Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Sotyktu

Active ingredient/s: Deucravacitinib

Sponsor: Bristol Myers Squibb Australia P/L

August 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
AEI	Adverse event of interest
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC	Area under the concentration time curve
AUC_{inf}	Area under the concentration time cure from zero to infinity
AUC_{tau}	Area under the concentration time curve from time zero to the end of the dosing interval
BMT-153261	Major active metabolite of deucravacitinib
BMT-158170	Active metabolite of deucravacitinib
BMT-334616	Active metabolite of deucravacitinib
BSA	Body surface area
CES2	Carboxylesterase 2
CI	Confidence interval
C_{max}	Maximum concentration
$C_{max,ss}$	Maximum concentration at steady state
CMI	Consumer Medicines Information
DLP	Data lock point
DLQI	Dermatology Life Quality Index
EAIR	Exposure-adjusted incidence rates
eGFR	Estimated glomerular filtration rate
EQ-5D-3L	Euro Quality of Life Five Dimensions Questionnaire – 3-Level Version
ESRD	End stage renal disease
EU	European Union
GM	Geometric mean
HADS	Hospital Anxiety and Depression Scale
IFN	Interferon
IL	Interleukin
JAK	Janus associated kinase
MACE	Major adverse cardiac events
NMSC	Non-melanoma skin cancers

Abbreviation	Meaning
OR	Odds ratio
PASE	Psoriatic Arthritis Screening and Evaluation Questionnaire
PASI	Psoriasis area and severity index
PD	Pharmacodynamics
PGI-C	Patient's Global Impression of Change
PGI-S	Patient's Global Impression of Severity
PI	Product Information
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSSD	Psoriasis Symptoms and Signs Diary
PSUR	Periodic safety update report
PT	Preferred Term
QoL	Quality of life
RMP	Risk management plan
SAE	Serious adverse event
SF-36	Short Form Health Survey-36 Item
SOC	System Organ Class
sPGA	Static physicians global assessment
STAT	signal transducer and activation of transcription
$T_{1/2}$	Half-life
TGA	Therapeutic Goods Administration
T_{max}	Time to maximum concentration
TNF	Tumour necrosis factor
TYK2	Tyrosine kinase type 2
UGT	UDP glucuronosyltransferase
US(A)	United States of America
VAS	Visual analog scale
WLQ	Work Limitation Questionnaire

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Sotyktu
Active ingredient:	Deucravacitinib
Decision:	Approved
Date of decision:	29 November 2022
Date of entry onto ARTG:	1 December 2022
ARTG number:	376290
▼*Black Triangle Scheme*	Yes
for the current submission:	This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd 4 Nexus Court, Mulgrave, VIC 3170, Australia
Dose form:	Film coated tablet
Strength:	6 mg
Container:	Blister pack
Pack sizes:	7 and 28
Approved therapeutic use for the current submission:	*Sotyktu is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*
Route of administration:	Oral
Dosage:	The recommended dose of Sotyktu is 6 mg once daily taken orally, with or without food. Do not crush, cut, or chew the tablet. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be

used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Bristol-Myers Squibb Australia Pty Ltd (the sponsor) to register Sotyktu (deucravacitinib) 6 mg, film coated tablet, blister pack for the following proposed indication:[1]

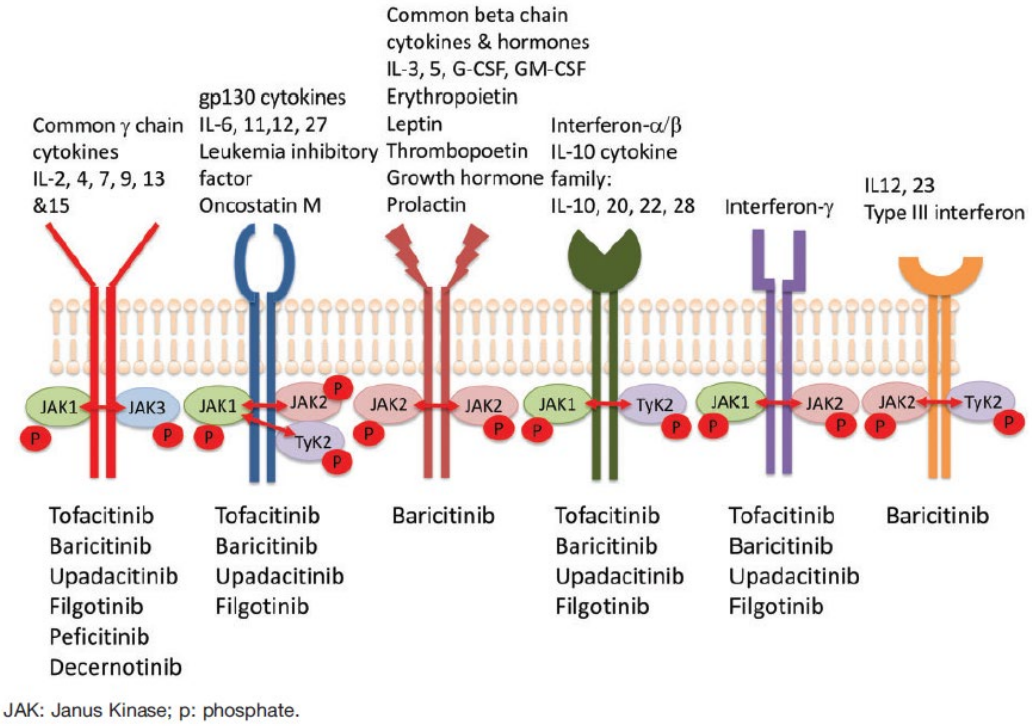
> *Sotyktu is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*

The sponsor describes deucravacitinib as a 'first in class, oral, selective tyrosine kinase type 2 (TYK2) inhibitor'. TYK2 is a member of the Janus associated kinase (JAK) family of intracellular kinases, which regulate signal transduction downstream of cytokine receptors. TYK2 is stated to be highly selective for the interleukin (IL)-23/IL-12 pathways where it pairs with JAK2, and the type I interferon family where it pairs with JAK1, to activate the associated signal transducer and activation of transcription (STAT) pathways. In his review of JAK inhibitor selectivity, Choy (2019) indicated that TYK2 may also be involved in regulation of IL-6, IL-11, and IL-27 pathways (see Figure 1).[2] The sponsor states that '*the binding mode of [deucravacitinib] takes advantage of unique structural features of the TYK2 pseudokinase domain to provide high biochemical and cellular functional selectivity. This approach differentiates [deucravacitinib] from inhibitors of the JAK kinases 1-3 that target the highly conserved active site of the kinase domain leading to lower selectivity*'.

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

[2] Choy EH. Clinical significance of Janus Kinase inhibitor selectivity [published correction appears in Rheumatology (Oxford). 2019 Jun 1;58(6):1122]. Rheumatology (Oxford). 2019;58(6):953-962

Figure 1: Cytokine signalling via JAK isoforms and their inhibitors



Source: Choy, (2019)

Condition

Psoriasis is a chronic, non-communicable and often debilitating disease affecting the skin and nails and is most common in age group 50-69 years.[3] The typical clinical features are of patches of scaling, induration and erythema. The classification of psoriasis can vary based on the clinical presentation. The most common subtype is chronic plaque psoriasis, with other major subtypes including guttate psoriasis, pustular psoriasis and erythrodermic psoriasis.[4] The disease can have a fluctuating relapsing course, with flares that may be induced by factors such as infections, trauma, smoking, and stress. Psoriasis can involve skin in any part of the body; particularly disabling is the involvement of specific anatomic regions, such as hands and feet (palmoplantar), face, scalp, and nails. The disease severity can be graded by body surface area (BSA) with mild less than 10% BSA, and moderate to severe greater than 10% BSA.

Psoriasis is associated with several co-morbidities and while the peak ages of onset are between 30 and 39 years and 50 and 69 years of age, it may be detected in children. The prevalence of psoriasis in Australia is estimated to be between 2.3 to 6.6%[3] Research has identified that psoriasis is a disease of immune dysfunction implicating T-lymphocytes, dendritic cells and cytokines including IL-23, IL-17 and tumour necrosis factor (TNF).[4]

Current treatment options

Mild or limited psoriasis may be managed in general practice with topical therapies including topical steroids, coal tar preparations and calcipotriol. Psoriasis that is extensive, does not

[3] Swanell C (2020) Psoriasis: comorbidities make it more than a skin disease. Med J Aust Published online: 11 May 2020.
[4] Feldman SR (2019) Psoriasis: epidemiology, clinical manifestations, and diagnosis. *UpToDate*https://www.uptodate.com/contents/psoriasis-epidemiology-clinical-manifestations-and-diagnosis?search=psoriasis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2, accessed 10 August 2022

respond to topical therapies or is associated with non-dermatological symptoms will require specialist therapy. Narrow band UVB therapy, conventional systemic anti-inflammatory medications such as methotrexate and ciclosporin, and the oral retinoid acitretin are generally trialled for more significant and widespread disease, but the oral medications in particular are associated with significant toxicities with long term use.

A small number of biological medicines, respectively secukinumab, ustekinumab, and TNF inhibitors (infliximab, etanercept, adalimumab) are available on the Pharmaceutical Benefits Scheme for the treatment of patients with moderate to severe psoriasis under the care of a dermatologist if their disease satisfies stringent criteria. Apremilast, a small-molecule inhibitor of phosphodiesterase 4, and monoclonal antibodies including risankizumab, ixekizumab and tildrakizumab, are registered but at the time of evaluation only available on private prescriptions.

Regulatory status

This product is considered a new chemical entity medicine for Australian regulatory purposes.

At the time the TGA considered this submission, a similar submission had been approved in United States of America (USA) on 10 September 2021. A similar submission was under consideration in European Union (EU) (submitted on 6 October 2021), Canada (submitted on 8 December 2021) and Switzerland (submitted on 15 November 2021).

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	10 September 2021	Approved on 9 September 2022	*Sotyktu is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.*
European Union Centralised procedure	6 October 2021	Under consideration	Under consideration
Canada	8 December 2021	Under consideration	Under consideration
Switzerland	15 November 2021	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2021-04758-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	30 November 2021
First round evaluation completed	9 May 2022
Sponsor provides responses on questions raised in first round evaluation	30 June 2022
Second round evaluation completed	18 August 2022
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	9 September 2022
Sponsor's pre-Advisory Committee response	23 September 2022
Advisory Committee meeting	6 and 7 October 2022
Registration decision (Outcome)	29 November 2022
Administrative activities and registration on the ARTG completed	1 December 2022
Number of working days from submission dossier acceptance to registration decision*	222

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- CHMP/EWP/2454/02 corr Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis.
- EMA 3CC3a Pharmacokinetic studies in man

Quality

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of deucravacitinib were assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

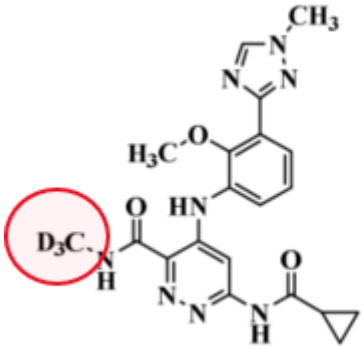
There are no British Phamacopoeia or United States Pharmacopeia monographs for the drug substance or the drug product.

Based on pH-dependent solubility data, the drug substance is a Biopharmaceutics Classification System Class II compound (high permeability, low solubility).

The drug product is a spray dried dispersion of deucravacitinib in hypromellose acetate succinate. Dry granulation, tablet compression and film-coating result in the final drug product. Excipients in the final product are listed in the PI.

Deucravacitinib, or 6-(cyclopropanecarbonylamido)-4-[2-methoxy-3-(1-methyl-1,2,4-triazol-3-yl)anilino]-N-(trideuteriomethyl)pyridazine-3-carboxamide, has three normal hydrogen atoms replaced by the stable hydrogen isotope deuterium. The sponsor states that there is evidence in the scientific literature that deuteration significantly reduced N-demethylation of an experimental drug in a mouse model and caused that drug to retain high TYK2 (JH2 domain) selectivity.

Figure 2: Chemical structure of deucravacitinib



→ → **Deucravacitinib**

The commercial dose form of deucravacitinib is a pink, round, biconvex, film-coated tablet laser printed with 'BMS 895 6 mg' on one side in two lines and no content on the other side.

Several deficiencies identified in the dossier during first round of evaluation have been addressed to the satisfaction of the evaluators. One assurance regarding storage time is outstanding and there is no major objection to the registration of deucravacitinib.

Nonclinical

There are no objections on nonclinical grounds to the registration of deucravacitinib for the treatment of adult patients with moderate to severe plaque psoriasis. The evaluator provided the following summary of the nonclinical evaluation:

In vitro, deucravacitinib and its major active human metabolite (BMT-153261) inhibited TYK2 with nanomolar potency. Another metabolite, BMT-158170 was considerably less potent than deucravacitinib and BMT-153261. Deucravacitinib, BMT-153261and BMT-158170 displayed greater potency at TYK2-dependent pathways than other JAK signalling pathways. While there are no animal models of psoriasis, deucravacitinib inhibited/decreased the pathophysiology of disease in mouse models of acanthosis and colitis and reduced pathophysiology of advanced

nephritis in lupus prone mice. The mechanism for efficacy in these models is expected to be similar to that in psoriasis.

No clinically relevant inhibition was seen on a set of potential off target sites including protein and lipid kinases and pseudokinases, receptors, ion channels, enzymes and transporters with deucravacitinib, BMT-153261 and BMT-158170.

