▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

SOTYKTU™ (DEUCRAVACITINIB)

1 NAME OF THE MEDICINE

Deucravacitinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 6 mg of deucravacitinib.

Excipient with known effect

Lactose

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Film-coated tablet

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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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.

Dosage Adjustment

Renal impairment

No dose adjustment is required in patients with renal impairment, including end stage renal disease (ESRD) on dialysis (see Section 5.2 Pharmacokinetic Properties).

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. SOTYKTU is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) (see Section 5.2 Pharmacokinetic Properties).

Paediatric population

The safety and efficacy of SOTYKTU in paediatric patients less than 18 years of age have not been established.

Elderly population

No dose adjustment required in patients aged 65 years and older. There is limited information in patients aged ≥ 75 years old.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

Hypersensitivity reactions have been reported in clinical trials with SOTYKTU, although causality is not established. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue SOTYKTU.

Infections

Serious infections have been reported in clinical trials with SOTYKTU (see Section 4.8 Adverse Effects [Undesirable Effects]).

Treatment with SOTYKTU should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. In patients with a chronic infection or a history of recurrent infection, deucravacitinib should be used with caution.

Patients treated with SOTYKTU should be instructed to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, the patient should be monitored closely and SOTYKTU discontinued until the infection resolves.

Viral Reactivation

Herpes virus reactivation (e.g. herpes zoster, herpes simplex) was reported in clinical trials with SOTYKTU (see Section 4.8 Adverse Effects [Undesirable Effects]).

The impact of SOTYKTU on chronic viral hepatitis reactivation is unknown. Patients with positive screening tests for hepatitis B or C, or chronic hepatitis B, or untreated hepatitis C were excluded from clinical trials. Consider viral hepatitis screening and monitoring for reactivation in accordance with clinical guidelines before starting therapy and during therapy with SOTYKTU.

Pre-treatment Evaluation for Tuberculosis

Prior to initiating treatment with SOTYKTU, patients should be evaluated for tuberculosis (TB) infection. Do not administer SOTYKTU to patients with active TB.

Anti-TB treatment should be considered prior to initiating SOTYKTU in patients with active TB or a past history of latent TB in whom an adequate course of treatment cannot be confirmed. Patients receiving SOTYKTU should be monitored for signs and symptoms of active TB.

Malignancies

The risk of malignancies is increased in patients with psoriasis. Malignancies, including lymphomas, were observed in clinical trials with SOTYKTU (see Section 4.8 Adverse Effects [Undesirable Effects]). Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with SOTYKTU, particularly in patients with a known malignancy (other than a successfully treated non-melanoma skin cancer [NMSC]) and patients who develop a malignancy when on treatment with SOTYKTU.

NMSCs have been reported in patients treated with SOTYKTU. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Immunisations

Prior to initiating therapy with SOTYKTU, consider completion of all age-appropriate immunisations according to current immunisation guidelines. Avoid use of live vaccines in patients being treated with SOTYKTU. The response to live or non-live vaccines has not been evaluated.

Potential risks of JAK inhibition

It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of Janus Kinase (JAK) inhibition (see Section 5.1 Pharmacodynamic Properties). In a large, randomised, postmarketing safety trial of a JAK inhibitor in rheumatoid arthritis (RA), patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer) were observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. SOTYKTU has not been studied nor approved for use in RA.

Laboratory abnormalities

Elevated CPK and rhabdomyolysis

Discontinue SOTYKTU if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever (see Section 4.8 Adverse Effects [Undesirable Effects]).

Triglyceride Elevations

Periodically evaluate serum triglycerides according to the clinical guidelines for hyperlipidemia while patients are receiving treatment with SOTYKTU. Manage patients according to clinical guidelines for the management of hyperlipidemia (see Section 4.8 Adverse Effects [Undesirable Effects]).

Liver Enzyme Elevations

Evaluate liver enzymes at baseline and thereafter in patients with known or suspected liver disease according to routine patient management. If treatment-related increases in liver enzymes occur and drug-induced liver injury is suspected, interrupt SOTYKTU until a diagnosis of liver injury is excluded (see Section 4.8 Adverse Effects [Undesirable Effects]).

Use in Elderly

Of the 1519 patients with plaque psoriasis treated with SOTYKTU, 152 patients were 65 years or older and 21 patients were 75 years or older (see Section 4.2 Dose and Method of Administration). No overall differences in deucravacitinib effectiveness were observed between patients 65 years of age and older and younger adult patients who received SOTYKTU.

During the Week 0-16 period, for those subjects (80 subjects ≥ 65 years old, including 12 subjects ≥ 75 years old) who received SOTYKTU without switching treatment arms, there was a higher rate of overall serious adverse events, including serious infections, and discontinuations due to adverse events compared with younger adults. Subjects in this age group who received placebo and apremilast also experienced a similar higher rate of overall serious adverse events.

