 100 at Week 16	Proportion of subjects with ≥ 100% improvement from baseline in the PASI score at Week 16 (vs placebo)
		PSSD Symptom Score 0 at Week 16	Proportion of subjects who achieved PSSD Symptom Score of 0 in subjects with a baseline PSSD Symptom Score ≥ 1 at Week 16 (vs placebo and vs apremilast)
		DLQI 0/1 at Week 16	Proportion of subjects who achieved DLQI 0/1 in subjects with a baseline DLQI score ≥ 2 at Week 16 (vs placebo)
		PGA-F 0/1 at Week 16	Proportion of subjects who achieved PGA-F 0/1 in subjects with ≥ 2-point improvement from baseline and a baseline PGA F score ≥ 3 at Week 16 (vs placebo)

		sPGA 0/1 at Week 24	Proportion of subjects who achieved sPGA 0/1 at Week 24 in subjects with ≥ 2-point improvement from baseline (vs apremilast)
		PASI 75 at Week 24	Proportion of subjects with ≥ 75% improvement from baseline in the PASI score at Week 24 (vs apremilast)
		PASI 90 at Week 24	Proportion of subjects with ≥ 90% improvement from baseline in the PASI score at Week 24 (vs apremilast)
		CFB in PSSD Symptom Score at Week 16	Mean change from baseline (CFB) in PSSD Symptom Score at Week 16 (vs apremilast)
		sPGA 0/1 at Week 52 & 24	Proportion of subjects who achieved sPGA 0/1 at Week 52 and 24 in subjects with ≥ 2-point improvement from baseline (vs apremilast)
		PASI 75 at Week 52 & 24	Proportion of subjects with ≥ 75% improvement from baseline in the PASI score at Week 52 and 24 (vs apremilast)
		PASI 90 at Week 52 & 24	Proportion of subjects with ≥ 90% improvement from baseline in the PASI score at Week 52 and 24 (vs apremilast)
		sPGA 0 at Week 16	Proportion of subjects who achieved sPGA 0 at Week 16 (vs apremilast)
		PSSD Symptom Score of 0 at Week 16	Proportion of subjects who achieved PSSD symptom score of 0 at Week 16 in subjects with a baseline PSSD symptom score ≥ 1 (vs apremilast)
Database lock	15-Oct-2020		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	DEUC 6 mg QD	Placebo	Apremilast
	Number of subject	332	166	168
	sPGA 0/1 at Week 16, % (95% CI)	53.6 (48.3, 59.0)	7.2 (3.3, 11.2)	32.1 (25.1, 39.2)
	PASI 75 at Week 16, % (95% CI)	58.4 (53.1, 63.7)	12.7 (7.6, 17.7)	35.1 (27.9, 42.3)
	PASI 90 at Week 16, % (95% CI)	35.5 (30.4, 40.7)	4.2 (1.2, 7.3)	19.6 (13.6, 25.7)

	ss-PGA 0/1 at Week 16, % (95% CI)	70.3 (64.1, 76.5)	17.4 (10.6, 24.1)	39.1 (30.0, 48.2)
	sPGA 0 at Week 16, % (95% CI)	17.5 (13.4, 21.6)	0.6 (0.0, 1.8)	4.8 (1.5, 8.0)
	PASI 100 at Week 16, % (95% CI)	14.2 (10.4, 17.9)	0.6 (0.0, 1.8)	3.0 (0.4, 5.5)
	PSSD Symptom Score 0 at Week 16, % (95% CI)	7.9 (4.8, 10.9)	0.7 (0.0, 2.0)	4.4 (1.2, 7.6)
	DLQI 0/1 at Week 16, % (95% CI)	41.0 (35.6, 46.4)	10.6 (5.9, 15.4)	28.6 (21.6, 35.5)
	PGA-F 0/1 at Week 16, % (95% CI)	20.9 (8.8, 33.1)	8.8 (0.0, 18.4)	35.3 (12.6, 58.0)
	sPGA 0/1 at Week 24, % (95% CI)	58.7 (53.4, 64.0)	NA	31.0 (24.0, 37.9)
	PASI 75 at Week 24, % (95% CI)	69.3 (64.3, 74.2)	NA	38.1 (30.8, 45.4)
	PASI 90 at Week 24, % (95% CI)	42.2 (36.9, 47.5)	NA	22.0 (15.8, 28.3)
	CFB in PSSD Symptom Score at Week 16, Adjusted Mean CFB (SE)	-26.7 (1.78)	-3.6 (2.13)	-17.8 (2.16)
	PASI 75 at Week 52 & 24, % (95% CI)	56.3 (51.0, 61.7)	NA	30.5 (23.6, 37.5)
	PASI 90 at Week 52 & 24, % (95% CI)	31.0 (26.0, 36.0)	NA	15.6 (10.1, 21.1)
	sPGA 0/1 at Week 52 & 24, % (95% CI)	45.5 (40.1, 50.8)	NA	22.2 (15.9, 28.5)

Effect estimate per comparison	Co-Primary endpoints (both)	Comparison groups	DEUC vs placebo
		P-value[a]	p < 0.0001
	Key Secondary endpoints (all)	Comparison groups	DEUC vs placebo
		P-value	p ≤ 0.0013 for all key secondary endpoints in the statistical testing hierarchy except PGA F 0/1 at Week 16 p = 0.1049 for PGA F 0/1 at Week 16 (last key secondary endpoint in the statistical testing hierarchy for DEUC vs placebo)
		Comparison groups	DEUC vs apremilast

		P-value[a]	p ≤ 0.0002 for all key secondary endpoints in the statistical testing hierarchy except PSSD Symptom Score 0 at Week 16 p = 0.1702 for PSSD Symptom Score 0 at Week 16 (last key secondary endpoint in the statistical testing hierarchy for DEUC vs apremilast)
[a]p-value was obtained using a stratified Cochran-Mantel-Haenszel test with stratification factors geographic region, body weight and prior biologic use per randomization.			
Abbreviations: CFB - change from baseline; CFB - change from baseline; CI - confidence interval; CSR - clinical study report; DEUC - deucravacitinib; DLQI - Dermatology Life Quality Index; PASI - Psoriasis Area and Severity Index; PGA-F - Physician's Global Assessment-Fingernail; PSSD - Psoriasis Symptoms and Signs Diary; QD - once daily; sPGA - static Physician's Global Assessment; ss PGA - scalp-specific Physician's Global Assessment			

Table 33 Summary of Efficacy for trial IM011047

Title: 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		
Study identifier	IM011047	
Design	52-week, randomized, double-blind, double-dummy, placebo and active comparator controlled Phase 3 study with randomized withdrawal and retreatment	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks not applicable not applicable
Hypothesis	Superiority of DEUC 6 mg QD to placebo and superiority of DEUC 6 mg QD to apremilast.	
Treatments groups	DEUC 6mg QD	Deucravacitinib 6 mg QD for 24 weeks At Week 24, subjects who achieved PASI 75 response were re-randomized 1:1, in a blinded manner, to placebo or DEUC, in order to evaluate maintenance and durability of response. If subjects re randomized to placebo experienced a relapse (defined as at least a 50% loss of Week 24 PASI percent improvement from baseline) they were to be switched in a blinded manner, to DEUC until Week 52. At Week 24, subjects who did not achieve PASI 75 response continued to receive DEUC, until Week 52. 511 randomized subjects

	Apremilast 30mg BID		Apremilast 30 mg BID for 24 weeks At Week 24, subjects who achieved PASI 75 response were to be switched (in a blinded manner), to placebo and those who did not achieve PASI 75 response were to be switched (in a blinded manner) to DEUC through Week 52. If subjects re randomized to placebo experienced a relapse (defined as at least a 50% loss of Week 24 PASI percent improvement from baseline) they were to be switched, in a blinded manner, to DEUC until Week 52. 254 randomized subjects
	Placebo		Placebo for 16 weeks At Week 16, subjects were switched to DEUC 6 mg QD 255 randomized subjects
Endpoints and definitions	Co-Primary endpoint	sPGA 0/1 at Week 16	Proportion of subjects who achieved an sPGA 0/1 at Week 16 in subjects with ≥ 2-point improvement from baseline (DEUC vs placebo)
		PASI 75 at Week 16	Proportion of subjects with ≥ 75% improvement from baseline in PASI score at Week 16 (DEUC vs placebo)

	Key Secondary endpoint	sPGA 0/1 at Week 16	Proportion of subjects who achieved sPGA 0/1 at Week 16 in subjects with ≥ 2-point improvement from baseline (vs apremilast)
		PASI 75 at Week 16	Proportion of subjects with ≥ 75% improvement from baseline in PASI score at Week 16 (vs apremilast)
		PASI 90 at Week 16	Proportion of subjects with ≥ 90% improvement from baseline in the PASI score at Week 16 (vs placebo and vs apremilast)
		ss-PGA 0/1 at Week 16	Proportion of subjects who achieved ss-PGA 0/1 in subjects with ≥ 2-point improvement from baseline and a baseline ss-PGA ≥ 3 at Week 16 (vs placebo and vs apremilast)
		sPGA 0 at Week 16	Proportion of subjects who achieved sPGA score of 0 at Week 16 (vs placebo and vs apremilast)
		PASI 100 at Week 16	Proportion of subjects with ≥ 100% improvement from baseline in the PASI score at Week 16 (vs placebo)
		PSSD Symptom Score 0 at Week 16	Proportion of subjects who achieved PSSD Symptom Score of 0 in subjects with a baseline PSSD Symptom Score ≥ 1 at Week 16 (vs placebo and vs apremilast)
		DLQI 0/1 at Week 16	Proportion of subjects who achieved DLQI 0/1 in subjects with a baseline DLQI score ≥ 2 at Week 16 (vs placebo)
		Time to Relapse through Week 52	Relapse is defined as ≥ 50% loss of Week 24 PASI percent improvement from baseline among Week 24 PASI 75 responders (vs placebo)
		PGA-F 0/1 at Week 16	Proportion of subjects who achieved PGA-F 0/1 in subjects with ≥ 2-point improvement from baseline and a baseline PGA F score ≥ 3 at Week 16 (vs placebo)

		sPGA 0/1 at Week 24	Proportion of subjects who achieved sPGA 0/1 at Week 24 in subjects with ≥ 2-point improvement from baseline (vs apremilast)
		PASI 75 at Week 24	Proportion of subjects with ≥ 75% improvement from baseline in the PASI score at Week 24 (vs apremilast)
		PASI 90 at Week 24	Proportion of subjects with ≥ 90% improvement from baseline in the PASI score at Week 24 (vs apremilast)
		CFB in PSSD Symptom Score at Week 16	Mean change from baseline (CFB) in PSSD Symptom Score at Week 16 (vs apremilast)
Database lock	22-Dec-2020		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	DEUC 6 mg QD	Placebo	Apremilast
	Number of subject	511	255	254
	sPGA 0/1 at Week 16, % (95% CI)	49.5 (45.2, 53.8)	8.6 (5.2, 12.1)	33.9 (28.0, 39.7)
	PASI 75 at Week 16, % (95% CI)	53.0 (48.7, 57.4)	9.4 (5.8, 13.0)	39.8 (33.7, 45.8)
	PASI 90 at Week 16, % (95% CI)	27.0 (23.2, 30.9)	2.7 (0.7, 4.8)	18.1 (13.4, 22.8)
	ss-PGA 0/1 at Week 16, % (95% CI)	59.7 (54.2, 65.2)	17.3 (11.7, 23.0)	36.7 (29.4, 44.1)
	sPGA 0 at Week 16, % (95% CI)	15.7 (12.5, 18.8)	1.2 (0.0, 2.5)	6.3 (3.3, 9.3)
	PASI 100 at Week 16, % (95% CI)	10.2 (7.6, 12.8)	1.2 (0.0, 2.5)	4.3 (1.8, 6.8)
	PSSD Symptom Score 0 at Week 16, % (95% CI)	7.5 (5.1, 9.9)	1.3 (0.0, 2.7)	4.3 (1.7, 6.9)
	DLQI 0/1 at Week 16, % (95% CI)	37.6 (33.3, 41.8)	9.8 (6.0, 13.5)	23.1 (17.8, 28.3)
	Time to Relapse (after Week 24) through Week 52, days (95% CI)	Median NA	Median NA	197.0 (125.0, N.A)

	PGA-F 0/1 at Week 16, % (95% CI)	20.3 (10.8, 29.8)	7.9 (0.0, 16.5)	27.7 (14.9, 40.4)
	sPGA 0/1 at Week 24, % (95% CI)	49.8 (45.4, 54.2)	NA	29.5 (23.9, 35.1)
	PASI 75 at Week 24, % (95% CI)	58.7 (54.4, 63.0)	NA	37.8 (31.8, 43.8)
	PASI 90 at Week 24, % (95% CI)	32.5 (28.4, 36.6)	NA	19.7 (14.8, 24.6)
	CFB in PSSD Symptom Score at Week 16, Adjusted Mean CFB (SE)	-28.3 (1.05)	-4.7 (1.41)	-21.1 (1.44)

Effect estimate per comparison	Co-Primary endpoints (both)	Comparison groups	DEUC vs placebo
		P-value[a]	$p < 0.0001$
	Key Secondary endpoints (all)	Comparison groups	DEUC vs placebo
		P-value	$p \leq 0.0005$ for all key secondary endpoints in the statistical testing hierarchy except PGA F 0/1 at Week 16) $p = 0.0621$ for PGA F 0/1 at Week 16 (last key secondary endpoint in the statistical testing hierarchy)
		Comparison groups	DEUC vs apremilast
		P-value[a]	$p \leq 0.0046$ for all key secondary endpoints in the statistical testing hierarchy except PSSD Symptom Score 0 at Week 16 $p = 0.0928$ for PSSD Symptom Score 0 at Week 16 (last key secondary endpoint in the statistical testing hierarchy)

[a]p-value was obtained using a stratified Cochran-Mantel-Haenszel test with stratification factors geographic region, body weight and prior biologic use per randomization.

Abbreviations: CFB - change from baseline; CI - confidence interval; CSR - clinical study report; DEUC - deucravacitinib; DLQI - Dermatology Life Quality Index; PASI - Psoriasis Area and Severity Index; PGA-F - Physician's Global Assessment-Fingernail; PSSD - Psoriasis Symptoms and Signs Diary; QD - once daily; sPGA - static Physician's Global Assessment; ss PGA - scalp-specific Physician's Global Assessment

2.6.5.3. Clinical studies in special populations

No specific clinical study was performed in special populations.

Table 34 Age Categorization of Subjects Treated with Deucravacitinib

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	67/842	13/842	0/842
Controlled and Non-controlled Trials	131/1519	21/1519[a]	0/1519[a]

[a] One subject in the 75-84 age group transitioned to the 85+ age group prior to the start of the IM011075 study.

Source: Refer to Table S.2.1.1 and Table S.2.1.2 in the SCS

Controlled Safety Pool = Includes subjects treated with DEUC in Studies IM011046 and IM011047
Phase 3 Safety Pool = Includes subjects treated with DEUC in Studies IM011046 and IM011047 and subjects treated with DEUC in Study IM011075 as of the safety cutoff date of 15-Jun-2021.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The controlled Phase 3 studies had identical study designs until Week 24. The characteristics of the 2 pivotal studies allowed the efficacy data from the first 24 weeks to be pooled across IM011046 and IM011047 for an integrated analysis of the efficacy of DEUC 6 mg QD in subjects with moderate-to-severe psoriasis.

Table 35 Studies Pooled for Efficacy Analysis

Analysis Sets	Studies Included	Study Population and Treatment Period	Treatment Groups	Rationale
Efficacy Pool (N = 1686; N=666 from IM011046; N=1020 from IM011047)	IM011046 IM011047	Subjects randomized to treatment Through Week 16 (DEUC, apremilast, and placebo) and through Week 24 (DEUC and apremilast)	DEUC 6 mg QD Placebo Apremilast	Evaluate the efficacy of DEUC in subjects with moderate-to-severe psoriasis through Week 16 for comparison to placebo and through Week 24 for comparisons to apremilast during the double-blind, placebo- and active-controlled period of the Phase 3 studies

Abbreviations: DEUC - deucravacitinib; QD - once daily; SAP - Statistical Analysis Plan; SCE - summary of clinical efficacy

In pooled analysis, results for co-primary endpoints at week 16 for DEUC vs placebo were (nominally significant p values):

- sPGA 0/1 51.1% vs 8.1% (p<0.0001, OR 11.87 with 95% CI 8.15, 17.28)

- PASI 75 55.2% vs 10.7% (p<0.0001, OR 10.36 with 95%CI 7.38, 14.54).

In addition to PASI 75 and sPGA 0/1 responses, DEUC was superior to placebo and apremilast across both studies in multiple other secondary endpoints including more stringent measures of disease activity (PASI

90/100, sPGA 0), clinically meaningful improvements in symptom burden (PSSD symptom score), and quality of life measures (DLQI).

At week 16, DEUC demonstrated superiority to placebo in treatment of scalp psoriasis, and superiority was also nominally significant in treatment of fingernail and palmoplantar psoriasis.

DEUS was superior also to apremilast at week 16 and week 24 in treatment of scalp psoriasis, however no meaningful difference between DEUC and apremilast was observed in the assessment of fingernail or palmoplantar psoriasis.

Regarding PROs, in the pooled analysis, nominal statistical significance was achieved compared to placebo for PSSD symptom score 0 at week 16, and a greater proportion of subjects in the DEUC group compared with the apremilast group achieved PSSD Symptom Score of 0 at Week 16 (nominal $p = 0.0321$) and at Week 24 (nominal $p = 0.0007$). Results for the pooled mean change from baseline analysis were consistent with those for the individual studies: nominal $p < 0.0001$ for the comparison of DEUC compared with the placebo and apremilast groups at Week 16 and also compared with the apremilast group at Week 24. In both studies, a greater proportion of subjects in the DEUC group at Week 16 achieved, as per Applicant, clinically meaningful thresholds of 15, 25 and 30 points on the PSSD Symptom Score when compared to subjects in the placebo and apremilast groups. A similar trend was maintained at Week 24 between the DEUC and apremilast groups.

Treatment with DEUC also achieved greater improvement in the impact of psoriasis on quality of life at Week 16 and Week 24 using the DLQI score. In the pooled analysis, the proportion of subjects who achieved DLQI 0/1 in the DEUC group and the mean reduction from baseline in DLQI were greater than that for the placebo group at Week 16 and greater than for the apremilast group at Weeks 16 and Week 24 (nominal $p <0.0001$ for all comparisons), consistent with the results observed in the individual studies.

Analyses for the co-primary endpoints PASI 75 and sPGA 0/1 were conducted for the pooled population of IM011046 and IM011047 subjects by the number of prior systemic biologic treatments (0, 1, or ≥2).

Consistent with the data reported in the submitted MAA for the overall study population, a treatment effect in favor of DEUC over placebo and apremilast was observed in the analyses of PASI 75 (**Table 36**) and sPGA 0/1 (**Table 37**, **Table 38**, **Table 39** and **Table 40**) at Week 16, regardless of the number of prior systemic biologics used.

Table 36 PASI 75 Response at Week 16 NRI by Number of Prior Systemic Biologic Treatment for PsO/PsA, Pooled IM011046 and IM011047

	BMS-986165 6 mg QD N = 843	Placebo N = 421	Apremilast N = 422
Number of Prior Systemic Biologics Used for Psoriasis/Psoriatic Arthritis: 0			
TOTAL NUMBER OF SUBJECTS	548	275	277
RESPONDERS (%)	316 (57.7)	34 (12.4)	122 (44.0)
RESPONSE RATE (95% CI)	57.7 (53.5, 61.8)	12.4 (8.5, 16.3)	44.0 (38.2, 49.9)
DIFFERENCE (95% CI)			
VS PLACEBO	45.3 (39.7, 51.0)	N.A.	31.7 (24.6, 38.7)
VS APREMILAST	13.6 (6.5, 20.8)	N.A.	N.A.
Number of Prior Systemic Biologics Used for Psoriasis/Psoriatic Arthritis: 1			
TOTAL NUMBER OF SUBJECTS	198	100	95
RESPONDERS (%)	106 (53.5)	9 (9.0)	28 (29.5)
RESPONSE RATE (95% CI)	53.5 (46.6, 60.5)	9.0 (3.4, 14.6)	29.5 (20.3, 38.6)
DIFFERENCE (95% CI)			
VS PLACEBO	44.5 (35.6, 53.5)	N.A.	20.5 (9.7, 31.3)
VS APREMILAST	24.1 (12.6, 35.6)	N.A.	N.A.
Number of Prior Systemic Biologics Used for Psoriasis/Psoriatic Arthritis: >=2			
TOTAL NUMBER OF SUBJECTS	97	46	50
RESPONDERS (%)	43 (44.3)	2 (4.3)	10 (20.0)
RESPONSE RATE (95% CI)	44.3 (34.4, 54.2)	4.3 (0.0, 10.2)	20.0 (8.9, 31.1)
DIFFERENCE (95% CI)			
VS PLACEBO	40.0 (28.2, 51.8)	N.A.	15.5 (2.9, 28.1)
VS APREMILAST	25.5 (11.0, 39.9)	N.A.	N.A.

PASI 75 responder defined as a 75% improvement from baseline in the PASI score.
NRI = Nonresponder imputation
Difference (95% CI) are obtained using a stratified Cochran-Mantel-Haenszel (CMH) test with study as the stratification factor.
Includes data from IM011046 and IM011047.
Source: SCE Table S.4.4.31

Table 37 PASI 75 Response at Week 16 NRI by Number of Prior Systemic Biologic Treatment for PsO/PsA, Pooled IM011046 and IM011047

	BMS-986165 6 mg QD N = 843	Placebo N = 421	Apremilast N = 422
Number of Prior Systemic Biologics Used for Psoriasis/Psoriatic Arthritis: 0			
TOTAL NUMBER OF SUBJECTS	548	275	277
RESPONDERS (%)	290 (52.9)	24 (8.7)	106 (38.3)
RESPONSE RATE (95% CI)	52.9 (48.7, 57.1)	8.7 (5.4, 12.1)	38.3 (32.5, 44.0)
DIFFERENCE (95% CI)			
VS PLACEBO	44.2 (38.9, 49.6)	N.A.	29.5 (22.9, 36.1)
VS APREMILAST	14.7 (7.6, 21.7)	N.A.	N.A.
Number of Prior Systemic Biologics Used for Psoriasis/Psoriatic Arthritis: 1			
TOTAL NUMBER OF SUBJECTS	198	100	95
RESPONDERS (%)	98 (49.5)	8 (8.0)	27 (28.4)
RESPONSE RATE (95% CI)	49.5 (42.5, 56.5)	8.0 (2.7, 13.3)	28.4 (19.4, 37.5)
DIFFERENCE (95% CI)			
VS PLACEBO	41.5 (32.7, 50.3)	N.A.	20.4 (9.9, 30.9)
VS APREMILAST	21.1 (9.6, 32.5)	N.A.	N.A.
Number of Prior Systemic Biologics Used for Psoriasis/Psoriatic Arthritis: >=2			
TOTAL NUMBER OF SUBJECTS	97	46	50
RESPONDERS (%)	43 (44.3)	2 (4.3)	7 (14.0)
RESPONSE RATE (95% CI)	44.3 (34.4, 54.2)	4.3 (0.0, 10.2)	14.0 (4.4, 23.6)
DIFFERENCE (95% CI)			
VS PLACEBO	40.0 (28.5, 51.5)	N.A.	9.5 (-1.8, 20.7)
VS APREMILAST	30.7 (17.0, 44.4)	N.A.	N.A.

sPGA 0/1 responder defined as sPGA score of 0 or 1 with at least 2-point improvement from baseline.
NRI = Nonresponder imputation
Difference (95% CI) and odds ratio (95% CI) are obtained using a stratified Cochran-Mantel-Haenszel (CMH) test with study as the stratification factor.
Includes data from IM011046 and IM011047.
Source: SCE Table S.4.4.8

Previous biologic treatments were categorized into 5 types: anti-IL-12/23, anti-IL-23, anti-IL-17, anti-TNFalpha, and other. Subjects in the "other" category received agents such as alefacept, efalizumab, etc. Analyses for the co-primary endpoints PASI 75 and sPGA 0/1 were conducted by each type of biologic treatment (Yes/No).