Safety pharmacology studies assessed effects on the cardiovascular system *in vivo* and *in vitro*, with effects on the respiratory and central nervous systems evaluated in repeat dose toxicity studies. No adverse effects on QTc interval or respiratory or central nervous system function are predicted during clinical use.

Overall, the pharmacokinetic profile in animals was adequately similar to that of humans. Following oral administration, deucravacitinib was readily and rapidly absorbed. Following intravenous dosing, plasma half-lives were moderate in mice and rats and longer in dogs and monkeys, and longer in humans following oral dosing. Plasma protein binding of deucravacitinib was moderate in all tested animal species and humans. Tissue distribution of drug related material was wide and penetration into the brain and spinal cord was limited. Retention in the melanin containing tissue of the uveal tract was high in pigmented rats but did not appear to be associated with any toxicity. Deucravacitinib was the predominant drug related circulating species in humans and laboratory animals. CYP1A2, carboxylesterase 2 (CES2) and UDP glucuronosyltransferase (UGT)1A9 were shown to be involved in the metabolism of deucravacitinib in humans. The three main human metabolites (BMT-153261, BMT-158170 and BMT-334616) were also metabolites in animals; however, metabolite:parent area under the concentration time curve (AUC) ratios were lower in animals than humans. The safety of the metabolites has been adequately assessed. Drug related material was excreted primarily via the faeces in animal species while in humans, excretion of radioactivity was similar in urine and faeces.

Aside from potential effects of CES2 inhibitors on deucravacitinib exposures, all potential pharmacokinetic drug interactions affecting deucravacitinib exposures appear to have been investigated in clinical studies. Based on in vitro data, deucravacitinib is not expected to alter exposures to co-administered drugs that are CYP450 substrates. A potentially clinically relevant effect on the exposures of co-administered MATE2K substrates cannot be completely dismissed but might be considered low given the margin in *in vitro* studies.

Deucravacitinib had a low order of acute oral toxicity in rats, dogs and monkeys.

Repeat dose toxicity studies by the oral route were conducted in mice (up to 28 days), rats (up to 6 months) and Cynomolgus monkeys (up to 9 months). Maximum exposures (AUC) were moderate to very high in mice, rats and monkeys. Adequate exposure to metabolites BMT-153261 and BMT-158170 was also achieved. Target organs for toxicity were the immune system (decreased lymphocytes, decreased spleen weight, lymphoid depletion, decreased lymphoid cellularity in the spleen and lymphoid tissues, suppression of T-cell dependent IgM and IgG responses) and haematolymphopoietic system (decreased red blood cell parameters and reticulocytes in all species, increased eosinophils in monkeys and megakaryocytes in the bone marrow of rats) in mice, rats and monkeys, and the skin in monkeys suggestive of infections (increased incidence of skin lesions, sores and/or scabs with associated microscopic findings in the epidermis). Due to decreases in circulating and tissue lymphocytes, immunocompetence in patients may be compromised with an associated increased risk of infection.

Deucravacitinib, BMT-153261 and BMT-158170 were not mutagenic in the bacterial mutation assay or clastogenic *in vitro* (in Chinese hamster ovary cells) or *in vivo* (in the rat micronucleus test). Deucravacitinib is not considered to pose a genotoxic concern.

In carcinogenicity studies, no treatment related increase in tumour incidence was observed in mice or rats at very high clinical exposures. However, TYK2, the pharmacological target for deucravacitinib, has been shown to play a role in tumour surveillance and an increased incidence of lymphoid tumours have been reported in Tyk2$^{-/-}$ mice. An increased risk of tumours exists in patients.

Fertility was unaffected in male and female rats treated with deucravacitinib at exposure levels greater than 100 times the clinical AUC. No treatment related effects were observed in embryofetal development studies in rats or rabbits at exposure levels 223 and 23 times the clinical AUC and free clinical AUC, respectively. Lower bodyweight gain was evident in breast fed pups of rats treated with deucravacitinib. Plasma levels of pharmacologically active material in breast fed pups were up to 11% of maternal plasma levels. A risk of infection in breast-fed infants following maternal exposure cannot be completely dismissed.

Deucravacitinib is not proposed for paediatric use. Studies in juvenile rats revealed findings that were similar to those seen in treated adults and included effects on the immune and haematopoietic systems.

Deucravacitinib was not phototoxic to Balb/C3T3 mouse fibroblasts, despite there being some binding of drug related material in melanin-containing tissues.

The proposed limits for three impurities in the drug substance have been adequately qualified by submitted toxicity data.

The collective safety studies indicate the following as potentially clinically relevant:

- decreases in lymphocytes and immunosuppression with a consequent higher risk of infection, and
- an increased risk of malignancies may be seen in patients.

Several amendments to the PI were recommended by the nonclinical evaluator. All were accepted by the sponsor.

Clinical

Summary of clinical studies

Two pivotal Phase III efficacy/safety studies, Studies IM011046 (POETYK-PSO-1) and IM011047 (POETYK-PSO-2), in adults with moderate to severe active psoriasis were supported by 18 pharmacokinetic/pharmacodynamic studies in healthy adult volunteers, adults with renal or hepatic impairment, and adults with psoriasis, a Phase II dose finding study, and a Phase III long term extension study. Data from the clinical study reports were variously included in a population pharmacokinetic analysis and/or integrated summaries of efficacy and safety.

Real-world data describing the epidemiology of infections, malignancies, major adverse cardiac events (MACE) and depression were used for indirect comparisons of adverse event rates in the treatment population.

Patient-reported outcomes measured in the clinical trials included validated measures of quality of life (QoL): Psoriasis Symptoms and Signs Diary (PSSD), Patient's Global Impression of Change (PGI-C) and Severity (PGI-S), Dermatology Life Quality Index (DLQI), Hospital Anxiety and Depression Scale (HADS), Short Form Health Survey-36 Item (SF-36), Euro Quality of Life Five Dimensions Questionnaire – 3-Level Version (EQ-5D-3L), Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire, visual analog scale (VAS) for assessment of peripheral joint

pain, VAS for assessment of peripheral joint disease, and a Work Limitation Questionnaire (WLQ).

Pharmacology

Pharmacokinetics

The pharmacokinetics (PK) of deucravacitinib were investigated in a series of Phase I clinical studies, and also by applying a population pharmacokinetic (popPK) model derived from results of measurements of PK in healthy volunteers, adults with varying degrees of renal or hepatic impairment and adults with psoriasis. The various PK studies were performed using single doses of between 1 mg and 40 mg deucravacitinib, or multiple doses of up to 12 mg twice daily for up to 14 days. Most studies did not specifically examine the proposed therapeutic oral dose of 6mg daily. Food and/or drug-drug interaction studies that used the 6 mg dosage explored pH effects (famotidine) and interactions with ciclosporin, pyrimethamine and diflunisal. The remaining PK studies generally assessed higher dosages or a range of dosages higher and lower than the proposed dose. Early studies used a solution formulation or capsule formulation of deucravacitinib, the Phase III studies used a tablet formulation essentially identical to the proposed commercial formulation.

Across the various studies, oral deucravacitinib was rapidly absorbed, with the time to maximums plasma concentrations (T_{max}) ranging between one and three hours. T_{max} was delayed under fed conditions (high fat/high calorie breakfast) compared to fasting conditions, and at higher doses. Although the maximum concentration (C_{max}) was generally lower when deucravacitinib was taken in the fed state, estimates of AUC were generally comparable. Deucravacitinib is moderately bound to plasma proteins (approximately 82%), and widely distributed into the tissues but not the brain.

The primary study investigating the PK of deucravacitinib was the four-part first in human study, Study IM011002. The C_{max} and AUC of deucravacitinib increased slightly more than proportionally with dose (1 mg, 3 mg, 10 mg, 20 mg and 40 mg orally as solution) in ascending single dose studies (eight adult participants). The estimated slope (90% confidence interval (CI)) of the relationship between dose and C_{max} was 1.295 (1.234, 1.355); and for area under the concentration time cure from zero to infinity (AUC_{inf}) was 1.244 [1.178, 1.31]. It is noted that in the clinical study report for Study IM011002,[5] the sponsor stated that the results of the dose proportionality studies should be interpreted with caution, as neither the single ascending dose or multiple ascending dose studies were *'optimally designed nor powered to confirm the presence or absence of meaningful departures from dose proportionality'*.

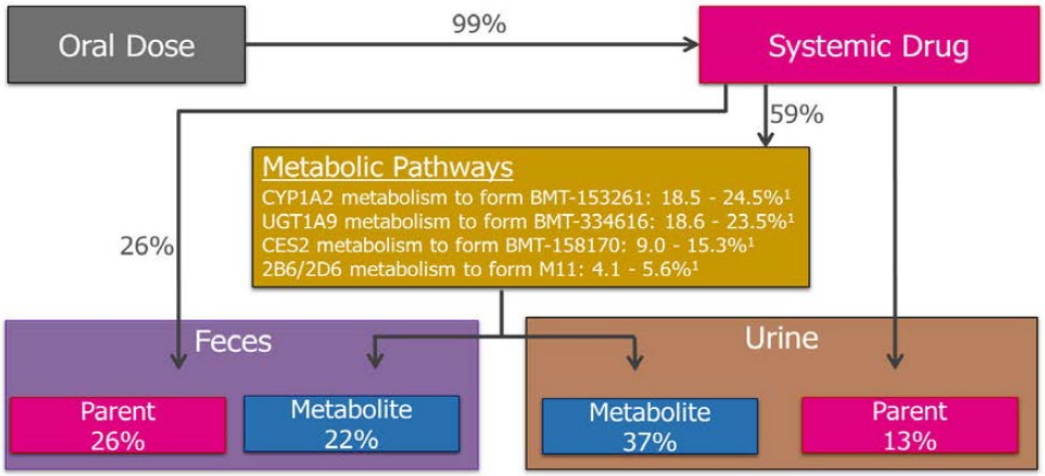
In the multiple ascending dose study with deucravacitinib solution (12 adult participants), the median T_{max} at steady state in healthy volunteers treated with deucravacitinib for 12 days over the dose range of 2 mg to 12 mg twice daily or 12 mg daily was one hour at all doses. Geometric mean (GM) maximum concentration at steady state ($C_{max,ss}$)(coefficient of variation) at 2 mg twice daily and 4 mg twice daily (closest comparable dosing to the proposed dose of 6 mg daily) was 15.2 ng/mL (40%) and 49.6 ng/mL (21%), respectively, and area under the concentration time curve from time zero to the end of the dosing interval (AUC_{tau}) was 90.5 ng.h/mL (43%) and 315 ng.h/mL (29%), respectively. The increase in exposures between doses of 4 mg twice daily to 12 mg twice daily appeared dose proportional, whereas below 4 mg twice daily it appeared to be greater than dose proportional. After multiple dosing, accumulation ratios of

[5] Randomised, double-blind, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of BMS-986165 in healthy participants and to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and clinical efficacy of BMS-986165 in participants with moderate to severe psoriasis, p.67

deucravacitinib at steady state (Day 5) ranged from 1.49 to 1.85 for doses between 2 mg twice daily and 12 mg twice daily.

Deucravacitinib is extensively metabolised, predominantly by four major pathways (see Figure 3) Approximately 59% of ingested deucravacitinib was metabolised, 13% was renally excreted as unmetabolised deucravacitinib and 26% was unmetabolized deucravacitinib measured in the faeces. The mean half-life ($T_{1/2}$) of deucravacitinib ranged from 7.93 hour to 15 hour with increasing dose, although the $T_{1/2}$ after single doses of deucravacitinib 3 mg or 10 mg (closest to the proposed oral dose of 6 mg) were similar (11 hour and 9.87 hour, respectively).

Figure 3: Mass balance model for deucravacitinib following oral administration based on human absorption, distribution, metabolism, and excretion, (Study IM011016) and absolute bioavailability (Study IM011067) studies



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

Values provided in the figure are expressed as percent of orally administered dose of [^{14}C] DEUC, based on ADME (IM011016)[32] and absolute bioavailability (IM011067)[52,53] studies

Up to 24.5% of deucravacitinib is metabolised by cytochrome P450 (CYP) 1A2 to form the active metabolite BMT-153261. Up to 15.3% of ingested deucravacitinib is metabolised by CES2 to the pharmacologically inactive (< 0.3% of parent activity) metabolite BMT-158170; and up to 13% is N-glucuronidated by UGT1A9 to the weakly active (< 10% of parent activity) metabolite BMT-334616. Mono-oxidation by CYP2B6 and 2D6 to metabolite M11 contributes to around 5% of metabolism.

The sponsor has stated that the active metabolites did not contribute significantly to the efficacy of deucravacitinib, however the pharmacological activity of BMT-153261 in *in vitro* whole blood assays was reportedly comparable to the parent drug.

The PK of BMT-153261, BMT-158170 and BMT-334616 were measured in plasma collected from healthy volunteers on Day 1 and Day 12 following the first dose of deucravacitinib (2 mg twice daily – 12 mg twice daily, 12 mg daily) in an exploratory bioanalytical study. Following doses of 12 mg deucravacitinib daily, the GM $C_{max,ss}$ and AUC_{tau} for the parent drug were 117 ng/mL and 803 ng.h/mL, respectively; for BMT-153261 were 18.3 ng/mL and 264 ng.h/mL, respectively; for BMT-158170 were 22.6 ng/mL and 254 ng.h/mL, respectively; and for BMT-334616 were 28.6 ng/mL and 230 ng.h/mL, respectively. The sponsor advised that the liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis of the metabolites was '*scientifically-sound*', but '*not validated following BAS SOP SPEC0008*'. This complicates the ability to assess the relative contributions of the active metabolites to the efficacy and safety of deucravacitinib *in vivo*.