Paediatric Use

The safety and efficacy of SOTYKTU in paediatric patients less than 18 years of age have not been established.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other medicinal products on deucravacitinib

Deucravacitinib is eliminated via multiple pathways, including Phase I and II metabolism, direct renal and faecal elimination with no single pathway predominantly responsible for elimination. Therefore, major drug interactions via inhibition or induction of a pathway are not anticipated.

Deucravacitinib is a substrate of efflux transporters, P-glycoprotein and breast cancer resistance protein (BCRP) and uptake transporter OCT1. Due to high passive permeability, high oral bioavailability and low affinity for these transporters, contribution of these transporters to deucravacitinib pharmacokinetics is minimal. Deucravacitinib is not a substrate of transporters OATP, NTCP, OAT1, OAT2, OAT3, OCT2, MATE1, or MATE2K.

In dedicated drug interaction studies, no clinically meaningful changes in deucravacitinib were noted following coadministration of ciclosporin (dual Pgp/BCRP inhibitor), fluvoxamine (CYP1A2 inhibitor), ritonavir (CYP1A2 inducer), diflunisal (UGT 1A9 inhibitor), pyrimethamine (OCT1 inhibitor), and gastric pH modulating agents like famotidine (H2 receptor antagonist) or rabeprazole (proton pump inhibitor).

No dose adjustment for deucravacitinib is required when coadministered with Pgp/BCRP inhibitors, strong CYP1A2 inhibitors, CYP1A2 inducers, UGT1A9 inhibitors, OCT1 inhibitors, or gastric pH modulators.

Effect of deucravacitinib on other medicinal products

Based on *in vitro* data for deucravacitinib and its major circulating metabolites and clinical drug interaction studies, co-administration of deucravacitinib at 6 mg daily is not expected to have clinically relevant effects on exposures of agents that are substrates of CYPs (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4), UGTs (1A1, 1A4, 1A6, 1A9, 2B7), CES2 and drug transporters (Pgp, NTCP, OATP1B1, OATP1B3, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2K).

In dedicated drug interaction studies, deucravacitinib did not have a meaningful effect on exposures of concomitant medications rosuvastatin, methotrexate, mycophenolate mofetil (MMF) or oral contraceptives (norethindrone acetate and ethinyl estradiol).

<u>Concomitant immunosuppressive therapy</u>

The safety and efficacy of deucravacitinib in combination with immunosuppressants, including biologics, have not been evaluated in patients with psoriasis.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The effect of deucravacitinib on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

In male rats, deucravacitinib had no effects on reproductive parameters (mating, fertility, and sperm morphology) or early embryonic development of their offspring at oral doses up to 50 mg/kg/day and exposure to total pharmacologically-active material approximately 248 times the maximum recommended human dose (MRHD).

In female rats, deucravacitinib had no effects on mating, fertility, or early embryonic parameters at oral doses up to 50 mg/kg/day and exposure approximately 144 times the MRHD.

Use in Pregnancy – Pregnancy Category B1

There are no adequate and well-controlled studies of deucravacitinib use in pregnant women. The data with deucravacitinib use in pregnant women are insufficient to inform on drug-associated risk. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Deucravacitinib was administered orally during the period of organogenesis at doses of up to 75 mg/kg/day in rats and up to 10 mg/kg/day in rabbits. Deucravacitinib was neither embryo-lethal nor teratogenic at the highest doses tested in either species. These doses resulted in maternal exposures (AUC) to total pharmacologically-active material that were approximately 223 times (rat) or 23 times (rabbit) the exposure at the MRHD.

In a pre- and post-natal development study in rats, deucravacitinib was administered from gestation day 6 through lactation day 20, at doses of 5, 15, or 50 mg/kg/day. At 50 mg/kg/day, pup body weight gain was lower, relative to control values, during the pre-weaning period; during post-weaning, their weights caught up and were comparable to those in control offspring after postnatal days 73 or 35 in males and females, respectively. There were no additional adverse findings in the F1 offspring, nor in F2 intrauterine survival. Maternal exposures to total pharmacologically-active material at 50 mg/kg/day were approximately 92 times the MRHD.

Use in Lactation

It is unknown whether deucravacitinib/metabolites are excreted in human milk.

A single oral dose of 5 mg/kg radiolabeled deucravacitinib was administered to lactating (post-partum days 8 to 12) rats. Deucravacitinib and/or its metabolites were present in the milk of lactating rats, with milk-to-plasma exposure ratio of 21. Deucravacitinib-related material was detected in breast-fed pups. Pup plasma levels of total pharmacologically-active material were 8–11% that in dams.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

SOTYKTU has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials, a total of 1519 patients with moderate-to-severe plaque psoriasis received deucravacitinib 6 mg once daily. Of these, 1141 patients were exposed to deucravacitinib for at least one year.

Data from two placebo- and active-controlled trials (POETYK PSO-1 and POETYK PSO-2) were pooled to evaluate the safety of SOTYKTU up to 16 weeks. In total, 842 patients were evaluated in the SOTYKTU group.

During the 16-week placebo-controlled period, the incidence of serious adverse events was low and similar across treatment groups (SOTYKTU 1.8%, placebo 2.9%, apremilast 1.2%) with no discernible trend in any specific type of serious adverse events.