Table 38 PASI 75 Response at Week 16 NRI by Type of Prior Systemic Biologic Treatment for Psoriasis/Psoriatic Arthritis (Full Analysis Set)

	BMS-986165 6 mg QD N = 843	Placebo N = 421	Apremilast N = 422
Prior Systemic Biologics: anti-IL-12/23 - Yes			
TOTAL NUMBER OF SUBJECTS	40	21	21
RESPONDERS (%)	18 (45.0)	2 (9.5)	3 (14.3)
RESPONSE RATE (95% CI)	45.0 (29.6, 60.4)	9.5 (0.0, 22.1)	14.3 (0.0, 29.3)
DIFFERENCE (95% CI)			
VS PLACEBO	35.7 (15.0, 56.4)	N.A.	4.7 (-15.7, 25.1)
VS APREMILAST	31.4 (10.4, 52.5)	N.A.	N.A.
Prior Systemic Biologics: anti-IL-23 - Yes			
TOTAL NUMBER OF SUBJECTS	29	21	25
RESPONDERS (%)	12 (41.4)	2 (9.5)	4 (16.0)
RESPONSE RATE (95% CI)	41.4 (23.5, 59.3)	9.5 (0.0, 22.1)	16.0 (1.6, 30.4)
DIFFERENCE (95% CI)			
VS PLACEBO	30.8 (8.0, 53.5)	N.A.	6.0 (-14.6, 26.6)
VS APREMILAST	25.4 (2.3, 48.5)	N.A.	N.A.
Prior Systemic Biologics: anti-IL-17 - Yes			
TOTAL NUMBER OF SUBJECTS	142	68	70
RESPONDERS (%)	73 (51.4)	3 (4.4)	17 (24.3)
RESPONSE RATE (95% CI)	51.4 (43.2, 59.6)	4.4 (0.0, 9.3)	24.3 (14.2, 34.3)
DIFFERENCE (95% CI)			
VS PLACEBO	46.1 (36.4, 55.9)	N.A.	19.5 (8.3, 30.7)
VS APREMILAST	27.6 (14.8, 40.5)	N.A.	N.A.
Prior Systemic Biologics: anti-TNF-alpha - Yes			
TOTAL NUMBER OF SUBJECTS	143	59	69
RESPONDERS (%)	72 (50.3)	4 (6.8)	18 (26.1)
RESPONSE RATE (95% CI)	50.3 (42.2, 58.5)	6.8 (0.4, 13.2)	26.1 (15.7, 36.4)
DIFFERENCE (95% CI)			
VS PLACEBO	44.7 (34.4, 55.1)	N.A.	19.7 (7.5, 32.0)
VS APREMILAST	24.4 (11.3, 37.4)	N.A.	N.A.
Prior Systemic Biologics: Other			
TOTAL NUMBER OF SUBJECTS	26	12	10
RESPONDERS (%)	11 (42.3)	3 (25.0)	3 (30.0)
RESPONSE RATE (95% CI)	42.3 (23.3, 61.3)	25.0 (0.5, 49.5)	30.0 (1.6, 58.4)
DIFFERENCE (95% CI)			
VS PLACEBO	16.9 (-15.1, 48.8)	N.A.	-6.9 (-45.0, 31.2)
VS APREMILAST	14.6 (-19.7, 48.9)	N.A.	N.A.

PASI 75 responder defined as a >= 75% improvement from baseline in the PASI score.
NRI = Nonresponder Imputation.
Subjects with multiple prior systemic biologic treatments for psoriasis/psoriatic arthritis are counted in each applicable Yes category.
Other category includes subjects with prior systemic biologic medications for psoriasis/psoriatic arthritis that were not in any of the types of interest.
Difference (95% CI), odds ratio (95% CI) and p-value are obtained using a stratified Cochran-Mantel-Haenszel (CMH) test with study as the stratification factor.
Includes data from IM011046 and IM011047.
Source: Table 2.11.1

Table 39 sPGA 0/1 Response at Week 16: NRI by Type of Prior Systemic Biologic Treatment for Psoriasis/Psoriatic Arthritis (Full Analysis Set)

	BMS-986165 6 mg QD N = 843	Placebo N = 421	Apremilast N = 422
Prior Systemic Biologics: anti-IL-12/23 - Yes			
TOTAL NUMBER OF SUBJECTS	40	21	21
RESPONDERS (%)	16 (40.0)	1 (4.8)	1 (4.8)
RESPONSE RATE (95% CI)	40.0 (24.8, 55.2)	4.8 (0.0, 13.9)	4.8 (0.0, 13.9)
DIFFERENCE (95% CI)			
VS PLACEBO	34.9 (16.9, 53.0)	N.A.	0.0 (-13.5, 13.6)
VS APREMILAST	35.4 (17.8, 53.1)	N.A.	N.A.
Prior Systemic Biologics: anti-IL-23 - Yes			
TOTAL NUMBER OF SUBJECTS	29	21	25
RESPONDERS (%)	13 (44.8)	2 (9.5)	4 (16.0)
RESPONSE RATE (95% CI)	44.8 (26.7, 62.9)	9.5 (0.0, 22.1)	16.0 (1.6, 30.4)
DIFFERENCE (95% CI)			
VS PLACEBO	35.0 (12.1, 58.0)	N.A.	6.0 (-14.6, 26.6)
VS APREMILAST	28.5 (5.3, 51.7)	N.A.	N.A.
Prior Systemic Biologics: anti-IL-17 - Yes			
TOTAL NUMBER OF SUBJECTS	142	68	70
RESPONDERS (%)	67 (47.2)	3 (4.4)	15 (21.4)
RESPONSE RATE (95% CI)	47.2 (39.0, 55.4)	4.4 (0.0, 9.3)	21.4 (11.8, 31.0)
DIFFERENCE (95% CI)			
VS PLACEBO	42.7 (33.1, 52.3)	N.A.	17.7 (6.9, 28.5)
VS APREMILAST	25.9 (13.2, 38.5)	N.A.	N.A.
Prior Systemic Biologics: anti-TNF-alpha - Yes			
TOTAL NUMBER OF SUBJECTS	143	59	69
RESPONDERS (%)	68 (47.6)	3 (5.1)	16 (23.2)
RESPONSE RATE (95% CI)	47.6 (39.4, 55.7)	5.1 (0.0, 10.7)	23.2 (13.2, 33.1)
DIFFERENCE (95% CI)			
VS PLACEBO	42.9 (32.9, 52.9)	N.A.	18.6 (7.0, 30.2)
VS APREMILAST	24.4 (11.6, 37.2)	N.A.	N.A.
Prior Systemic Biologics: Other			
TOTAL NUMBER OF SUBJECTS	26	12	10
RESPONDERS (%)	13 (50.0)	3 (25.0)	2 (20.0)
RESPONSE RATE (95% CI)	50.0 (30.8, 69.2)	25.0 (0.5, 49.5)	20.0 (0.0, 44.8)
DIFFERENCE (95% CI)			
VS PLACEBO	22.0 (-9.9, 53.9)	N.A.	-3.4 (-45.1, 38.2)
VS APREMILAST	31.7 (-1.6, 64.9)	N.A.	N.A.

sPGA 0/1 responder defined as sPGA score of 0 or 1 with at least 2-point improvement from baseline.
NRI = Nonresponder Imputation.
Subjects with multiple prior systemic biologic treatments for psoriasis/psoriatic arthritis are counted in each applicable Yes category.
Other category includes subjects with prior systemic biologic medications for psoriasis/psoriatic arthritis that were not in any of the types of interest.
Difference (95% CI), odds ratio (95% CI) and p-value are obtained using a stratified Cochran-Mantel-Haenszel (CMH) test with study as the stratification factor.
Includes data from IM011046 and IM011047.
Source: Table 2.11.2

In subjects who had previously received a prior systemic biologic treatment for psoriasis or psoriatic arthritis, the reported reason for discontinuation was further examined. On the CRF, options for the reason for discontinuation were as follows: lack of efficacy; loss of access to treatment; side effects; or other. "Other" was selected as the most common reason for discontinuation and was chosen by investigators when the major reason for discontinuation did not fall into one of the alternative categories. Further descriptions of the "other" category described in a free text field were diverse, eg, end of a clinical trial, completion of treatment course, patient choice, and unknown. The category "loss of access to treatment" generally consisted of insurance issues or other socioeconomic factors. The category "side effects" suggested adverse events or intolerance as the reason for discontinuation.

Of the 586 subjects who received prior biologic treatment, 95 (16.2%) specified that discontinuation of prior biologic treatment was due to lack of efficacy. If lack of efficacy was the reported reason for discontinuation of prior biologic treatment, further specification was requested, with the following options: "failure to respond

at all" (ie, primary failure); "loss of initial response" (ie, loss of response); "specifics not known." This request was for each biologic, so a subject could have multiple reasons for discontinuation recorded if they had received two or more biologics and discontinued use for different reasons.

Regardless of the reason for discontinuation of prior systemic biologic treatment, DEUC response rates were generally consistent with that reported in the overall population. Greater responses were observed with DEUC compared to placebo across all prior biologic-treated subgroups. Responses observed with DEUC were generally numerically greater than apremilast as well, except in subgroups with small sample sizes limiting interpretability of the results (eg, PASI 75 results for the subgroup that discontinued due to side effects/intolerance).

Overall, results for the pooled analysis were consistent with those in the individual studies showing DEUC superiority over placebo across various endpoints and time-points and over apremilast, except in treatment of fingernail and palmoplantar psoriasis.

2.6.5.6. Supportive studies

Two studies were considered as supportive in terms of efficacy and pharmacodynamic data:

- IM011075 Long-Term Extension Phase 3 Study with efficacy data for persistency of response
- IM011084 Phase 2 study in psoriatic arthritis with pharmacodynamic objectives by biomarkers explorations.

IM011075 is a multi-year, multi-centre, open-label, Phase 3b study to evaluate the long-term safety, tolerability, and efficacy of DEUC 6 mg QD in the treatment of psoriasis of subjects who were previously enrolled in the parent studies. Applicable parent studies include IM011046, IM011047, IM011065 and IM011066.

IM011065 and IM011066 studies are 2 regional, ongoing Phase 3 studies in psoriasis with DEUC 6 mg QD. IM011065 is a double-blind, placebo-controlled, 52-week study being conducted in China, Singapore, South Korea, and Taiwan; IM011066 is a single-arm, open-label study being conducted in Japan.

An interim clinical study report presented safety, tolerability, and efficacy data from subjects who completed the parent studies IM011046 and IM011047 (both global studies) only.

A total of 1221 patients were treated with DEUC. As of 15-JUN-2021 cut-off date, there were 1163 subjects who had a total exposure to DEUC for at least 6 months (26 weeks), and 573 subjects for at least 52 weeks. The mean and median durations of exposure to DEUC were 358.3 and 357 days, respectively.

In the total population (N= 1221), sPGA 0/1 and PASI 75 response rates were improved or maintained over time.

- sPGA 0/1 response rates were 50.9% at Week 0 and improved through Week 48 (56.4%) and Week 60 (57.3%).

Table 40 sPGA 0/1 Response Over Time – As Observed (IM011075)

Group	Week 0	Week 16	Week 36	Week 48	Week 60
DEUC to DEUC	56.0% (529/944)	59.1% (535/905)	53.9% (440/817)	53.8% (315/586)	55.1% (98/178)
Placebo to DEUC	25.4% (50/197)	74.2% (144/194)	62.4% (103/165)	66.0% (66/100)	61.5% (16/26)
Apremilast to DEUC	53.8% (43/80)	66.2% (49/74)	76.1% (54/71)	66.1% (39/59)	75.0% (12/16)
Total	50.9% (622/1221)	62.1% (728/1173)	56.7% (597/1053)	56.4% (420/745)	57.3% (126/220)

Note: The Apremilast to DEUC group includes subjects in IM011046 who had PASI 50 response at Week 24 and continued on to enroll in IM011075

sPGA 0/1 response: score of 0 or 1 in subjects with ≥ 2-point improvement from baseline

Abbreviations: CSR - clinical study report; DEUC - deucravacitinib; sPGA - static Physician's Global Assessment

Source: Table S.5.1.1 in the IM011075 Interim CSR[7]

- PASI 75 response rates were 65.1% at Week 0 and were improved through Week 48 (75.7%) and maintained through Week 60 (75.0%).

Table 41 PASI 75 Response Over Time – As Observed (IM01175)

Group	Week 0	Week 16	Week 36	Week 48	Week 60
DEUC to DEUC	70.8% (668/944)	75.9% (687/905)	73.8% (603/817)	72.9% (427/586)	73.6% (131/178)
Placebo to DEUC	34.5% (68/197)	84.0% (163/194)	84.2% (139/165)	89.0% (89/100)	80.8% (21/26)
Apremilast to DEUC	73.8% (59/80)	86.5% (64/74)	91.5% (65/71)	81.4% (48/59)	81.3% (13/16)
Total	65.1% (795/1221)	77.9% (914/1173)	76.6% (807/1053)	75.7% (564/745)	75.0% (165/220)

Note: The Apremilast to DEUC group includes subjects in IM011046 who had PASI 50 response at Week 24 and continued on to enroll in IM011075

PASI 75: ≥ 75% improvement from baseline in the PASI score

Abbreviations: CSR - clinical study report; DEUC - deucravacitinib; PASI - Psoriasis Area and Severity Index

Source: Table S.5.1.2 in the IM011075 Interim CSR[7]

In subjects who were last treated with DEUC in their respective parent study (DEUC to DEUC; n = 944), sPGA 0/1 and PASI 75 response rates were maintained over time indicating long term maintenance of response up to at least Week 60.

- sPGA 0/1 response rates were 56.0% at Week 0 and were maintained through Week 48 (53.8%) and Week 60 (55.1%).
- PASI 75 response rates were 70.8% at Week 0 and were maintained through Week 48 (72.9%) and Week 60 (73.6%).

Similarly, subjects who were last treated with Apremilast in their respective parent study (IM011046 only) and switched to DEUC at Week 0 (Apremilast to DEUC; n = 80) demonstrated maintenance of sPGA 0/1 and PASI 75 response rates.

- sPGA 0/1 response rates were 53.8% at Week 0 and were maintained or improved through Week 48 (66.1%) and Week 60 (75.0%).
- PASI 75 response rates were 73.8% at Week 0 and were maintained through Week 48 (81.4%) and Week 60 (81.3%).

Subjects who were last treated with placebo in their respective parent study (IM011047 only) and switched to DEUC at Week 0 (placebo to DEUC; n = 197) experienced increases in sPGA 0/1 and PASI 75 response rates starting at Week 8 and were maintained through Week 60.

- sPGA 0/1 response rates increased from 25.4% at Week 0 to 63.6% at Week 8 and 74.2% at Week 16, and were maintained through Week 48 (66.0%) and Week 60 (61.5%).
- PASI 75 response rates were increased from 34.5% at Week 0 to 71.3% at Week 8 and 84.0% at Week 16, and maintained through Week 48 (89.0%) and Week 60 (80.8%).

Other measures of efficacy, including sPGA 0, PASI 90, PASI 100, and BSA involvement demonstrated similar trends.

IM011084 (Part A) was a Phase 2 study of DEUC in psoriatic arthritis of 16 weeks (completed, double-blind, and placebo-controlled). At the time of submission, a Part B of 36 weeks was ongoing with switch to DEUC or ustekinumab.

A total of 203 subjects were randomized. Baseline characteristics were similar across the 3 groups. A significant PASI 75 dose response relationship with DEUC was observed at Week 16 for subjects with baseline BSA 3% or more (secondary endpoint: 42.4% in the DEUC 6 mg QD group, 59.6% in the DEUC 12 mg QD group, and 20.4% in the placebo group; $p < 0.001$ for the dose-response relationship of DEUC).

It is of note that results indicated higher PASI response for 12 mg QD vs 6 mg QD.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy of deucravacitinib (DEUC) in the treatment of moderate to severe plaque psoriasis in adults is substantiated by 4 psoriasis studies including one Phase 2 study (IM011011), two Phase 3 studies (IM011046 and IM011047) and one ongoing Phase 3 open-label, long-term extension (LTE) study (IM011075) of the 2 pivotal studies. Development was in line with regulatory feedback received from the FDA and from the CHMP and is generally in line with the CHMP Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis (CHMP/EWP/2454/02 corr, effective June 2005). All clinical studies were GCP-compliant.

The dose ranging study**, IM011011** was a 12 week, randomized, double blind, placebo controlled, parallel group, Phase 2 study in subjects with moderate to severe plaque psoriasis. Subjects were randomly assigned to receive BMS-986165 (3 mg every other day [QOD], 3 mg once daily [QD], 3 mg twice daily [BID], 6 mg BID, 12 mg QD) or placebo.

The Applicant provided the rationale for deucravacitinib dose selection for Phase 3 clinical trials. The dose of 6 mg QD is based on data from FIH trial, Phase 2 dose-finding study, and E-R modelling (see section 2.6.3). The decision was based on efficacy exposure-response analysis, safety and tolerability profile of deucravacitinib, and convenience of QD over BID dosing. Of note, the concerned 6mg QD dose was not included in the dose-finding study or modelling exercise. It was concluded, based on simulations, that profiles of 3mg BID and 6mg QD would be comparable.

The 2 pivotal studies **(IM011046 and IM011047)** were multicentre, randomized, double-blind, placebo- and/or active comparator-controlled evaluations of the proposed dose and dosing regimen (deucravacitinib 6 mg QD) in adults with stable moderate to severe chronic plaque psoriasis ≥ 6 months; with or without psoriatic arthritis; body surface area (BSA) involvement ≥ 10%; PASI score ≥ 12; sPGA ≥ 3; and candidate for systemic therapy or phototherapy.

The enrollment criteria were in accordance with the EMA psoriasis guideline requirements. Following patients were excluded: those who had non-plaque forms of psoriasis, were using any restricted medication, had recent major surgery or underwent organ transplantation, had a history of malignancy, had concurrent chronic or relevant acute infections including active tuberculosis, HIV or viral hepatitis or women who were pregnant.

The statistical methods used for analysis of the primary and secondary endpoints were appropriate. The testing procedure adequately controlled the type I error for the co-primary and ranked secondary endpoints. The use of non-responder imputation as the primary method for handling missing data is considered acceptable in the context of the disease under study, the limited amount of missing data observed in each treatment group and the magnitude of the observed treatment effect.

Both study designs were in line with the current EMA guidance on clinical investigation of products for the treatment of psoriasis. The subsequent withdrawal phase allows examining the duration of response, rebound and time to relapse. The double-blind period of 16 weeks was deemed sufficient by the CHMP to establish short-term efficacy. The time for the assessment of the primary endpoint was scheduled on week 16 (in line with other phase 3 studies).

Across the 2 Phase 3 studies, the majority of subjects were White (approximately 87%) and male (approximately 67%), with a mean age of approximately 47 years with approximately 10% of subjects being ≥ 65 years of age. The overall proportions of female subjects and male subjects were similar, but the distribution by sex varied slightly across the treatment groups. Within each study the distribution of race was similar among the treatment groups; however, due to the different geographic footprints of the 2 studies there was a greater proportion of Asian race in IM011046 (total 18.2%) compared with IM011047 (total 4.3%). The studies population was appropriate and reflected the intended patient population.

Both pivotal studies assessed the co-primary endpoints of PASI 75 and sPGA of clear or almost clear (0 or 1) at Week 16 versus placebo and further evaluated deucravacitinib therapy over a longer duration in responder patients.

The sPGA was considered to be a validated, standardised, global score that is recommended to be used in conjunction with PASI. sPGA 0/1 endpoint was endorsed by CHMP, however PASI 75 is a less strict measure of efficacy (compared to PASI 90) and is considered acceptable only if a sufficient proportion of patients with severe psoriasis is included in the trials. Pivotal studies included somewhat lower proportion of severe patients according to sPGA compared to other studies in the field (only about 20% of patients had sPGA 4), however more than 40% of subject had PASI >20 and nearly 50% had BSA >20%, both of which also indicate severe psoriasis. Overall, considering the included population, PASI 75 is an acceptable efficacy

endpoint. Therefore, the use of PASI 75 and Static Physician Global Assessment (sPGA) (0 or 1) at Week 16 as co-primary endpoints was endorsed by CHMP.

Key secondary endpoints included more stringent measures of disease activity (PASI 90/100, sPGA 0), variation of the PASI adapted for the scalp psoriasis (ss-PGA) and the condition of the nails (PGA-F 0/1). Key secondary endpoints also included the Dermatology Life Quality Index (DLQI) and the Psoriasis Symptoms and Signs Diary (PSSD). The DLQI is a self-administered, 10-question, validated health-related quality of life (HRQoL) questionnaire that covers 6 domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The higher the score, the more the HRQoL is impaired. The PSSD is an 11-item subject-reported instrument used to assess the severity of symptoms and subject-observed signs commonly associated with plaque psoriasis.

Deucravacitinib was also evaluated versus Apremilast (second line treatment). As the pursued indication is treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy, the applicant considered that an oral compound would be a more appropriate choice than a biologic, and therefore apremilast was chosen. Additionally, the Applicant explained that methotrexate, cyclosporine, and fumarate preparations are approved systemic agents for the treatment of psoriasis in Europe, but due to significant toxicities associated with chronic use or only modest efficacy (fumarates) they were considered less suitable than apremilast as the active comparator in Phase 3 studies in psoriasis. The inclusion of an active comparator, in addition to placebo, in both clinical trials meets the CHMP guideline (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis, EMEA/CHMP/EWP/2454/02) requirement that a three-armed, parallel-group studies with the active agent, placebo and comparative active treatment are strongly recommended. A comparator with the same claimed indication, i.e. treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy may have been chosen. However this is considered acceptable for a marketing authorisation application as in line with the guideline and scientific advice, also taking into account that both studies met their objectives demonstrating superiority of deucravacitinib over placebo and over apremilast.

Additionally, both pivotal studies included a very heterogeneous population of patients regarding previous psoriasis treatment, with study IM011046 including 37% and study IM011047 46% of naive patients (overall 42.4% naïve subjects). Additional analyses for the co-primary endpoints PASI 75 and sPGA 0/1 in subgroups of patients with different prior systemic non-biologic therapies were performed, results are discussed below.

Key secondary endpoints versus Apremilast included sPGA 0/1 at Week 16, 24 and 52, PASI 75 and 90 at Week 16, 24 and 52. PSSD symptom score of 0 at week 16 and change from baseline in PSSD symptom score at Week 16. Ss-PGA 0/1 at Week 16 and sPGA 0 at Week 16.

Efficacy data and additional analyses

Study IM011011 (Phase 2)

The proportion of subjects who achieved PASI-75 on week 12 (Day 85) was statistically significantly higher than placebo in each of the active treatment groups (nominal p-values: 0.0003 for DEUC 3 mg QD and <0.0001 for DEUC 3 mg BID, DEUC 6 mg BID, and DEUC 12 mg QD).

The Applicant provided discussion on adequacy of the 6 mg QD dose in the context of the results from the population pharmacokinetic (PPK) and E-R analysis, which have been revised to address the concerns that were raised regarding the appropriateness of these models.

Studies IM011046 and IM011047 (Pivotal Phase 3 studies)

The Co-primary endpoints were met and the results were both clinically and statistically significant.

DEUC was superior to placebo for the co-primary endpoints at week 16: PASI 75 (58.4%-53.0% vs 12.7%-9.4% DEUC versus placebo respectively in studies 046 and 047) and sPGA of clear or almost clear (53.6%-49.5% vs 7.2%-8.6% DEUC versus placebo respectively in studies 046 and 047) ($p < 0.0001$).

DEUC was also superior to Apremilast at week 16 for PASI 75 (58.4% vs 35.1% in 046 and 53.0% vs 39.8% in 047) and sPGA 0/1 (53.6% vs 32.1% in 046 and 49.5% vs 33.9% in 047) both $p < 0.001$.

Apremilast also performed significantly better than placebo which supports internal validity of results.

Deucravacitinib also demonstrated superiority over placebo in all secondary endpoints at week 16, except in nail psoriasis (PGA-F 0/1). Deucravacitinib was superior to placebo in stricter measures of disease severity, i.e. PASI 90 (35.5% vs 4.2% and 27% vs 2.7% in studies 046 and 047, respectively) and PASI 100 (14.2% vs 0.6% and 10.2% vs 1.2% in studies 046 and 047, respectively), all $p<0.0001$.

Deucravacitinib also demonstrated superiority over apremilast in all secondary endpoints at week 16, except in PSSD symptom score 0. Deucravacitinib was superior to apremilast in stricter measure of disease severity, i.e. PASI 90 at week 16 (35.5% vs 19.6% and 27.0% vs 18.1%, in studies 046 and 047, respectively; both $p<0.005$) and at week 24 (42.2% vs 22.0% and 32.5% vs 19.7% in studies 046 and 047, respectively; both $p\leq0.0001$).

Deucravacitinib was superior to placebo for improving the extent and severity of scalp psoriasis in patients with baseline ssPGA $\geq$ 3 as demonstrated by statistically significant differences ($p< 0.0001$ for each comparison) between treatment groups at week 16 - ss-PGA 0/1 70.3% vs 17.4% and 59.7% vs 17.3% in studies 046 and 047, respectively and PSSI 90 57.9% vs 11.6% and 45.6% vs 9.8% in studies 046 and 047, respectively. Superiority of deucravacitinib in treatment of scalp psoriasis was also demonstrated compared to apremilast at week 16 and week 24.

The trials demonstrated a statistically and clinically significant improvement in plaque psoriasis in the patient population compared to placebo and compared with active comparator apremilast. Starting at Week 4, statistically significant differences in favour of deucravacitinib for proportions of subjects who achieved all levels of sPGA and PASI 75 response were observed.