In the same study, the relative proportion of measured total parent drug and major metabolites in the circulation was calculated by dividing the molar AUC (AUC_{tau}/molecular weight) of an individual drug-related component (parent drug or metabolite) in plasma by the sum of molar AUC for all measured circulating components. Following deucravacitinib doses of 6 mg twice daily and 12 mg twice daily, unmetabolised deucravacitinib represented 49% of the total of parent and metabolites in plasma at steady state, while metabolites BMT-153261, BMT-158170 and BMT-334616 represented approximately 20%, 20% and 9% respectively. Based on AUC_{tau} values, for the 6 mg and 12 mg twice daily groups, BMT-153261 showed the greatest degree of accumulation (1.9- to 2.9-fold), followed by BMT-158170 (1.9- to 2-fold), and then BMT-334616 (1.2- to 1.4-fold). The metabolite ratio vs parent drug for AUC_{tau} at steady state (Day 12) was 0.34 to 0.46 for BMT-153261, 0.38 to 0.44 for BMT-158170, and 0.15 to 0.20 for BMT-334616.

The sponsor has stated that no dose adjustment is required in patients with mild or moderate hepatic impairment, and that use is not recommended in patients with Child-Pugh Class C hepatic impairment. The PK of deucravacitinib and of the active metabolite BMT-153261 were examined in adults with impaired hepatic function following a single 12 mg oral dose of the tablet formulation under fasted conditions (Study IM11062). The GM C_{max} of total deucravacitinib in plasma was generally comparable in adults with normal hepatic function, and with mild, moderate or severe hepatic impairment (range 83.6 ng/mL to 92.3 ng/mL). There was greater variability in the measurement of unbound fraction of deucravacitinib, with GM C_{max} of the unbound fraction approximately 14%, 26% and 62% higher in participants with mild, moderate and severe hepatic impairment respectively, compared to participants with normal hepatic function. AUC_{0-t} and AUC_{inf} also appeared to increase with increasing hepatic impairment, and were approximately 11%, 40% and 43% higher in participants with mild, moderate and severe hepatic impairment, respectively, compared to participants with normal hepatic function.

Measures of exposure to BMT-153261 were generally lower in patients with mild, moderate or severe hepatic impairment compared to exposure in participants with normal hepatic function.

The sponsor has stated that no dose adjustment is required in patients with any degree of renal impairment, including end stage renal disease (ESRD) requiring dialysis. The PK of deucravacitinib and of BMT-153261 were examined in adults with impaired renal function following a single 12 mg oral dose of the tablet formulation under fasted conditions (Study IM011061). The GM C_{max} of total deucravacitinib in plasma was comparable in adults with normal renal function (estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73m^2), mild (eGFR ≥ 60 to < 90 mL/min/1.73m^2), moderate (eGFR≥30-<60 mL/min/1.73m2) or severe (eGFR<30 mL/min/1.73m2) renal impairment and adults with ESRD requiring dialysis (eGFR < 15 mL/min/1.73m2), ranging between 97.5 ng/mL and 120 ng/mL with no clear relationship with eGFR. The GM C_{max} of unbound deucravacitinib ranged between 11.2 ng/mL and 12.8 ng/mL and was highest in participants with ESRD requiring dialysis (14.2 ng/mL). Deucravacitinib AUC_{0-t} and AUC_{inf} were comparable in participants with normal renal function and mild renal impairment, but between 28 to 40% higher in moderate renal impairment, severe renal impairment and ESRD compared to normal function. Consideration of the clinical importance of these differences is complicated, as coefficient of variation for measures of AUC in the groups with more significant impairment were greater than 40%.

Renal impairment may have greater impact on the PK of BMT-153261. While GM C_{max} was comparable in participants with normal renal function (9.01 ng/mL), mild renal impairment (8.02 ng/mL), and moderate renal impairment (8.31 ng/mL); C_{max} in participants with ESRD requiring hemodialysis (9.78 ng/mL, 9% increase) and in severe renal impairment (11.6 ng/mL, 28% increase) appeared to trend upwards. The GM AUC_{inf} of BMT-153261 was similar in participants with normal renal function and mild renal impairment, whereas, it was increased by

24 to 27% in moderate renal impairment and ESRD and by 81% in severe renal impairment. The coefficient of variation for measures of AUC in participants with moderate renal impairment and requiring dialysis exceeded 40%.

Regarding drug-drug interactions with deucravacitinib, the sponsor concluded that because deucravacitinib is eliminated via multiple pathways, major interactions via inhibition of induction of any one pathway was unlikely. The dedicated drug-drug interactions studies are summarised in Table 3.

Table 3: Summary of drug drug interaction studies

Drug/dose	Deuc dose	Metabolic process	Effect on deuc	Effect on other
Fluvoxamine 100mg daily	Single 12mg	CYP1A2 inhibitor	15% ↓ Cmax >50% ↑ AUC >40% ↑ $T_{1/2}$	BMT-153261: >90% ↓ Cmax, AUC
Ritonavir single 100mg	Single 12mg	CYP1A2 inducer	↔	BMT-153261: >30% ↑ Cmax, AUC
Ritonavir 100mg daily	Single 12mg	CYP1A2 inducer P-gp inhibitor OCT1 inhibitor	↔	BMT-153261: 16% ↑ Cmax ↔ AUC
Ciclosporin single 500mg	6mg daily (steady state)	BCRP inhibitor P-gp inhibitor	↔ Cmax 29% ↑ AUC	BMT-153261: ↔ Cmax 21% ↑ AUC
Pyrimethamine single 50mg	Single 6mg	OCT1 inhibitor	↔	
Rabeprazole 20mg daily	Single 12mg	PPI (↑ gastric pH)	↔	BMT-153261: ↔
Famotidine single 40mg	Single 6mg	H_2 antagonist	↔ Cmax, AUC, $T_{1/2}$ ↓ T_{max}	
Methotrexate single 7.5mg	12mg daily			Methotrexate ↔
Mycophenolate mofetil single 1g	12mg daily			Mycophenolate ↔
Diflunisal 500mg twice daily	Single 6mg	UGT1A9 inhibitor	↔ Cmax 19% ↑ AUC	BMT-153261: >20% ↑ Cmax >50% ↑ AUC
Loestrin single	12mg twice daily			Norethisterone, ethinyl oestradiol ↔
Rosuvastatin single 10mg	12mg daily			Rosuvastatin 14% Cmax, AUC

Population pharmacokinetics data

Population pharmacokinetic analyses were performed to characterise the PK of deucravacitinib and BMT-153261 in healthy adults and in adults with moderate to severe psoriasis, to assess the impact of baseline PASI score, baseline eGFR, age, body weight, race, gender, presence or absence of psoriasis,[6] deucravacitinib formulation,[7] prandial state and other factors on exposure to deucravacitinib, and to assess the impact of baseline eGFR, age, body weight, race, gender, presence or absence of psoriasis, hepatic impairment and other factors on exposure to BMT-153261.

The deucravacitinib dataset included 18,781 values for deucravacitinib concentrations, collected from 1060 adults with psoriasis and 328 adults without psoriasis (including small numbers with

[6] This was recorded in the report as "Participant Type" with categories "Phase 1" vs "Phase 2/3 PsO"

[7] This was reported with two different comparisons: "Capsule" vs "Tablet" and separately "Liquid" vs "Tablet"

hepatic impairment or renal impairment), in ten Phase I studies, one Phase II study and two Phase III studies. The BMT-153261 dataset included 13,503 values for BMT-153261 concentrations, collected from 919 adults with psoriasis and 233 adults without psoriasis, in ten Phase I studies, one Phase II study and two Phase III studies.

Separate models for deucravacitinib and BMT-1532161 were applied using a nonlinear mixed-effects modelling (NONMEM) software program. Both analyses applied a structural model describing plasma concentrations as a function of dose and time, a random effects model that described interindividual variability in the structural model parameters (clearance, central volume of distribution, intercompartmental clearance, peripheral volume of distribution, absorption rate constant and dose-dependence), as well as clearance for individuals with psoriasis, a residual effects model that accounted for the remaining unexplained random variability within individuals and covariate models that described relationships between the structural model parameter values and the covariates.

The initial base models were conducted with data from all the listed studies except the Phase III study, Study IM011047 (POETYK-PSO-2 trial), then re-estimated when the additional data became available. The full model developed from the first stage was refitted to the entire dataset and served as the starting point for backward elimination to obtain the final model. The results from the full model were used to infer the covariate effects on the PK parameters.

Covariates included in the final model for deucravacitinib were: weight, age, baseline eGFR (based on MDRD equation), baseline PASI,[8] gender and population (psoriasis, healthy adult, renal impairment, hepatic impairment) on clearance; weight, population, gender and disease duration on deucravacitinib central volume of distribution; and formulation and prandial state on absorption rate constant. Covariates included in the final model for BMT-153261 were: age, hepatic impairment, eGFR and race on clearance; age, disease status, race and hepatic impairment on BMT-153261 VC and weight (applied *a priori*) on clearance, central volume of distribution, peripheral volume of distribution and intercompartmental clearance.

The final model for deucravacitinib was also used to generate Empirical Bayesian Estimate (EBE) parameter values for each individual that were further used to develop the BMT-153261 PopPK model, and the EBE parameter values derived from the final deucravacitinib and BMT-153261 PopPK models for each participant were used to simulate exposure (for example, minimum concentration, C_{max} and average concentration) of the dosing regimen of interest (6 mg four time daily), and for further assessment of the impact of intrinsic and extrinsic factors on the pharmacokinetics of deucravacitinib and BMT-153261. The models were evaluated by assessments of Goodness-of-Fit, Uncertainty of Parameter Estimates, and Visual Predictive Checks.

Deucravacitinib concentration-time profiles were adequately described with a two compartment model with zero order followed by first order absorption with a small lag time and linear elimination where the bioavailability (logit transformed) was described by a dose-dependent E_{max} function. The sponsor reported that while the included parameter-covariate relationships were statistically significant, none of them were considered clinically important.

The study reported the following conclusions:

> 'The effects of intrinsic and extrinsic factors such as race, participant type (Phase I participants versus participants with [psoriasis]), baseline PASI, and smoking status on deucravacitinib exposures were small as geometric mean exposures ($C_{max,ss}$ and $C_{avg,ss}$) were comparable and differed by ≤ 20% between relevant comparisons.

[8] Psoriasis Area and Severity Index, a validated tool for assessing psoriasis

> Age, body weight, and sex had a modest effect (< 50%) on deucravacitinib exposures ($C_{max,ss}$ and $C_{avg,ss}$):
>
> Participants with [psoriasis] aged > 65 years had higher deucravacitinib $C_{max,ss}$ (19.5%) and $C_{avg,ss}$ (31%) compared to those aged 40 to 65 years.
>
> Relative to a reference [weight] range of 60 to 90 kg, participants with [psoriasis] with [weight] above 90 kg had a lower deucravacitinib $C_{max,ss}$ (24.8%) and $C_{avg,ss}$ (19.3%). Conversely, participants with [psoriasis] with [weight] below 60 kg had a higher Cmaxss (36.4%) and $C_{avg,ss}$ (24.2%) relative to the reference.
>
> Female participants with [psoriasis] were predicted to have a higher deucravacitinib $C_{max,ss}$ (31.6%) and $C_{avg,ss}$ (28.7%) compared to male participants with [psoriasis].'

A two compartment model with linear elimination was able to adequately capture BMT-153261 concentrations in Phase I participants or participants with psoriasis. The fraction of deucravacitinib dose that is metabolised to BMT-153261was fixed to 0.22 based on results from ADME studies. The sponsor concluded that:

> 'The effects of intrinsic and extrinsic factors such as age, sex, race, smoking status, and baseline PASI on BMT-153261 exposures were small as geometric mean exposures (C_{maxss} and C_{avgss}) were comparable and differed by ≤ 20% between relevant comparisons.
>
> Baseline body weight and participant type (Phase I participants versus participants with [psoriasis]), had a modest effect (< 50%) on BMT-153261 exposures (C_{maxss} and C_{avgss}).
>
> Relative to a reference weight range of 60 to 90 kg, participants with [psoriasis] with [weight] above 90 kg had a lower BMT-153261 C_{maxss} (24.4%) and C_{avgss} (22.5%). Conversely, participants with [psoriasis] with [weight] below 60 kg had a higher BMT-153261 C_{maxss} (44%) and C_{avgss} (36.9%) relative to the reference.'

Based on the population pharmacokinetic analysis, the sponsor considered that no dosage adjustment to the proposed 6mg daily was justified based on any intrinsic or extrinsic factor, other than a recommendation not to use deucravacitinib in patients with severe hepatic impairment. Notably, renal impairment did not appear to have a significant effect on the estimated exposures with the proposed dose.

Pharmacodynamics

Human pharmacodynamic studies included assessments of inhibition of interferon (IFN)α mediated phosphorylation of STAT5 after single ascending doses of deucravacitinib. Dose dependent inhibition was reported at doses between 1 mg and 10 mg, with maximal inhibition with doses 10 mg and over. In multiple dose studies, maximal inhibition was observed at all doses greater than 2 mg twice daily. In multiple dose studies, deucravacitinib also inhibited IFNα mediated gene transcription (of interferon-response genes) in a dose dependent manner.

Single and multiple doses of deucravacitinib inhibited IL-12 and IL-18- IFNγ production in a dose dependent manner, with maximal inhibition with single doses of 10 mg or greater.

In the Phase II and Phase III studies, deucravacitinib administration reduced levels of serum biomarkers for the IL-23/Th17 pathway, which were associated with psoriasis disease activity. Median levels of IL-17A, IL-19 and β defensin were reduced by 48 to 50%, 72% and 81 to 84%, respectively.