Discontinuation of therapy due to adverse events during the 16-week placebo-controlled period was SOTYKTU 2.4%, compared to placebo 3.8% and apremilast 5.2%.

Tabulated Summary of Adverse Events

Adverse events reported by ≥ 2% of subjects in any treatment group are provided in Table 1.

Table 1: Adverse Events Reported in ≥ 2% of Subjects in Any Treatment Group - Controlled Safety Pool (Week 0-16) - As-treated Population

Preferred Term	SOTYKTU N = 842 n (%)	Apremilast N = 422 n (%)	Placebo N = 419 n (%)
Nasopharyngitis	76 (9.0)	37 (8.8)	36 (8.6)
Upper respiratory tract infection	46 (5.5)	17 (4.0)	17 (4.1)
Headache	38 (4.5)	45 (10.7)	19 (4.5)
Diarrhoea	37 (4.4)	50 (11.8)	25 (6.0)
Blood creatine phosphokinase increased	23 (2.7)	3 (0.7)	5 (1.2)
Arthralgia	19 (2.3)	12 (2.8)	8 (1.9)
Hypertension	15 (1.8)	11 (2.6)	1 (0.2)
Psoriasis	12 (1.4)	9 (2.1)	14 (3.3)
Nausea	14 (1.7)	42 (10.0)	7 (1.7)
Back pain	10 (1.2)	11 (2.6)	5 (1.2)
Rhinitis	7 (0.8)	10 (2.4)	5 (1.2)

Description of Selected Adverse Events

The following adverse events have been reported in patients treated with SOTYKTU. A causal relationship to SOTYKTU is not established.

Tuberculosis

In clinical trials, of 4 subjects with latent TB who were treated with SOTYKTU and received appropriate TB prophylaxis, no subjects developed active TB (during the mean follow-up of 34 weeks). One subject, who did not have latent TB, developed active TB after receiving 54 weeks of SOTYKTU.

Laboratory abnormalities

Elevated CPK and rhabdomyolysis

Cases of rhabdomyolysis were reported in patients treated with SOTYKTU resulting in interruption or discontinuation of SOTYKTU dosing. In the 16-week placebo-controlled period, increased CPK (including Grade 4) was reported in 23 subjects (9.3 per 100 patient-years) treated with SOTYKTU, and 5 subjects (4.1 per 100 patient-years) treated with placebo.

Triglyceride Elevations

Mean triglycerides concentrations increased by 10.3 mg/dL during the 16-week treatment period in subjects treated with SOTYKTU and by 9.1 mg/dL during the 52-week treatment period. The effect of this elevated parameter on cardiovascular morbidity and mortality has not been determined.

Liver Enzyme Elevations

There was an increased incidence of liver enzyme elevation with SOTYKTU treatment compared to treatment with placebo. Liver serum transaminase elevations ≥ 3 times the ULN were reported in subjects treated with SOTYKTU. In the 16-week placebo-controlled period:

- ALT elevations ≥3 times the ULN was reported in 9 subjects (3.6 per 100 patient- years) treated with SOTYKTU, and 2 subjects (1.6 per 100 patient-years) treated with placebo.
- AST elevations ≥3 times the ULN was reported in 13 subjects (5.2 per 100 patient- years) treated with SOTYKTU, and 2 subjects (1.6 per 100 patient-years) treated with placebo.

Tabulated List of Adverse Drug Reactions (ADRs)

Adverse drug reactions that occurred in patients treated with SOTYKTU during the 16-week controlled period are presented in Table 2 below. Through Week 52, no new ADRs were identified with SOTYKTU and the incidence rates of common ADRs did not increase compared to those observed during the first 16 weeks of treatment.

These reactions are presented by MedDRA System Organ Class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000).

Table 2: List of Adverse Drug Reactions

Frequency	ADRs
Infections and infestations	
Very common	Upper respiratory infections[a]
Common	Herpes simplex infections[b]
Uncommon	Herpes zoster
Gastrointestinal disorders	
Common	Oral ulcers[c]
Skin and subcutaneous tissue disorders	
Common	Acneiform rash[d], folliculitis

[a] Upper respiratory infections include nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, pharyngitis, sinusitis, acute sinusitis, rhinitis, tonsillitis, peritonsillar abscess, laryngitis, tracheitis, and rhinotracheitis.

[b] Herpes simplex infections include oral herpes, herpes simplex, genital herpes, and herpes viral infection.

[c] Oral ulcers include aphthous ulcer, mouth ulceration, tongue ulceration, and stomatitis.

[d] Acneiform rash includes acne, dermatitis acneiform, rash, rosacea, pustule, rash pustular, and papule.

Description of Selected Adverse Reactions

Infections

In POETYK PSO-1 and POETYK PSO-2 during the first 16 weeks, infections occurred in 29.1% of patients in the deucravacitinib group (116.0 events per 100 person-years) compared to 21.5% of patients in the placebo group (83.7 events per 100 person-years). The majority of infections were non-serious and mild to moderate in severity and did not lead to discontinuation of deucravacitinib. The incidence of serious infections in the deucravacitinib group was 0.6% (2.0 events per 100 person-years) and in the placebo group was 0.5% (1.6 events per 100 person-years).