Different Patient-reported Outcomes (PRO) and Health-related Quality of Life Measures were assessed such as PSSD Symptom and Sign scores and DLQI. Statistically significant differences in favour of deucravacitinib versus placebo were observed for improvement for these scores in both pivotal studies. Significant difference between deucravacitinib and apremilast were also observed at week 16 which was maintained at Week 24.

The DLQI 0/1 response rates for deucravacitinib vs placebo at week 16 were 41.0% vs 10.6% in IM011046, and 37.6% vs 9.8% in IM011047, respectively. DLQI 0/1 response was most frequent in patients with baseline DLQI 2-5 (small effect) and 6-10 (moderate effect), and the proportion of patients achieving DLQI 0/1 response diminished with higher baseline DLQI score, as could be expected. However, proportion of patients with DLQI 0/1 response at week 16 was in all categories highest in the deucravacitinib group compared to apremilast and placebo group.

Similar finding was observed regarding PSSD score – as could be expected, PSSD 0 symptom score was most frequent in patients with lower baseline PSSD score, i.e. 0-11 and 11-21, however, and as for DLQI 0/1 response, proportion of patients achieving PSSD 0 score at week 16 was highest in deucravacitinib group compared to placebo and apremilast arm in all categories, except PSSD 61-71. PSSD symptom score 0

response rates at week 16 for deucravacitinib vs placebo were 7.9% vs 0.7% in IM011046 and 7.5% vs 1.3% in IM011047, respectively. There was no significant difference in PSSD symptom score 0 response rates at week 16 between deucravacitinib and apremilast.

Considering that most patients had baseline DLQI score between 6 and 20 (moderate to severe effect) and baseline PSSD score above 21, change from baseline score to DLQI 0/1 and PSSD 0 could be considered relevant in overall population. These results have been included in section 5.1 of the SmPC.

Subgroup analysis

In both pivotal studies, the treatment effect of deucravacitinib versus placebo and versus Apremilast observed across subgroups was generally consistent with the overall treatment effect. Stratification factors for randomisation were geographic region, body weight and prior biologic therapy.

However, some inconsistencies in response rates were noted in few subgroups. Patients with body weight >90 kg had lower response rates compared to patients with body weight <90 kg. At the CHMP request, the Applicant provided additional data regarding this issue showing that superior efficacy of deucravacitinib compared to apremilast and placebo was maintained also in patients with higher body weight. Additionally, according to PK analyses, increasing deucravacitinib dose and consequently exposure, is not expected to meaningfully increase PASI 75 or sPGA0/1 response rates in patients with body weight >90 kg.

The Applicant provided analyses for the co-primary endpoints PASI 75 and sPGA 0/1 according to the number of prior systemic biologic therapies received and additional analyses by each of the 5 types of biologic treatment along with reasons for discontinuation.

Provided data are consistent with the results for the overall study population. As could be expected, the highest response rates were observed in patients naïve to biologics, and became lower with use of 2 or more previous biologic therapies in all three groups. However, regardless of number or type of previous biologic therapies, response rates for both co-primary endpoints at week 16 were consistently favouring deucravacitinib over placebo and apremilast.

Additional analyses were conducted to show deucravacitinib efficacy in subgroups of patients with various reasons for discontinuation of previous biologic therapy. Overall, 37.3% of patients who reported lack of efficacy with previous biologic therapy (primary failure or loss of response or not known), achieved PASI 75 and sPGA 0/1 response at week 16 in deucravacitinib group. PASI 75 and sPGA 0/1 response rates in patients who did not report lack of efficacy with previous biologic therapy was 53.3% and 50%, respectively.

Long-term results

IM011046: The maximum effect of deucravacitinib 6 mg QD was seen at week 24 then a decrease was observed until week 52. The PASI 75 response in subjects initially randomized to deucravacitinib was 58.4% at Week 16. The proportion of subjects achieving PASI 75 response continued to increase through Week 24 (69.3%) and persisted at Week 52 (65.1%).

Among subjects who were randomized to deucravacitinib on Day 1 and achieved:
- PASI 75 response at Week 24, 81.3% maintained PASI 75 response at Week 52.
- sPGA 0/1 response at Week 24, 77.4% maintained sPGA 0/1 response at Week 52.

The co-primary endpoints examined at week 52 showed consistent effects with week 16 results and achieved slightly lower efficacy, sPGA 0/1 (45.5% vs 22.2%) and PASI 75 (56.3% vs 30.5%) deucravacitinib vs apremilast respectively in study 046.

Around 80% of deucravacitinib responders at week-24 maintained their response through week-52 for the ss-PGA 0/1 and PSSI90 scalp assessment, demonstrating deucravacitinib ability to maintain efficacy also in scalp psoriasis.

IM011047: Given the randomized maintenance and withdrawal design of the study, maintenance and durability could both be assessed in IM011047. Subjects initially randomized to the deucravacitinib group on Day 1, who had achieved a PASI 75 response at Week 24, were re-randomized 1:1 to either continue deucravacitinib treatment (maintenance group) or to be withdrawn from deucravacitinib treatment and treated with placebo (withdrawal group).

Among subjects who were randomized to deucravacitinib on Day 1 and achieved:

- PASI 75 response at Week 24, 80.4% (119/148) of subjects re-randomized to deucravacitinib had PASI 75 response at Week 52 compared with 31.3% (47/150) of subjects who were re-randomized to placebo.
- sPGA 0/1 response at Week 24, 70.3% (83/118) of subjects re-randomized to deucravacitinib had sPGA 0/1 response at Week 52 compared with 23.5% (28/119) of subjects who were re-randomized to placebo.

These results reflected only the maintenance of deucravacitinib effects in the subgroup of patients responders at week 24 who continued on deucravacitinib until week 52. This is not an image of deucravacitinib global effect from week 1 to week 52.

The time to loss of effect was defined as the time to the first loss of PASI 75 or sPGA 0/1 response after re-randomization at Week 24 (Randomized Withdrawal and Maintenance Period). A lower proportion of subjects re-randomized to deucravacitinib experienced relapse (5.5%) compared with those re-randomized to placebo (45.3%) by Week 52. Since less than 50% subjects relapsed before Week 52 in each subpopulation, a median time to relapse could not be estimated. Among subjects re-randomized from deucravacitinib to placebo at Week 24, the loss of PASI 75 response occurred as early as the first assessment, approximately 4 weeks after withdrawal of therapy (at Week 24). The median time to loss of PASI 75 response was approximately 12 weeks and a median time to loss of sPGA 0/1 response was approximately 8 weeks.

Data on recapture rate upon retreatment are not available due to the IRT technical issues that prevented relapsed patients to be switched back to deucravacitinib in study IM011047. Due to this, no information on recapture of efficacy after retreatment could be obtained and no conclusion on continuous vs on demand treatment could be made.

A retrospective post-hoc review was conducted and no subjects rebounded (had worsening psoriasis over baseline [measured as a PASI score >125% over the baseline PASI score] or had new pustular, erythrodermic or more inflammatory psoriasis occurring within 2 months [60 days] of stopping therapy) in any treatment group.

Switching to deucravacitinib for subjects who had inadequate initial response to Apremilast (<PASI 50 for study 046 and <PASI 75 at Week 24 for study 047) led to improvement in PASI 75 and sPGA 0/1 response that were observed as early as Week 32 (8 weeks after the switch), with responses continuing to improve through Week 52.

Supportive data: Study IM011075

Study IM011075 is an OLE/ LTE study to characterise deucravacitinib long-term safety and efficacy. Data as of cut-off date of 15 Jun 2021 are submitted within the initial MAA. Planned duration is 240 Weeks.

IM011075 is a multi-year, multi-centre, open-label, Phase 3b study to evaluate the long-term safety, tolerability, and efficacy of deucravacitinib 6 mg QD in the treatment of psoriasis of subjects who were previously enrolled in the parent studies. An interim clinical study report presented safety, tolerability, and efficacy data from subjects who completed the parent studies IM011046 and IM011047 (both global studies) only.

As of cut-off date, 1221 patients have been enrolled and treated: 944 continuing deucravacitinib treatment, others being switched from placebo (197) or apremilast (80). Overall, 10% of patients did not complete the treatment.

There were 1163 subjects who had a total exposure to deucravacitinib for at least 6 months (26 weeks), and 573 subjects for at least 52 weeks. The mean and median durations of exposure to deucravacitinib were 358.3 and 357 days, respectively.

In the total population (N= 1221), sPGA 0/1 and PASI 75 response rates were improved or maintained over time. In the total population, sPGA 0/1 response rates were 50.9% at Week 0 and 57.3% at Week 60; and PASI 75 response rates were 65.1% at Week 0 and 75.0% at Week 60. In participants continuing on deucravacitinib treatment (n= 944), sPGA 0/1 response rates were 56.0% at Week 0 and 55.1% at Week 60; and PASI 75 response rates were 70.8% at Week 0 and 73.6% at Week 60. Available data on secondary efficacy endpoints to Week 60 supports maintenance of deucravacitinib's effect.

Results at the entry of study IM011075 in terms of co-primary endpoints are higher especially for PASI 75 in every group compared to the results at week 16 in parents study IM011046 and -047. The applicant explained that difference for the following reasons:

- subjects being re-randomized from placebo or apremilast to deucravacitinib in the parent study,
- improving response rates with continued active treatment,
- differences in statistical analysis methods for the blinded vs open-label extension studies.

This was agreed by CHMP.

In order to further substantiate the long-term efficacy of deucravacitinib, the final CSR is awaited. The Applicant committed to submit these data in a future variation for additional efficacy and safety implementation in the SmPC, and the study has been included in the RMP as a category 3 study.

2.6.7. Conclusions on the clinical efficacy

This is the first application of a TYK2 inhibitor intended to treat moderate to severe plaque psoriasis.

In the pivotal Phase 3 studies subjects with moderate to severe plaque psoriasis who were treated with deucravacitinib experienced substantial skin clearance and clinical improvement in the extent and severity of plaque psoriasis.

The oral dose (6 mg QD) carried forward to phase 3 studies is considered acceptable.

The efficacy of deucravacitinib was consistent across studies irrespective of demographic, disease or geographic characteristics or previous psoriasis therapies applied. Primary endpoints were supported by all secondary and other endpoints.

In addition to this impact on extent and severity of psoriasis, deucravacitinib also was superior to placebo in improving psoriasis signs and symptoms (itching, pain, redness, and burning) and quality of life (QoL).

Deucravacitinib effect was also maintained over time. Long term results from the OLE study are expected in order to further substantiate the long-term efficacy of deucravacitinib.

In conclusion, the CHMP considered that the efficacy data available supports the following indication: *Sotyktu is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.*

2.6.8. Clinical safety

2.6.8.1. Patient exposure

The safety evaluation plan assessing the safety of DEUC in the treatment of psoriasis includes 2 completed Phase 3 controlled studies (IM011046 and IM011047) and 1 ongoing open-label LTE study (IM011075). Safety data were pooled from these three studies with a data cutoff date of 15-Jun-2021.

These safety data provide a direct comparison of the DEUC safety profile with that of a placebo control as well as the active comparator Apremilast. Analysis periods for the "Control Safety Pool" were chosen to reflect the study designs.

In the "Controlled Safety Pool", safety data were summarized over 3 different time periods:

- Placebo-controlled Period (Week 0-16),
- Apremilast-controlled Period (Week 0-24),
- DEUC Exposure Period (Week 0-52).

In the Controlled Safety Pool (pool of phase 3 studies IM011046 and IM011047) and in the Phase 3 Safety Pool (pool phase 3 studies IM011046, IM011047 and IM011075), 1364 patients and 1519 patients were enrolled and all received at least one dose of DEUC, respectively. The total exposure in person-years was 969 and 2166.9, respectively.

The number of patients who received at least 52 weeks of continuous exposure was n= 503 in the Control Safety Pool and n=1068 in the Phase 3 safety Pool.

A summary of the total exposure to DEUC in the Controlled Safety Pool and in the Phase 3 Safety Pool is presented in the following **Table 42**:

Table 42 Summary of Extent of DEUC Exposure in the Controlled Safety Pool and Phase 3 Safety Pool

	Controlled Safety Pool (IM011046 and IM011047 only)	Phase 3 Safety Pool (IM011046, IM011047, and IM011075[a])
	DEUC 6 mg QD N = 1364	DEUC 6 mg QD N = 1519
At least one dose (%)	1364 (100)	1519 (100)
At least 16 weeks of continuous exposure (%)	1257 (92.2)	1405 (92.5)
At least 26 weeks of continuous exposure (%)	1050 (77.0)	1312 (86.4)
At least 52 weeks of continuous exposure (%)	503 (36.9)	1068 (70.3)
At least 52 weeks of total exposure (%)	-	1141 (75.1)
At least 78 weeks of total exposure (%)	-	855 (56.3)
At least 104 weeks of total exposure (%)	-	296 (19.5)
Total exposure in person-years	969.0	2166.9

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.
Frequency of exposure in weeks is a cumulative frequency.
Continuous exposure is based on longest exposure of BMS-986165 6 mg QD.
Abbreviations: DEUC = deucravacitinib; QD = once daily.
Source: Table S.4.1.3 and Table S.4.1.4

[a] as of data cut-off date 15-Jun-2021

At the CHMP request, the applicant provided updated long term safety data with a cut-off data of 01 October 2021 and then with a cut-off date of 15 June 2022. As of 15-Jun-2022, there was a total of 3260.7 p-y of exposure to DEUC, with 65.3% of subjects continuously exposed to DEUC for ≥ 104 weeks and a median exposure to DEUC of 932.0 days (see **Table 43**).

Table 43 Summary of Extent of DEUC Exposure in the Phase 3 Safety Pool

	Phase 3 Safety Pool Through 01-Oct-2021	Phase 3 Safety Pool Through 15-Jun-2022
	DEUC 6 mg QD N = 1519	DEUC 6 mg QD N = 1519
At least 1 dose (%)	1519 (100)	1519 (100)
At least 16 weeks of continuous exposure (%)	1405 (92.5)	1405 (92.5)
At least 26 weeks of continuous exposure (%)	1312 (86.4)	1312 (86.4)
At least 52 weeks of continuous exposure (%)	1179 (77.6)	1199 (78.9)
At least 104 weeks of continuous exposure (%)	584 (38.4)	992 (65.3)
At least 130 weeks of continuous exposure (%)	91 (6.0)	760 (50.0)
At least 52 weeks of total exposure (%)	1200 (79.0)	1206 (79.4)
At least 78 weeks of total exposure (%)	994 (65.4)	1127 (74.2)
At least 104 weeks of total exposure (%)	606 (39.9)	1028 (67.7)
At least 130 weeks of total exposure (%)	102 (6.7)	830 (54.6)
Total exposure in person-years	2482.0	3260.7
Median duration of exposure in days (min, max)	682.0 (1, 1132)	932.0 (1, 1467)

Exposure is summarized according to the number of subjects exposed to DEUC 6 mg QD.
Total exposure in person-years is calculated as the sum of exposure from all subjects divided by 365.25.
Frequency of exposure in weeks is a cumulative frequency.
Continuous exposure is based on longest exposure of DEUC 6 mg QD.
Abbreviations: DEUC, deucravacitinib; QD, once daily.
Source: D120 SUR Table S.4.1.4 and Table 180.2.1.

General baseline demographic characteristics: in the pooled analyses of the 2 Phase 3 studies, from IM011046 and IM011047, mean age was approximately 47 years old, and most subjects were between 40 and 64 years of age. The elderly population represented 10% of subjects. The majority of subjects were male (66.8%) and white (87.2%). The mean body weight was 90.71 kg and the mean body mass index (BMI) was 30.54 kg/m^2.

The mean age at disease onset was 28.8 years, and mean duration of disease was 18.65 years.

Baseline demographics and disease characteristics were representative of a moderate-to-severe psoriasis population within the individual pivotal Phase 3 studies (IM011046 and IM011047) and across the pooled safety analyses (Controlled Safety Pool and Phase 3 Safety Pool).

2.6.8.2. Adverse events

Overview of Treatment-Emergent Adverse Events (TEAEs) The **Table 44** below summarizes the overall incidence of AEs in the DEUC (BMS-986165), placebo and Apremilast groups in the control safety pool.

Table 44 Overall incidence of AEs in the controlled safety pool

AEs	Deucravacitinib	Placebo	Apremilast
Week 0-16 Placebo-controlled Period	469/842 (**55.7%**) 305.7 IR/100 P-Y	208/419 (**49.6%**) 263.2 IR/100 P-Y	243/422 (**57.6%**) 341.3 IR/100 P-Y
Week 0-24 Apremilast-controlled Period	680/1199 (**56.7%**) 281.3 IR/100 P-Y	208/419 (**49.6%**) 263.2 IR/100 P-Y	281/422 (**66.6%**) 305.4 IR/100 P-Y
Week 0-52 DEUC Exposure Period	995/1364 (**72.9%**) 229.2 IR/100 P-Y	347/666 (**52.1%**) 217.4 IR/100 P-Y	299/422 (**70.9%**) 281.1 IR/100 P-Y

Safety data issued from the Phase 3 Safety Pool did not differ from those issued from the Controlled Safety Pool: the overall incidence of AEs in the DEUC group during Phase 3 Safety Pool was 162.1/100 P-Y (78.2%, 1188/ 1519)(data cut-off 15-JUN-2021) and 145.2/100 P-Y (83.6%, 1270/1519) (data cut-off 15-JUN-2022).

Common TEAES

The following **Table 45** summarizes the main AEs ≥ 1% reported by SOC and Preferred Terms:

Table 45 Most Common Adverse Events (⩾ 1% of Subjects in deucravacitinib Group) - Controlled Safety Pool (Data for P3 Safety pool is based on 15-JUN-2021)

	Control safety Pool									Phase 3 SP
	PCP (week 0-16)			APR CP (week 0-24)			DEUC EP (week 0-52)			
	DEUC (n=842)	PBO (n=419)	APR (n=422)	DEUC (n=1199)	PBO (n=419)	APR (n=422)	DEUC (n=1364)	PBO (n=666)	APR (n=422)	DEUC (n=1519)
Common AEs (% and EAIR /100 P-Y)										
Infections	29.1% 116	21.5% 83.7	22% 84.8	31.1% 110.6	21.5% 83.7	29.9% 84.4	46.6% 95.4	23.7% 74.6	32.7% 77	52.1% 63.1
Nasopharyngitis	9% 31.7	8.6% 30.6	8.8% 31.1	10.8% 32.9	8.6% 30.6	11.1% 28	16.8% 26.1	8.1% 22.7	12.8% 25.9	17.2% 14.2
Upper respiratory tract infection	5.5% 18.8	4.1% 14	4% 13.9	5.9% 17.5	4.1% 14	5.9% 14.3	9.1% 13.4	5% 13.5	6.4% 12.4	9.5% 7.2
Folliculitis	1.7% 5.6	0	0	1.7% 4.8	0	0.5% 1.1	2% 2.8	0	0.5% 0.9	2% 1.4
Oral herpes	1.3% 4.4	0.2% 0.8	0.2% 0.8	1.3% 3.6	0.2% 0.8	0.5% 0.1	2.1% 2.9	0.3% 0.8	0.5% 0.9	2.2% 1.5
Pharyngitis	1.2% 4	0	0.5% 1.6	1.5% 4.3	0	0.9% 2.2	3% 4.2	0.6% 1.6	1.2% 2.2	3.6% 2.6
Viral upper respiratory tract infection	1.2% 4	1.2% 4.1	0.5% 1.6	1.1% 3.1	1.2% 4.1	0.5% 1.1	2.2% 3.1	0.9% 2.4	0.7% 1.3	2.1% 1.5
Sinusitis	1.1% 3.6	0.5% 1.6	1.4% 4.8	1.3% 3.8	0.5% 1.6	1.4% 3.4	1.8% 2.5	0.6% 1.6	1.4% 2.7	2% 1.5
Urinary tract infection	1% 3.2	1% 3.3	0.7% 2.4	1.3% 3.6	1% 3.3	0.9% 2.2	2.1% 3	1.2% 3.2	0.9% 1.8	2.2% 1.6

	Control safety Pool									Phase 3 SP
	PCP (week 0-16)			APR CP (week 0-24)			DEUC EP (week 0-52)			
	DEUC (n=842)	PBO (n=419)	APR (n=422)	DEUC (n=1199)	PBO (n=419)	APR (n=422)	DEUC (n=1364)	PBO (n=666)	APR (n=422)	DEUC (n=1519)
Common AEs (% and EAIR /100 P-Y)										
Skin disorders	8.9% 31.7	5.3% 18.5	5.9% 20.8	9% 27.4	5.3% 18.5	7.3% 18.1	13.6% 20.7	7.4% 20.7	8.3% 16.4	17.8% 14.2
Psoriasis	1.4% 4.8	3.3% 11.6	2.1% 7.3	1.3% 3.8	3.3% 11.6	2.4% 5.6	2.1% 3	4.7% 12.8	2.4% 4.5	3.7% 2.6
Acne	1.2% 4	0.2% 0.8	0	1.4% 4.1	0.2% 0.8	0	2.1% 2.9	0.2% 0.4	0	2.2% 1.5
Pruritus	1.1% 3.6	1% 3.3	1.2% 4	0.9% 2.6	1% 3.3	1.4% 3.4	1.2% 1.7	0.8% 2	1.7% 3.1	1.4% 1
Rash	1% 3.2	0	0.2% 0.8	0.8% 2.1	0	0.2% 0.6	1.2% 1.6	0	0.2% 0.4	1.3% 0.9
Rosacea	1% 3.2	0	0.5% 1.6	0.8% 2.1	0	0.5% 1.1	1% 1.3	0.2% 0.4	0.5% 0.9	1.5% 1.1
Gastrointestinal disorders	12% 43.8	13.1 49.4	25.8% 108.3	11.3% 35.1	13.1% 49.3	28.7% 85.1	15% 23.4	11% 31.4	29.4% 71	17.2% 13.9
Diarrhoea	4.4% 15.2	6% 21.3	11.8 % 43.9	4.3% 12.5	6% 21.3	12.8% 33.2	5.1% 7.3	4.2% 11.5	12.8% 26.5	5.4% 3.9
Nausea	1.7% 5.6	1.7% 5.8	10% 36.4	1.4% 4.1	1.7% 5.8	11.1% 28.5	1.5% 2.1	1.5% 4	11.1% 22.9	1.7% 1.2
Aphthous ulcer	1.3% 4.4	0	0	1.1% 3.1	0	0	1.3% 1.8	0	0	1.4% 1
Musculoskelatal And connectivite disorders	7.8% 27.3	7.6% 27.2	10.2% 36.7	7.7% 23	7.6% 27.2	12.6% 32	12% 17.9	8.6% 23.9	14.7% 30	15.9% 12.6
Arthralgia	2.3% 7.6	1.9% 6.6	2.8% 9.7	2.3% 6.7	1.9% 6.6	3.3% 7.9	4% 5.7	3.2% 8.5	4% 7.7	4.9% 3.6
Back pain	1.2% 4	1.2% 4.1	2.6% 8.9	1.2% 3.3	1.2% 4.1	3.8% 9.1	2% 2.8	1.2% 3.2	4% 7.7	3% 2.1
Investigations	6.2% 21.6	6.9% 24.9	1.9% 6.5	6.9% 20.7	6.9% 24.9	5% 11.9	10.6% 15.7	6% 16.7	6.6% 12.9	15.3% 12
Blood CPK increased	2.7% 9.3	1.2% 4.1	0.7% 2.4	2.3% 6.5	1.2% 4.1	1.4% 3.4	3.3% 4.7	1.7% 4.5	1.9% 3.6	4.5% 3.3

	Control safety Pool									Phase 3 SP
	PCP (week 0-16)			APR CP (week 0-24)			DEUC EP (week 0-52)			
	DEUC (n=842)	PBO (n=419)	APR (n=422)	DEUC (n=1199)	PBO (n=419)	APR (n=422)	DEUC (n=1364)	PBO (n=666)	APR (n=422)	DEUC (n=1519)
Common AEs (% and EAIR /100 P-Y)										
General disorders etc.	3.9% 13.4	3.3% 11.7	3.1% 10.6	3.8% 11	3.3% 11.7	4.3% 10.2	4.9% 7	3.6% 9.8	4.7% 9.1	6.4% 4.7
Fatigue	1.4% 4.8	1.2% 4.1	0.5% 1.6	1.2% 3.3	1.2% 4.1	0.9% 2.2	1.5% 2.1	0.8% 2	1.2% 2.2	1.5% 1.1
Vascular disorders	2.3% 7.6	2.4% 8.3	3.1% 10.6	2.3% 6.7	0.7% 2.5	4% 9.6	3.8% 5.4	1.2% 3.2	4.7% 9.1	5.6% 4.1
Hypertension	1.8% 6	0.2% 0.8	2.6% 8.9	1.8% 5.3	0.2% 0.8	3.3% 7.9	2.9% 4	0.8% 2	3.8% 7.2	4.4% 3.2
Respiratory thoracic and mediastinal disorders	4% 13.8	3.8% 13.4	2.6% 8.9	4.3% 12.4	3.8% 13.4	3.8% 9.1	7.5% 10.9	4.1% 11.1	5% 9.6	9% 6.7
Cough	1.2% 4	1.2% 4.1	0.7% 2.4	1% 2.9	1.2% 4.1	0.9% 2.2	1.9% 2.7	1.1% 2.8	0.9% 1.8	2.1% 1.5
Oropharyngeal pain	1.1% 3.6	0.7% 2.4	0.5% 1.6	1.2% 3.3	0.7% 2.4	0.7% 1.7	1.9% 2.7	0.8% 2	0.9% 1.8	2% 1.5
Nervous system disorders	7.2% 25.5	6.2% 22.1	14.7% 55.2	7.6% 22.8	6.2% 22.1	16.8% 44.7	9.9% 14.7	5% 13.6	17.8% 38	5.6% 5.8
Headache	4.5% 15.6	4.5% 16	10.7% 39.1	4.7% 13.8	4.5% 16	11.8% 30.5	5.9% 8.5	3.2% 8.6	12.6% 26	5.9% 8.5

Severity of TEAEs

Across treatment periods (Control Safety Pool: Week 0-16, Week 0-24, Week 0-52), treatment groups (DEUC, placebo, and Apremilast) as well as during phase 3 Safety Pool, AEs were predominantly mild to moderate in severity.