Exposure response and exposure safety analyses were performed to characterise the relationship between exposures to deucravacitinib and its active metabolite and efficacy as

assessed by psoriasis area and severity index (PASI) 50/75/90/100;[9] and static physicians global assessment (sPGA) 0/1;[10] and separately to characterise the relationship between deucravacitinib/metabolite and selected safety endpoints (infections and infestations, major adverse cardiac event, extended major adverse cardiac event, serious infections, herpes zoster, malignancy and elevated creatine phosphokinase). The models were developed with data from Study IM011011 and the two pivotal efficacy and safety studies.

The exposure-response efficacy analysis reported that the 6 mg daily dose achieves near-maximal PASI 75 and sPGA 0/1 responses with further increases in deucravacitinib exposures predicted to result in only modest improvements. According to the model a 50% lowering of deucravacitinib exposure, relative to median exposures achieved with the 6 mg daily dose, resulted in a modest reduction in PASI 75 response and sPGA 0/1 response.

The exposure-response safety analysis did not identify any notable safety trends.

Efficacy

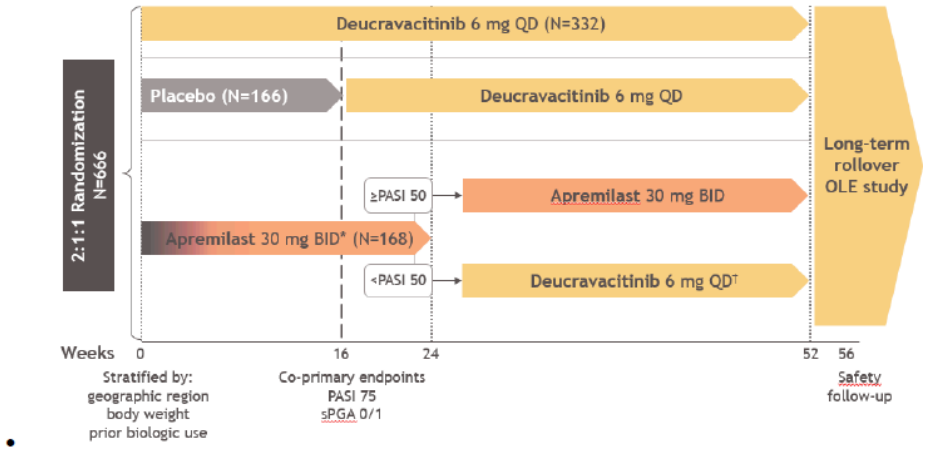
POETYK-PSO-1 trial

POETYK-1 trial was a Phase III, multicentre, randomised, double blind, double dummy, placebo- and active-controlled study to compare the efficacy and safety of deucravacitinib 6 mg daily versus placebo and apremilast 30 mg twice daily in 666 adults with moderate to severe plaque psoriasis.

The primary objective of the study was to assess if deucravacitinib was superior to placebo at Week 16 in terms of efficacy, applying co-primary endpoints of response rates sPGA of psoriasis score of 0 or 1 (sPGA 0/1, maximum score 4) and 75% improvement from baseline PASI (PASI 75). The secondary endpoint was to assess whether deucravacitinib was superior to the active control, apremilast, at Week 16 and at Week 52. The study schematic of POETYK-1 trial is outlined in Figure 4

The primary, secondary and additional endpoints are listed in Table 4.

Figure 4: POETYK-1 trial schematic



[9] The PASI is a scoring system to evaluate baseline and response of therapy in psoriasis.

[10] The sPGA is used to determine a single estimate of the patient's overall severity of disease at a given point in time. Psoriatic lesions are graded for induration, erythema, and scaling based on scales of 0 to 5 that are then averaged over all lesions

Table 4: POETYK-1 trial objectives and endpoints

Objective	Assessments and/or Endpoints	Reported in this CSR (Yes/No)
Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment	• sPGA 0/1 response	Yes
	• PASI 75 response	Yes
	• PASI 90 response	Yes
	• sPGA 0 response	Yes
	• PASI 100 response	Yes
	• Change from baseline and percent change from baseline in PASI	Yes
	• Change from baseline and percent change from baseline in BSA	Yes
	• Change from baseline and percent change from baseline in BSA x sPGA	Yes
Assess whether BMS-986165 is superior to apremilast over 52 weeks of treatment	• sPGA 0/1 response	Yes
	• PASI 75 response	Yes
	• PASI 90 response	Yes
	• sPGA 0 response	Yes
	• PASI 100 response	Yes
	• Change from baseline and percent change from baseline in PASI	Yes
	• Change from baseline and percent change from baseline in BSA	Yes
	• Change from baseline and percent change from baseline in BSA x sPGA	Yes
Assess whether BMS-986165 is superior to placebo in scalp psoriasis through Week 16 in those subjects who have baseline ss-PGA score ≥3	• ss-PGA 0/1 response	Yes
	• Change from baseline in the PSSI	Yes
	• PSSI 90 response	Yes
Assess whether BMS-986165 is superior to apremilast in scalp psoriasis through Week 52 in those subjects who have baseline ss-PGA score ≥3	• ss-PGA 0/1 response	Yes
	• Change from baseline in PSSI score	Yes
	• PSSI 90 response	Yes
Assess whether BMS-986165 is superior to placebo in nail psoriasis through Week 16 in those subjects who have baseline PGA-F psoriasis score ≥3	• PGA-F 0/1 response	Yes
	• Change from baseline in the mNAPSI	Yes
	• mNAPSI 75 response	Yes
Assess whether BMS-986165 is superior to apremilast in nail psoriasis through Week 52 in those subjects who have baseline PGA-F score ≥3	• PGA-F 0/1 response	Yes
	• Change from baseline in mNAPSI	Yes
	• mNAPSI 75 response	Yes
Assess whether BMS-986165 is superior to placebo in palmoplantar psoriasis through Week 16 in those	• pp-PGA 0/1 response	Yes
	• Change from baseline in the pp-PASI	Yes

Table 4: POETYK-1 trial objectives and endpoints, continued'

Objective	Assessments and/or Endpoints	Reported in this CSR (Yes/No)
Assess whether BMS-986165 is superior to placebo over the first 16 weeks of treatment	• sPGA 0/1 response	Yes
	• PASI 75 response	Yes
	• PASI 90 response	Yes
	• sPGA 0 response	Yes
	• PASI 100 response	Yes
	• Change from baseline and percent change from baseline in PASI	Yes
	• Change from baseline and percent change from baseline in BSA	Yes
	• Change from baseline and percent change from baseline in BSA x sPGA	Yes
Assess whether BMS-986165 is superior to apremilast over 52 weeks of treatment	• sPGA 0/1 response	Yes
	• PASI 75 response	Yes
	• PASI 90 response	Yes
	• sPGA 0 response	Yes
	• PASI 100 response	Yes
	• Change from baseline and percent change from baseline in PASI	Yes
	• Change from baseline and percent change from baseline in BSA	Yes
	• Change from baseline and percent change from baseline in BSA x sPGA	Yes
Assess whether BMS-986165 is superior to placebo in scalp psoriasis through Week 16 in those subjects who have baseline ss-PGA score ≥3	• ss-PGA 0/1 response	Yes
	• Change from baseline in the PSSI	Yes
	• PSSI 90 response	Yes
Assess whether BMS-986165 is superior to apremilast in scalp psoriasis through Week 52 in those subjects who have baseline ss-PGA score ≥3	• ss-PGA 0/1 response	Yes
	• Change from baseline in PSSI score	Yes
	• PSSI 90 response	Yes
Assess whether BMS-986165 is superior to placebo in nail psoriasis through Week 16 in those subjects who have baseline PGA-F psoriasis score ≥3	• PGA-F 0/1 response	Yes
	• Change from baseline in the mNAPSI	Yes
	• mNAPSI 75 response	Yes
Assess whether BMS-986165 is superior to apremilast in nail psoriasis through Week 52 in those subjects who have baseline PGA-F score ≥3	• PGA-F 0/1 response	Yes
	• Change from baseline in mNAPSI	Yes
	• mNAPSI 75 response	Yes
Assess whether BMS-986165 is superior to placebo in palmoplantar psoriasis through Week 16 in those	• pp-PGA 0/1 response	Yes
	• Change from baseline in the pp-PASI	Yes

Table 4: POETYK-1 trial objectives and endpoints, continued'

subjects who have baseline palmoplantar pp-PGA score ≥3		
Evaluate improvement in PROs for BMS-986165 compared with placebo through Week 16	• Change from baseline in PSSD symptom score, sign score, and total score	Yes
Evaluate improvement in PROs for BMS-986165 compared with apremilast through Week 52	• PSSD total score of 0 (among subjects with a baseline PSSD total score of at least 1)	Yes
	• PSSD symptom score of 0 (among subjects with a baseline PSSD symptom score of at least 1)	Yes
	• PSSD sign score of 0 (among subjects with a baseline PSSD sign score of at least 1)	Yes
	• PGI-C	Yes
	• Change from baseline in the PGI-S	Yes
	• Change from baseline in DLQI score	Yes
	• DLQI 0/1 (among subjects with a baseline DLQI score ≥2)	Yes
	• Change from baseline in joint pain VAS score in subjects with baseline joint pain VAS score ≥30 mm	Yes
	• Change from baseline in subject's global assessment of joint disease (VAS score) in subjects with baseline joint pain VAS score ≥30 mm	Yes
	• Change from baseline in HADS anxiety component score and depression component score	Yes
	• Change from baseline in total score, PCS and MCS of the SF-36[a]	No
	• Change from baseline in the 3-level version of the EQ-5D-3L utility scores[b]	Yes
	• Change from baseline in the WLQ score[c]	Yes
Evaluate maintenance of response of BMS-986165 through Week 52	• Time to first loss of PASI 75 among subjects that are PASI 75 responders at Week 24	Yes
	• PASI 75 responders at Week 52 and Week 24	Yes
	• sPGA 0/1 responders at Week 52 and Week 24	Yes
	• PASI 90 responders at Week 52 and Week 24	Yes

a PCS and MCS of the SF-36 were reported per the Statistical Analysis Plan. Total score endpoint was reported.

b CSR is reporting Change from Baseline in the EQ-5D-3L VAS score, per the Statistical Analysis Pan.

c CSR s reporting Changefrom Baselinein the WLQ At-Work Productiveity Loss Score per the Statistical Analysis Plan.

Abbreviations: BSA – body surface area; DLQI = Dermatology Life Quality Index; EQ-5D-3L = Euro QoL Five Dimensions Questionnaire; HADS = Hospital Anxiety and Depression Scale; MCS = mental component score;; mNAPSI = modified nail psoriasis severity index; PCS = physical component score; PGA-F = Physician's Gobal Assessment Fingemail; PGI-C = Patient's Gobal Impression of Change; PGI-S = Patient's Gobal Impression of Sevreity; pp-PASI = palmoplantar Psoriasis Area and Severity Index; pp-PGA = palmpplantar Physician's Global Assessment; PRO = patient-repoerted outcome; PSSD = Psoriasis Symptoms and Signs Diary; PSSI = Poriasis Scalp Severity Index; SF-36 = 36 items Short Form Health Survey; sPGA = Static Physician's Global Assessment; ss-PGA = scalp severity Physician's Gobal Assessment; VAS = visual analog scale; WLQ = Work limitataions questionnaire.

The major inclusion criteria were adult males and females who had plaque psoriasis, PASI score ≥ 12, sPGA ≥ 3, and BSA involvement ≥ 10% at both Screening Visit and Day 1, who the investigator deemed candidates for phototherapy or systemic therapy. Plaque psoriasis should have been stable (defined as no morphology changes or significant flares of plaque psoriasis in the opinion of the investigator) for six months or more. The complete list of all inclusion criteria is provided in the clinical evaluation report. The exclusion criteria were typical for this population, excluding from participation those with non-plaque psoriasis; at risk of or currently infected (acute or chronic) with serious or severe infections including herpes zoster, hepatitis B, hepatitis C, human immunodeficiency virus or tuberculosis; with a history of or current immune related conditions; serious or severe conditions affecting any major organ system, recent history of malignancy other than resected non-melanoma skin cancer or carcinoma of the cervix. The complete list of exclusion criteria is provided in the clinical evaluation report.

Tests of significance of deucravacitinib 6 mg daily versus placebo at Week 16 for the co-primary endpoints were two sided with a significance level of 0.05. Two sided 95% CI were provided for all efficacy estimates. Both co-primary endpoints needed to demonstrate statistical significance to result in a successful study. Once both co-primary endpoints were found to be statistically significant, a hierarchical testing approach was used for testing the key secondary endpoints. Analysis of covariance models were used to compare the differences between deucravacitinib 6 mg daily and placebo or between deucravacitinib 6 mg four times a day and apremilast at each timepoint of comparison. Non-responder imputation or modified baseline observation carried forward was applied to missing values as appropriate. Sensitivity analyses included multiple imputation and tipping point methods.

Overall, 666 adults were randomized in a 2:1:1 ratio to one of the three treatment groups (332, 166 and 168 participants to deucravacitinib 6 mg daily, placebo and apremilast, respectively), and 665 participants were treated across all groups (one participant in the placebo group was not treated).

Most participants completed the placebo controlled period. Completion rates in the deucravacitinib group were somewhat higher than in the placebo and apremilast treatment groups (92.5%, 87.9% and 86.3% respectively). Adverse events (AEs) were the most common reason for discontinuations (1.5%, 4.2%, and 6.0%, respectively).