The rate of infections in the deucravacitinib group did not increase through Week 52 (95.4 events per 100 person-years). The rate of serious infections in the deucravacitinib group did not increase through Week 52 (1.7 events per 100 person-years).

In the 16-week placebo-controlled period, herpes simplex infections were reported in 17 subjects (6.8 per 100 patient-years) treated with SOTYKTU, and 1 subject (0.8 per 100 patient-years) treated with placebo. Multidermatomal herpes zoster was reported in a subject who received SOTYKTU.

During PSO-1, PSO-2, and the open-label extension trial in which subjects who completed the controlled trials could enrol, the majority of subjects (10/18) who reported events of herpes zoster while receiving SOTYKTU were under 50 years of age.

Malignancies

During the 52-week treatment period of the two controlled psoriasis clinical studies (total exposure of 969.0 person-years with deucravacitinib), malignancies (excluding non-melanoma skin cancers) were reported in 0.2% of deucravacitinib-treated patients (0.3 events per 100 person-years), including one lymphoma. Lymphomas were also reported with deucravacitinib in the open-label, long-term extension and in an open-label regional study. The potential role of deucravacitinib in the development of malignancies is unclear.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Deucravacitinib has been administered in healthy subjects as single doses up to 40 mg (>6 times the recommended human dose of 6 mg/day [RHD]) and in multiple doses up to 24 mg/day (12 mg twice daily) for 14 days without dose-limiting toxicity.

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately. Dialysis does not substantially clear deucravacitinib from systemic circulation (5.4% of dose cleared per dialysis treatment).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Deucravacitinib is a small molecule that selectively inhibits the tyrosine kinase 2 (TYK2) enzyme. Deucravacitinib binds to the regulatory domain of TYK2, stabilising an inhibitory interaction between the regulatory and the catalytic domains of the enzyme. This results in allosteric inhibition of receptor-mediated activation of TYK2 and its downstream functions in cells. TYK2 is a member of the Janus kinase (JAK) family. JAK kinases, including TYK2, function in pairs to mediate JAK-STAT pathways. TYK2 pairs with JAK1 to mediate multiple cytokine pathways and also pairs with JAK2 to transmit signals. The pairing of TYK2 with either JAK1 or JAK2 mediates signalling of a narrower range of cytokines compared with the pairings of JAKs 1/2/3 with each other. The allosteric mechanism of action of deucravacitinib has been shown to inhibit TYK2 with minimal or no inhibition of JAK 1/2/3. TYK2 mediates signalling of interleukin-23 (IL-23) cytokine, interleukin-12 (IL-12) cytokine, and type I interferons (IFN), which are naturally occurring cytokines involved in inflammatory and immune responses. Deucravacitinib inhibits

signalling from IL-23, IL-12 and type I IFN and the downstream release of proinflammatory cytokines and chemokines.

Pharmacodynamic Effects

In healthy volunteers, the administration of deucravacitinib resulted in a dose- and concentration-dependent inhibition of two TYK2-dependent pathways indicating robust target engagement. These include IFN-alpha-induced STAT5 phosphorylation (mediated by TYK2/JAK1), and IL-12-induced IFN-gamma production (mediated by TYK2/JAK2) in *ex vivo* whole blood assays. The maximal inhibition was observed one hour after dosing which returned to near baseline by the end of dosing interval (12 or 24 hours). Further, IFN-regulated gene expression was inhibited *in vivo* in a dose dependent manner in subjects administered IFN-alpha, confirming that deucravacitinib inhibits TYK2 *in vivo*.

In a Phase 2 sub-study in subjects with psoriasis, deucravacitinib reduced psoriasis associated gene expression in psoriatic skin in a dose dependent manner, notably including reductions in IL-23-pathway and type I IFN pathway regulated genes. In Phase 2 and Phase 3 studies, deucravacitinib reduced levels of serum biomarkers associated with psoriasis disease activity. In Phase 3, IL-17A IL-19 and beta-defensin were reduced with deucravacitinib treatment by 47-50%, 72% and 81-84% respectively.

Cardiac Electrophysiology

At 7 times the maximum exposure achieved by the 6 mg once daily dose in psoriasis subjects, there was no clinically relevant effect on the QTc interval.

Clinical Trials

Plaque Psoriasis

The efficacy and safety of SOTYKTU 6 mg once daily were assessed in two multi-centre, randomised, double-blind, placebo- and active-controlled clinical studies, POETYK PSO-1 and POETYK PSO-2, which enrolled patients 18 years of age and older with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Patients had a body surface area (BSA) involvement of ≥ 10%, a Psoriasis Area and Severity Index (PASI) score ≥ 12, and a static Physician's Global Assessment (sPGA) ≥ 3 (moderate or severe) on a 5-point scale of overall disease severity.