Related TEAES

Adverse events considered treatment-related by the investigator occurred at a higher frequency in the DEUC group than the placebo group during the Placebo-controlled period (Weeks 0-16). During the DEUC exposure period (Weeks 0-52), AEs considered treatment-related by the investigator occurred in DEUC-treated subjects at a lower frequency and lower exposure-adjusted incidence rate (EAIR) than in apremilast-treated subjects and at a lower EAIR than in placebo treated subjects. For each of the treatment periods, the most common SOCs and PTs of treatment-related AEs were the same as those identified as most common for overall AEs.

Overall, no new safety findings were observed with longer DEUC treatment (DEUC exposure period). In the DEUC group, treatment-related AEs were most commonly reported in the SOCs of Infections and Infestations, Gastrointestinal Disorders, and Skin and Subcutaneous Tissue Disorders.

EAIRs for the SOCs of Infection and Infestations and Skin and Subcutaneous Tissue Disorders were similar between DEUC and apremilast groups. The EAIR for the SOC of Gastrointestinal Disorders was lower in the DEUC group than in the apremilast group (DEUC: 7.4/100 p-y; apremilast: 37.2/100 p-y) as was that of Nervous System Disorders (DEUC: 3.3/100 p-y; apremilast: 11.6/100 p-y) (**Table 46**):

Table 46 Most Common Treatment-related Adverse Events (≥ 0.5% of Subjects in Any Treatment Group) Controlled Safety Pool (Week 0-52) – As-Treated Population

	BMS-986165 6 mg QD N = 1364			Placebo N = 666			Apremilast N = 422		
Preferred Term	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y
Nasopharyngitis	33 (2.4)	969.6	3.4	6 (0.9)	248.7	2.4	5 (1.2)	224.8	2.2
Upper respiratory tract infection	30 (2.2)	972.2	3.1	9 (1.4)	247.9	3.6	12 (2.8)	222.9	5.4
Diarrhoea	29 (2.1)	967.9	3.0	16 (2.4)	246.1	6.5	31 (7.3)	214.1	14.5
Headache	23 (1.7)	972.2	2.4	8 (1.2)	248.2	3.2	20 (4.7)	218.0	9.2
Blood creatine phosphokinase increased	14 (1.0)	979.8	1.4	4 (0.6)	248.8	1.6	1 (0.2)	226.0	0.4
Nausea	13 (1.0)	976.6	1.3	4 (0.6)	249.0	1.6	36 (8.5)	211.9	17.0
Acne	12 (0.9)	979.8	1.2	0			0		
Oral herpes	12 (0.9)	980.9	1.2	1 (0.2)	249.9	0.4	1 (0.2)	225.9	0.4
Aphthous ulcer	11 (0.8)	980.4	1.1	0			0		
Pharyngitis	10 (0.7)	982.6	1.0	2 (0.3)	249.4	0.8	3 (0.7)	225.9	1.3
Sinusitis	9 (0.7)	982.1	0.9	1 (0.2)	249.5	0.4	0		
Fatigue	8 (0.6)	981.2	0.8	1 (0.2)	249.7	0.4	4 (0.9)	224.9	1.8
Leukopenia	8 (0.6)	983.2	0.8	2 (0.3)	249.7	0.8	1 (0.2)	226.0	0.4
Psoriasis	8 (0.6)	983.6	0.8	10 (1.5)	246.9	4.0	3 (0.7)	225.8	1.3
Rash	8 (0.6)	984.4	0.8	0			1 (0.2)	226.3	0.4
Urticaria	8 (0.6)	983.2	0.8	1 (0.2)	249.7	0.4	3 (0.7)	225.5	1.3
Folliculitis	7 (0.5)	983.3	0.7	0			0		
Abdominal pain	5 (0.4)	983.2	0.5	2 (0.3)	249.6	0.8	6 (1.4)	224.6	2.7
Dyspepsia	5 (0.4)	983.8	0.5	0			2 (0.5)	225.1	0.9
Pruritus	6 (0.4)	983.6	0.6	3 (0.5)	249.1	1.2	4 (0.9)	225.3	1.8
Abdominal pain upper	4 (0.3)	983.6	0.4	1 (0.2)	249.7	0.4	4 (0.9)	225.2	1.8
Back pain	4 (0.3)	983.6	0.4	0			2 (0.5)	226.2	0.9
Insomnia	4 (0.3)	985.0	0.4	0			2 (0.5)	225.8	0.9
Arthralgia	3 (0.2)	985.0	0.3	4 (0.6)	249.1	1.6	3 (0.7)	225.5	1.3
Flatulence	3 (0.2)	984.8	0.3	0			3 (0.7)	225.5	1.3
Myalgia	3 (0.2)	985.8	0.3	0			2 (0.5)	225.6	0.9
Rhinitis	3 (0.2)	984.9	0.3	0			3 (0.7)	225.6	1.3
Vomiting	3 (0.2)	985.9	0.3	0			4 (0.9)	225.2	1.8
Abdominal discomfort	2 (0.1)	985.6	0.2	0			2 (0.5)	226.2	0.9
Anxiety	1 (0.1)	986.5	0.1	1 (0.2)	249.7	0.4	2 (0.5)	226.2	0.9
Blood triglycerides increased	1 (0.1)	986.5	0.1	0			2 (0.5)	226.1	0.9
Dizziness	2 (0.1)	984.9	0.2	0			3 (0.7)	224.5	1.3

Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
n = number of subjects; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.
MedDRA: 23.1
Includes data from IM011046 and IM011047.
Source: Refer to Table 8.5.4.37 in the SCS

Adverse events of special interest

Specific AEs were identified for monitoring during the clinical studies based on the mechanism of action (MOA) of DEUC (e.g, suppression of IL-23/IL-17, IL-12, and Type 1 IFNs via inhibition of TYK2), observed safety profile of DEUC in prior studies (i.e. acneiform rash and folliculitis), known comorbidities, including cardiovascular disease, depression and suicidality, associated with psoriasis, and safety concerns that have been identified with currently marketed JAK inhibitors. Hence, considering the mechanism of action of deucravacitinib, special attention was given to infections, skin events, malignancies, MACE, extended MACE, peripheral arterial events, venous thromboembolic events, other cardiovascular events, and depression and suicidal ideation or behavior.

◇ Infections

The **Table 47** and **Table 48** presents the incidence rate of overall AEs of infections across treatment group and periods:

Table 47 Overall Infection AEs (cut-off date 15-JUN-2021)

Overall Infections n (%); IR/100 p-y	DEUC	Placebo	Apremilast
Controlled Safety Pool: Week 0-16, N	842	419	422
Infection (SOC)	245 (29.1); 116	90 (21.5); 83.7	93 (22.0); 84.8
Serious infection	5 (0.6); 2.0	2 (0.5); 1.6	2 (0.5); 1.6
Controlled Safety Pool: Week 0-52, N	1364	666	422
Infection (SOC)	636 (46.6); 95.4	158 (23.7); 74.6	138 (32.7); 77.0
Serious infection	17 (1.2); 1.7	2 (0.3); 0.8	4 (0.9); 1.8
Phase 3 Safety Pool, N	1519	-	-
Infection (SOC)	792 (52.1); 63.1	-	-
Serious infection	59 (3.9); 2.8	-	-

Source: Table S.5.4.1, Table S.5.8.1.1, Table S.5.4.3, Table S.5.9.2, Table S.5.4.4, Table S.5.9.3 in the SCS[56]

Table 48 Infection Serious Adverse Events – Controlled Safety Pool (Week 0-52) and Phase 3 Safety Pool – All Treated Subjects

	CONTROLLED SAFETY POOL			PHASE 3 SAFETY POOL		
	BMS-986165 6 mg QD N = 1364			BMS-986165 6 mg QD N = 1519		
System Organ Class Preferred Term	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y
Infections and infestations	17 (1.2)	981.1	1.7	59 (3.9)	2143.2	2.8
Pneumonia	3 (0.2)	985.4	0.3	4 (0.3)	2173.2	0.2
COVID-19	2 (0.1)	986.2	0.2	27 (1.8)	2167.9	1.2
Anal abscess	1 (0.1)	986.6	0.1	1 (0.1)	2177.0	0.0
Carbuncle	1 (0.1)	986.5	0.1	1 (0.1)	2176.0	0.0
Diverticulitis	1 (0.1)	985.9	0.1	2 (0.1)	2174.4	0.1
Infectious mononucleosis	1 (0.1)	986.5	0.1	1 (0.1)	2175.7	0.0
Pharyngotonsillitis	1 (0.1)	986.7	0.1	1 (0.1)	2176.0	0.0
Pilonidal cyst	1 (0.1)	986.1	0.1	1 (0.1)	2175.5	0.0
Purulence	1 (0.1)	986.3	0.1	1 (0.1)	2176.1	0.0
Pyelonephritis	1 (0.1)	986.0	0.1	1 (0.1)	2175.3	0.0
Sepsis	1 (0.1)	986.6	0.1	1 (0.1)	2177.0	0.0
Streptococcal bacteraemia	1 (0.1)	986.6	0.1	1 (0.1)	2177.0	0.0
Upper respiratory tract infection	1 (0.1)	986.4	0.1	1 (0.1)	2175.7	0.0
Vascular graft infection	1 (0.1)	986.0	0.1	1 (0.1)	2175.8	0.0
COVID-19 pneumonia	0			13 (0.9)	2171.5	0.6
Gastroenteritis	0			1 (0.1)	2175.7	0.0
Pneumonia viral	0			1 (0.1)	2176.6	0.0
Tubo-ovarian abscess	0			1 (0.1)	2176.4	0.0
Post procedural sepsis	0			1 (0.1)	2176.8	0.0

Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.
MedDRA: 23.1
Note: Exposure in p-y is presented in the table only for those PTs where there is at least one event.
Controlled Safety Pool:
Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
Includes data from IM011046 and IM1011047.
Note: **DEUC Exposure Period** (Treatment Duration Week 0-52):
DEUC: Includes subjects treated with DEUC at any time. This includes subjects randomized to DEUC at Week 0, or switched from placebo to DEUC at Week 16, or switched from apremilast to DEUC at Week 24.
Source: Table S.5.9.2
Phase 3 Safety Pool:
Includes events with a start date between first dose and +30 days post last dose date (discontinued subjects) or through safety cutoff date.
Includes subjects who were assigned to BMS-986165 in IM011046, IM011047, or IM011075.
Includes data from IM011046, IM011047, and IM011075 (Safety Cutoff Date = 15-JUN-2021).
Source: Table S.5.9.3

◇ Skin events

The **Table 49** presents skin AEs during Deucravacitinib Exposure Period (week 0-52):

Table 49 Skin AEs during Deucravacitinib Exposure Period (week 0-52)

Protocol: SCS-Deucravacitinib Psoriasis

Adverse Events of Interest Summary
Exposure Adjusted Incidence Rate
Skin Events
Controlled Safety Pool
Week 0 through Week 52
As-treated Population

	BMS-986165 6 mg QD N = 1364			Placebo N = 666			Apremilast N = 422		
Preferred Term	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	163 (12.0)	905.1	18.0	19 (2.9)	245.1	7.8	19 (4.5)	220.2	8.6
Acne	28 (2.1)	970.6	2.9	1 (0.2)	250.0	0.4	0		
Folliculitis	27 (2.0)	973.4	2.8	0			2 (0.5)	225.9	0.9
Pruritus	17 (1.2)	977.8	1.7	5 (0.8)	248.5	2.0	7 (1.7)	223.9	3.1
Rash	16 (1.2)	980.7	1.6	0			1 (0.2)	226.3	0.4
Rosacea	13 (1.0)	979.3	1.3	1 (0.2)	249.9	0.4	2 (0.5)	226.1	0.9
Urticaria	12 (0.9)	981.3	1.2	2 (0.3)	249.2	0.8	5 (1.2)	225.2	2.2
Eczema	10 (0.7)	980.9	1.0	1 (0.2)	249.9	0.4	1 (0.2)	226.2	0.4
Seborrhoeic dermatitis	10 (0.7)	983.2	1.0	0			0		
Dermatitis contact	8 (0.6)	983.9	0.8	1 (0.2)	249.9	0.4	1 (0.2)	226.1	0.4
Blister	4 (0.3)	984.8	0.4	1 (0.2)	249.7	0.4	1 (0.2)	226.4	0.4
Dermatitis	4 (0.3)	984.3	0.4	1 (0.2)	249.9	0.4	0		
Paronychia	4 (0.3)	985.3	0.4	3 (0.5)	249.5	1.2	0		
Perioral dermatitis	3 (0.2)	984.5	0.3	0			0		
Skin infection	3 (0.2)	984.2	0.3	0			0		
Subcutaneous abscess	3 (0.2)	985.5	0.3	0			0		
Dermatitis acneiform	2 (0.1)	985.1	0.2	0			0		
Dyshidrotic eczema	2 (0.1)	985.6	0.2	0			0		
Impetigo	2 (0.1)	985.7	0.2	0			0		
Intertrigo	2 (0.1)	986.0	0.2	1 (0.2)	249.4	0.4	0		
Mechanical urticaria	2 (0.1)	985.3	0.2	0			0		
Rash pustular	2 (0.1)	985.6	0.2	0			0		

Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
n = number of subjects; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.
MedDRA: 23.1
Includes data from IM011046 and IM011047.
Program Source: \BMSSTATS-BSTATS\SAS\Report\SCSSCE\rt-ae-009-sum-eair.sas 28JUL2021:14:30:27

During the Placebo-Controlled Period, 8.6% of patients experienced skin adverse events in DEUC group, which is about 3-fold higher than apremilast group and placebo. This rate is maintained during the Apremilast Controlled Period and slightly increased during Deucravacitinib-Exposure Period as well as in the Phase 3 Safety Pool. However, on a patient-year perspective, the EAIR appears to decrease overtime: EAIR for skin AEs in DEUC group of 25.2 /100 P-Y (8.3%) (week 0-24), 18.0/100 P-Y (12%) (week 0-52) and 11.2/100 P-Y (14.4%) (Phase 3 SP), respectively.

◇ Malignancies

Ten patients out of 1364 treated with DEUC have experienced an event from the Standardized MedRA Queries for Malignancies during Deucravacitinib Exposure Period (week 0-52):

Table 50 Adverse Events of Interest Summary – Exposure Adjusted Incidence Rate – Malignancy Events by Category – Controlled Safety Pool (Week 0 - 52) – As-treated Population

High Level Category Low Level Category Preferred Term (%)	BMS-986165 6 mg QD N = 1364 n(%)	P-Y	IR/ 100 P-Y	Placebo N = 666 n(%)	P-Y	IR/ 100 P-Y	Apremilast N = 422 n(%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	10 (0.7)	983.2	1.0	0			2 (0.5)	226.0	0.9
NMSC	7 (0.5)	983.4	0.7	0			1 (0.2)	226.1	0.4
BASAL CELL CARCINOMA	4 (0.3)	985.3	0.4	0			0		
Basal cell carcinoma	4 (0.3)	985.3	0.4	0			0		
SQUAMOUS CELL CARCINOMA	2 (0.1)	985.7	0.2	0			1 (0.2)	226.1	0.4
Squamous cell carcinoma	1 (0.1)	986.2	0.1	0			1 (0.2)	226.1	0.4
Squamous cell carcinoma of skin	1 (0.1)	986.2	0.1	0			0		
OTHER	1 (0.1)	985.8	0.1	0			0		
Malignant sweat gland neoplasm	1 (0.1)	985.8	0.1	0			0		
MALIGNANCIES EXCLUDING NMSC	3 (0.2)	986.5	0.3	0			1 (0.2)	226.4	0.4
MALIGNANCIES EXCLUDING NMSC - SOLID	2 (0.1)	986.5	0.2	0			1 (0.2)	226.4	0.4
BREAST CANCER	1 (0.1)	986.6	0.1	0			0		
Breast cancer	1 (0.1)	986.6	0.1	0			0		
LIVER CANCER	1 (0.1)	986.6	0.1	0			0		
Hepatocellular carcinoma	1 (0.1)	986.6	0.1	0			0		
LUNG CANCER	0			0			1 (0.2)	226.4	0.4
Lung adenocarcinoma	0			0			1 (0.2)	226.4	0.4
MALIGNANCIES EXCLUDING NMSC - HEMATOLOGIC	1 (0.1)	986.6	0.1	0			0		
LYMPHOMA	1 (0.1)	986.6	0.1	0			0		
Hodgkin's disease	1 (0.1)	986.6	0.1	0			0		

Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075
Abbreviation: NMSC = nonmelanoma skin cancer.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.
MedDRA: 23.1; Includes data from IM011046 and IM011047.
Malignancy is defined as any event in Malignancy Event cSMQ used in the clinical safety program.
Source: Table S.6.2.10

From the SOC "Neoplasm benign, malignant" for W0-52, n=22 patients.

The EAIR of malignancies in DEUC group was 0.4/100 P-Y (0.1%), 0.2/100 P-Y (0.1%) and 1.0/100 P-Y (0.7%) in the Placebo-Controlled Period, Apremilast-Controlled Period and DEUC exposure Period. In the Phase 3 Safety Pool, total 19 patients experienced malignancies, the EAIR of all malignancies was 0.9/100 P-Y, with an EAIR for malignancies excluding NMSC and NMSC of 0.5/100 P-Y (0.7%) each.

◇ MACE, extended MACE, peripheral arterial events, venous thromboembolic events, other cardiovascular events

Table 51 Subjects with MACE and Extended MACE based on Cardiovascular Committee Term

MACE Category, n(%); IR/100 p-y	DEUC	Placebo	Apremilast
Adjudicated MACE			
Controlled Safety Pool: Week 0-16	2 (0.2); 0.8	3 (0.7); 2.4	1 (0.2); 0.8
Controlled Safety Pool: Week 0-52	3 (0.2); 0.3	3 (0.5); 1.2	2 (0.5); 0.9
Phase 3 Safety Pool	9 (0.6); 0.4	--	--
Adjudicated extended MACE			
Controlled Safety Pool: Week 0-16	2 (0.2); 0.8	3 (0.7); 2.4	1 (0.2); 0.8
Controlled Safety Pool: Week 0-52	4 (0.3); 0.4	3 (0.5); 1.2	2 (0.5); 0.9
Phase 3 Safety Pool	11 (0.7); 0.5	--	--

One subject in the apremilast group incorrectly received 2 weeks of DEUC.
Note: Controlled Safety Pool (Week 0-16): DEUC: N=842, Placebo: N=419, Apremilast: N=422
Controlled Safety Pool (Week 0-52): DEUC N=1364, Placebo: N=666, Apremilast: N=422
Phase 3 Safety Pool: DEUC N=1519
Source: Table 2.7.4.3-1 in SCS[56]

Three patients treated with DEUC have experienced a VTE event:

Table 52 Venous Thromboembolic Events – Phase 3 Psoriasis Studies

Age/ Sex/ Race/	Treatment Sequence	Preferred Term/ Study Day/ Seriousness/Relatedness	Relevant Medical History Risk Factors	Adjudicated Term	Other Relevant AEs	Action Taken with Study Treatment	Comment
48/M/A	DEUC (W0-52)	Pulmonary embolism/ D338/ SAE/Not related	Hypertension, obesity, prior smoking (≥30 years)	Pulmonary Embolism	Aortic dissection/ D338/ SAE	Drug interrupted for 6 days/ Completed study and rolled over to LTE	On D338, hospitalized with acute aortic dissection concident with pulmonary embolism. CT pulmonary angiogram revealed Type A dissection from aortic root to upper abdominal aorta, with saddle thrombosis/pulmonary embolus extending into lower right middle lobe and left upper lobe. Underwent aortic graft repair and aortic valve replacement. Events resolved after aortic dissection repair and aortic valve replacement. On D344, discharged and resumed DEUC treatment. No DVT, PE or other cardiac PTs reported into LTE. Cases of dissection in the ascending aorta with coincidental findings of thrombi in the adjacent pulmonary artery have been described in the literature..
19/F/W	DEUC (W0-16)	Deep vein thrombosis/ D16/ AE/Not related	Current smoker/ taking oral contraceptive (drospirenone; ethinylestradiol)	NA	SAE: Streptococcal bacteraemia (D9-18)	Treatment discontinued on D4/ Withdrew consent from study on D23	On D9, hospitalized for streptococcal bacteremia and treated with IV antibiotics via a peripheral cannula (IV) in the right radial vein. On D16, she had an ultrasound of the right upper extremity which showed non-compressible radial vein with signs of thrombosis. Possible cause of radial vein blockage due to receiving IV as a procedure for antibiotic treatment. Treated with enoxaparin. Started hormonal contraceptive approximately 4-6 weeks prior to event. Event resolved on D24.
48/M/W	DEUC (W0-24), Placebo (W24-52)	Venous thrombosis of left lower leg/ D72/SAE/ not related	Factor V Leiden mutation positive, Previous pulmonary embolism 31 May 2008, former smoker 1985-2008 (1 pack/week)	Deep venous thrombosis lower extremity	Thrombophlebitis (D16 to D72 IM011075), COVID-19 (D11 to 21) and Pneumonia (D4 to 26)	Dose not changed	Subject with COVID-19 infection and pneumonia developed thrombophlebitis of left lower leg. Subject was treated with Clexane 6000 IU QD. This progressed to a DVT 56 days later. Duplex ultrasound confirmed deep and superficial venous thrombosis of left lower leg. Clexane was increased to 10000 IU QD.

Bolded treatment is treatment at time of event

For IM011075 events, the parent study PID is provided in parentheses

Source: IM011046: Appendix 6.1, Appendix 6.4, Appendix S.6.5.1, Appendix 6.2, Appendix 4.3.1, Appendix 3.1, Appendix 2.3, Appendix 2.4, Appendix 4.1, and Table S.600

IM011047: Appendix 6.1, Appendix S.6.5.1, Appendix 6.2, Appendix 4.3.1, Appendix 4.3.2, Appendix 4.3.4, Appendix 3.1, Appendix 3.2, Appendix 2.3, Appendix 2.4, Appendix 4.1, and Table S.600

IM011075: Appendix 6.1, Appendix 6.5.1, Appendix 6.4, Appendix 6.3, Appendix 4.4, Appendix 2.1, Appendix 4.1, Appendix 3.3, Table S.6.9.1, and Table S.600

▪ Peripheral arterial events

Two patients treated with DEUC have experienced a peripheral arterial event versus 1 treated with placebo:

Table 53 Peripheral Arterial Events Summary Controlled Safety Pool (Week 0-52) – As-treated Population

Preferred Term	BMS-986165 6 mg QD N=1364 n (%)	P-Y	IR/ 100 P-Y	Placebo N=666 n (%)	P-Y	IR/ 100 P-Y	Apremilast N=422 n (%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN AIE EVENT	2 (0.1)	986.3	0.2	1 (0.2)	249.8	0.4	1 (0.2)	226.0	0.4
Leriche syndrome	1 (0.1)	986.4	0.1	0			0		
Thrombosis	1 (0.1)	986.6	0.1	0			0		
Iliac artery occlusion	0			1 (0.2)	249.8	0.4	0		
Peripheral arterial occlusive disease	0			0			1 (0.2)	226.0	0.4
Peripheral artery occlusion	0			1 (0.2)	250.0	0.4	1 (0.2)	226.1	0.4

Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
AEs are sorted in descending order for percentage in the BMS-986165 treatment group and then alphabetically.
Abbreviations: VTE = Venous Thromboembolic; AIE = peripheral arterial event
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/ total exposure time for the selected AE under each treatment.
MedDRA 23.1. Includes data from IM011046 and IM011047
Note: Exposure in p-y is presented in the table only for those PTs where there is at least one event.
Source: Table S.6.12.3

▪ Other serious CV events

The EAIRs of other serious CV events in the DEUC group during Placebo-controlled Period and DEUC Exposure Period were 0.8/100 P-Y (0.2%) and 1.2/100 P-Y (0.9%) and none in the apremilast group. In the Phase 3 Safety Pool, the EAIR for other serious CV events for DEUC was 1.0/100 p-y (1.2%).