Overall, 535 (80.3%) participants completed the study (Week 0 to 52), of which 517 (77.6%) participants rolled over to the long term extension study (Study IM011075). The most common reasons for discontinuation from the study overall were: 62 (9.3%) participants due to withdrawal by participant, 27 (4.1%) participants due to AEs, and 21 (3.2%) participants lost to follow up. The most common protocol deviations included noncompliance with treatment (defined as < 75% study treatment compliance during the first 16 weeks of the study) with similar incidence across treatment groups.

Results

Baseline demographic, disease features and treatment history were comparable in the three treatment groups. Most participants (78.7%) had an sPGA score of 3 (moderate disease), and the remaining 21.2% of participants had an sPGA score of 4 (severe disease). The mean PASI score was 21.4 and 43.4% of participants had PASI greater than 20. Mean BSA involvement was 26.3% across treatment groups and 48.5% of participants had BSA involvement greater than 20%. Most participants (88.9%) had scalp psoriasis present at Baseline; 38.3% participants had fingernail psoriasis, and 13.8% participants had palmoplantar psoriasis present at baseline. Overall, 62.8% (418 out of 666) had received any prior systemic treatment (including biologic and/or non-biologic systemic treatment); 38.9% (259 out of 666) had received a prior biologic systemic treatment and 23.9% (159 out of 666) had received a prior non-biologic systemic

treatment and had never received a prior biologic treatment. In addition, 37.2% (248 out of 666) reported no prior systemic treatment and 35.9% (239 out of 666) of participants received prior phototherapy.

Deucravacitinib was statistically significantly superior to placebo in achieving the co-primary efficacy outcomes. In the deucravacitinib treatment group, 53.6% of participants achieved sPGA response of 0 or 1 at Week 16, compared to 7.2% in the placebo treatment group (odds ratio (OR) = 18.71 (95% CI: 9.51, 36.81), p< 0.0001). In the deucravacitinib group, 58.4% of participants achieved a 75% improvement in PASI score at Week 16, compared to 12.7% in the placebo group (OR = 11.09 (95% CI: 6.49, 18.95), p< 0.0001, Table 5).

Table 5: POETYK-1 trial Response rates for the co-primary efficacy outcomes

Endpoint	DEUC N = 332	Placebo N = 166	P-value
sPGA 0/1, n (%)	178 (53.6%)	12 (7.2%)	< 0.0001
PASI 75, n (%)	194 (58.4%)	21 (12.7%)	< 0.0001

Response Definitions:

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

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

p-value was obtained using a stratified Cochran-Mantel-Haenszel test.

Abbreviations: sPGA - Static Physician's Global Assessment, PASI - Psoriasis Area and Severity Index.

Deucravacitinib was also statistically significantly superior to placebo, and to apremilast, in achieving most of the ranked key secondary endpoints (Table 6, Table 7). The first secondary endpoint that failed to achieve statistical significance against placebo was improvement in the fingernail psoriasis PGA score (PGA-F 0/1) at Week 16. The first secondary endpoint that failed to achieve statistical significance against apremilast was the patient-reported outcome for improvement in the PSSD at 16 weeks.

Table 6: POETYK-1 trial Response rates versus placebo at Week 16

Rank	Endpoint	DEUC N = 332	Placebo N = 166	P-value
1	PASI 90	35.5%	4.2%	< 0.0001
2	ss-PGA 0/1	70.3%	17.4%	< 0.0001
3	sPGA 0	17.5%	0.6%	< 0.0001
4	PASI 100	14.2%	0.6%	< 0.0001
5	PSSD Symptom Score 0	7.9%	0.7%	0.0013
6 *	DLQI 0/1	41.0%	10.6%	< 0.0001
7	PGA-F 0/1	20.9%	8.8%	0.1049

Table 7: POETYK-1 trial Response rates versus apremilast

Rank	Endpoint	DEUC N = 332	Apremilast N = 168	P-value
1	sPGA 0/1 at Week 16	53.6%	32.1%	< 0.0001
2	PASI 75 at Week 16	58.4%	35.1%	< 0.0001
3	PASI 90 at Week 16	35.5%	19.6%	0.0002
4	sPGA 0/1 at Week 24	58.7%	31.0%	< 0.0001
5	PASI 75at Week 24	69.3%	38.1%	< 0.0001
6	PASI 90 at Week 24	42.2%	22.0%	< 0.0001
7	CFB in PSSD Symptom Score at Week 16	-29.4	-22.8	< 0.0001
8	ss-PGA 0/1 at Week 16	70.3%	39.1%	< 0.0001
9	sPGA 0/1 at Week 52 and at Week 24	45.5%	22.2%	< 0.0001
10	PASI 75 at Week 52 and at Week 24	56.3%	30.5%	< 0.0001
11	PASI 90 at Week 52 and at Week 24	31.0%	15.6%	0.0002
12	sPGA 0 at Week 16	17.5%	4.8%	< 0.0001
13	PSSD Symptom Score 0 at Week 16	7.9%	4.4%	0.1702

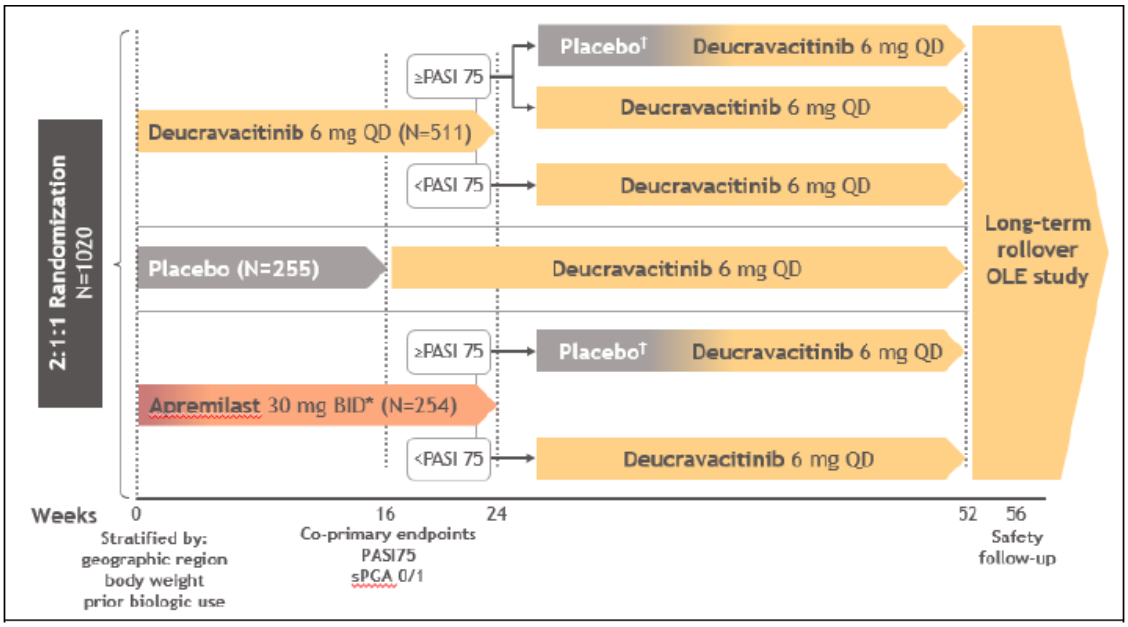
sPGA 0/1: sPGA score of 0 or 1 in subjects with ≥ 2-point improvement from baseline
ss-PGA 0/1: ss-PGA of 0 or 1 in subjects with ≥ 2-point improvement from baseline and a baseline ss-PGA ≥ 3
sPGA 0: sPGA score of 0 with at least 2-point improvement from baseline
PASI 75: a ≥ 75% improvement from baseline in the PASI score
PASI 90: a ≥ 90% improvement from baseline in the PASI score
PSSD symptom score of 0: PSSD symptom score of 0 in subjects with a baseline PSSD symptom score ≥ 1
Abbreviations: CFB - change from baseline, PASI - Psoriasis Area and Severity Index; sPGA - Static Physician's Global Assessment; ss-PGA - scalp-specific PGA; PSSD - psoriasis symptoms and signs diary

Sensitivity analyses supported the primary analyses. Response curves over time favouring deucravacitinib, subgroup analyses and assessments of long-term efficacy of deucravacitinib were also supportive.

POETYK-PSO-2 trial

POETYK-2 trial was also a Phase III, multi centre, randomised, double blind, double dummy, placebo- and active-controlled study to compare the efficacy and safety of deucravacitinib 6 mg daily versus placebo and apremilast 30 mg twice daily in adults with moderate to severe plaque psoriasis, which beyond the first 16 weeks intended to assess the response to withdrawal and retreatment with deucravacitinib in the maintenance phase (Figure 5).

Figure 5: POETYK-2 trial schematic



*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

At Week 16, participants originally randomized to placebo were switched to (blinded) deucravacitinib 6mg daily and maintained on this treatment until the end of study.

At Week 24 participants were assessed for PASI response and were managed as follows:

- Participants originally randomised to deucravacitinib, who did not achieve PASI 75 response, continued to receive deucravacitinib. Participants originally randomised to deucravacitinib, who achieved PASI 75 response, were re-randomised in a 1:1 ratio to either deucravacitinib or placebo. If participants re-randomized to placebo experienced a relapse (at least a 50% loss of Week 24 PASI percent improvement from Baseline) at any visit during this period, they were to be switched back to deucravacitinib through Week 52.
- Participants originally randomised to apremilast who did not achieve PASI 75 response at Week 24, were switched to deucravacitinib. Participants originally randomized to apremilast who achieved PASI 75 response, were switched to placebo. If participants re-randomised to placebo experienced a relapse at any visit during this period, they were to be switched to deucravacitinib through Week 52.
- All participants originally randomised to placebo at Week 0 and switched to deucravacitinib at Week 16 remained on deucravacitinib through Week 52.
- Participants who had a sPGA of at least 3 or scalp specific-PGA of at least 3 were permitted to start treatment with restricted topicals or shampoos on the body and scalp lesions at Week 24 and continue these treatments through Week 52, at the investigator's discretion. These treatments may have been only initiated at Week 24, and not at earlier or subsequent time points.

Participants concluded the treatment period of the study at Week 52, but eligible participants could continue treatment under a separate long term extension protocol IM011075 (approximately 5 years).

Inclusion and exclusion criteria were the same as in POETYK-1.trial

Essentially the same efficacy outcomes were assessed as in POETYK-1 trial, but additional endpoints were included to evaluate the maintenance and durability of efficacy of deucravacitinib during the randomized withdrawal period through Week 52 among Week 24 PASI 75 responders continuing on treatment compared with those re-randomised to placebo. The additional endpoints were

- Maintenance of PASI 75 response at Week 52
- Maintenance of sPGA 0/1 response at Week 52 among participants with a Week 24 sPGA 0/1 response
- Disease relapse (proportion of participants with at least 50% loss of Week 24 PASI percent improvement from baseline)
- Time to relapse until Week 52
- Disease rebound (proportion of participants with worsening of psoriasis over baseline [measured as a PASI score greater than 125% over baseline PASI score] or new pustular, erythrodermic or more inflammatory psoriasis occurring within two months of stopping therapy) in participants re-randomised to placebo
- Time to rebound in participants re-randomised to placebo
- Recapture rate (PASI 75 response at Week 52) in participants re-randomised to placebo who are retreated with deucravacitinib 6 mg daily after relapse.

Most of the 1018 participants who were randomised and received treatment completed the placebo controlled period (89.4%, 83.5% and 85.4% in the deucravacitinib, placebo, and apremilast treatment groups, respectively). The most common reasons for discontinuation were AEs (2.2%, 2.8%, and 4.7%), 'other' reasons (2.5%, 3.5%, 2.8%), and withdrawal by participant (2.7%, 3.5%, 3.5%).

Overall, 884 participants entered the weeks 16 to 24 period. Of these, 455 were participants originally randomised to deucravacitinib and continued on deucravacitinib, 212 were participants originally administered placebo then switched to deucravacitinib at 16 weeks and 217 were participants originally randomised to apremilast and continued on apremilast until Week 24.

At Week 24, 860 continued into the next phase of the study:

- 212 who switched from placebo to deucravacitinib at Week 16 (PBO/DEUC/DEUC group);
- 142 participants originally randomised to deucravacitinib who failed to achieve PASI 75 at Week 24 continued on deucravacitinib without re-randomisation (DEUC/DEUC/DEUC, nrr group);
- 148 participants originally randomized to deucravacitinib who achieved PASI 75 at Week 24 and re-randomised to continue deucravacitinib (DEUC/DEUC/DEUC, rr group);
- 150 participants originally randomized to deucravacitinib who achieved PASI 75 at Week 24 and re-randomised to placebo (DEUC/DEUC/PBO group);
- 111 participants originally randomized to apremilast who failed to achieve PASI 75 at Week 24 switched to (blinded) deucravacitinib (APR/APR/DEUC group); and
- 97 participants originally randomized to apremilast who achieved PASI 75 at Week 24 switched to (blinded) placebo (APR/APR/PBO group).

Between Weeks 24 and 52, a total 33 participants randomised to placebo treatment were switched to deucravacitinib following a relapse, of these 17 were in the DEUC/DEUC/PBO group and 16 were in the APR/APR/PBO group. An additional 106 participants who experienced relapse while on placebo were not switched to deucravacitinib because of a system failure. This affected the assessment of retreatment efficacy. Seventeen participants discontinued in this phase for COVID-19 related reasons. Protocol deviations were uncommon (5.7%) and predominantly related to failure to return pill bottles for assessments of treatment compliance.