POETYK PSO-1 and POETYK PSO-2 evaluated a total of 1686 patients with 843 randomised to SOTYKTU 6 mg once daily, 422 to apremilast 30 mg twice daily, and 421 to placebo.

In both studies, patients receiving placebo switched to SOTYKTU at Week 16, which continued up to Week 52. Patients randomised to apremilast who did not achieve a PASI 50 (POETYK PSO-1) or PASI 75 (POETYK PSO-2) response at Week 24 switched to SOTYKTU and continued up to Week 52. In POETYK PSO-1 patients who were randomised to SOTYKTU continued treatment up to Week 52. In POETYK PSO-2, SOTYKTU-treated patients who achieved PASI 75 at Week 24 were re-randomised 1:1 to continue SOTYKTU (maintenance) or were switched to placebo (withdrawal).

Both studies assessed the responses at Week 16 compared to placebo for the two co-primary endpoints:

- the proportion of patients who achieved a sPGA score of 0 (clear) or 1 (almost clear)
- the proportion of patients who achieved at least a 75% improvement in the PASI scores (PASI 75) from baseline

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

- the proportion of patients who achieved PASI 90, PASI 100, sPGA 0, scalp-specific PGA (ss-PGA) score of 0 (clear) or 1 (almost clear), and Psoriasis Symptoms and Signs Diary (PSSD) Symptom Score of 0 (symptom-free).

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

- at Week 16 and 24 (POETYK PSO-1 and POETYK PSO-2), the proportion of patients who achieved PASI 75, PASI 90, and sPGA 0/1
- at Week 16 (POETYK PSO-1 and POETYK PSO-2), the proportion of patients who achieved sPGA 0 and ssPGA 0/1 (scalp)

Baseline disease characteristics were consistent for the study population in both studies with an overall median PASI score of 18.7, and a median BSA of 20%. Baseline sPGA score was 3 (moderate) in 79.8% of patients and 4 (severe) in 20.2%. Median Dermatology Life Quality Index (DLQI) score was 11. A total of 18.4% of study patients had a history of psoriatic arthritis.

Across both studies, 40% of patients had received prior phototherapy, 42.4% were naive to any systemic therapy (including biologic and/or non-biologic treatment), 41% received prior non-biologic systemic treatment, and 34.8% had received prior biologic therapy (16% TNF, 5% IL-12/23, 17% IL-17 and 4% IL-23 inhibitors).

Table 3 presents the efficacy results demonstrating superiority of SOTYKTU compared to apremilast and placebo.

Table 3: Efficacy Results in Adults with Plaque Psoriasis (Non-responder Imputation - NRI)

Endpoint	POETYK PSO-1			POETYK PSO-2		
	SOTYKTU N = 332 n (%)	**Apremilast N = 168 n (%)**	**Placebo N = 166 n (%)**	**SOTYKTU N = 511 n (%)**	**Apremilast N = 254 n (%)**	**Placebo N = 255 n (%)**
sPGA 0/1						
Week 16	178 (53.6)	54 (32.1)[d]	12 (7.2)[a,d]	253 (49.5)	86 (33.9)[d]	22 (8.6)[a,d]
Week 24	195 (58.7)	52 (31.0)[d]	-	251 (49.8)[b]	75 (29.5)[d]	-
sPGA 0						
Week 16	58 (17.5)	8 (4.8)[d]	1 (0.6)[d]	80 (15.7)	16 (6.3)[e]	3 (1.2)[d]
Week 24	67 (20.2)	17 (10.1)[f]	-	86 (17.1)	20 (7.9)[e]	-
PASI 75						
Week 16	194 (58.4)	59 (35.1)[d]	21 (12.7)[a,d]	271 (53.0)	101 (39.8)[e]	24 (9.4)[a,d]
Week 24	230 (69.3)	64 (38.1)[d]	-	296 (58.7)[b]	96 (37.8)[d]	-
PASI 90						
Week 16	118 (35.5)	33 (19.6)[e]	7 (4.2)[d]	138 (27.0)	46 (18.1)[f]	7 (2.7)[d]
Week 24	140 (42.2)	37 (22.0)[d]	-	164 (32.5)[b]	50 (19.7)[d]	-
PASI 100						
Week 16	47 (14.2)	5 (3.0)[d]	1 (0.6)[d]	52 (10.2)	11 (4.3)[f]	3 (1.2)[d]
Week 24	58 (17.5)	11 (6.5)[e]	-	66 (13.1)	17 (6.7)[f]	-
ss-PGA 0/1 (scalp)	**N=209**	**N=110**	**N=121**	**N=305**	**N=166**	**N=173**
Week 16	147 (70.3)	43 (39.1)[d]	21 (17.4)[d]	182 (59.7)	61 (36.7)[d]	30 (17.3)[d]
Week 24	151 (72.2)	47 (42.7)[d]	-	180 (59.0)	69 (41.6)[e]	-