◇ Depression and suicidal ideation or behavior

The **Table 54** presents AEs of Psychiatric disorders during DEUC exposure Period (week 0-52):

Table 54 Summary of AEs of Psychiatric Disorders – Exposure Adjusted Incidence Rate – Controlled Safety Pool – Week 0-52 As-treated Population

System Organ Class Preferred Term	BMS-986165 6 mg QD N = 1364 n (%)	P-Y	IR/ 100 P-Y	Placebo N = 666 n (%)	P-Y	IR/ 100 P-Y	Apremilast N = 422 n (%)	P-Y	IR/ 100 P-Y
Psychiatric disorders	45 (3.3)	967.4	4.7	13 (2.0)	247.7	5.2	16 (3.8)	221.3	7.2
Anxiety	10 (0.7)	984.0	1.0	1 (0.2)	249.7	0.4	3 (0.7)	226.1	1.3
Depression	8 (0.6)	982.9	0.8	4 (0.6)	249.5	1.6	1 (0.2)	226.2	0.4
Insomnia	8 (0.6)	983.5	0.8	2 (0.3)	249.7	0.8	5 (1.2)	224.0	2.2
Depressed mood	7 (0.5)	984.0	0.7	1 (0.2)	249.8	0.4	2 (0.5)	225.9	0.9
Mood altered	3 (0.2)	985.4	0.3	1 (0.2)	249.7	0.4	0		
Panic attack	3 (0.2)	986.2	0.3	0			0		
Libido decreased	2 (0.1)	985.6	0.2	1 (0.2)	249.7	0.4	0		
Sleep disorder	2 (0.1)	985.1	0.2	0			1 (0.2)	226.0	0.4
Abnormal dreams	1 (0.1)	985.7	0.1	0			0		
Affect lability	1 (0.1)	986.6	0.1	0			0		
Alcohol withdrawal syndrome	1 (0.1)	986.6	0.1	0			0		
Anxiety disorder	1 (0.1)	985.7	0.1	1 (0.2)	249.7	0.4	0		
Distractibility	1 (0.1)	985.7	0.1	0			0		
Hallucination	1 (0.1)	985.9	0.1	0			0		
Mood swings	1 (0.1)	986.6	0.1	0			0		
Suicidal ideation	1 (0.1)	986.6	0.1	1 (0.2)	249.9	0.4	1 (0.2)	226.4	0.4
Aggression	0			0			1 (0.2)	226.0	0.4
Anger	0			0			1 (0.2)	226.0	0.4
Attention deficit hyperactivity disorder	0			1 (0.2)	250.0	0.4	0		
Bruxism	0			0			1 (0.2)	226.2	0.4
Initial insomnia	0			1 (0.2)	249.8	0.4	0		
Major depression	0			1 (0.2)	249.9	0.4	0		
Negative thoughts	0			0			1 (0.2)	226.4	0.4

Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
Abbreviations: n = number of subjects; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.
AEs are sorted in descending order for percentage in the BMS-986165 treatment group and then alphabetically.
MedDRA: 23.1. Includes data from IM011046 and IM011047.
Note: Exposure in p-y is presented in the table only for those PTs where there is at least one event.
Note: DEUC Exposure Period (Treatment Duration Week 0-52):
DEUC: Includes subjects treated with DEUC at any time. This includes subjects randomized to DEUC at Week 0, or switched from placebo to DEUC at Week 16, or switched from apremilast to DEUC at Week 24.
Placebo: Includes subjects randomized to placebo at Week 0 who received at least 1 dose of placebo during Week 0-16 and subjects who switched from DEUC or apremilast to placebo at Week 24 in IM011047.
Apremilast: Includes subjects randomized to apremilast at Week 0 and received at least 1 dose of apremilast during Week 0-52.
Source: Table S.5.4.3

The EAIR of depression in DEUC group was higher compared to apremilast during all time periods of Controlled Safety Pool (2.0/100 P-Y (0.6%), 1.4/100 P-Y (0.5%) and 0.8/100 P-Y (0.6%)). In the Phase 3 Safety Pool, EAIR of depression in DEUC group was 0.5/100 P-Y (0.7%).

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

The **Table 55** presents serious AEs during Apremilast-controlled Period (Week 0-24):

Table 55 Serious Adverse Events – Controlled Safety Pool (Week 0 – 24) – Subjects Who Were Randomized to and Continued on the Same Active Treatment Groups – As-treated Population

	BMS-986165 6 mg QD N = 842			Apremilast N = 422		
System Organ Class Preferred Term	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y
IMMUNE SYSTEM DISORDERS	1 (0.1)	367.3	0.3	0	0	0
ANAPHYLACTIC REACTION	1 (0.1)	367.3	0.3	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1)	367.4	0.3	0	0	0
TOXICITY TO VARIOUS AGENTS	1 (0.1)	367.4	0.3	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.1)	367.5	0.3	0	0	0
OSTEOARTHRITIS	1 (0.1)	367.5	0.3	0	0	0
NERVOUS SYSTEM DISORDERS	1 (0.1)	367.4	0.3	2 (0.5)	180.1	1.1
STATUS EPILEPTICUS	1 (0.1)	367.4	0.3	0	0	0
ISCHAEMIC STROKE	0	0	0	2 (0.5)	180.1	1.1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1)	367.4	0.3	0	0	0
ORGANISING PNEUMONIA	1 (0.1)	367.4	0.3	0	0	0
VASCULAR DISORDERS	1 (0.1)	367.3	0.3	0	0	0
MALIGNANT HYPERTENSION	1 (0.1)	367.3	0.3	0	0	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	0	0	0	1 (0.2)	180.3	0.6
GASTROINTESTINAL ARTERIOVENOUS MALFORMATION	0	0	0	1 (0.2)	180.3	0.6
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	0	1 (0.2)	180.2	0.6
LUNG ADENOCARCINOMA	0	0	0	1 (0.2)	180.2	0.6
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	1 (0.2)	180.2	0.6
OVARIAN CYST	0	0	0	1 (0.2)	180.2	0.6

Includes events with a start date between first dose and the Week 24 visit date.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.
AEs are sorted in descending order for percentage in the BMS-986165 treatment group and then alphabetically.
MedDRA: 23.1. Includes data from IM011046 and IM011047.
Note: Exposure in p-y is presented in the table only for those PTs where there is at least one event.
Subjects that switched to a different treatment group during Week 0 through Week 24 were excluded.
Source: S.5.9.34

The **Table 56** presents serious AEs during Deucravacitinib Exposure Period (week 0-52):

Table 56 Serious Adverse Events in ≥ 2 Subjects in any Treatment Group – Controlled Safety Pool (Week 0-52) – As-Treated Population

Preferred Term	BMS-986165 6 mg QD N = 1364 n (%)	P-Y	IR/ 100 P-Y	Placebo N = 666 n (%)	P-Y	IR/ 100 P-Y	Apremilast N = 422 n (%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	55 (4.0)	969.1	5.7	14 (2.1)	247.5	5.7	9 (2.1)	224.3	4.0
Pneumonia	3 (0.2)	985.4	0.3	0			0		
Acute kidney injury	2 (0.1)	986.4	0.2	0			0		
Atrial fibrillation	2 (0.1)	986.1	0.2	0			0		
Cholecystitis acute	2 (0.1)	986.0	0.2	0			0		
COVID-19	2 (0.1)	986.2	0.2	0			0		
Pericarditis	2 (0.1)	986.5	0.2	0			0		
Ischaemic stroke	0			0			2 (0.5)	225.8	0.9

Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.
AEs are sorted in descending order for percentage in the BMS-986165 treatment group and then alphabetically.
MedDRA: 23.1; Includes data from IM011046 and IM011047.
Note: Exposure in p-y is presented in the table only for those PTs where there is at least one event.
Note: DEUC Exposure Period (Treatment Duration Week 0-52):
DEUC: Includes subjects treated with DEUC at any time. This includes subjects randomized to DEUC at Week 0, or switched from placebo to DEUC at Week 16, or switched from apremilast to DEUC at Week 24.
Placebo: Includes subjects randomized to placebo at Week 0 who received at least 1 dose of placebo during Week 0-16 and subjects who switched from DEUC or apremilast to placebo at Week 24 in IM011047.
Apremilast: Includes subjects randomized to apremilast at Week 0 and received at least 1 dose of apremilast during Week 0-52.
Note: Exposure in p-y is presented in the table only for those PTs where there is at least one event.
Source: Table S.5.9.2

Deaths

There were 4 deaths reported in Studies IM011046 and IM011047 (2 in the DEUC group and 1 each in the placebo and Apremilast groups) and 6 deaths reported in IM011075 (as of the 15-Jun-2021 safety data cutoff date). Five of the 6 deaths in IM011075 were due to COVID-19 and 1 death was attributed to ruptured thoracic aortic aneurysm.

As of the 15-Jun-2021 safety data cutoff date, 7 additional deaths were reported in the blinded, ongoing studies (IM011084 (PsA) [2 deaths reported in Part B of the study after Part A - Week 16 database lock (DBL)], IM011024 (UC) [2 deaths], IM011021 (SLE), IM011023 (Crohn's disease), and IM011074 (SLE) [one death reported in each study]).

2.6.8.4. Laboratory findings

Laboratory monitoring included assessment of routine hematology (neutrophils, lymphocytes, haemoglobin, platelets) and clinical chemistry parameters (ALT, AST, bilirubin, creatinine), CPK and lipid parameters.

Routine laboratory monitoring of hematology, chemistry parameters, and lipids showed no meaningful differences in the DEUC group compared with placebo and Apremilast groups in the parameters over time or incidence of markedly abnormal values (by CTCAE grading). Markedly abnormal laboratory parameters among DEUC-treated subjects over the longer term were infrequent and transient and did not result in treatment discontinuation.

There were no clinically meaningful changes from baseline or trends over time in hematology parameters for subjects receiving DEUC in the controlled Phase 3 Safety pool compared with placebo and apremilast during the placebo-controlled period. With longer exposure beyond 16 weeks on DEUC the findings were consistent with the placebo-controlled period and no new trends were observed. Any markedly abnormal hematologic laboratory test was infrequent and transient with low frequency of Grade 3 worst toxicity and no Grade 4.

There were no clinically meaningful changes from baseline or trends over time in chemistry parameters (mean +/- SD) for subjects receiving DEUC in the Controlled Phase 3 Safety Pool compared with placebo and

apremilast during the placebo-controlled period; with longer exposure beyond 16 weeks on DEUC the findings were consistent with the placebo-controlled period and no new trends were observed. Any markedly abnormal chemistry laboratory test was infrequent and transient. There was a low frequency of Grade 3 and no Grade 4 worst toxicity observed for ALT, AST, and bilirubin parameters.

Table 57 Maximum Elevations in Alanine Aminotransferase, Aspartate Aminotransferase, and Bilirubin

Abnormality (n, %)	Controlled Safety Pool (Week 0-16)			Controlled Safety Pool (Week 0-52)			Phase 3 Safety Pool
	DEUC N = 842	Placebo N = 419	Apremilast N = 422	DEUC N = 1364	Placebo N = 666	Apremilast N = 422	DEUC N = 1519
ALT							
Number of subjects with an assessment	**833**	**413**	**419**	**1351**	**658**	**419**	**1504**
> 3x ULN	9 (1.1)	5 (1.2)	2 (0.5)	25 (1.9)	12 (1.8)	4 (1.0)	37 (2.5)
> 5x ULN	0	3 (0.7)	0	6 (0.4)	3 (0.5)	0	12 (0.8)
> 10x ULN	0	0	0	1 (0.1)	0	0	3 (0.2)
> 20x ULN	0	0	0	0	0	0	0
AST							
Number of subjects with an assessment	**833**	**413**	**419**	**1351**	**658**	**419**	**1504**
> 3x ULN	13 (1.6)	2 (0.5)	3 (0.7)	26 (1.9)	7 (1.1)	3 (0.7)	42 (2.8)
> 5x ULN	3 (0.4)	1 (0.2)	1 (0.2)	10 (0.7)	1 (0.2)	1 (0.2)	21 (1.4)
> 10x ULN	0	0	0	2 (0.1)	0	0	3 (0.2)
> 20x ULN	0	0	0	0	0	0	0
Total Bilirubin							
Number of subjects with an assessment	**833**	**413**	**419**	**1351**	**658**	**419**	**1504**
> 1.5x ULN	10 (1.2)	6 (1.5)	2 (0.5)	27 (2.0)	8 (1.2)	4 (1.0)	37 (2.5)
> 3x ULN	1 (0.1)	0	0	1 (0.1)	0	0	2 (0.1)
> 10x ULN	0	0	0	0	0	0	0

Includes postbaseline values only. Subjects are counted once in each relevant category.

Controlled Safety Pool: Includes data from IM011046 and IM011047.
Source: Table S.7.5.1 and Table S.7.5.3

Phase 3 Safety Pool: Includes subjects who were assigned to BMS-986165 in IM011046, IM011047, or IM011075.
Includes data from IM011046, IM011047, and IM011075 (Safety Cutoff Date = 15-Jun-2021).
Source: Table S.7.5.4

No clinically meaningful increases from baseline in mean triglyceride levels were observed in the DEUC group compared with placebo and apremilast during the placebo-controlled period, or with longer exposure beyond 16 weeks on DEUC without corresponding changes in total cholesterol and low density lipoprotein (LDL) levels. Worst toxicity values of triglyceride levels of Grade 3 or higher occurred at low and similar frequencies across all treatment groups. There were no subjects with Grade 3 or higher worst toxicity levels for total cholesterol.

During the Placebo-Controlled Period (Week 0-16), worst toxicity values of ≥Grade 3 CPK occurred at low and similar frequencies in all treatment groups. Of the Grade 4 elevations, none were consecutive. AEs of CPK increase were predominantly mild or moderate and not serious.

Table 58 Worst Toxicity Grades of Creatine Phosphokinase Increased

Parameter	Grade	DEUC	Placebo	Apremilast
Controlled Safety Pool, Week 0 - 16, n (%)	N	833	413	419
	Grade 3	5 (0.6)	3 (0.7)	2 (0.5)
	Grade 4	6 (0.7)	1 (0.2)	1 (0.2)
Controlled Safety Pool, Week 0 - 52, n (%)	N	1351	658	419
	Grade 3	19 (1.4)	4 (0.6)	7 (1.7)
	Grade 4	13 (1.0)	3 (0.5)	1 (0.2)
Phase 3 Safety Pool, n (%)	N	1504	-	-
	Grade 3	23 (1.5)	-	-
	Grade 4	26 (1.7)		

Source: Table S.7.2.1, Table S.7.2.3, and Table S.7.2.4

Abbreviations: CPK = Creatine phosphokinase

Table 59 Creatine Phosphokinase Increased AE Summary – Controlled Safety Pool (Week 0-16)

n (%/) IR / 100 p-y	DEUC N = 842	Placebo N = 419	Apremilast N = 422
Total Subjects with an Event	23 (2.7) / 9.3	5 (1.2) / 4.1	3 (0.7) / 2.4
Severe	1 (0.1) / NA	0	0
Serious	0	0	0
Led to Treatment Discontinuation	1 (0.1) / NA	0	1 (0.2/ NA)
Treatment Related	8 (1.0) / NA	3 (0.7) / NA	1 (0.2) / NA

Includes events with a start date between first dose and the Week 16 visit date.

Abbreviations: n = number of subjects; P-Y = person-years of exposure based on time to first onset; NA = not available

MedDRA: 23.1. Includes data from IM011046 and IM011047.

Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.

Note: Exposure in p-y is presented in the table only for those PTs where there is at least one event.

Source: Table S.5.4.1 (AEs), Table S.5.7.1 (Severity), Table S.5.8.1 (Serious AEs), Table S.5.10 (AEs leading to treatment discontinuation), Table S.5.3.12 (treatment related AEs)

Table 60 Creatinine Phosphokinase Increased AE Summary – Controlled Safety Pool (Week 0-52)

n (%) IR / 100 p-y	DEUC N = 1364	Placebo N = 666	Apremilast N = 422
Total Subjects with an Event	45 (3.3) / 4.7	11 (1.7) / 4.5	8 (1.9) / 3.6
Severe	1 (0.1) / NA	1 (0.2) / NA	0
Serious	0	0	0
Led to Treatment Discontinuation	2 (1.0) / 0.2	0	1 (0.2) / 0.4
Treatment Related	14 (1.0) / 1.4	4 (0.6) / 1.6	1 (0.2) / 0.4

Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.

Abbreviation: NA = not available

Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.

Denominators are based on the number of subjects exposed to each treatment. Worst severity determined for each treatment and AE per subject.

MedDRA: 23.1. Includes data from IM011046 and IM011047.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

▪ Age, sex, race, ethnicity and BMI: The effects of intrinsic factors (age, sex, race, body weight) and extrinsic factors (geographic region and prior treatments) on the incidence of AEs and SAEs were examined for subjects in the Control Safety Pool and the Phase 3 Safety Pool.

A summary of total AEs by age subgroup has been provided for the Controlled Safety Pool (Week 0-52) in **Table 61** and for the Phase 3 Safety Pool in **Table 62** and **Table 63**. As there were no subjects > 85 years, this subgroup is not included in the summary.

Table 61 Adverse Events Summary by Age Group, Controlled Safety Pool (Week 0-52) – As Treated Population

	Age < 65 Years N = 1514			Age 65 - 74 Years N = 146			Age 75 - 84 Years N = 23		
AE Category n(%)	BMS N= 1231	PBO N= 587	APR N= 384	BMS N= 114	PBO N= 71	APR N= 34	BMS N= 19	PBO N= 8	APR N= 4
AEs	894(72.6)	306(52.1)	274(71.4)	85(74.6)	37(52.1)	22(64.7)	16(84.2)	4(50.0)	3(75.0)
SAEs	42(3.4)	11(1.9)	8(2.1)	9(7.9)	3(4.2)	0	4(21.1)	0	1(25.0)
Fatal	1(0.1)	1(0.2)	0	0	0	0	1(5.3)	0	1(25.0)
Initial/prolonged hospitalization	35(2.8)	9(1.5)	7(1.8)	9(7.9)	3(4.2)	0	4(21.1)	0	1(25.0)
Life-threatening	5(0.4)	0	1(0.3)	3(2.6)	1(1.4)	0	2(10.5)	0	1(25.0)
Disability/incapacity	1(0.1)	0	0	0	0	0	0	0	0
Other medically important	9(0.7)	3(0.5)	3(0.8)	0	0	0	0	0	0
AE leading to treatment discontinuation	32(2.6)	20(3.4)	22(5.7)	7(6.1)	2(2.8)	4(11.8)	4(21.1)	1(12.5)	0
Psychiatic Disorders	39(3.2)	10(1.7)	16(4.2)	6(5.3)	3(4.2)	0	0	0	0
Nervous System Disorders	120(9.7)	30(5.1)	69(18.0)	12(10.5)	3(4.2)	5(14.7)	3(15.8)	0	1(25.0)
Accidents and injuries	69(5.6)	21(3.6)	14(3.6)	7(6.1)	1(1.4)	7(20.6)	1(5.3)	1(12.5)	2(50.0)
Cardiac Disorders	20(1.6)	5(0.9)	4(1.0)	2(1.8)	4(5.6)	0	2(10.5)	0	0
Vascular Disorders	44(3.6)	5(0.9)	18(4.7)	6(5.3)	3(4.2)	1(2.9)	2(10.5)	0	1(25.0)
Cerebrovascular disorders	0	0	1(0.3)	2(1.8)	0	0	1(5.3)	0	1(25.0)
Infections and infestations	581(47.2)	144(24.5)	128(33.3)	45(39.5)	14(19.7)	9(26.5)	10(52.6)	0	1(25.0)
Anticholinergic syndrome	35(2.8)	6(1.0)	13(3.4)	1(0.9)	0	1(2.9)	1(5.3)	0	1(25.0)
Quality of life decreased	0	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	23(1.9)	9(1.5)	9(2.3)	1(0.9)	0	1(2.9)	1(5.3)	0	1(25.0)

AEs occurring more frequently in older patients	260 (21.1)	76 (12.9)	128 (33.3)	48 (42.1)	20 (28.2)	8 (23.5)	6 (31.6)	2 (25.0)	1 (25.0)
Abdominal pain	10 (0.8)	4 (0.7)	7 (1.8)	5 (4.4)	1 (1.4)	1 (2.9)	1 (5.3)	0	0
Actinic keratosis	2 (0.2)	0	0	1 (0.9)	0	1 (2.9)	1 (5.3)	0	0
Aphthous ulcer	14 (1.1)	0	0	3 (2.6)	0	0	1 (5.3)	0	0
Arthralgia	44 (3.6)	18 (3.1)	15 (3.9)	10 (8.8)	2 (2.8)	2 (5.9)	1 (5.3)	1 (12.5)	0
Back pain	24 (1.9)	7 (1.2)	16 (4.2)	3 (2.6)	1 (1.4)	1 (2.9)	0	0	0
Benign prostatic hyperplasia	0	1 (0.2)	1 (0.3)	3 (2.6)	0	0	0	0	0
Bronchitis	22 (1.8)	4 (0.7)	5 (1.3)	5 (4.4)	0	0	0	0	0
COVID-19	3 (0.2)	2 (0.3)	0	2 (1.8)	0	0	0	0	0
COVID-19 pneumonia	0	0	1 (0.3)	0	0	0	0	0	0
Constipation	7 (0.6)	4 (0.7)	1 (0.3)	1 (0.9)	2 (2.8)	0	1 (5.3)	0	0
Dermatitis contact	4 (0.3)	0	1 (0.3)	3 (2.6)	1 (1.4)	0	1 (5.3)	0	0
Diarrhoea	60 (4.9)	20 (3.4)	51 (13.3)	8 (7.0)	8 (11.3)	3 (8.8)	1 (5.3)	0	0
Glomerular filtration rate decreased	2 (0.2)	0	0	4 (3.5)	1 (1.4)	0	1 (5.3)	0	0
Hypertension	34 (2.8)	4 (0.7)	15 (3.9)	5 (4.4)	1 (1.4)	0	0	0	1 (25.0)
Nausea	14 (1.1)	8 (1.4)	45 (11.7)	4 (3.5)	2 (2.8)	2 (5.9)	2 (10.5)	0	0
Oral herpes	24 (1.9)	1 (0.2)	2 (0.5)	4 (3.5)	1 (1.4)	0	0	0	0
Rhinitis	22 (1.8)	5 (0.9)	10 (2.6)	3 (2.6)	0	1 (2.9)	1 (5.3)	0	0
Rosacea	8 (0.6)	1 (0.2)	2 (0.5)	4 (3.5)	0	0	1 (5.3)	0	0
Urinary tract infection	24 (1.9)	5 (0.9)	4 (1.0)	2 (1.8)	3 (4.2)	0	3 (15.8)	0	0
Vertigo	6 (0.5)	0	1 (0.3)	2 (1.8)	2 (2.8)	0	1 (5.3)	1 (12.5)	0

Includes events with a start date between first dose and +30 days post last dose date or upon rollover into IM011075.
n = number of subjects; EMS = EMS-986165 6mg QD; PBO = Placebo; APR = Apremilast
MedDRA: 23.1
Includes data from IM011046 and IM011047.
Source: Table 3.7.1

Table 62 Adverse Events Summary by Age Group, Phase 3 Safety Pool (Week 0 [Parent Study] through IM011075 Safety 01-Oct-2021 Data Cutoff Date) – As Treated Population