Results

Baseline demographic, disease features and treatment history were comparable in the three treatment groups except that the proportion of males was somewhat higher in the placebo treatment group (71%) than in the deucravacitinib (65.8%) or apremilast (61.8%) groups. Most patients (80.5%) had a sPGA score of 3 (moderate disease) while the remaining 19.5% of participants had an sPGA score of 4 (severe disease). The mean PASI score was 21.04 and 41.9% of participants had PASI greater than 20 (severe disease). Mean BSA involvement was 26.5% across treatment groups and 50.6% of participants had BSA involvement greater than 20%. Most participants (86.1%) had a history of scalp psoriasis; 44.5% had a history of fingernail psoriasis, and 18% had a history of palmoplantar psoriasis. The prior treatment experience was generally consistent across treatment groups.

As in POETYK-1 trial, deucravacitinib was statistically significantly superior to placebo in achieving the co-primary efficacy outcomes. In the deucravacitinib treatment group, 49.5% of participants achieved sPGA response of 0 or 1 at Week 16, compared to 8.6% in the placebo treatment group (OR = 10.55 (95% CI: 6.54,17), p< 0.0001). In the deucravacitinib group, 53% of participants achieved a 75% improvement in PASI score at Week 16, compared to 9.4% in the placebo group (OR = 10.49 (95% CI: 6.65, 16.55), p< 0.0001). Deucravacitinib was also statistically significantly superior to placebo, and to apremilast, in achieving most of the ranked key secondary endpoints (Table 8).

Table 8: POETYK-2 trial Key secondary outcomes

DEUC vs Placebo (2-sided alpha=0.025)					DEUC vs Apremilast (2-sided alpha=0.025)				
Rank	Endpoint	DEUC N = 511	Placebo N = 255	p-value	Rank	Endpoint	DEUC N = 511	Apremilast N = 254	p-value
1	PASI 90 at W16	27.0%	2.7%	< 0.0001	1	sPGA 0/1 at W16	49.5%	33.9%	< 0.0001
2	ss-PGA 0/1 at W16	59.7%	17.3%	< 0.0001	2	PASI 75 at W16	53.0%	39.8%	0.0004
3	sPGA 0 at W16	15.7%	1.2%	< 0.0001	3	PASI 90 at W16	27.0%	18.1%	0.0046
4	PASI 100 at W16	10.2%	1.2%	< 0.0001	4	sPGA 0/1 at W24	49.8%	29.5%	< 0.0001
5	PSSD Symptom Score 0 at W16	7.5%	1.3%	0.0005	5	PASI 75 at W24	58.7%	37.8%	< 0.0001
*	DLQI 0/1 at W16	37.6%	9.8%	< 0.0001	6	PASI 90 at W24	32.5%	19.7%	0.0001
*	Time To Relapse until W52 in Wk 24 PASI 75 responders[a]	--[b]	--[b]	< 0.0001	7	Change from baseline in PSSD Symptom Score at W16	-28.3	-21.1	< 0.0001
6	PGA-F 0/1 at W16	20.3%	7.9%	0.0621	8	ss-PGA 0/1 at W16	59.7%	36.7%	< 0.0001
					9	sPGA 0 at W16	15.7%	6.3%	0.0002
					10	PSSD Symptom Score 0 at W16	7.5%	4.3%	0.0928

* Endpoint in the Ex-US hierarchy only

[a] Median times are not estimable. P-value is for comparison of the distribution of time to relapse.

[b] Kaplan-Meier estimations. Time to relapse and median time to relapse are not available.

Endpoint Definitions:

sPGA 0/1: sPGA score of 0 or 1 in subjects with ≥ 2-point improvement from baseline
PASI 75: a ≥ 75% improvement from baseline in the PASI score
PASI 90: a ≥ 90% improvement from baseline in the PASI score
PASI 100: a 100% improvement from baseline in the PASI score
ss-PGA 0/1: ss-PGA of 0 or 1 in subjects with ≥ 2-point improvement from baseline and a baseline ss-PGA ≥ 3
PSSD symptom score of 0: PSSD symptom score of 0 in subjects with a baseline PSSD symptom score ≥ 1
DLQI 0/1: DLQI score of 0 or 1 in subjects with a baseline DLQI score ≥ 2
PGA-F 0/1: PGA-F score of 0 or 1 in subjects with ≥ 2-point improvement from baseline and a baseline PGA-F score ≥ 3
Relapse: ≥ 50% loss of Week 24 PASI percent improvement from baseline in Week 24 DEUC PASI 75 responders after switching to placebo through Week 52

The first secondary endpoint that failed to achieve statistical significance against placebo was improvement in the fingernail psoriasis PGA score (PGA-F 0/1) at Week 16. The first secondary endpoint that failed to achieve statistical significance against apremilast was the patient-reported outcome for improvement in the PSSD at 16 weeks. Sensitivity analyses supported the primary analyses. Response curves over time favouring deucravacitinib, subgroup analyses and assessments of long-term efficacy of deucravacitinib were also supportive.

Regarding the maintenance of responses to deucravacitinib, 70.3% of participants in the DEUC/DEUC/DEUC,rr group had sPGA 0/1 at Week 52, compared to 23.5% in the DEUC/DEUC/PRO group; PASI 75 responses at 52 weeks in the same groups were 80.4% and 31.3%, respectively. Of the responders to deucravacitinib at Week 24, 46.6% in the DEUC/DEUC/DEUC,rr group compared to 87.4% in the DEUC/DEUC/PRO group lost the sPGA 0/1 response; 26.9% in the DEUC/DEUC/DEUC,rr group compared to 78.7% in the DEUC/DEUC/PRO group lost the PASI 75 response. In the same comparator groups, 5.5% in the DEUC/DEUC/DEUC,rr group experienced relapse by Week 52, whereas 45.4% in the DEUC/DEUC/PRO group experienced relapse by Week 52.

In the groups originally treated with apremilast and achieved sPGA 0/1 and PASI 75, 89.9% in the APR:APR:PBO group lost sPGA 0/1 response, 80% lost PASI75 response by Week 52 and 50.5% experienced relapse by Week 52.

Several other analyses were supportive of efficacy, including maintenance and durability of response claims for deucravacitinib.

The open label extension study, Study IM011075 provided supportive evidence for long term maintenance of efficacy: participants who were last treated with deucravacitinib in their

respective parent study maintained sPGA 0/1 and PASI 75 response rates up to Week 60 of open label treatment in the long term extension study. Participants who were last treated with apremilast in their respective parent study and switched to deucravacitinib also maintained sPGA 0/1 and PASI 75 response rates. Participants who were last treated with placebo in their respective parent study and switched to deucravacitinib in the long term extension experienced increases in sPGA 0/1 and PASI 75 rates up to Week 16 that were maintained through Week 60. In this group sPGA 0/1 rates were 25.4%, 63.6%, 74.2%, 66% and 61.5% at Week 0, Week 8, 16, 48 and 60, respectively; PASI 75 response rates were 34.5%, 71.3%, 84.0%, 89% and 80.8%, respectively.

Safety

The main studies providing safety data included two pivotal Phase III studies, POETYK-1 trial, POETYK-2 trial and one open label, long term extension Phase III study, Study IM011075. Supportive safety data was also provided by a Phase II clinical trial in psoriasis (Study IM011011), a Phase II clinical trial in adults with psoriatic arthritis (Study IM011084, Part A) and the 18 clinical pharmacology studies. Further supportive safety information was provided from ongoing studies with deucravacitinib in patients with psoriasis and non-psoriasis indications. The provided narratives, which were not included in the integrated safety analysis, referred to deaths, serious adverse events, and adverse events leading to treatment discontinuation, and from the unblinded studies also suspected unexpected serious adverse reactions and any pregnancy outcomes.

Safety evaluations included general medical history (including history of tobacco use), psoriasis-related history including prior systemic treatment, other prior and concomitant treatments, physical examinations and measurements, vital signs, electrocardiograms, chest imaging, and laboratory tests. Pre-specified AEs of interest, which represent potential safety concerns related to the drug's mechanism of action, observations from prior clinical studies with deucravacitinib and with inhibitors of IL-23, IL-12, and/or IL-17, and/or the underlying disease state included infections, skin events, malignancy, cardiac events, thromboembolic events, and suicidal ideation and behaviour.

The integrated safety analysis was done in two safety pools:

- A controlled safety pool drawn from active and placebo-controlled periods of POETYK-1 and POETYK-2 trials, which had identical eligibility criteria and were of identical study designs until Week 24.
- A Phase III safety pool drawn from the uncontrolled periods of POETYK-1 and POETYK-2 trials, and from the extension study (Study IM011075) up to the safety cutoff date of 15 June 2021.

In the Phase III safety pool 1519 participants received at least one dose of deucravacitinib 6 mg with a total exposure of 2166.9 patient-years. Of these, 1317 participants had a total exposure to deucravacitinib of at least 26 weeks and 1312 received continuous exposure for at least 26 weeks, 1141 had total exposure of at least 52 weeks and 1068 had continuous exposure for at least 52 weeks, and 296 participants had total exposure of at least 104 weeks (Table 9). The mean and median durations of exposure to deucravacitinib were 521 and 588 days, respectively.

In the controlled safety pool, a total of 1364 participants received at least one dose of deucravacitinib, 666 received at least one dose of placebo, and 422 received at least one dose of apremilast. The mean duration of exposure was consistent across the treatment groups, with a median duration of exposure of 112 days (16 weeks) for each group during the placebo controlled period.

Table 9: Exposure to deucravacitinib by safety pool in psoriasis studies

	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.
[a] as of data cut-off date 15-Jun-2021

In the controlled safety pool, AE irrespective of relationship to treatment were more frequent in the deucravacitinib- (55.7%) and apremilast-treated (57.6%) arms than in the placebo treated arm (49.6%, Table 10). Similarly, treatment-related AEs were also more frequent in the active treatment arms. This general pattern was maintained over the 52-week treatment period.

Table 10: Overall safety summary – controlled safety pool (Week 0 to 16)

	BMS-986165 6 mg QD N = 842		Placebo N = 419		Apremilast N = 422	
Adverse Event Category (%)	n (%)	IR/ 100 P-Y	n (%)	IR/ 100 P-Y	n (%)	IR/ 100 P-Y
AEs	469 (55.7)	305.7	208 (49.6)	263.2	243 (57.6)	341.3
RELATED AEs	164 (19.5)	-	65 (15.5)	-	109 (25.8)	-
SEVERE AEs	15 (1.8)	-	11 (2.6)	-	9 (2.1)	-
SAEs	15 (1.8)	6.0	12 (2.9)	9.9	5 (1.2)	4.0
DISCONTINUED TREATMENT DUE TO AEs	20 (2.4)	8.0	16 (3.8)	13.2	22 (5.2)	17.9
DEATHs	1 (0.1)	-	1 (0.2)	-	1 (0.2)	-

Abbreviations: AE = adverse event; SAE = serious adverse event.
Includes events with a start date between first dose and the Week 16 visit date.
Treatment associated with the event is the treatment the subject was taking on the event start date.
MedDRA: 23.1.
Includes data from IM011046 and IM011047.

In the deucravacitinib- and placebo-treated arms, the MedDRA System Organ Classification (SOC) with most frequently reported AEs in the placebo-controlled period was infections and infestations (29.1% and 21.5%, respectively). In the apremilast treated arm, infections and infestations were recorded by 22% but the most frequently reported AEs were in the SOC gastrointestinal disorders (25.8%), with incidence rates around twice as high as reported in the deucravacitinib- and placebo-treated arms. AE reports in the SOC skin and subcutaneous tissues were higher in the deucravacitinib arm (8.9%) than in placebo (5.3%) or apremilast (5.9%) arms. Other SOC with AE reports of at least 5% in the deucravacitinib-treated arm were musculoskeletal and connective tissue disorders (7.8%), nervous system disorders (7.2%) and investigations (6.2%).

The most frequently reported AE by preferred term (PT) in any treatment arm during the 16 week placebo controlled period were nasopharyngitis in the deucravacitinib (9%) and placebo (8.6%), and diarrhoea (11.8%), headache (10.7%) and nausea (10%) in the apremilast arm. By PT, upper respiratory tract infection was slightly more frequently reported in the deucravacitinib group (5.5%) than in either the placebo (4.1%) or apremilast (4%) groups. Additional analyses applying customised groupings of related PTs confirmed that participants treated with deucravacitinib generally reported a higher incidence of URTIs (18.9%, 16.6% and 14.8% in deucravacitinib, apremilast and placebo groups, respectively), acneiform rash (3.6%, 0.9% and 0.2%, respectively), oral ulcers (1.9%, 0% and 0%, respectively) and herpes simplex infection (2%, 0.5% and 0.2%, respectively) than participants treated with placebo or apremilast.

There were no clinically meaningful changes from baseline in haematology or chemistry parameters, including creatinine phosphokinase and lipids. Laboratory abnormalities were infrequent, balanced across the deucravacitinib, placebo, and apremilast treatment groups, and showed no evidence of organ toxicity. Laboratory abnormalities observed were mostly associated with transient changes generally not leading to dose interruption or discontinuation. Creatinine phosphokinase elevations of at least 2.5x upper limit of normal (Grade 2 elevation) were categorized as events of interest and occurred more frequently in the deucravacitinib treatment group.

Reports of serious AEs (SAEs) were relatively low in the 16 week placebo controlled period (Table 10); over the 52 week study period, few SAEs were reported by more than one participant in any treatment arm but more frequently in the deucravacitinib arm (Table 11).

Table 11: Serious adverse events in at least two participants in any treatment group over Weeks 0 to 52 Controlled Safety Pool

	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	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

Exposure-adjusted incidence rates (EAIR) calculated over the total 52 week exposure period of the controlled study safety pool, and from the Phase III safety pool did not flag any new or significant issues. The EAIR of AEs trended to be lower over the longer evaluation periods than reported in the placebo-controlled (and apremilast controlled) periods.