[a] Co-primary endpoints comparing SOTYKTU with placebo

[b] N=504 accounting for missed assessments due to COVID-19 pandemic

[c] Includes only subjects with baseline ss-PGA score of ≥ 3

[d] $p \leq 0.0001$ for comparison between SOTYKTU and placebo or SOTYKTU and apremilast

[e] $p < 0.001$ for comparison between SOTYKTU and apremilast

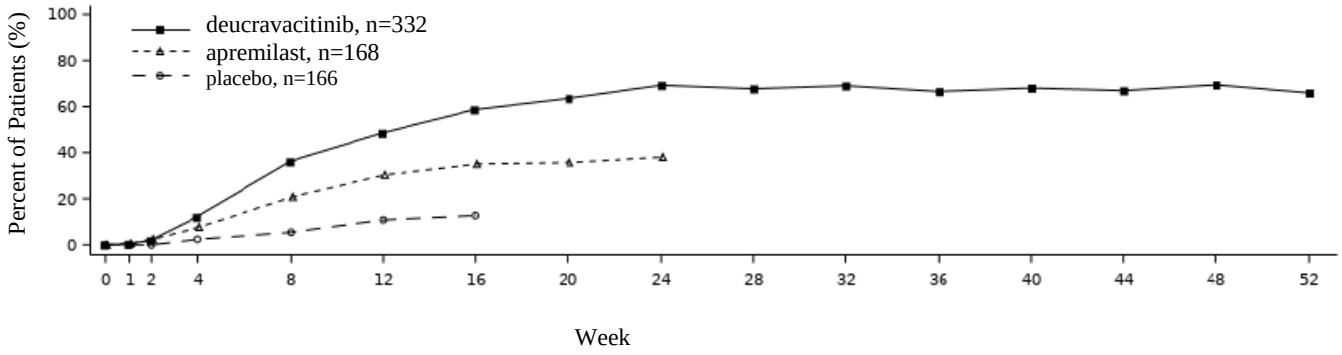
[f] $p < 0.01$ for comparison between SOTYKTU and apremilast

Examination of age, gender, race, body weight, duration of disease, baseline disease severity, and previous treatment with biologic or non-biologic agents did not identify differences in response to SOTYKTU among these subgroups.

Response over time

SOTYKTU demonstrated rapid onset of efficacy, with higher percent improvement in PASI from baseline as compared with placebo as early as Week 1 (POETYK PSO-1 and PSO-2). The percentage of patients achieving a PASI 75 response was higher for SOTYKTU compared to placebo by Week 4, with maximum PASI 75 response achieved by Week 24 (POETYK PSO-1 and PSO-2) and maintained through Week 52 (POETYK PSO-1) (see Figure 1).

Figure 1: PASI 75 response (NRI) through Week 52 by visit in POETYK PSO-1



In POETYK PSO-1, among patients initially randomised to apremilast who did not achieve PASI 50 response and were switched to SOTYKTU at Week 24, 46.3% achieved PASI 75 response by Week 52.

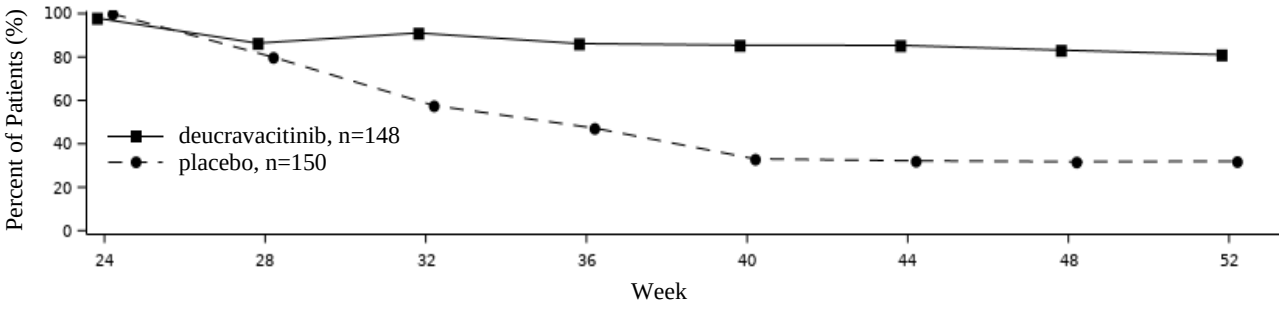
Maintenance and Durability of Response

In POETYK PSO-1, among patients who received SOTYKTU and achieved PASI 75 response at Week 24, 81.3% of patients who continued on SOTYKTU maintained PASI 75 response at Week 52. Among PASI 90 responders at Week 24, 73.6% of patients maintained PASI 90 response at Week 52. Among sPGA 0/1 responders at Week 24, 77.4% of patients maintained sPGA 0/1 response at Week 52.

In POETYK PSO-2, to evaluate maintenance and durability of response, patients who were originally randomised to SOTYKTU and were PASI 75 responders at Week 24, were re-randomised to either continue treatment on SOTYKTU or receive placebo. At Week 52, 80.4% of patients who continued on SOTYKTU maintained PASI 75 compared to 31.3% of patients who were re-randomised to placebo withdrawn from SOTYKTU. For responders at Week 24 who were re-randomised to placebo, the median time to loss of PASI 75 was approximately 12 weeks.