	EMS-986165 6 mg QD (N = 1519)								
	Age < 65 Years (N = 1367)			Age 65 - 74 Years (N = 131)			Age 75 - 84 Years (N = 21)		
AE Category	n (%)	P-Y	IR/100 P-Y	n (%)	P-Y	IR/100 P-Y	n (%)	P-Y	IR/100 P-Y
AEs	1092 (79.9)	717.0	152.3	104 (79.4)	60.3	172.4	18 (85.7)	8.9	202.5
SAEs	119 (8.7)	2162.6	5.5	19 (14.5)	196.4	9.7	7 (33.3)	25.7	27.3
Fatal	8 (0.6)	2252.6	0.4	0			2 (9.5)	30.1	6.7
Initial/prolonged hospitalization	101 (7.4)	2170.0	4.7	18 (13.7)	196.5	9.2	7 (33.3)	25.7	27.3
Life-threatening	21 (1.5)	2241.3	0.9	6 (4.6)	210.4	2.9	3 (14.3)	29.8	10.1
Disability/incapacity	4 (0.3)	2251.0	0.2	0			0		
Other medically important	25 (1.8)	2243.3	1.1	2 (1.5)	213.8	0.9	1 (4.8)	30.1	3.3
AE leading to treatment discontinuation	55 (4.0)	2246.8	2.4	9 (6.9)	213.4	4.2	5 (23.8)	29.6	16.9
Psychiatric Disorders	58 (4.2)	2193.6	2.6	8 (6.1)	205.9	3.9	0		
Nervous System Disorders	173 (12.7)	2041.4	8.5	16 (12.2)	196.1	8.2	3 (14.3)	23.5	12.8
Accidents and injuries	121 (8.9)	2125.2	5.7	14 (10.7)	196.7	7.1	1 (4.8)	29.6	3.4
Cardiac Disorders	45 (3.3)	2213.8	2.0	4 (3.1)	210.2	1.9	4 (19.0)	28.0	14.3
Vascular Disorders	81 (5.9)	2164.9	3.7	10 (7.6)	203.9	4.9	3 (14.3)	26.8	11.2
Cerebrovascular disorders	4 (0.3)	2251.1	0.2	3 (2.3)	212.9	1.4	1 (4.8)	27.7	3.6
Infections and infestations	735 (53.8)	1248.3	58.9	65 (49.6)	129.0	50.4	14 (66.7)	17.1	81.9
Anticholinergic syndrome	56 (4.1)	2189.6	2.6	2 (1.5)	211.4	0.9	1 (4.8)	29.9	3.3
Quality of life decreased	0			0			0		
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	46 (3.4)	2209.3	2.1	3 (2.3)	212.0	1.4	1 (4.8)	27.7	3.6
AEs occurring more frequently in older patients	447 (32.7)	1725.7	25.9	65 (49.6)	123.1	52.8	9 (42.9)	21.5	41.9
Abdominal pain	15 (1.1)	2236.1	0.7	6 (4.6)	204.5	2.9	1 (4.8)	30.1	3.3
Actinic keratosis	2 (0.1)	2249.6	0.1	6 (4.6)	208.4	2.9	1 (4.8)	29.1	3.4
Aphthous ulcer	17 (1.2)	2230.1	0.8	4 (3.1)	208.3	1.9	1 (4.8)	27.4	3.6
Arthralgia	70 (5.1)	2173.5	3.2	14 (10.7)	194.0	7.2	1 (4.8)	29.8	3.4
Back pain	45 (3.3)	2195.0	2.1	5 (3.8)	207.9	2.4	1 (4.8)	29.7	3.4
Benign prostatic hyperplasia	1 (0.1)	2252.7	0.0	5 (3.8)	206.7	2.4	0		
Bronchitis	32 (2.3)	2217.2	1.4	7 (5.3)	203.1	3.4	0		
COVID-19	116 (8.5)	2173.9	5.3	7 (5.3)	209.6	3.3	1 (4.8)	29.7	3.4
COVID-19 pneumonia	11 (0.8)	2246.3	0.5	4 (3.1)	211.0	1.9	1 (4.8)	30.1	3.3

Table 63 Adverse Events Summary by Age Group, Phase 3 Safety Pool (Week 0 [Parent study] through IM011075 Safety 01-Oct-2021 Data Cutoff Date) – As Treated Population

	BMS-986165 6 mg QD (N = 1519)								
	Age < 65 Years (N = 1367)			Age 65 - 74 Years (N = 131)			Age 75 - 84 Years (N = 21)		
AE Category	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y
Constipation	8 (0.6)	2240.4	0.4	3 (2.3)	211.1	1.4	1 (4.8)	29.8	3.4
Dermatitis contact	16 (1.2)	2238.5	0.7	5 (3.8)	206.3	2.4	1 (4.8)	28.1	3.6
Diarrhoea	73 (5.3)	2157.1	3.4	10 (7.6)	198.7	5.0	1 (4.8)	29.8	3.4
Glomerular filtration rate decreased	2 (0.1)	2251.0	0.1	4 (3.1)	211.9	1.9	1 (4.8)	30.1	3.3
Hypertension	66 (4.8)	2178.5	3.0	7 (5.3)	206.0	3.4	1 (4.8)	29.5	3.4
Nausea	19 (1.4)	2226.1	0.9	5 (3.8)	210.3	2.4	2 (9.5)	29.1	6.9
Oral herpes	29 (2.1)	2206.8	1.3	4 (3.1)	207.7	1.9	0		
Rhinitis	29 (2.1)	2221.9	1.3	3 (2.3)	210.0	1.4	1 (4.8)	30.1	3.3
Rosacea	18 (1.3)	2233.5	0.8	4 (3.1)	208.0	1.9	1 (4.8)	27.5	3.6
Urinary tract infection	30 (2.2)	2215.1	1.4	2 (1.5)	210.7	0.9	3 (14.3)	28.0	10.7
Vertigo	10 (0.7)	2240.2	0.4	2 (1.5)	212.1	0.9	2 (9.5)	29.3	6.8

Includes events with a start date between first dose and +30 days post last dose date (discontinued subjects) or through 120 day safety cutoff date.
n = number of subjects; P-Y = person-years of exposure based on time to first onset.
Incidence rate per 100 person-years of exposure (IR/100 P-Y): 100*365.25*(total number of subjects with the AE)/total exposure time for the selected AE under each treatment.
MedDRA: 23.1
Includes subjects who were assigned to BMS-986165 in IM011046, IM011047, or IM011075.
Includes data from IM011046, IM011047, and IM011075 (120 Day Safety Data Cutoff Date = 01OCT2021).

Source: Table 3.7.2

The significant increases in AEs for the age group 75-84 Years compared to group <65 Years were observed, which additionally increased with the long-term use of deucravacitinib:

- SAEs (33.3% vs 8.7%) including fatal (9.5% vs 0.6%), initial/prolonged hospitalization (33.3% vs 7.4%), life-threatening (14.3% vs 1.5%); AE leading to the treatment discontinuation (23.8% vs 4.0%)
- SOC Cardiac disorders (19.0% vs 3.3%); SOC Infections and infestations (66.7% vs 53.8%)
- Urinary tract infection (14.3% vs 2.2%) and Nausea (9.5% vs 1.4%)

The incidence of AEs, SAEs, and AEs leading to treatment discontinuation did not reveal any clinically relevant concerns with DEUC treatment in any age group compared with placebo and Apremilast. Approximately 10% of the subjects were in the age group ≥ 65 years. There was no increased risk of infection in the age group ≥ 65 years. With additional open-label exposure to DEUC beyond 52 Weeks, the overall incidence of infections was not higher in the age group ≥ 65 years with the exception of COVID-19 SAEs in consideration of their known higher risk of COVID-19 complications and study conduct during the global pandemic.

Approximately 67% of the subjects were male. There were small differences in the incidence of AEs between male and female subgroups that were not clinically meaningful and there were no differences in SAEs and AEs leading to discontinuation. Approximately 87% of subjects were White and approximately 10% were Asian. The incidence of AEs (Week 0-16) in the Asian subgroup was higher across the treatment groups compared to the White subgroup, mostly due to AEs in the Skin and Subcutaneous Tissue Disorders SOC.

The proportion of subjects with body weight < 90 kg and > 90 kg were approximately evenly distributed between the weight subgroups.

The proportion of subjects from the EU was 44.9% compared with 30.5% from the US, and 24.6% from rest of world (ROW). The incidence of AEs in the US was similar to the EU and lower than in the ROW. During the

placebo-controlled period, the incidence of AEs in the most common SOC of Infections and Infestations was lower in the US (23.2%) compared with the EU (30.6%) or ROW (34.6%), mostly due to the lower AE incidence of nasopharyngitis (US: 3.7%; EU: 11.4%, and ROW: 11.9%).

The proportion of subjects who received prior treatment with systemic (biologic and nonbiologic) medication was 57.5%, 34.8% previously received biologics. The incidence of AEs was higher among subjects who were naive to prior treatment compared to those with prior treatment in the DEUC and Apremilast groups compared to the placebo group where the incidence was generally similar.

▪ Hepatic impairment and renal impairment: see section 2.6.2.1 "Clinical Pharmacology, sub-section Pharmacokinetic in special population".

▪ Pregnancy: Across the entire deucravacitinib clinical program, 15 pregnancies were reported in subjects or their partners treated with deucravacitinib as of the cutoff date (7 subject pregnancies and 8 partner pregnancies). The data on pregnancies reported after exposure to deucravacitinib are limited, but do not suggest a specific safety concern. No congenital anomalies have been reported.

▪ Breastfeeding: No information is available on the clinical use of deucravacitinib during breastfeeding, on the presence of deucravacitinib in human milk, on the effect on the breastfed infant, or effects on milk production.

▪ Overdose: No overdoses were reported.

▪ Drug abuse: There was no evidence of drug abuse observed during the DEUC clinical trials conducted to date.

▪ Withdrawal and rebound: No withdrawal or rebound were reported.

▪ Effects on ability to drive or operate machinery or impairment of mental ability

No studies of the effects on the ability to drive and use machines have been performed. Based on the class of drug the Applicant concluded that DEUC is not expected to affect/impair the ability to drive and use machines.

2.6.8.7. Immunological events

Anti-drug antibodies (ADA) were not identified with DEUC. This is consistent with small molecule inhibitors with which ADA are not expected.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Safety related to DDI and other interactions has been broadly discussed previously through the section "Clinical Pharmacology".

2.6.8.9. Discontinuation due to adverse events

The **Table 64** and **Table 65** present discontinuations due to adverse events during the Placebo-Controlled Period (week 0-16) and Deucravacitinib-Exposure Period (week 0-52):

Table 64 AEs Leading to Treatment Discontinuation – Controlled Safety Pool (Week 0-16) – As-treated Population

System Organ Class Preferred Term	BMS-986165 6 mg QD N = 842 n(%)	P-Y	IR/ 100 P-Y	Placebo N = 419 n(%)	P-Y	IR/ 100 P-Y	Apremilast N = 422 n(%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	20 (2.4)	249.5	8.0	16 (3.8)	121.1	13.2	22 (5.2)	122.8	17.9
Investigations	5 (0.6)	251.2	2.0	2 (0.5)	122.8	1.6	1 (0.2)	125.3	0.8
Glomerular filtration rate decreased	4 (0.5)	251.3	1.6	1 (0.2)	122.9	0.8	0		
Blood creatine phosphokinase increased	1 (0.1)	252.0	0.4	0			1 (0.2)	125.3	0.8
Aspartate aminotransferase increased	0			0			1 (0.2)	125.3	0.8
Liver function test abnormal	0			1 (0.2)	123.0	0.8	0		
Psychiatric disorders	5 (0.6)	251.5	2.0	2 (0.5)	122.8	1.6	4 (0.9)	124.8	3.2
Insomnia	2 (0.2)	251.8	0.8	0			1 (0.2)	125.1	0.8
Depressed mood	1 (0.1)	252.0	0.4	0			0		
Mood altered	1 (0.1)	252.0	0.4	0			0		
Panic attack	1 (0.1)	252.0	0.4	0			0		
Anxiety	0			0			3 (0.7)	125.0	2.4
Depression	0			1 (0.2)	123.0	0.8	0		
Major depression	0			1 (0.2)	122.9	0.8	0		
Suicidal ideation	0			0			1 (0.2)	125.3	0.8
Gastrointestinal disorders	3 (0.4)	251.7	1.2	2 (0.5)	122.9	1.6	13 (3.1)	124.1	10.5
Diarrhoea	2 (0.2)	251.8	0.8	1 (0.2)	123.0	0.8	6 (1.4)	124.7	4.8
Abdominal pain	1 (0.1)	252.0	0.4	0			2 (0.5)	125.2	1.6
Vomiting	1 (0.1)	252.0	0.4	0			2 (0.5)	125.2	1.6
Abdominal discomfort	0			0			1 (0.2)	125.3	0.8
Abdominal pain upper	0			0			1 (0.2)	125.3	0.8
Constipation	0			1 (0.2)	123.0	0.8	0		
Flatulence	0			0			1 (0.2)	125.3	0.8
Gastrointestinal pain	0			0			1 (0.2)	125.2	0.8
Gastrooesophageal reflux disease	0			0			1 (0.2)	125.3	0.8
Lip swelling	0			0			1 (0.2)	125.3	0.8
Nausea	0			0			4 (0.9)	125.0	3.2
General disorders and administration site conditions	3 (0.4)	251.8	1.2	1 (0.2)	123.0	0.8	1 (0.2)	125.2	0.8
Fatigue	2 (0.2)	251.9	0.8	0			1 (0.2)	125.2	0.8
Chest pain	1 (0.1)	252.0	0.4	0			0		
Hernia perforation	0			1 (0.2)	123.0	0.8	0		
Infections and infestations	2 (0.2)	251.8	0.8	2 (0.5)	122.9	1.6	1 (0.2)	125.3	0.8
Folliculitis	1 (0.1)	251.9	0.4	0			0		
Pneumonia	1 (0.1)	252.0	0.4	0			0		
Cellulitis	0			1 (0.2)	123.0	0.8	1 (0.2)	125.3	0.8
Gastroenteritis	0			1 (0.2)	123.0	0.8	0		
Skin and subcutaneous tissue disorders	2 (0.2)	251.9	0.8	5 (1.2)	122.3	4.1	2 (0.5)	125.2	1.6
Psoriasis	1 (0.1)	252.0	0.4	4 (1.0)	122.6	3.3	1 (0.2)	125.3	0.8
Rosacea	1 (0.1)	252.0	0.4	0			0		
Erythema	0			1 (0.2)	122.8	0.8	0		
Rash	0			0			1 (0.2)	125.3	0.8
Blood and lymphatic system disorders	1 (0.1)	252.0	0.4	0			0		
Lymphopenia	1 (0.1)	252.0	0.4	0			0		
Cardiac disorders	1 (0.1)	252.0	0.4	0			1 (0.2)	125.3	0.8
Myocardial infarction	1 (0.1)	252.0	0.4	0			1 (0.2)	125.3	0.8
Arteriosclerosis coronary artery	0			0			1 (0.2)	125.3	0.8
Coronary artery disease	0			0			1 (0.2)	125.3	0.8
Hepatobiliary disorders	1 (0.1)	252.0	0.4	0			0		
Hepatic function abnormal	1 (0.1)	252.0	0.4	0			0		
Immune system disorders	1 (0.1)	252.0	0.4	1 (0.2)	122.9	0.8	0		
Hypersensitivity	1 (0.1)	252.0	0.4	1 (0.2)	122.9	0.8	0		
Musculoskeletal and connective tissue disorders	1 (0.1)	252.0	0.4	1 (0.2)	122.9	0.8	3 (0.7)	124.9	2.4
Myalgia	1 (0.1)	252.0	0.4	0			2 (0.5)	125.0	1.6
Muscle spasms	0			0			1 (0.2)	125.3	0.8
Psoriatic arthropathy	0			1 (0.2)	122.9	0.8	0		
Metabolism and nutrition disorders	0			1 (0.2)	123.0	0.8	0		
Decreased appetite	0			1 (0.2)	123.0	0.8	0		

Table 65 AEs Leading to Discontinuation of Study Treatment – Controlled Safety Pool (Week 0-52) – Subjects Who Were Randomized to and Continued on the Same Active Treatment Groups – As-treated Population

System Organ Class Preferred Term	BMS-986165 6 mg QD N = 692 n (%)	P-Y	IR/ 100 P-Y	Apremilast N = 160 n (%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	32 (4.6)	596.4	5.4	26 (16.3)	103.3	25.2
INVESTIGATIONS	7 (1.0)	599.3	1.2	1 (0.6)	106.3	0.9
GLOMERULAR FILTRATION RATE DECREASED	5 (0.7)	600.1	0.8	0		
BLOOD CREATINE PHOSPHOKINASE INCREASED	2 (0.3)	600.3	0.3	1 (0.6)	106.3	0.9
ASPARTATE AMINOTRANSFERASE INCREASED	0			1 (0.6)	106.3	0.9
PSYCHIATRIC DISORDERS	7 (1.0)	600.2	1.2	5 (3.1)	105.7	4.7
INSOMNIA	2 (0.3)	600.9	0.3	1 (0.6)	106.1	0.9
AFFECT LABILITY	1 (0.1)	601.1	0.2	0		
DEPRESSED MOOD	1 (0.1)	600.9	0.2	0		
DEPRESSION	1 (0.1)	601.0	0.2	0		
MOOD ALTERED	1 (0.1)	601.0	0.2	0		
PANIC ATTACK	1 (0.1)	601.0	0.2	0		
SUICIDAL IDEATION	1 (0.1)	601.0	0.2	1 (0.6)	106.3	0.9
ANXIETY	0			3 (1.9)	106.0	2.8
NEGATIVE THOUGHTS	0			1 (0.6)	106.3	0.9
GASTROINTESTINAL DISORDERS	6 (0.9)	600.5	1.0	14 (8.8)	104.9	13.3
DIARRHOEA	2 (0.3)	600.8	0.3	6 (3.8)	105.8	5.7
VOMITING	2 (0.3)	600.9	0.3	2 (1.3)	106.2	1.9
ABDOMINAL PAIN	1 (0.1)	601.0	0.2	3 (1.9)	106.1	2.8
NAUSEA	1 (0.1)	601.0	0.2	5 (3.1)	105.8	4.7
PANCREATIC MASS	1 (0.1)	601.1	0.2	0		
ABDOMINAL DISCOMFORT	0			1 (0.6)	106.3	0.9
ABDOMINAL PAIN UPPER	0			1 (0.6)	106.3	0.9
FLATULENCE	0			1 (0.6)	106.3	0.9
GASTROINTESTINAL PAIN	0			1 (0.6)	106.2	0.9
GASTROOESOPHAGEAL REFLUX DISEASE	0			1 (0.6)	106.3	0.9
LIP SWELLING	0			1 (0.6)	106.3	0.9
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (0.4)	600.7	0.5	1 (0.6)	106.3	0.9
FATIGUE	2 (0.3)	600.8	0.3	1 (0.6)	106.3	0.9
CHEST PAIN	1 (0.1)	601.0	0.2	0		

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

Deucravacitinib is a selective TYK2 inhibitor (TYK2 belongs to the JAK family). Its mechanism of action differs from apremilast, which is also an immunosuppressant agent (by acting as an inhibitor of phosphodiesterase 4). Hence, the safety profile of deucravacitinib is not expected to be similar to Apremilast. Moreover, special attention has been paid with regards to the known adverse reactions related to JAK inhibitors, notably the increased risks of serious infections, Major Adverse Cardiovascular Events (MACE), veno-thromboembolic events and malignancies.

The safety profile of deucravacitinib, oral administration 6 mg QD regimen, was supported by a pooled analysis of 3 clinical studies:

- 2 phase 3 completed pivotal controlled studies in 1686 patients (IM011046 and IM011047) corresponding to the Controlled Safety Pool.

- 1 ongoing phase 3 open-label Long-Term Extension study (IM011075) with a data cutoff date of 15-Jun-2021, in 1519 patients treated with deucravacitinib. Safety data from this LTE study was pooled with those observed from the two phase 3 pivotal studies constituting the Phase 3 Safety Pool.

Of note, pooled safety analyses were based on the as-treated Population which included all subjects who received at least 1 dose of study drug.

Based on limited data from the LTE study (IM011075) (cut off 15-Jun-2021), safety data in the Phase 3 Safety Pool did not differ significantly from that observed in the Controlled Safety Pool. In order to support the long-term deucravacitinib safety, additional long term data were requested by the CHMP. The Applicant provided an updated deucravacitinib 6 mg QD safety data (data cut-off date 01-Oct-2021) obtained on 606 patients (39.9%) with at least total exposure of 104 weeks and 1179 patients (77.6%) with at least continuous exposure of 52 weeks. No significant difference was seen in deucravacitinib 6 mg safety profile reported in the updated period (data cut-off date 01-Oct-2021) compared to the previous period. However, these updated long-term safety data were based on only 3.5 months period difference compared to the initial MAA submission. That is too short to notice any significant difference in the safety profile in the context of deucravacitinib long term use for psoriasis treatment (chronic disease). Additional updated safety data with a cut-off date of 15-Jun-2022 including more long-term data (922 subjects (65.3%) with exposure > 2 years and 760 subjects (50%) with exposure > 2.5 years) were provided by the Applicant. No new safety issues were observed with deucravacitinib use compared to that as of 01-Oct-2021. However, given that psoriasis is a chronic indication, more long-term data (5-years exposure) will be necessary in order to confirm the favourable safety profile of deucravacitinib in the context of long-term use. Long term safety has been included in the missing information of the RMP and 3 Category 3 studies are planned to obtain more information on long term safety.

Overall Treatment Emergent Adverse Events (TEAEs)

In the Control Safety Pool, the incidence rates (Exposure-Adjusted Incidence Ratio - EAIR) of Adverse Events (AEs) in deucravacitinib group were 305.7/100 P-Y (55.7%) and 281.3/100 P-Y (56.7%) during the Placebo-Controlled Period (week 0-16) and the Apremilast-Controlled Period (week 0-24). Hence, more than half of patients experienced at least one adverse event after a deucravacitinib exposure of 16 and 24 weeks. During deucravacitinib Exposure Period (week 0 to 52), the EAIR of AEs was 229.2/100 P-Y (72.9%) in deucravacitinib group.

Common TEAEs

In the Control Safety Pool, during the Placebo-Controlled Period (week 0-16), AEs were most commonly (> 5% in any treatment group) reported in the SOCs of "Infections and Infestations", "Gastrointestinal Disorders", "Skin and Subcutaneous Tissue Disorders", "Musculoskeletal and Connective Tissue Disorders", "Nervous System Disorders, and Investigations".

Adverse events were predominantly mild or moderate in intensity across treatment periods in deucravacitinib group. The number of severe AEs increased with deucravacitinib exposure: 18 severe AEs week 0-16, 31 severe AEs week 0-24 and 66 severe AEs week 0-52. But, by comparing exposure adjusted incidence rates with longer exposure to DEUC there was no evidence of increased incidence of severe AEs.

Treatment related AEs

In both Control Safety Pool and Phase 3 Safety Pool, the main AEs related to deucravacitinib were diarrhoea, nausea, dyspepsia, aphthous ulcer, folliculitis, upper respiratory tract infection, nasopharyngitis, oral herpes, sinusitis, blood CPK increased, fatigue, headache, dizziness, rash, acne, rosacea, urticaria, leukopenia and lymphopenia.

In addition, pneumonia, abdominal pain upper, vomiting, abdominal discomfort, eczema, somnolence, pyrexia, depressed mood and bronchitis were also considered for inclusion in the section 4.8 of SmPC. This is

based on analysis of uncommon TEAEs with deucravacitinib use in the IM011046, IM011047 and IM011075 studies occurred with frequency ≥0.5% and <1% (e.g. occurred in at least 4 subjects in the Placebo Controlled Period). However, no conclusion could be drawn on the association of these AEs with deucravacitinib. Hence, they are not listed in section 4.8 of the SmPC.

Adverse Events of Special Interest (AESI)

Adverse events of special interest were infections, skin events, malignancies, MACE, extended MACE, peripheral arterial events, VTE, other serious CV events, depression and suicidal ideation or behaviour.

- Infections

Data from adverse events in the SOC "Infections and infestations" clearly put forward the increased risk of infections with deucravacitinib which is maintained throughout the treatment duration. Hence, in the Control Safety Pool, the incidence rates (IR) of AEs for the SOC "Infections and Infestations" for each treatment period, Placebo-Controlled Period (week 0-16), Apremilast-Controlled Period (week 0-24) and Deucravacitinib-Exposure Period (0-52 week) were 116 /100 P-Y (29.1%), 110.6/100 P-Y (31.1%) and 95.4/100 P-Y (46.6%), respectively and always higher than placebo and Apremilast incidence rates.

The most common AE in deucravacitinib group during the Placebo-Controlled Period (week 0-16) were nasopharyngitis (9.0%), upper respiratory tract infection (5.5%), folliculitis (1.7%), oral herpes (1.3%), and pharyngitis (1.2%). The severity of AEs was predominantly mild (18.9%) or moderate (9.6%).

The main AEs related to deucravacitinib were upper respiratory tract infection (1.5%), nasopharyngitis (1.4%), oral herpes (0.8%), folliculitis (0.4%), herpes simplex, pharyngitis, sinusitis and urinary tract infection (0.2% each). One patient experienced herpes zoster (0.1%).

During the DEUC Exposure Period (Week 0-52), the incidence of serious infection AEs and AEs leading to treatment discontinuation with deucravacitinib was 1.7/100 P-Y (1.2%) and 0.5/100 P-Y (0.5%).

In the Phase 3 Safety Pool, with additional long-term exposure on deucravacitinib, the incidence rate of AEs in the SOC "Infections and Infestations" was lower 63.1/100 P-Y (52.1%) compared with the Control Safety Pool (Week 0-16), EAIRs =116/100 P-Y (29.1%). The most common serious AEs were COVID-19-related infections (1.8%) and COVID-19 pneumonia (0.9%). Cases of herpes zoster and herpes simplex were reported but none were serious, disseminated, or led to treatment discontinuation. Tuberculosis was reported in 4 patients (1 active, and 3 latent TB) in the Phase 3 Safety Pool but cases are insufficiently documented to establish any causal relationship with deucravacitinib.