Four deaths were reported in POETYK-1 and POETYK-2 trials. One 75 year old female in the deucravacitinib group had multiple episodes of cardiac arrest on Day 12 and was resuscitated and died on Day 13. This patient had discontinued deucravacitinib on Day 4 as she was taking leflunomide (prohibited by protocol) and was withdrawn from the study. Relevant medical history included hypertension, prior cerebrovascular accident (CVA) and cardiac pacemaker. A 54 year old male in the deucravacitinib group had a poorly differentiated hepatocellular carcinoma diagnosed following investigations for gastrointestinal symptoms on Day 212 and

died at home on Day 298. A 57 year old female in the placebo group with hypertensive disease, obesity and sleep apnoea died on Day 23 (placebo was ceased on Day 17), and a 76 year old male in the apremilast group was diagnosed with lung cancer on Day 109 and developed a gastrointestinal bleed on Day 135, investigation identified a gastrointestinal arteriovenous malformation. All deaths were considered unrelated to study treatment.

Six deaths were reported in the long term extension study (as of 15 June 2021). Five of the six deaths in the long term extension study were due to COVID-19 (58 year old male, Day 157 of long term extension (515 days on deucravacitinib); 84 year old male Day 111 of long term extension (476 days on deucravacitinib), multiple comorbidities; 61 year old male Day 274 of long term extension (639 days on deucravacitinib), Type 2 diabetes mellitus, hypertension, hypercholesterolaemia; 64 year old female Day 203 of long term extension; apremilast for first 24 weeks, comorbid diabetes, asthma, sleep apnoea and others; 68 year old male Day 186 of long term extension, had been on apremilast to Week 24 and then placebo to Week 52 of parent trial). One death in the long term extension was attributed to a ruptured thoracic aortic aneurysm. This 58 year old male had been in the PBO/DEUC arm of POETYK-1 trial, and had comorbidities of hypertension, obesity, sinus tachycardia and smoking, and had also experienced AEs including chronic pancreatitis, chronic cholecystitis, liver haemangioma, nasopharyngitis, respiratory disorder and AST increased.

Adverse events of interest

Adjudication committees were used to adjudicate specified AEs during the studies, specifically an Infection Adjudication Committee, Cardiovascular Adjudication Committee, and Suicidal Ideation and Behavior Adjudication Committee. Each committee was distinct from the Data Monitoring Committee, and each was composed of individuals with relevant expertise. Adjudication Committee members were not investigators in the study and were blinded to participant treatment assignment.

Skin and subcutaneous tissues

The incidence of skin adverse event of interest (AEI) in the 16 week placebo controlled period was higher in the deucravacitinib group (8.6%) compared with the placebo (2.4%) and apremilast (2.8%) groups. The most common events were folliculitis and acne which typically occurred on the face, chest or back, and resolved spontaneously or with topical or oral antimicrobial treatments and mostly occurred within the first eight weeks of treatment. None of the skin AEIs was serious. Skin AEIs rarely led to discontinuation of study treatment with one event each of folliculitis and rosacea in the deucravacitinib group and one event of rash in the apremilast group leading to treatment discontinuation. EAIR of skin infections remained higher in the deucravacitinib group than in the apremilast group throughout the 52 week study period, and in the long term extension study. There was no evidence of increasing incidence with increasing exposure time.

Infections and infestations

As reported above, during the 16 week placebo controlled period the incidence of AEs in the SOC of infections and infestations was higher in the deucravacitinib group compared with placebo and apremilast groups. The most common AE was nasopharyngitis and the second most common infection AE was upper respiratory tract infection. Folliculitis, oral herpes, pharyngitis, viral upper respiratory tract infection, sinusitis and urinary tract infection were all more frequently reported in the deucravacitinib group. Overall, the infection AEs were predominantly mild or moderate in severity. Over the longer study periods the EAIRs of infections (including pharyngitis, viral upper respiratory tract infection, urinary tract infections, oral herpes, bronchitis, and folliculitis) remained higher in the deucravacitinib group compared to

apremilast group, although the EAIR of serious infections were comparable in the two groups. There was no evidence of increasing rates of infection AEs with longer exposure. Common severe AEs in the long-term extension study were COVID-19 related infections (1.6%) and COVID-19 pneumonia (0.8%).

Based on the mechanism of action of deucravacitinib and the safety profiles of antibodies targeting cytokines whose signalling is mediated by TYK2, AEs of herpes zoster, influenza, opportunistic infections, and tuberculosis were pre-specified as infection AEIs in the Phase III studies. Review of reported influenza cases by the adjudication committee did not confirm higher rates of influenza in patients treated with deucravacitinib compared to placebo and apremilast. Reports of herpes simplex were more common in deucravacitinib treated patients. While the EAIR of herpes simplex in deucravacitinib treated participants decreased over longer exposure times, they remained higher than in the apremilast group.

Reports of herpes zoster infections were comparable between participants treated with deucravacitinib and placebo during the placebo-controlled period, and a total of 15 participants in the Phase III safety pool had confirmed AE of herpes zoster. Most reports were while taking deucravacitinib, with one study participant experiencing one episode while taking placebo and a second event while on deucravacitinib; four participants reported herpes zoster while taking apremilast.

Reports of opportunistic infections, and of tuberculosis were infrequent across the study.

Malignancies including non-melanoma skin cancers

No malignancies were reported in the deucravacitinib treated patients, and one malignancy (lung adenocarcinoma) was reported in an apremilast treated patient, during the controlled safety pool 16 week placebo controlled period. Over the 52 week exposure period, seven non-melanoma skin cancers (NMSC) were reported among participants originally randomised to deucravacitinib, none from those originally randomized to placebo, and one from those originally randomised to apremilast. Furthermore, among participants originally randomised to deucravacitinib, one reported breast cancer, one reported hepatocellular cancer and one reported Hodgkin's disease during the 52 week exposure period, whereas no new malignancies were identified among the participants originally randomized to placebo or apremilast. Noting that study participants were re-randomised at Week 16 or Week 24, and may therefore have had varying exposures to deucravacitinib, apremilast or placebo over the 52 week period, EAIR were provided (Table 12). The EAIR for individual malignancies in participants originally randomised to deucravacitinib were comparable to or lower than the EAIR in patients originally randomised to apremilast.

Table 12: Malignancy events – controlled safety pool (W0-52), exposure-adjusted incidence rates

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.

Most participants who reported malignancies had at least one recognised risk factor, for example, most participants who reported NMSC had had a previous NMSC; the participant with hepatocellular carcinoma had a history of hepatitis C with cirrhosis.

Three additional cases of lymphoma were reported in the Phase III safety pool. Expert reviews of individual cases could not definitely conclude that there was a relationship with deucravacitinib use.

Indirect comparisons with malignancy rates in the general population of adults with psoriasis did not identify higher rates in the deucravacitinib-treated population.

Major adverse cardiovascular events

Nonfatal myocardial infarction, nonfatal stroke and cardiovascular death were defined as MACE by the adjudication committee, and MACE plus unstable angina requiring hospitalisation was defined as extended MACE. The committee also reviewed reports of other cardiovascular events including revascularization procedures, heart failure, dysrhythmias, heart blocks, thrombotic events and deaths.

In the controlled safety pool, Week 0 to 16, SAEs were adjudicated as MACE in two participants in the deucravacitinib group (EAIR 0.8/100 p-y), three participants in the placebo group (2.4/100 p-y), and one participant in the apremilast group (0.8/100 p-y, Table 13). One additional MACE was reported in each of the deucravacitinib and apremilast groups up to 52 weeks of the study. All the participants considered to have had a MACE carried additional risk factors for cardiovascular disease, and investigators considered the event unrelated to study medication. Eleven adjudicated other cardiovascular events were reported by 11 participants (all originally randomised to deucravacitinib) during the 52-week exposure period; these included atrial fibrillation (two cases), pericarditis (two cases), aortic dissection, arteriosclerosis coronary artery, malignant hypertension, myocardial ischemia, transient ischemic attack, ventricular tachycardia shock, supraventricular tachycardia (one case each). The EAIR for these events (combined) was 1.2/100 p-y. One patient originally randomized to placebo experienced a pericardial effusion.

Table 13: Adjudicated major adverse cardiac events and extended major adverse cardiac events in the controlled safety pool

MACE Category, n (%) / EAIR	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	--	--

1 subject in the DEUC group had 2 event terms (cardiac arrest and cardiac failure) adjudicated as sudden death
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

In the Phase III safety pool, adjudicated MACE events were reported in 9 out of 1519 study participants (EAIR 0.4/100 p-y) and extended MACE in 11 out of 1519 participants (EAIR 0.5/100 p-y; these rates were consistent with the rates observed in the controlled safety pool (Week 0 to 52). Of note, four MACE or extended MACE events occurred in males younger than 50 years of age (one during treatment with apremilast), and one 34 year old female with a history of smoking less than 10 cigarettes a day experienced an ischaemic stroke while taking deucravacitinib.

The sponsor considered that the rates of cardiovascular events in the deucravacitinib psoriasis studies were comparable to the rates reported in the general psoriasis population.

Thromboembolic disease (venous or arterial)

No venous thromboembolic events were reported in the controlled safety pool during the placebo controlled period. Over the 52 week study period, one participant in the deucravacitinib group experienced a non-serious deep vein thrombosis of a radial vein associated with intravascular cannulation. A second participant in the deucravacitinib group experienced a SAE of aortic dissection and coincident pulmonary embolism. The EAIR for the combined events was 0.1/100 p-y. No thromboembolic events were reported in the groups originally randomised to placebo or apremilast. An SAE of deep vein thrombosis in a participant with comorbid COVID-19 infection and thrombophlebitis was reported in the Phase III safety pool.

In the placebo controlled period of the two pivotal studies, one 66 year old male in the placebo treated group developed an iliac artery occlusion on Day 24. Subsequently the male had vascular surgery on Day 106 for another, peripheral arterial, occlusion. A 55 year old female in the apremilast group also experienced peripheral arterial occlusion on Day 9 and Day 23 of treatment. There were no arterial thrombotic events during the placebo controlled period in participants treated with deucravacitinib. Two additional reports of arterial thrombosis were made during the Week 0 to 52 period, both participants were taking deucravacitinib at the time. A 64 year old male developed right popliteal arterial thrombosis (Day 189, 77 days on deucravacitinib) and a 57 year old male was diagnosed with Leriche syndrome (obstruction of common femoral and superficial femoral arteries) on Day 261.

All affected participants had additional risks for thromboembolic disease. The sponsor indicated that the EAIR for venous thromboembolism in the clinical studies were comparable to the patient population with psoriasis.

Depression and suicidal ideation

The most frequently reported psychiatric AEs in the deucravacitinib group were depression and insomnia, and in the apremilast group were insomnia and anxiety across the safety pools. Overall, reports in the SOC of psychiatric disorders were comparable to rates reported in the patient population with psoriasis. There were no SAEs reported. Reporting rates did not appear to increase or decrease with longer exposure to deucravacitinib. The adjudication committee confirmed three AEs of suicidal ideation, one in each treatment group.

Diverticulitis and gastrointestinal perforation

Diverticulitis and gastrointestinal perforation were not considered AEIs during the psoriasis study. The TGA and major international regulators are currently investigating, among other concerns, an apparent increased risk of diverticulitis and gastrointestinal perforation with the use of registered JAK inhibitors. In view of the ongoing review, it was considered appropriate to examine the safety data from the psoriasis program for possible signals. During the placebo-controlled periods of the pivotal Phase III studies, SAEs of diverticulitis were reported in one participant in the deucravacitinib arm and one participant in the placebo arm, with no reports in the apremilast arm, whereas gastrointestinal haemorrhage was reported by one participant in the deucravacitinib arm and one in the apremilast arm. A small intestinal perforation was reported in the placebo arm (Table 14). In the 24 week apremilast-controlled arm, EAIR in patients taking deucravacitinib were estimated at 0.3/100 p-y for diverticulitis and for gastrointestinal haemorrhage (Table 15).