Figure 2 shows the PASI 75 responses in the two arms from Week 24-52.

Figure 2: PASI 75 response (NRI) after re-randomisation at Week 24 in POETYK PSO-2



Patient Reported Outcomes

Significantly greater improvements in psoriasis symptoms (itch, pain, burning, stinging, and skin tightness) at Week 16 were observed with SOTYKTU compared to apremilast in both studies based on the Psoriasis Symptoms and Signs Diary (PSSD) (Table 4). Significantly greater proportions of patients on SOTYKTU compared to placebo achieved a PSSD symptom score of 0 (symptom-free) at Week 16 in both studies (Table 4).

Significantly greater proportions of patients on SOTYKTU compared to placebo achieved a Dermatology Life Quality Index (DLQI) score of 0/1 (no effect at all on patient's life) at Week 16 in both studies (Table 4).

Improvement of these responses in patients receiving continuous SOTYKTU treatment was observed through Week 24 and was maintained through Week 52 in POETYK PSO-1.

Table 4: Patient reported outcomes in POETYK PSO-1 and POETYK PSO-2

	POETYK PSO-1		**POETYK PSO-2**	
	SOTYKTU	**Apremilast**	**SOTYKTU**	**Apremilast**
PSSD symptom score Change from baseline (mBOCF) *	N=306	N=158	N=466	N=233
Week 16, mean (SE)	-26.7 (1.8)	-17.8 (2.2) [a]	-28.3 (1.1)	-21.1 (1.4) [a]
	POETYK PSO-1		**POETYK PSO-2**	
	SOTYKTU	**Placebo**	**SOTYKTU**	**Placebo**
PSSD symptom score Patients achieving 0 (NRI) ***	N=305	N=149	N=466	N=238
Week 16, n (%)	24 (7.9)	1 (0.7) [c]	35 (7.5)	3 (1.3) [b]
DLQI Patients achieving 0 or 1 (NRI) **	N=322	N=160	N=495	N=246
Week 16, n (%)	132 (41.0)	17 (10.6) [a]	186 (37.6)	24 (9.8) [a]

NRI: Non-responder imputation

* Adjusted mean change; mBOCF – modified baseline observation carried forward; standard error (SE)

** Patients with baseline score ≥ 2

*** Patients with baseline score ≥ 1

[a] p <0.0001 for multiplicity adjusted comparison between SOTYKTU and placebo or SOTYKTU and apremilast

[b] p ≤ 0.001 for multiplicity adjusted comparison between SOTYKTU and placebo

[c] p < 0.01 for multiplicity adjusted comparison between SOTYKTU and placebo

In addition, SOTYKTU patients had significantly greater improvement from baseline compared to placebo in health-related quality of life at Week 16 as measured by the 36-item Short Form physical component summary

(SF-36 PCS) and EQ-5D-3L Visual Analogue Scale (VAS). These improvements were maintained through Week 52.

5.2 PHARMACOKINETIC PROPERTIES

Deucravacitinib exhibited consistent oral absorption, dose-related increase in exposure, and no evident time-dependent pharmacokinetics. The pharmacokinetics of deucravacitinib administered as tablets was linear across a 3 mg to 36 mg dose range.

Absorption

Following oral administration of tablets, deucravacitinib exhibited rapid and near complete absorption. The median T_{max} ranged from 2 to 3 hours and absolute oral bioavailability was 99%. Modest accumulation (<1.4-fold) was observed following once daily dosing.

Deucravacitinib can be administered without consideration for food or gastric pH modulators (H2 receptor blockers and proton pump inhibitors). Co-administration of food or gastric pH modulators did not affect total exposure ($AUC_{[INF]}$) of deucravacitinib.

Distribution

The volume of distribution at steady state (Vss), at 140 L, is greater than total body water [42 L] indicating extravascular distribution. Deucravacitinib is 81.6% bound to human plasma proteins. Deucravacitinib distributes similarly between plasma and red blood cell components with blood-to-plasma concentration ratio of 1.26.

Metabolism

In humans, deucravacitinib is mainly metabolised via three primary biotransformation pathways, which include N-demethylation at the triazole moiety by cytochrome P-450 (CYP) 1A2 to form major metabolite BMT-153261, cyclopropyl carboxamide hydrolysis by carboxylesterase 2 (CES2) to form major metabolite BMT-158170 and N-glucuronidation by uridine glucuronyl transferase (UGT) 1A9 to form BMT-334616.

At steady state, deucravacitinib is the major circulating species constituting 49% of measured drug-related components. Two major circulating metabolites, BMT-153261 and BMT-158170, were identified, both of which have half-lives comparable to the parent deucravacitinib. BMT-153261 has comparable potency to the parent drug and BMT-158170 has no clinically-relevant pharmacological activity. The circulating exposure of BMT-153261 accounts for approximately 20% of the systemic exposure of the total drug-related components.

Excretion

Deucravacitinib is eliminated via multiple pathways including Phase I and II metabolism along with direct renal and faecal elimination. Additionally, no single enzyme or pathway contributed more than 26% of total clearance. Deucravacitinib was extensively metabolised, with 59% of the orally administered [^{14}C]-deucravacitinib dose eliminated as metabolites in urine (37% of the dose) and faeces (22% of the dose). Unchanged deucravacitinib in urine and faeces represented 13% and 26% of the dose, respectively.

Terminal half-life in healthy human volunteers is 10 hours. Renal clearance of deucravacitinib ranges from 27 to 54 mL/min.

Special population

Renal impairment

Renal impairment has no clinically meaningful effect on deucravacitinib exposures (see Section 4.2 Dose and Method of Administration).

Compared to the normal renal function group, deucravacitinib C_{max} was 14% lower and 6% higher in patients with mild (eGFR ≥60 to <90 mL/min/1.73m^2) and moderate (eGFR ≥30 to <60 mL/min/1.73m^2) renal impairment, no change in C_{max} was observed in patients with severe (eGFR <30 mL/min/1.73m^2) renal impairment, and ESRD (eGFR <15 mL/min/1.73m^2) on dialysis. Deucravacitinib $AUC_{[INF]}$ was unchanged in patients with mild renal impairment but higher by 39%, 28% and 34% in patients with moderate, severe and ESRD on dialysis, respectively, compared to subjects with normal renal function.

BMT-153261 C_{max} was 11% lower, 8% lower, 28% higher and 9% higher in patients with mild, moderate, severe renal impairment and ESRD on dialysis, respectively, compared to subjects with normal renal function. BMT-153261 $AUC_{[INF]}$ was 2% lower, 24% higher, 81% higher and 27% higher in patients with mild, moderate, severe renal impairment and ESRD on dialysis, respectively, compared to subjects with normal renal function.

Dialysis did not substantially clear deucravacitinib from systemic circulation (5.4% of dose cleared per dialysis).

Hepatic impairment

Mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment has no clinically meaningful effect on deucravacitinib exposures (see Section 4.2 Dose and Method of Administration).

Compared to normal hepatic function group, total deucravacitinib C_{max} was higher by 4%, 10% and 1% in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment, respectively. Deucravacitinib $AUC_{[INF]}$ was higher by 10%, 40% and 43% in patients with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function.

BMT-153261 C_{max} was lower by 25%, 59% and 79% in patients with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. BMT 153261 $AUC_{[INF]}$ was lower by 3%, 20% and 50% in patients with mild, moderate, and severe hepatic impairment, respectively, compared to subjects with normal hepatic function.

Paediatric and adolescent

The safety and efficacy of deucravacitinib in paediatric patients less than 18 years of age have not been established.

Intrinsic factors

Body weight, gender, race, and ethnicity did not have a clinically meaningful effect on deucravacitinib exposure.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Deucravacitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in an *in vitro* chromosomal aberration assay (cultured Chinese hamster ovary cells) or *in vivo* in a rat peripheral blood micronucleus assay.

Carcinogenicity

The carcinogenic potential of deucravacitinib was assessed in 6-month rasH2 transgenic mouse and 2-year rat studies. No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received deucravacitinib at oral doses up to 60 mg/kg/day and exposure to total pharmacologically-active material 160 times the MRHD. No evidence of tumorigenicity was observed in male or female rats that received

deucravacitinib at oral doses up to 15 mg/kg/day and exposure to total pharmacologically-active material approximately 43 times the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Hypromellose acetate succinate
Lactose
Microcrystalline cellulose
Croscarmellose sodium
Silicon dioxide
Magnesium stearate
Film-coating: Opadry II Complete Film Coating System 85F140184 Pink (PI 141510)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Polyvinyl chloride (PVC) / polychlorotrifluoroethylene (PCTFE) / aluminium foil blisters.

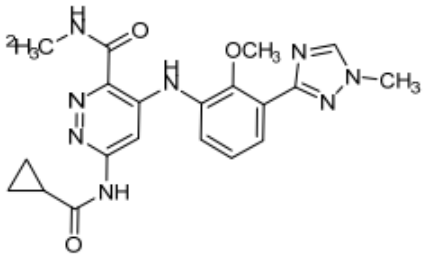
Pack sizes: 7 and 28 film-coated tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Molecular formula	$C_{20}H_{19}{}^{2}H_3N_8O_3$
Molecular weight	425.47
Chemical name	6-(cyclopropanecarboxamido)-4-[2-methoxy-3-(1-methyl-1*H*-1,2,4-triazol-3-yl)anilino]-*N*-($^{2}H_3$)methylpyridazine-3-carboxamide
Chemical Abstract Service (CAS) registry number	1609392-27-9

Chemical structure	

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave,
Victoria 3170, Australia.
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9 DATE OF FIRST APPROVAL

1 December 2022

10 DATE OF REVISION

5 July 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
6.7	Removal of ATC Code

SOTYKTU is a trademark of Bristol-Myers Squibb Company.