Based on the appraisal of safety data from the Control Safety Pool, the SmPC section 4.8 on adverse reactions includes the following AEs related to the SOC "Infections and infestations": Upper respiratory infections (include nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, pharyngitis, sinusitis, acute sinusitis, rhinitis, tonsillitis, peritonsillar abscess, laryngitis, tracheitis, and rhinotracheitis), Herpes simplex infections (include oral herpes, herpes simplex, genital herpes, and herpes viral infection) and Herpes Zoster.

Furthermore, the use of deucravacitinib in patients with a chronic infection or a history of recurrent infection has been the subject of further explanation from the Applicant. Hence, 32 patients with medical history of chronic infections (chronic sinusitis, chronic tonsillitis, and bronchitis chronic) were included in Phase 3 psoriasis studies. The most common TEAEs from SOC Infections and Infestations occurred in deucravacitinib-treated patients with history of chronic infection during Week 0 -52 were nasopharyngitis (27.8%, EAIR 50.2/100 p-y), sinusitis (22.2%, EAIR 42.7/100 p-y) and bronchitis (11.1%; EAIR 17.9/100 p-y). The

frequencies were higher compared to overall deucravacitinib -treated patients (nasopharyngitis (16.8%, EAIR 26.1/100 p-y); sinusitis (1.8%; EAIR 2.5/100 p-y) and bronchitis (2.0%, EAIR 2.8/100 p-y). Therefore, deucravacitinib may increase the risk of infections and caution should be exercised when considering the use of deucravacitinib in patients with a chronic infection or a history of recurrent infection. As infections have been observed with deucravacitinib, the Applicant has adequately included a product specific warning in section 4.4 of the SmPC regarding the use of deucravacitinib in these patients, and serious infection has been included in the RMP as an important potential risk. In addition deucravacitinib is contraindicated in patients with clinically important active infections (e.g. active tuberculosis) (SmPC section 4.3).

Given the increased incidence of pneumonia in deucravacitinib group during deucravacitinib Exposure Period (Week 0 -52 compared to placebo and apremilast group (DEUC: EAIR 1.1/100 P-Y (0.8%), 11 subjects; placebo: EAIR 0.4/100 P-Y (0.2%), 1 subject; apremilast: 0), inclusion of pneumonia as uncommon ADRs in the section 4.8 of SmPC was raised. However, based on provided safety data, no firm conclusion on association of pneumonia with deucravacitinib use could be drawn. Pneumonia events will continue to be monitored via pharmacovigilance activities.

◇ Skin events

During the Placebo-Controlled Period (week 0-16), 8.6% of patients experienced skin adverse events in deucravacitinib group, which is about 3-fold higher than apremilast group. The main events were folliculitis (15/100 P-Y, 1.7%), acne (10/100 P-Y, 1.2%), rash (10/100 P-Y, 1%) and rosacea (8/100 P-Y, 1%). Similar incidence rates were observed during the Apremilast Controlled Period (week 0-24), and the Deucravacitinib-Exposure Period (week 0-52). None of the skin AEIs was serious.

Therefore, in section 4.8 of the SmPC, under the frequency common, in the SOC Skin and subcutaneous disorders the following AEs are included: Acneiform rash (includes acne, dermatitis acneiform, rash, rosacea, pustule, rash pustular and papule) and Folliculitis (as folliculitis reported with deucravacitinib may be either a microbial or a non-microbial origin the Applicant decided to include it in the above-mentioned SOC).

◇ Malignancies

During the Placebo-Controlled-Period (week 0-16), the EAIR of malignancy was 0.4/100 P-Y (0.1%) in deucravacitinib group and 1.6/100 P-Y (0.5%) in apremilast group. No event of malignancy was reported in the placebo group.

Furthermore, during Deucravacitinib-Exposure Period (week 0-52), ten patients experienced malignancies (1/100 P-Y, 0.7%) in the deucravacitinib group, among them 7 were NMSC (0.7/100 P-Y (0.5%)). No case in placebo group was reported. Basal cell carcinoma was the most common, occurring in 4 subjects (0.4/100 P-Y, 0.3%) with squamous cell carcinoma occurring in 2 subjects (0.2/100 P-Y, 0.1%). Other malignancies represented 3 subjects, corresponding to an incidence rate of 0.3/100 P-Y (0.2%) with 1 case of breast cancer (0.1/100 P-Y, 0.1%), 1 hepatocellular carcinoma (0.1/100 P-Y, 0.1%), and 1 Hodgkin’s disease (0.1/100 P-Y, 0.1%).

In the Phase 3 Safety Pool, the incidence rate of all malignancies was consistent with those observed in the Control Safety Pool (Week 0-52). Nonetheless, 10 subjects (n=10, EAIR= 0.5 /100 P-Y, 0.7%) experienced an NMSC and 7 had a medical history of NMSC. All cases of malignancies presented confounding factors as medical history or medical family history or risk factors such as sun exposure, smoking, that could have also contributed to the event of malignancy.

Even though no clear relationship with deucravacitinib can be made, the compatible time-to-onset and the occurrence of these adverse events, mainly in deucravacitinib group, none in placebo and very few in

Apremilast group during different periods warrants to consider malignancies (including NMSC) as an important potential risk in the RMP. These risks will be further monitored as part of Long-Term studies (IM011194, IM0111130 and IM011075) and in the forthcoming PSURs. In addition, due to the conclusion of the Article 20 referral on the JAK inhibitors, a specific warning on malignancies for deucravacitinib has been added in section 4.4 of the SmPC, taking into consideration the differences in mechanism of action and uncertainties with regards to the long term safety profile.

◇ MACE, extended MACE and other serious cardiovascular events

Patients with psoriasis have an increased risk of major adverse cardiovascular events (MACE) beyond that attributable to standard cardiovascular (CV) risk factors (smoking, excess alcohol intake, obesity, hypertension, dyslipidemia, and insulin resistance).

MACE occurred in 3 patients (0.2%, EAIR 0.3/100 P-Y) and adjudicated extended MACE in 4 patients (0.3%, EAIR 0.4/100 P-Y) in deucravacitinib group during week 0 - 52. With longer deucravacitinib exposure (after first year of treatment), 9 patients experienced MACE (0.6%, EAIR 0.4/100 P-Y), while extended MACE was reported in 11 patients (0.7%, EAIR 0.5/100 P-Y).

The EAIRs for serious CV events during deucravacitinib Exposure Period (Week 0-52) was 1.2/100 P-Y in deucravacitinib group and none in the apremilast group. The events in deucravacitinib group were atrial fibrillation, pericarditis, aortic dissection, arteriosclerosis coronary artery, malignant hypertension, myocardial ischemia, transient ischemic attack, ventricular tachycardia shock, supraventricular tachycardia. All events occurred in a single subject with the exception of atrial fibrillation and pericarditis which were reported in 2 subjects each.

In the Control Safety Pool, during deucravacitinib - Exposure Period (Week 0-52), there were 2 VTE (0.1%, EAIR 0.2/100 p-y) in the deucravacitinib group, one of which was serious. This patient had an aortic dissection and a coincident pulmonary embolism. The second event was a non-serious VTE of the radial vein (deep vein thrombosis-DVT) which occurred in a subject post cannular placement for an IV antibiotic. There were no events reported in the placebo or apremilast groups.

In the Control Safety Pool (Week 0-52), there were 2 peripheral arterial events (0.1%, EAIR 0.2 / 100 P-Y) in deucravacitinib group, 1 (0.2%, EAIR 0.4 / 100 P-Y) in placebo group and in Apremilast group.

These adverse events corresponded to two peripheral arterial events in the deucravacitinib group, one of which was serious. The serious event of thrombosis (adjudicated as peripheral artery occlusion) occurred in a subject with risk factors of obesity, smoking and sleep apnea. There was one subject in the deucravacitinib group with a non-serious arterial event of Leriche syndrome with risk factors of obesity, smoking and cardiovascular disease. However, although the patient had confounding factors, and even no clear mechanism was identified, one cannot discard that deucravacitinib would have precipitated this thrombosis event. No event of thrombosis occurred in placebo and apremilast group.

In conclusion, regarding MACE, extended MACE and other cardiovascular adverse events, there is a trend to CV AEs in the deucravacitinib group compared to apremilast considering the homogenous baseline characteristics in deucravacitinib, placebo and apremilast group. This leads to not conclude on a causal relationship of deucravacitinib in the CV events but the compatible TTO cannot allow to discard it. Therefore, even though the primary pharmacology data indicated deucravacitinib selectivity for TYK2, and due to the conclusion of the Article 20 referral on the JAK inhibitors, MACE and VTE have been added as important potential risks in the safety concerns of deucravacitinib RMP. Furthermore, acknowledging the differences in

mechanisms of action and given the uncertainties with regards to the long-term safety profile, a specific warning on MACE and VTE (DVT/PE) risk for deucravacitinib was added in section 4.4 of the SmPC.

◇ Depression, suicidal ideation, behaviour

In the Control Safety Pool, during the Placebo-Controlled Period (week 0-16), the incidences rates of AEs in the SOC "Psychiatric Disorders" was EAIR=9.3/100 P-Y (2.7%) in deucravacitinib group, 9.7/100 P-Y (2.8%) in Apremilast group and 8.3/100 P-Y (2.4%) in placebo. The most frequently reported AEs were depression (EAIR=2/100 P-Y, 0.6%), insomnia, (EAIR=2/100 P-Y, 0.6%), depressed mood (EAIR=1.6/100 P-Y, 0.5%), mood altered and panic attack (EAIR= 0.8/100 P-Y, 0.2%). Surprisingly, these events occurred less or even none in Apremilast group whilst depression is a common AE in Apremilast SmPC. With a longer exposure (week 0-52), the incidence rate of depression remains higher in deucravacitinib group than in Apremilast: 0.8/100 P-Y (0.6%, 8 patients) and 0.4/100 P-Y (0.2%, 1 patient). The Applicant discussed the cases of depression reported as part of the phase 3 Safety Pool. Although, the incidence rates of depression remain higher in the deucravacitinib group than in apremilast, the description of the case cannot allow any causal association with deucravacitinib to be made. As a matter of fact, either most of patients were medical history of depression and /or anxiety before initiating deucravacitinib treatment or the narratives are insufficiently documented. Depression and other symptoms related will be monitored as part of the forthcoming PSURs.

Safety considerations on AEs from other SOCs

Different types of injuries and fractures (SMQ Accidents and injuries) were observed with uncommon frequency in the deucravacitinib group during the first 52 week of treatment (some fractures considered serious). It seems that EAIR of bone fractures with deucravacitinib (as of 01-Oct-2021) was similar to EAIR for Week 0 -52 (9 events, EAIR 0.9/100 p-y vs 25 events, EAIR 1.0/100 p-y).Data as of 01-Oct-2021 do not suggest an increased risk for injuries or fractures in deucravacitinib-treated patients. It is acknowledged that overall EAIR of fractures and injuries events in deucravacitinib group decreased with longer deucravacitinib exposure as well as overall EAIR of fractures and injuries in deucravacitinib group was lower compared to that in placebo and apremilast group up to Week 0-52.

In conclusion, based on submitted data on use up to Week 52, increased EAIR of some individual AEs (ligament sprain, muscle strain, skin laceration and joint injury) in deucravacitinib group was seen compared to apremilast, and it seems that decreases with longer treatment duration. In the absence of long-term controlled data, the final conclusion on increased risk of fractures and injuries with deucravacitinib use cannot be drawn. No amendment of SmPC is warranted at this moment. Given that psoriasis population is at increased risk of fractures and possible future deucravacitinib use in adolescents, closely monitoring of fractures and injuries with deucravacitinib use is recommended.

Serious events and deaths

▪ Serious AEs

In the Control Safety Pool, during the Placebo-Controlled Period (week 0-16), the incidence of serious adverse events was higher in deucravacitinib group than in Apremilast group: 6/100 P-Y (1.8%) versus 4/100 P-Y (1.2%), respectively. The frequency of SAE was nonetheless the highest in the placebo group, EAIR= 9.9 /100 P-Y (2.9%). The most frequently reported SAE terms were in the SOC "Infections and Infestations" (2/100 P-Y, 0.6%), followed by "Cardiac disorders" (1.2/100 P-Y, 0.4%).

During the Apremilast-Controlled Period (week 0-24) and the deucravacitinib Exposure Period (Week 0-52), the incidence or type of SAE were consistent with the Placebo-Controlled Period (Week 0-16).

▪ Deaths

There were 4 deaths reported in the pivotal phase III studies IM011046 and IM011047 of which 2 in the deucravacitinib group (the two others in the placebo and Apremilast groups). Six other deaths were reported in the long-term extension study IM011075. Five of the 6 deaths were due to COVID-19 and 1 death was attributed to ruptured thoracic aortic aneurysm. Despite a compatible time-to-onset, either the narratives were insufficiently documented to allow any causal association with deucravacitinib treatment to be established, or underlying diseases (notably COVID 19 disease) may have contributed to the patient's death.

Discontinuations

In the Control Safety Pool, during the Placebo-Controlled Period (week 0-16), the incidence rate of AEs leading to treatment discontinuation was 8/100 P-Y in the DEUC group (2.4%) and 17.9/100 P-Y in Apremilast (5.2%) groups. In the deucravacitinib group, AEs leading to treatment discontinuation reported in 2 or more subjects included glomerular filtration rate (GFR) decreased (4 subjects, 0.5%), diarrhea, fatigue, and insomnia (2 subjects each, 0.2%).

Similar incidence rates and AEs were observed during the Apremilast-Controlled Period (week 0-24) and the Deucravacitinib-Exposure Period (week 0-52).

EAIR of AEs leading to treatment interruption in the deucravacitinib group in the Phase 3 Safety Pool (EAIR 3.0/100 p-y as of 15-Jun-2021, 8.8/100 p-y as of 15-Jun-2022) slightly declined compared to that observed at Week 0 – 52 (EAIR 4.4/100 p-y).

The most frequently affected SOCs with corresponding EAIRs of AEs leading to treatment interruption were Infections and infestations (5.1/100 p-y in Week 0-52, 5.9/100 p-y as of 15-Jun-2021, 5.3/100 p-y as of 15-Jun-2022), Investigations (0.8/100 p-y in Week 0-52, 1.3/100 p-y as of 15-Jun-2021, 0.9/100 p-y as of 15-Jun-2022) and Gastrointestinal disorders (1.9/100 p-y in Week 0-52, 1.4/100 p-y as of 15-Jun-2021, 1.0/100 p-y as of 15-Jun-2022).

With the exemption of COVID-19 infection, the most commonly AEs leading to treatment interruption in the deucravacitinib group in the Phase 3 Safety Pool were consistent with those observed at Week 0- 52. For those AEs, EAIR decreased with longer deucravacitinib exposure.

Based on the submitted documentation, no safety issue has been identified.

Laboratory findings

▪ Haematology

In the Control Safety Pool, during the Placebo-Controlled Period (week-0-16), a net difference in treatment related AEs from the SOC "Blood and lymphatic disorders" was observed with an increase in AEs in the deucravacitinib group compared to apremilast and placebo: in deucravacitinib group 9 patients (1.1%) experienced 18 AEs belonging to this SOC, mainly leukopenia (4 patients) and lymphopenia (4 patients), whilst placebo and Apremilast groups reported 1 and 3 adverse events respectively which occurred in 1 and 2 patients, respectively. One subject in the deucravacitinib group discontinued treatment due to an AE of lymphopenia. The subject had a Grade 1 lymphocyte count decreased at baseline, Grade 3 at Week 4. Treatment was discontinued, and lymphocyte count returned to Grade 2. There were no associated infection AEs.

With longer exposure to deucravacitinib (week 0-52) and in the Phase 3 Safety Pool, AE findings were consistent with the Placebo-controlled Period (Week 0-16).

The overall data on hematologic parameters highlight a trend in blood and lymphatic disorder increase, notably, lymphopenia and leukopenia, in deucravacitinib group compared to apremilast and placebo groups, and across every periods. The Applicant considered hematologic events unrelated to deucravacitinib because mean hematologic parameters remained similar across the 3 treatment groups during the controlled trial, and the majority of events were transient and resolved while the subjects remained on therapy with deucravacitinib and without any specific treatment.

Based on the provided data, there are not sufficient evidence to conclude on any deucravacitinib causality in the hematologic abnormalities observed. No SmPC amendment at this time is therefore warranted.

Given that cases of 'eosinophil count increased' or 'eosinophilia' use were mild and transient, and available data do not indicate that risk of these adverse effects increases with longer deucravacitinib exposure, at this moment no amendments of SmPC are warranted. However, these ADRs should be monitored with deucravacitinib use.

Hepatic parameters: Across periods, the AEs related to increased AST, ALT and bilirubin were higher in deucravacitinib group than in placebo and Apremilast groups. No increased bilirubin ≥ 10N were reported with deucravacitinib, but increased ALT and AST were experienced by 5 patients during deucravacitinib Exposure Period (week 0-52) (n=3) and the Phase 3 Safety Pool (n=2). Considering the additional data discussed by the Applicant and notably the lack of meaningful changes from baseline in ALT and AST noted in Phase 3 studies in subjects with psoriasis (IM011046 and IM011047) which included women of child-bearing potential on oral contraceptives, no clinically relevant mean changes. No further action is presently needed however this should be closely monitor as part of the forthcoming PSURs.

As regards *blood creatine phosphokinase*, although incidence of toxicities of CPK increased of Grade 3 and Grade 4 were low in deucravacitinib group, it increased with longer treatment. Similar was shown for incidence of shifts from baseline of > 2 CTCAE grades in deucravacitinib group (Week 0 -16: 1.2%, Week 0 - 52: 1.8%, LTE study: 2.6%). Furthermore, during the Deucravacitinib-Exposure Period (week 0-52), fourteen (n=14) cases of Blood CPK increased related to deucravacitinib were reported, and in 2 patients the event of blood CPK increased led to deucravacitinib discontinuation. Based on the assessment of provided cases, blood CPK increased was added in the section 4.8 of the SmPC.

Safety in special population

No safety issues related to age, sex, race, BMI, ethnicity/region has been identified.

Approximately 10% of the subjects were in the age group ≥ 65 years. There was no increased risk of infection in the age group ≥ 65 years. With additional open-label exposure to deucravacitinib beyond 52 Weeks, the overall incidence of infections was not higher in the age group ≥ 65 years with the exception of COVID-19 SAEs in consideration of their known higher risk of COVID-19 complications and study conduct during the global pandemic. Therefore, no dose adjustment or restriction is proposed for patients ≥ 65 years to < 75 years.

However, the available safety data in very small number of patients aged ≥ 75 years (n=21) suggest that there is 3 fold higher EAIR of SAEs in this elderly subgroup compared to that in group 65 - 74 years.

Therefore, the following statement was included in the section 4.2 of the SmPC: "Clinical experience in patients ≥ 75 years is very limited and deucravacitinib should be used with caution in this group of patients".

It is noted that all JAK inhibitors registered so far in immunology are contraindicated in pregnant women based on non-clinical findings. Nevertheless, no effects on embryo-foetal development were observed with

oral administration of deucravacitinib to rats and rabbits during organogenesis. During the clinical development program, pregnant women were excluded from study participation and women of childbearing potential were required to use effective contraception while receiving study medication. Across the entire deucravacitinib clinical program, 15 pregnancies were reported in subjects or their partners treated with deucravacitinib. The data on pregnancies reported after exposure to deucravacitinib are limited, but do not suggest a specific safety concern. No congenital anomalies have been reported. Considering that there are limited data on the use of deucravacitinib in pregnant women, deucravacitinib should be avoided during pregnancy as a precautionary measure (adequate information has been added in section 4.6 of the SmPC). In addition, use in pregnancy and lactation was added as missing information in the RMP: a category 3 study should be conducted to further assess the use of deucravacitinib in pregnancy.

2.6.10. Conclusions on the clinical safety

Deucravacitinib is a selective TYK 2 inhibitor belonging to the JAK family. The safety profile of deucravacitinib is consistent with its mechanism of action (MOA).

More than 50% of patients experienced at least one adverse events and this increases with deucravacitinib exposure. Due to its immunosuppressant properties related to its MOA, deucravacitinib substantially increases risk of infections notably upper respiratory tract infections and skin disorders. These AEs were mainly mild to moderate in intensity. Although no clear relationship with deucravacitinib can be presently established, in view of the conclusion of the Article 20 referral on the JAK inhibitor, risk of malignancies, NMSC, MACE and other cardiovascular AEs cannot be fully discarded. Hence, pending the results from the Long-term Extension study, the safety concerns of the RMP were further strengthened and "MACE" and "VTE (DVT/PE)" were added as "Important potential risks".

Overall the safety profile of Deucravacitinib in the target indication is considered acceptable and adequately characterised by the submitted safety data.

2.7. Risk Management Plan

2.7.1. Safety concerns

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

2.7.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Not applicable				
Category 2 – Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Long-term, observational cohort study of adults with plaque psoriasis, who are new users of deucravacitinib, non-TNFi (tumour 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. Study protocol finalization 2. Progress updates 3. Interim report submission (1,000 p-y) 4. Final report submission	Q4 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	Q3 2023 Dec 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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	Q1 2024 PSUR Q1 2029
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 2. Progress updates 3. Interim report submission 4. Final report submission	05-Feb-2019 PSUR Oct-2021 Dec-2026

[a] US FDA study commitment.
[b] Extension of the Phase 3 clinical studies IM011046 and IM011047.

2.7.3. Risk minimisation measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Clinical trial long-term extension (IM011075)
Malignancies	**Routine risk minimisation measures:** SmPC (Section 4.4); PL (Section 2) **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: 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) **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: 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)
VTE (DVT/PE)	**Routine risk minimisation measures:** SmPC (Section 4.4); PL (Section 2) **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: 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)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnancy and lactation	**Routine risk minimisation measures:** SmPC (Section 4.6); PL (Section 2) **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: Pregnancy study (IM011201)
Long-term safety	**Routine risk minimisation measures:** None **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: 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)

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 09 September 2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Sotyktu (deucravacitinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Deucravacitinib is intended for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriasis is a chronic debilitating immunologic disease characterized by marked inflammation and thickening of the epidermis that result in thick, scaly plaques involving the skin. The reported prevalence of psoriasis in countries ranges between 0.09% and 11.4%.

Plaque psoriasis is the most common form, affecting approximately 80% to 90% of patients. In patients with plaque psoriasis, approximately 80% have mild to moderate disease, with 20% having moderate to severe disease.

3.1.2. Available therapies and unmet medical need

Topical corticosteroids are commonly used for mild to moderate cases. Other topical medications include keratolytic agents, anthralin, coal tar, vitamin D analogs, and retinoids. For more widespread disease, phototherapy (ultraviolet B [UVB] or psoralen with ultraviolet A [PUVA]) is commonly used. Systemic therapy, including methotrexate (MTX), cyclosporine, synthetic retinoids, and fumaric acid are often effective in patients with moderate or severe disease. Due to the potential adverse side effects of systemic agents, these medications are generally administered in rotation to avoid long-term or cumulative toxicities. Apremilast, an oral selective inhibitor of the enzyme phosphodiesterase 4, is also approved for the treatment of psoriasis.

Biological therapies have emerged as an alternative treatment option for patients with moderate to severe psoriasis in need of systemic therapy.

Expression of tumour necrosis factor (TNF)-induced proteins in psoriatic plaques provided the rationale for the development of TNF-neutralizing therapies for psoriasis, and the anti-TNF agents etanercept, adalimumab, and infliximab are approved for the treatment of moderate to severe psoriasis. Ustekinumab, a p40 IL 12/23 inhibitor, is approved for the treatment of moderate to severe psoriasis.

More targeted biological therapies such as guselkumab and risankizumab, IL-23 inhibitors and anti-IL-17 monoclonal antibodies such as brodalumab, ixekizumab, and secukinumab are also available with higher results in terms of PASI 90 (about 70-75% at week 16).

These more targeted therapies such as IL-17 and IL-12/23 inhibitors have added incremental clinical benefit. While there is not a large unmet need, newer more efficacious treatments are welcome to improved quality of life of plaque psoriasis patients.

3.1.3. Main clinical studies

The deucravacitinib psoriasis clinical development program designed to support the proposed indication included 2 pivotal Phase 3 studies of the dose and dosing regimen (6 mg once daily) in adults who had stable moderate to severe chronic plaque psoriasis ≥ 6 months (with or without psoriatic arthritis), defined as body surface area (BSA) involvement ≥ 10%; Psoriasis Area and Severity Index (PASI) score ≥ 12; Static Physician Global Assessment (sPGA) ≥ 3. These 2 pivotal, double-blind, placebo- and active-controlled 52-week Phase 3 studies (IM011046 and IM011047) are completed.

In addition a dose-finding, placebo-controlled, 12-week Phase 2 study IM011011 was completed.

And a Phase 3 open-label, long-term extension (LTE) study, IM011075 is ongoing for eligible subjects who completed the Phase 3 parent studies (IM011046, IM011047) and where all subjects received deucravacitinib 6 mg QD.

3.2. Favourable effects

A total of 1686 subjects were randomized in the 2 Phase 3 studies:, 843 subjects were randomized to deucravacitinib, 421 to placebo and 422 to Apremilast. Among these Phase 3 patients, 1221 subjects switched to deucravacitinib in the open-label extension Study IM011075. Demographic characteristics and disease severity were balanced across treatment groups and studies and were consistent with those seen in other recent trials of biologics in plaque psoriasis.

The co-primary endpoint in both studies were PASI 75 at week 16 and sPGA of clear or almost clear (0 or 1) at week 16 versus placebo.

Deucravacitinib was superior to placebo as demonstrated by statistically significant differences ($p < 0.0001$) between groups in the proportions of subjects who achieved PASI 75 (58.4%-53.0% vs 12.7%-9.4% deucravacitinib versus placebo respectively in studies 046 and 047) and sPGA of clear or almost clear (53.6%-49.5% vs 7.2%-8.6% deucravacitinib versus placebo respectively in studies 046 and 047).

Deucravacitinib also demonstrated superiority over placebo in all secondary endpoints at week 16, except in nail psoriasis (PGA-F 0/1). Deucravacitinib was superior to placebo in stricter measures of disease severity, i.e. PASI 90 (35.5% vs 4.2% and 27% vs 2.7% in studies 046 and 047, respectively) and PASI 100 (14.2% vs 0.6% and 10.2% vs 1.2% in studies 046 and 047, respectively), all $p \leq 0.0001$.

Deucravacitinib was superior to apremilast for both co-primary endpoints at week 16 PASI 75 (58.4% vs 35.1% in 046 and 53.0% vs 39.8% in 047) and sPGA 0/1 (53.6% vs 32.1% in 046 and 49.5% vs 33.9% in 047) both $p < 0.001$.

Deucravacitinib also demonstrated superiority over apremilast in all secondary endpoints at week 16, except in PSSD symptom score 0. Deucravacitinib was superior to apremilast in stricter measure of disease severity, i.e. PASI 90 at week 16 (35.5% vs 19.6% and 27.0% vs 18.1%, in studies 046 and 047, respectively; both $p<0.005$) and at week 24 (42.2% vs 22.0% and 32.5% vs 19.7% in studies 046 and 047, respectively; both $p<0.0001$).

In both pivotal studies, the treatment effect observed at week 16 across subgroups (geographic region, sex, race, age, weight, BMI, prior psoriasis therapy (phototherapy, conventional systemic therapy, and biologic therapy), baseline sPGA score, baseline PASI score, BSA involvement, duration of disease) consistently

favoured deucravacitinib over placebo and apremilast, although some differences in effect size were noted depending on geographic region, weight/BMI and sex.

Deucravacitinib was superior to placebo for improving the extent and severity of scalp psoriasis in patients with baseline ssPGA ≥3 as demonstrated by statistically significant differences (p< 0.0001 for each comparison) between treatment groups at week 16 - ss-PGA 0/1 70.3% vs 17.4% and 59.7% vs 17.3% in studies 046 and 047, respectively and PSSI 90 57.9% vs 11.6% and 45.6% vs 9.8% in studies 046 and 047, respectively. Superiority of deucravacitinib in treatment of scalp psoriasis was also demonstrated compared to apremilast at week 16 and week 24.

Across the pivotal studies significant improvements in patient-reported outcomes of DLQI (DLQI 0/1) and PSSD (clinically meaningful change in both symptom and sign scores) were observed. 41.0% and 37.6% (study 046 and 047) of subjects in the deucravacitinib group achieved DLQI of 0 or 1 (psoriasis had no impact on subject's quality of life) at Week 16 compared with 10.6% and 9.8% of subjects who received placebo and compared with 28.6% and 23.1% in apremilast arm. In subjects initially randomized to deucravacitinib on Day 1, the proportion of subjects with a DLQI 0/1 response remained relatively consistent at Week 24 (48.1%) and Week 52 (43.2%) in study 046.

At week 52, consistent effects with week 16 results were achieved with a slightly lower efficacy: sPGA 0/1 (45.5% vs 22.2%) and PASI 75 (56.3% vs 30.5%) deucravacitinib vs apremilast respectively in study 046.

Switching to deucravacitinib for subjects who had inadequate initial response to apremilast (<PASI 50 for study 046 and <PASI 75 at Week 24 for study 047) led to improvement in PASI 75 and sPGA 0/1 response that were observed as early as Week 32 (8 weeks after the switch), with responses continuing to improve through Week 52.

Maintenance and durability of response

A lower proportion of subjects re-randomized to deucravacitinib experienced relapse (5.5%) compared with those re-randomized to placebo (45.3%) by Week 52. Since less than 50% subjects relapsed before Week 52 in each subpopulation, a median time to relapse could not be estimated. In subjects re-randomized from deucravacitinib to placebo at Week 24, the median time to loss of PASI 75 response was approximately 12 weeks and a median time to loss of sPGA 0/1 response was approximately 8 weeks.

3.3. Uncertainties and limitations about favourable effects

The inclusion of an active comparator, in addition to placebo, in both clinical trials meets the CHMP guideline (Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis, EMEA/CHMP/EWP/2454/02) requirement that a three-armed, parallel-group studies with the active agent, placebo and comparative active treatment are strongly recommended. A comparator with the same claimed indication, i.e. treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy may have been chosen. However this is considered acceptable for a marketing authorisation application as in line with the guideline and scientific advice, also taking into account that both studies met their objectives demonstrating superiority of deucravacitinib over placebo and over apremilast.

Overall the majority of patients had moderate disease as baseline sPGA score was severe in 20.2% of subjects (sPGA=4). Although it is agreed that the indication is for moderate and severe plaque psoriasis as the analysis included both populations the effects in each subgroups were not studied separately.

In patients with fingernail psoriasis, no meaningful difference of PGA-F 0/1 score was observed between deucravacitinib vs placebo and deucravacitinib vs apremilast neither at week 16 nor at week 24 in both pivotal studies. Deucravacitinib vs apremilast did not show either a meaningful improvement for the assessment of palmoplantar psoriasis with pp-PGA 0/1 or pp-PASI at weeks 16 and 24.

Data on recapture rate upon retreatment are not available due to the IRT technical issues that prevented relapsed patients to be switched back to deucravacitinib in study IM011047. Therefore, no conclusion on continuous versus on demand treatment could be made.

No subjects aged ≥85 years were recruited to the pivotal studies and thus exposure for this age group are not available. In addition clinical experience in patients >75 years is very limited. Therefore section 4.2 of the SmPC was updated to mention that deucravacitinib should be used with caution in this age group.

As requested, the effect of gender, race / ethnicity and body weight were reassessed using model-based predictions from the updated population PK models. The Applicant provided a discussion and concluded that flat dose of 6 mg QD is recommended in all patients regardless of gender, race/ethnicity and body weight.

Given that results from both models are comparable, females are still expected to have an about 30 % higher deucravacitinib mean exposure compared to male, and patients with lower body weight a higher geometric mean C_{maxss} (37.4%) and C_{avgss} (24.8%). Patients with a higher body weight are expected to have a lower geometric mean C_{maxss} (24.8%) and C_{avgss} (19.6%).

Model-based results reveal that exposure-response relationships for efficacy and safety measures are relatively flat for $C_{avg,ss}$ and $C_{min,ss}$, respectively. The probability of infections and infestations with increasing exposure seem to approach a limit from approximately 20 ng/mL $C_{min,ss}$ and onwards. Thus an increase in exposure seems not be associated with a remarkable change in safety (doses up to 12 mg QD or 6 mg BID).

However, it is noted that acceptance of up to 2-fold increased exposure in some groups of patients is not generally appreciated from the PK point of view. The fact that only one dose / strength as a film-coated tablet was selected to be investigated in pivotal trials is not ideal. It was missed to further investigate whether some patients could benefit from dose adjustments and the current drug formulation also does not allow any. With the proposed ”one-fits-all” dosing of 6 mg QD, some patients will be exposed to unnecessarily higher concentrations, much higher than needed to achieve levels that are efficacious, while other individuals could be at risk of under-dosing (e.g. patients with higher body weight). Nonetheless, these risks appear to be covered by the flat exposure-response relationships for efficacy and safety.

3.4. Unfavourable effects

Adverse events

In the Controlled Safety Pool, the overall incidences of TEAEs (treatment-emergent adverse events) in deucravacitinib group were 55.7% (week 0 – 16), 56.7% (week 0 -24) and 72.9% (week 0 -52).

In the Controlled Safety Pool (week 0 - 52), the most commonly reported SOCs for TEAEs in deucravacitinib group were Infections and infestations (46.6%), Gastrointestinal disorders (15.0%), Skin and subcutaneous tissue disorders (13.6%), Musculoskeletal and connective tissue disorders (12.0%), Investigations (10.6%) and Nervous system disorders (9.9%).

The most commonly TEAEs reported in deucravacitinib group were nasopharyngitis (16.8%), upper respiratory tract infection (9.1%), headache (5.9%), diarrhea (5.1%), arthralgia (4.0%) and blood creatine phosphokinase increased (3.3%).

Adverse events were predominantly mild or moderate in intensity across treatment periods.

Treatment-related adverse events

In the treatment period week 0 – 52, treatment-related TEAEs were observed in 22.3% deucravacitinib - treated subjects, 14.4% placebo-treated subjects and 30.1% apremilast-treated subjects.

In both Control Safety Pool and Phase 3 Safety Pool, the main AEs related to deucravacitinib were diarrhoea, nausea, dyspepsia, aphthous ulcer, folliculitis, upper respiratory tract infection, nasopharyngitis, oral herpes, sinusitis, blood CPK increased, fatigue, headache, dizziness, rash, acne, rosacea, urticaria, leukopenia and lymphopenia.

Serious adverse events and deaths

In the treatment period week 0 – 52, serious TEAEs occurred in 4.0% deucravacitinib-treated subjects compared to 2.1% in placebo and apremilast groups. The most frequently reported (in ≥2 patients) SAEs in deucravacitinib group were pneumonia, acute kidney injury, atrial fibrillation, cholecystitis acute, pericarditis and COVID-19.

There were in total 10 deaths in the Controlled Safety Pool and Phase 3 Safety Pool (8 in deucravacitinib group, 1 in the placebo and 1 in the apremilast group).

Adverse events leading to treatment discontinuation

In the treatment period week 0 – 52, incidences of TEAEs leading to treatment discontinuation were 3.2%, 3.5% and 6.2% in the deucravacitinib, placebo and apremilast groups, respectively. GFR decreased, COVID-19, blood CPK increased, psoriasis, rash, diarrhoea, fatigue, insomnia and vomiting were in ≥2 deucravacitinib-treated subjects led to treatment discontinuation.

Adverse events of particular interest

Adverse events of particular interest were skin events, infections, malignancies, MACE, extended MACE, peripheral arterial events, VTE, other serious CV events, depression and suicidal ideation or behaviour.

Skin events were reported in 13.6% deucravacitinib-treated subjects and 7.4% placebo-treated and 8.3% apremilast-treated subjects during first year of treatment. 0.1% of skin AEs was serious, and incidence of skin AEs led to treatment discontinuation was 0.5%. The EAIR of skin AEs in deucravacitinib-treated group was 20.7/100 P-Y in week 0 – 52.

Infections occurred in 46.6% deucravacitinib-treated subjects, compared to 23.7% and 32.7% in placebo and apremilast group during first year of treatment, respectively. Incidence of SAEs of infections in deucravacitinib group was low (1.2%) (mainly reported pneumonia) and increased after the first year of treatment (3.9%) (due to COVID-19). Incidence of infections AEs leading to treatment discontinuation was low (0.4%).

Malignancies were reported in 10 patients (0.7%, EAIR 1.0/100 P-Y) in the deucravacitinib group and in 2 patients (0.5%, EAIR 0.9/100 P-Y) in apremilast group during week 0 - 52. NMSC occurred in 7 deucravacitinib-treated patients (0.5%, EAIR 0.7/100 P-Y) and in 1 apremilast-treated patient (0.2%, EAIR 0.4/100 P-Y). With longer deucravacitinib exposure (after first year of treatment) 19 deucravacitinib-treated

patients experienced malignancies (1.3%, EAIR 0.9/100 P-Y), of which in 10 patients occurred NMSC (0.7%, EAIR 0.5/100 P-Y).

MACE occurred in 3 patients (0.2%, EAIR 0.3/100 P-Y) and adjudicated extended MACE in 4 patients (0.3%, EAIR 0.4/100 P-Y) in deucravacitinib group during week 0 -52. With longer deucravacitinib exposure (after first year of treatment), 7 patients experienced MACE (0.5%, EAIR 0.3/100 P-Y), while extended MACE reported in 10 patients (0.7%, EAIR 0.5/100 P-Y).

In the Controlled Safety Pool (week 0 -52), there were 2 peripheral arterial events (0.1%, EAIR 0.2/ 100 P-Y), 2 VTEs (0.1%, EAIR 0.1/100 P-Y) and 12 other serious CV events (EAIR 1.2/100 P-Y) in deucravacitinib-treated group.

Suicidality and depression: In the Controlled Safety Pool (week 0 -52), the incidence of depression in the deucravacitinib group was 0.6% (2.0/100 P-Y, 5 subjects) compared to 0 cases in the apremilast group. With a longer exposure (week 0-52), the incidence rate of depression remains higher in the deucravacitinib group than in apremilast: 0.8/100 P-Y (0.6%, 8 patients) and 0.4/100 P-Y (0.2%, 1 patient). Suicidal ideation was reported in 1 patient in each treatment group.

Laboratory findings

Haematology: The incidence of treatment-related AEs in the SOC Blood and lymphatic system disorders were higher in deucravacitinib (1.0%) compared placebo (0.5%) and apremilast group (0.7%) during 52 weeks of treatment. The most common treatment-related AEs were leukopenia and lymphopenia occurred with incidence of 0.6% and 0.3% in deucravacitinib group, which was higher than in the placebo and apremilast group.

Hepatic parameters: Incidences of treatment-related ALT increased, AST increased and total were higher in deucravacitinib group compared to apremilast and placebo group.

In conclusion, the appraisal of AESI with deucravacitinib is consistent with its mechanism of action. Deucravacitinib substantially increases risk of infections notably upper respiratory tract infections and skin disorders. The overall AEs were mainly mild to moderate in intensity.

3.5. Uncertainties and limitations about unfavourable effects

Mature long-term safety data from the LTE study (IM011075) are required for this application, and are awaited.

Data from adverse events of interest for the SOC "Infections and infestations" clearly put forward the increased risk of infections with deucravacitinib which is maintained throughout the treatment duration. Furthermore, the use of deucravacitinib in patients with a chronic infection or a history of recurrent infection has been further assessed. The most common TEAEs from SOC Infections and Infestations occurred in deucravacitinib-treated patients with history of chronic infection during Week 0 -52 were nasopharyngitis (27.8%, EAIR 50.2/100 p-y), sinusitis (22.2%, EAIR 42.7/100 p-y) and bronchitis (11.1%; EAIR 17.9/100 p-y). The frequencies were higher compared to overall deucravacitinib -treated patients (nasopharyngitis (16.8%, EAIR 26.1/100 p-y); sinusitis (1.8%; EAIR 2.5/100 p-y) and bronchitis (2.0%, EAIR 2.8/100 p-y). Therefore, deucravacitinib may increase the risk of infections and caution should be exercised when considering the use of deucravacitinib in patients with a chronic infection or a history of recurrent infection. The Applicant has adequately included a warning in section 4.4 of the SmPC regarding the use of

deucravacitinib in these patients. In addition deucravacitinib is contraindicated in patients with clinically important active infections (e.g. active tuberculosis) (SmPC section 4.3).

Deucravacitinib is a selective TYK 2 inhibitor. TYK2 belongs to the JAK family but its TYK 2 selectivity sets it apart from other drugs belonging to this therapeutic class.

The Article 20 referral for JAK inhibitors used in chronic inflammatory disorders finalised on January 2023 (CHMP Opinion) recommended measures to mimimise the risk of serious adverse events associated with JAK inhibitors; compared with TNF-alpha inhibitors, JAK inhibitors used to treat chronic inflammatory disorders are linked to a higher risk of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, serious infections and all-cause mortality.

Although, deucravacitinib is a TYK2 inhibitor, and no clear relationship with deucravacitinib can be presently established, the risks of malignancies, NMSC, MACE and other cardiovascular AEs cannot be fully discarded based on the available data from the phase 3 studies. Patients medical history and co-medications are confounding factors pre-empting a definitive conclusion. However, the compatible time-to-onset observed after deucravacitinib discontinuation for some of the reported cases lead to not discard the causality of deucravacitinib. Overall, as these adverse reactions cannot be fully excluded with deucravacitinib use and given the uncertainties with regards to the long-term safety profile, it remains important to monitor for MACE, VTE, malignancies and serious infections in the post-marketing setting. Therefore, malignancies, MACE and VTE have been added as important potential risks in the RMP and category 3 studies are planned to further evaluate these AEs. In addition warnings were included in section 4.4 of the SmPC to recommend caution prior to initiating treatment.

Deucravacitinib has not been studied in pregnant women, during the clinical development program, pregnant women were excluded from study participation and women of childbearing potential were required to use effective contraception while receiving study medication. Across the entire deucravacitinib clinical program, 15 pregnancies were reported in subjects or their partners treated with deucravacitinib. There is currently insufficient clinical data to draw conclusions about the safety of using deucravacitinib during pregnancy. No effects on embryo-foetal development were observed with oral administration of deucravacitinib to rats and rabbits during organogenesis. As a precautionary measure, it is recommended to avoid the use of deucravacitinib during pregnancy. Use in pregnant and lactating women has been added as a missing information in the list of safety concerns in the RMP. The safety of deucravacitinib use in pregnant and lactating women will be monitored in a category 3 study.

3.6. Effects Table

Table 66 Effects Table for Sotyktu for the treatment of moderate to severe plaque psoriasis (data cut-off: 15 Jun 2021)

Effect	Short Description	Unit	DEUC	Placebo	Apremilast	Uncertainties/ Strength of evidence	Ref
	Favourable Effects						
sPGA 0/1	sPGA success (score 0/1) at wk 16 in subjects with ≥ 2-point improvement from baseline	%	53.6%	7.2%	32.1%	DEUC showed superior efficacy over placebo and Apremilast across the 2 Apremilast & placebo-controlled studies. Results were statistically significant and adjusted for multiplicity. Efficacy was consistent across studies and across several subgroups by demographics, geographics, disease characteristics and psoriasis medication history. The co-primary and all major secondary objectives were met (p<0.001) except for nail and palmoplantar scores	Study IM011046
			49.5%	8.6%	33.9%		Study IM11047
PASI 75	75% reduction on PASI score at wk 16	%	58.4%	12.7%	35.1%		Study IM011046
			53.0%	9.4%	39.8%		Study IM11047
PASI 90	90% reduction on PASI score at wk 16		35.5%	4.2%	19.6%		Study IM011046
			27.0%	2.7%	18.1%		Study IM11047
PASI 100	100% reduction in PASI score at wk 16	%	10.2%	1.2%	-		Study IM011047
ss-PGA 0/1	ss-PGA success (score 0 or 1) at wk 16 in subjects with ≥ 2-point improvement from baseline and a baseline ss-PGA score ≥ 3	%	70.3%	17.4%	39.1%		Study IM011046
			59.7%	17.3%	36.7%		Study IM011047
sPGA 0	sPGA success (score 0) at wk 16		17.5%	0.6%	4.8%		Study IM011046
			15.7%	1.2%	6.3%		Study IM11047
PGA-F 0/1	score of 0 or 1 in		20.9%	8.8% P=0.1049	-		Study IM011046

Effect	Short Description	Unit	DEUC	Placebo	Apremilast	Uncertainties/ Strength of evidence	Ref
	subjects with ≥ 2-point improvement from baseline and a baseline PGA-F score ≥ 3		20.3%	7.9% P=0.0621	-		Study IM11047
PSSD Symptom Score 0	PSSD Symptom Score of 0 in subjects with a baseline PSSD Symptom Score ≥ 1		7.9%	0.7% P=0.0013	4.4% P=0.1702		Study IM011046
			7.5%	1.3% P=0.0005	4.3% P=0.0928		Study IM011047
	Unfavourable Effects						
Nasopharyngitis	AEs related to DEUC >1%	% P-Y	1.4% EAIR= 15/100 P-Y	1.4% EAIR= 6/100 P-Y		Related to DEUC and lower EAIR in placebo group	Control safety pool (week 0-16)
Upper Respiratory Tract infection	AEs related to DEUC >1%	% P-Y	1.5% EAIR= 15/100 P-Y	1% EAIR= 4/100 P-Y		Related to DEUC and lower EAIR in placebo group.	Control safety pool (week 0-16)
Diarrhoea	AEs related to DEUC >1%	% P-Y	2.7% EAIR= 26/100 P-Y	3.8% EAIR= 17/100 P-Y		Related to DEUC and lower rate in placebo group	Control safety pool (week 0-16)
Headache	AEs related to DEUC >1%	% P-Y	1.8% EAIR= 18/100 P-Y	1.7% EAIR= 7/100 P-Y		Related to DEUC and lower rate in placebo group	Control safety pool (week 0-16)
Nausea	AEs related to DEUC >1%	% P-Y	1.4% EAIR= 12/100 P-Y	0.7% EAIR= 3/100 P-Y		Related to DEUC and lower rate in placebo group	Control safety pool (week 0-16)
Blood CPK increased	AEs related to DEUC >1%	% P-Y	1% EAIR= 8/100 P-Y	0.7% EAIR= 3/100 P-Y		Related to DEUC and lower rate in placebo group	Control safety pool (week 0-16)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Deucravacitinib is an oral, selective tyrosine kinase 2 (TYK2) inhibitor. TYK2 is an intracellular non-receptor kinase that mediates the signaling of the pro-inflammatory cytokines interleukin (IL)-23, IL-12, and Type I interferons (IFN). IL-23, IL-12, and type I IFNs are naturally occurring cytokines that are upregulated in inflammatory and immune responses.

Deucravacitinib has shown to work effectively in a very heterogeneous populations with moderate to severe plaque psoriasis. Statistically significant results were demonstrated versus placebo and when compared with active treatment- apremilast, this translated into an improvement in the overall quality of life. Improvements in regional psoriasis such as scalp.

Deucravacitinib demonstrated superiority over placebo and apremilast for improving the extent and severity of scalp psoriasis. Superiority over placebo was nominally significant in treatment of fingernail and palmoplantar psoriasis. No meaningful difference between deucravacitinib and apremilast was observed in the assessment of fingernail or palmoplantar psoriasis. Furthermore improvements were demonstrated in patients not achieving an adequate response to apremilast therapy (non-responder with < PASI 50 or PASI 75) which may be a more treatment resistant population. Therefore deucravacitinib provides additional treatment options for a certain range of patients from naïve to systemic therapy through to those patients who are not adequately controlled on apremilast.

Maintenance of effect was demonstrated. Patients with continuous deucravacitinib treatment at 52 weeks maintained their initial PASI and sPGA responses as observed at week 16.

Subgroups analyses showed a consistently superior effect compared to placebo and active comparator apremilast.

The safety profile of deucravacitinib is consistent with its mechanism of action (MOA). More than 50% of patients experienced at least one adverse event and this increases with deucravacitinib exposure. Due to its immunosuppressant properties related to its MOA, deucravacitinib substantially increases risk of infections notably upper respiratory tract infections and skin disorders. These AEs were mainly mild to moderate in intensity.

Further data on long term safety of deucravacitinib in plaque psoriasis will be provided through the post-marketing setting.

3.7.2. Balance of benefits and risks

The efficacy of oral deucravacitinib in the treatment of moderate to severe plaque psoriasis was demonstrated across an heterogenous population (irrespective of demographic, disease or geographic characteristics or previous psoriasis therapies applied). Deucravacitinib was superior to placebo and apremilast showing meaningful improvement. The onset was achieved near maximal effect at week 24 and maintenance of effect was seen until 52 weeks. Similar improvements were seen across subgroups.

The most significant safety concern associated with deucravacitinib treatment is infection which is expected for this class of product. The safety profile is favourable based on the current safety dataset. It is currently not known whether TYK2 inhibition may be associated with the adverse reactions of JAK inhibition. Therefore,

as precautionary measure, warnings on malignancies and MACE and VTE were included in the SmPC and these risks will be further evaluated in the post-authorisation setting for deucravacitinib.

Overall, based on the data presented, the beneficial effects of deucravacitinib outweigh the unfavourable effects observed in the clinical programme.

Third party intervention during the evaluation of Sotyktu.

During the assessment of Sotyktu, the CHMP received a third party intervention which expressed concerns about an increased risk of malignancies with TYK2 inhibition.

The CHMP considered this intervention in the context of its assessment and concluded that the observations put forward by the third party were already assessed by the CHMP, and as such had no impact on the CHMP assessment or its conclusions.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Sotyktu is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Sotyktu is favourable in the following indication:

Sotyktu is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that deucravacitinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 26 January 2023