Table 14: Summary of clinical safety – Serious Adverse Event Summary, Controlled Safety Pool, Week 0 – Week 16, Diverticulitis, gastrointestinal perforation

System Organ Class Preferred Term [n (%) n]	BMS-986165 6 mg QD N = 842		Placebo N = 419		Apremilast N = 422	
INFECTIONS AND INFESTATIONS	5 (0.6)	5	2 (0.5)	2	2 (0.5)	2
DIVERTICULITIS	1 (0.1)	1	1 (0.2)	1	0	
GASTROINTESTINAL DISORDERS	1 (0.1)	1	1 (0.2)	3	2 (0.5)	2
GASTROINTESTINAL HAEMORRHAGE	1 (0.1)	1	0		1 (0.2)	1
ABDOMINAL PAIN UPPER	0		0		1 (0.2)	1
ENTEROCUTANEOUS FISTULA	0		1 (0.2)	1	0	
INTRA-ABDOMINAL FLUID COLLECTION	0		1 (0.2)	1	0	
SMALL INTESTINAL PERFORATION	0		1 (0.2)	1	0	

Table 15: Summary of clinical safety - Serious Adverse Events, Controlled Safety Pool, Week 0 - 24, Subjects Who Were Randomized to and Continued on the Same Active Treatment Groups, Diverticulitis, gastrointestinal perforation

System Organ Class Preferred Term	BMS-986165 6 mg QD N = 842			Apremilast N = 422		
	n (%)	P-Y	IR/ 100 P-Y	n (%)	P-Y	IR/ 100 P-Y
TOTAL SUBJECTS WITH AN EVENT	25 (3.0)	364.1	6.9	8 (1.9)	179.3	4.5
INFECTIONS AND INFESTATIONS	7 (0.8)	366.6	1.9	3 (0.7)	179.9	1.7
DIVERTICULITIS	1 (0.1)	367.3	0.3	0	0	0
GASTROINTESTINAL DISORDERS	2 (0.2)	367.4	0.5	2 (0.5)	180.2	1.1
GASTROINTESTINAL HAEMORRHAGE	1 (0.1)	367.5	0.3	1 (0.2)	180.3	0.6
OBSTRUCTIVE PANCREATITIS	1 (0.1)	367.4	0.3	0	0	0
ABDOMINAL PAIN UPPER	0	0	0	1 (0.2)	180.2	0.6

All-cause mortality

In addition to the deaths that were reported in the psoriasis treatment program, the sponsor provided safety narratives for deaths that were reported in other ongoing studies with deucravacitinib. A total of seven deaths were reported in blinded, ongoing studies in psoriatic arthritis, ulcerative colitis, Crohn's disease, lupus nephritis and systemic lupus erythematosus. An 18 year old female with systemic lupus erythematosus developed a toxic skin eruption on Day 2 of blinded study treatment, study treatment was withdrawn on Day 3. The eruption was treated with acyclovir, ceftriaxone and doxycycline, was later diagnosed as 'herpes simplex,

complicated by pyoderma' which resolved. She did not recommence study treatment and died three months later with pulmonary heart disease. Relationship to study treatment could not be ascertained. A 51 year old female with Crohn's disease and co-morbid Type 2 diabetes, hyperlipidaemia, hypertension, obesity, and other conditions experienced cardiac arrest at home 36 days after discontinuing blinded drug therapy owing to Crohn's disease flare, diabetic foot infection and cellulitis on Day 21 of the trial. An autopsy identified atherosclerosis of one of the coronary arteries. A 38 year old male with ulcerative colitis died on Day 135 (blinded therapy Day 0 to 84, open label deucravacitinib from Day 85 to 129) after hospitalisation on Day 129 for confirmed COVID-19 pneumonia. There were no known underlying co-morbidities. The sponsor considers the death unrelated to study drug. A 52 year old man with ulcerative colitis died between Day 61 and Day 77 with confirmed COVID-19 pneumonia. The man had been taking blinded drug therapy between Day 0 and Day 47 and had been hospitalised in intensive care since Day 52, commencing ECMO on Day 61. The sponsor considered the death unrelated to study treatment. A 63 year old female with psoriatic arthritis in a blinded trial of deucravacitinib died as a result of road traffic accident on Day 192.

A 53 year old female with systemic lupus erythematosus who was enrolled in a long-term extension study, with no known cardiac risk factors, and co-morbid illness not directly related to cardiac disease, experienced cardiogenic shock and acute myocardial infarction on Day 68 of deucravacitinib treatment (dose blinded in this study). Her condition deteriorated resulting in death on Day 69 despite treatment with vasopressors, thrombolysis and mechanical ventilation.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 1.0 (02 September 2021; data lock point (DLP) 15 June 2021) and Australia specific annex (ASA) version 1.0 (20 September 2021) in support of this application

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 15. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 16: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Serious infections	✓	✓*	✓	–
	Malignancies	✓	✓*	✓	–
Missing information	Use in pregnancy and lactation	✓	–	✓	–
	Long-term safety	✓	✓*	–	–

* Study IM011075 (includes Australian patients) and Study IM011194

The RMP evaluation considered the summary of safety concerns acceptable, noting that any safety concerns raised by the nonclinical evaluator should be assessed by the sponsor for inclusion in RMP or ASA updates.

Routine and additional pharmacovigilance is proposed, in line with the EU-RMP. Additional pharmacovigilance activities include one ongoing and one planned post authorisation study to further characterise the safety profile of deucravacitinib. Minor changes to the pharmacovigilance plan in the ASA have been requested, to be included in the next ASA update.

Routine risk minimisation activities only are proposed to address all safety concerns. At second round evaluation, amendments were made to the CMI as requested. The risk management plan is considered is acceptable.

The sponsor was recommended to reference event-specific follow-up questionnaires for 'Pregnancy', 'Malignancies', and 'Infections/Opportunistic Infections' as part of routine pharmacovigilance in the ASA. This may be included in the next revision of the ASA. The sponsor should continue to evaluate whether these general questionnaires are appropriate for the product-specific risks.

The sponsor agreed to include planned US post-marketing study, Study IM011201 in the ASA. The sponsor was also requested to add study IM011193 to the additional pharmacovigilance activities table in the ASA, including details of the planned completion date of these studies (when known). Any safety findings from the studies should be reflected in a revised RMP/ASA as appropriate.

RMP evaluator recommendations regarding condition/s of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> 'The Sotyktu (deucravacitinib) EU-RMP (version 1.0, dated 02 September 2021, DLP 15 June 2021), with ASA (version 1.0, dated 20 September 2021), included with submission PM-2021-04758-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.'

The following wording is recommended for the PSUR requirement:

> 'An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.
>
> If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.'

As Sotyktu is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> 'Sotyktu (deucravacitinib) is to be included in the Black Triangle Scheme. The PI and CMI for Sotyktu must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.'

Risk-benefit analysis

Delegate's considerations

Results from the submitted studies confirmed that oral administration of deucravacitinib 6 mg daily is effective in the treatment of patients with moderate to severe psoriasis who are candidates for systemic therapy. In these studies, clinically meaningful improvements in the signs and symptoms of plaque psoriasis, scalp psoriasis, and associated improvements in disease-related patient-reported symptoms and quality of life measures were observed with deucravacitinib compared with placebo and deucravacitinib compared with apremilast, an approved oral treatment for moderate-to-severe psoriasis. The efficacy was observed in all subgroups with evidence to support maintenance and durability of response.

Adverse events assessed as possibly related to deucravacitinib were not unexpected given the mechanism of action and include upper respiratory infections, acneiform rash, herpes simplex infection, oral ulcers, folliculitis, and herpes zoster infection. Although there was a higher rate of these events in the deucravacitinib treatment group compared with the placebo and apremilast groups, these events were predominantly mild or moderate in severity, only one AE of upper respiratory infection was serious, and none lead to discontinuation with no evidence of increased risk of these events with long-term use.

Reports of serious adverse events and deaths while on study were infrequent. No death was considered likely to be associated with deucravacitinib exposure, however analyses, particularly in the long-term extension studies, may have been complicated by the high number of COVID-19 infections in the study population. The relatively young age at which four study participants experienced MACE events may be a function of increased cardiovascular risk in patients with psoriasis but could merit further consideration. The increased incidence of malignancies, including NMSCs and lymphomas in the deucravacitinib group should be noted, notwithstanding the presence of additional risk factors.

While efficacy of deucravacitinib has been confirmed, and no apparent significant safety issues have been identified in the clinical studies to date, it is not completely clear to this delegate that the targeted mechanism of action of deucravacitinib on TYK2 is sufficient to support claims by the sponsor that distinguish deucravacitinib from other JAK inhibitor drugs and class-based risks that are being investigated. Selection of the proposed dose of 6mg deucravacitinib daily was based on a population pharmacokinetic model that was developed after results of the first pivotal study had been completed. Phase I and II studies used a range of different doses and formulations, and some studies, specifically those examining the role of deucravacitinib metabolites did not use validated measurement techniques. The sponsor has stated that the single ascending dose or multiple ascending dose sub-studies of the key PK study, Study IM011011 were not "optimally designed nor powered to confirm the presence or absence of meaningful departures from dose proportionality" which may challenge the validity of assumptions were made in choosing a therapeutic dose.

Proposed action

Notwithstanding the Delegate's concerns about the early clinical program in psoriasis, deucravacitinib has shown superior efficacy over placebo and apremilast for the treatment of moderate to severe psoriasis, and all evaluators of the submitted dossier were supportive of registration of deucravacitinib, and the proposed indication:

> *Sotyktu is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please clarify why the activity of the active metabolite BMS-153261 is not considered to significantly contribute to the efficacy of deucravacitinib.***

In subjects with psoriasis, the projected steady state exposure (average plasma concentration at steady state [C_{avgss}] or area under the concentration time curve [AUC]) of BMT-153261 was about 22% of the parent, deucravacitinib. Given comparable potencies, selectivity and terminal half-life of BMT-153261 and deucravacitinib, the pharmacological contribution of BMT-153261 was estimated based on ratio of BMT-153261 Cavgss relative to sum of BMT-153261 and deucravacitinib Cavgss. Based on this assessment, BMT-153261 is expected to contribute to about 18% of the total pharmacological activity after deucravacitinib administration with the rest of pharmacological activity (about 82%) attributed to the parent.

In the mass balance study in healthy subjects (Study IM011016), terminal half-lives of deucravacitinib and total radioactivity (TRA) were comparable, indicating that there was no long-lived circulatory metabolite. Based on the AUC($_{0\text{-}24h}$) values (generated using radioactivity concentrations), the plasma exposure for deucravacitinib and BMT-153261,was 43% and 11%, respectively, of the total plasma exposure indicating that these species contribute to majority of radioactivity in circulation. Since deucravacitinib and BMT-153261 are the major active metabolites (> 10% of total plasma exposure), the contribution of BMT-153261 to the total pharmacologic activity was estimated to be approximately 20%.

In subjects with psoriasis, the geometric mean steady-state exposure (C_{avgss} or AUC[$_{TAU}$]) of BMT-153261 was calculated at approximately 20% of the parent exposure at a 6 mg daily dose, based on the population pharmacokinetic (PPK) model. Based on this exposure ratio and similar in-vitro potency (IC_{50}) and selectivity between parent molecule deucravacitinib and BMT-153261, the contribution of BMT-153261 to overall pharmacological activity was estimated to be 17% (20 / [100 + 20]). This indicated that the contribution of BMT-153261 to the overall pharmacologic activity of deucravacitinib was relatively minor (< 20%) and similar in healthy subjects and psoriasis patients.

Consistent with this assessment, incorporation of BMT-153261 exposures in the exposure-response models that describe deucravacitinib exposure and key measure of efficacy (PASI and sPGA responses) and selected safety endpoints resulted in no further improvements in model performance. This indicates BMT-153261 exposures are not anticipated to meaningfully impact efficacy and safety profile of deucravacitinib in psoriasis patients.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

1. ***Is the mechanism of action of deucravacitinib sufficiently different from that of the other small molecule JAK inhibitors to justify claims for long-term clinical safety?***

The ACM was of the opinion that although the mechanism of action seems to be different from other available JAK inhibitors as it targets TYK2, there is no certainty of long-term safety yet. There are still low-level signals of malignancy, venous thromboembolism, serious infection in the available trials and so far, less than 3000 patients have been trialled and the follow-up is less than 3 years. These numbers are not sufficient to draw firm safety data. Therefore, the ACM recommended that, if approved, cautionary statements be included in the PI to the effect that although causality has not been firmly established, the data are not yet available to give certainty that deucravacitinib will be safer than other JAK-STAT agents approved for this condition.

2. ***Has the proposed dose of 6 mg daily been adequately justified in the relative absence of Phase I and dose-finding studies using this dose?***

The ACM felt the 6 mg daily dose had not adequately been justified as the most appropriate regimen in the sponsor's submission. A dose-dependent inhibition at 1-10 mg was noted and maximal inhibition occurred ≥10 mg. The 6 mg dose choice was based on exposure-response modelling. The ACM considered that there may be a time lag in improvement in PASI score following lower doses of deucravacitinib. The ACM suggested that more data were needed to ascertain whether while appropriate as a starting dose, 6 mg daily may not necessarily be the most appropriate maintenance dose. For several other biological medicines, a higher loading dose followed by a lower maintenance dose is often used. The ACM was not able to determine from the data whether this may also be the case for JAK-STAT agents in general, and for deucravacitinib specifically.

3. ***Does the Committee have any other advice regarding the registration of deucravacitinib?***

The ACM raised concerns regarding the current recommendation of no dosage modification for renally impaired patients in the draft PI since the exposure (AUC) was increased in this cohort of patients. Deucravacitinib is also moderately protein-bound which will slow its elimination. The ACM recommended the Delegate request more data on the 6 mg dose administered to renally impaired patients and for this information to be included in the PI.

The ACM also recommended that, if approved, the indications should be amended and 'chronic' be included for consistency with indications for biological medicines:

> *Sotyktu is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy*

In addition, the ACM recommended that the sponsor conduct further investigations to exclude increases in chronic/latent infections such as tuberculosis. This is important in the Australian context where there is greater risk of exposure to endemic populations.

The ACM also recommended that adults with psoriasis should be counselled about the risk of herpetic infection and if appropriate consider vaccination against the varicella zoster virus. Furthermore, regular skin examination for skin cancer by general practitioners and/or treating dermatologists should be recommended in the PI as well as blood pressure monitoring, in light of the pharmacologic action of deucravacitinib, and hypertension being reported.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Sotyktu is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy.*

Amendments to the product information to identify areas of uncertainty regarding safety are recommended.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Sotyktu (deucravacitinib) 6 mg, film coated tablet, blister pack, indicated for:

> *Sotyktu is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*

Specific conditions of registration applying to these goods

- Sotyktu (deucravacitinib) is to be included in the Black Triangle Scheme. The PI and CMI for Sotyktu must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Sotyktu (deucravacitinib) EU-RMP (version 1.0, dated 02 September 2021, data lock point 15 June 2021), with Australian Specific Annex (version 1.0, dated 20 September 2021), included with submission PM-2021-04758-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

  If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes.

  Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The PI for Sotyktu approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication #