NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Deucravacitinib for treating moderate to severe plaque psoriasis {ID3859]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Deucravacitinib for treating moderate to severe plaque psoriasis {ID3859]

Contents:

The following documents are made available to stakeholders:

1. **Company submission** from Bristol Myers-Squibb:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. British Association of Dermatologists
   b. Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
   c. Psoriasis Association

4. **External Assessment Report** prepared by University of Aberdeen HTA Group

5. **External Assessment Group response to factual accuracy check of EAR**

6. **Technical engagement response** from Bristol Myers-Squibb
   a. TE Response from Company
   b. TE response appendix

7. **Technical engagement response & personal statement from experts:**
   a. Abbvie
   b. Janssen
   c. Novartis
   d. UCB Pharma

8. **External Assessment Group critique of company response to technical engagement** prepared by University of Aberdeen HTA Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Deucravacitinib for treating moderate-to-severe plaque psoriasis [ID3859]

Document B

Company evidence submission

April 2022

File name	Version	Contains confidential information	Date
[ID3859] Company submission [26 April 2022]	v1.1	Yes	26 April 2022

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Abbreviations

ADM	adalimumab
ADORA3	adenosine A3 receptor
AE	adverse event
AEI	adverse event of interest
AESI	adverse event of special interest
AIC	Akaike information criteria
ANCOVA	Analysis of covariance
APT	apremilast
ATP	adenosine triphosphate
BAD	British Association of Dermatologists
BIC	Bayesian information criteria
BID	twice daily
BIM	bimekizumab
BIW	twice weekly
BMI	body mass index
BMS	Bristol Myers Squibb
BNF	British National Formulary
BRO	brodalumab
BSA	body surface area
BSC	best supportive care
CER	certolizumab pegol
CG	clinical guideline
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CrI	credible interval
CSR	clinical study report
CZP	certolizumab pegol
DEU	deucravacitinib
DSA	deterministic sensitivity analysis
DLQI	Dermatology Life Quality Index
DMF	dimethyl fumarate
DSU	Decision Support Unit
EAIR	exposure-adjusted incidence rate
ECG	electrocardiograms
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions
EQ-5D-3L	EuroQol 5-Dimensions 3-Level
EQ-5D-5L	EuroQol 5-Dimensions 5-Level
ERG	Evidence Review Group
ETC	etanercept
EU	European Union
FAS	full analysis set
FE	fixed effects
GB	Great Britain
GH	growth hormone
GM-CSF	granulocyte macrophage colony-stimulating factor

GUS	guselkumab
HADS	hospital anxiety and depression scale
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
HRCU	healthcare resource use
HTA	health technology assessment
ICER	incremental cost-effectiveness ratios
IFN	interferon
IFX	infliximab
IL	interleukin
ILC	innate lymphoid cell
INF	infliximab
IPD	individual patient-level data
IR	incidence rate
IRT	interactive response technology
ITC	indirect treatment comparison
ITT	intention-to-treat
IXE	ixekizumab
JAK	janus kinase
LS	least squares
LTE	long-term extension
KM	Kaplan-Meier
MAPP	Multinational Assessment of Psoriasis and PsA
max	maximum
mBOCF	modified baseline observation carried forward
MHC	major histocompatibility complex
MHRA	Medicines and Healthcare Products Regulatory Agency
min	minimum
mNAPSI	modified Nail Psoriasis Severity Index
MOA	mechanism of action
N	number
N/A	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
NYHA	New York Heart Association
NRI	non-responder imputation
OLE	open-label extension
PASI	Psoriasis Area Severity Index
PGA-F	Physician's Global Assessment-Fingernail
PGI-C	Patient's Global Impression of Change
PGI-S	Patient's Global Impression of Severity
PK	pharmacokinetic
PLC	placebo
PP	per protocol
pp-PASI	palmoplantar psoriasis-Psoriasis Area and Severity Index
pp-PGA	palmoplantar psoriasis-Physician's Global Assessment
PRO	patient-reported outcome
PsA	psoriatric arthritis
PSSD	Psoriasis Symptoms and Signs Diary

PSSI	Psoriasis Scalp Severity Index
PSSUR	Personal Social Services Research Unit
PUVA	psoralen plus ultraviolet A
p-y	person.years
QALY	quality-adjusted life year
QD	once daily
QoL	quality of life
QW	once weekly
Q2W	every two weeks
RCT	randomised controlled trial
RE	random effects
RIS	risankizumab
ROW	rest of world
SA	sensitivity analysis
SAE	serious adverse event
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SD	standard deviation
SE	standard error
SEC	secukinumab
SF-12	12-item short-form
SF-36	36-item short-form
SLR	systematic literature review
SmPC	summary of product characteristics
SOC	System Organ Class
sPGA	static Physician's Global Assessment
ss-PGA	scalp-specific Physician's Global Assessment
TA	technology appraisal
TB	tuberculosis
Th	T helper
TIL	tildrakizumab
TNFα	tumour necrosis factor-alpha
TYK2	tyrosine kinase 2
TRAE	treatment-related adverse event
UK	United Kingdom
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
UST	ustekinumab
UTI	urinary tract infection
VAS	visual analogue scale
vs	versus
VURI	vital upper respiratory tract infection
WTP	willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

- Psoriasis is a chronic, immune-mediated inflammatory skin disease which is associated with multisystem comorbidities.
- Alongside the clinical burden of psoriasis, the humanistic burden of the disease is substantial as patients have a higher risk of developing comorbidities and suffer from a reduced health-related quality of life and mental health. On a broader level, psoriasis causes a considerable burden to the NHS and the wider economy due to high healthcare resource utilisation and associated costs.
- Dysregulation of the immune system, specifically the Type I interferon and interleukin (IL)-23/IL-17 signalling cascades play significant roles in the pathogenesis of psoriasis and these have been the targets of focus in therapeutic development.
- Deucravacitinib is an oral, selective TYK2 inhibitor with a unique mechanism of action, representing a new class of small molecules. It achieves a higher degree of selectivity than other approved JAK 1, 2 and 3 inhibitors by binding to the TYK2 regulatory domain instead of the more conserved kinase domain, resulting in allosteric inhibition of TYK2 and its downstream functions in cells and reducing the risk of off target effects.
- Despite advances in the treatment of psoriasis, there is a need for more effective and well-tolerated oral therapies for patients with moderate-to-severe psoriasis. Despite the availability of effective systemic therapy, many patients with psoriasis remain undertreated or even untreated, and many are dissatisfied with current treatments.
- Deucravacitinib is positioned as an alternative to current injectable biologics or other systemic oral non-biologics for treatment for patients with moderate-to-severe plaque psoriasis.
- Administered as a once daily oral drug, deucravacitinib has the potential to become a treatment of choice and new standard of care for patients who require systemic therapy for their moderate-to-severe plaque psoriasis.

B.1.1 Decision problem

The marketing authorisation for deucravacitinib is expected to be for [redacted] The submission focuses on a narrower population, specifically adult patients with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option (inadequately effective, not tolerated or contraindicated). A summary of the decision problem is provided in Table B.1.1.1.

Table B.1.1.1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with moderate-to-severe plaque psoriasis	Adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option	Aligns with expected use of deucravacitinib in NHS clinical practice
Intervention	Deucravacitinib	As per scope	N/A
Comparators	If systemic non-biological treatment or phototherapy is suitable: • Systemic non-biological therapies (including methotrexate, ciclosporin, and acitretin) • Phototherapy with or without psoralen For people with severe or very severe psoriasis [defined by a total PASI of 10 or more, and a DLQI of more than 10] for whom systemic non-biological treatment (including methotrexate, ciclosporin and acitretin) and phototherapy are inadequately effective, not tolerated or contraindicated: • TNF-α inhibitors (adalimumab, etanercept, infliximab [for very severe plaque psoriasis, as defined by a total PASI of 20 or more, and a DLQI of more than 18] and certolizumab pegol) • IL-17 family inhibitors or receptor inhibitors (brodalumab, ixekizumab, secukinumab and bimekizumab) • IL-23 inhibitors (guselkumab, tildrakizumab and risankizumab) • IL-12/IL-23 inhibitors (ustekinumab) • Apremilast • Dimethyl fumarate • Best supportive care	If systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or contraindicated: • TNF-α inhibitors (adalimumab, etanercept, and certolizumab pegol) • IL-17 family inhibitors or receptor inhibitors (brodalumab, ixekizumab, secukinumab and bimekizumab) • IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab) • IL-12/IL-23 inhibitors (ustekinumab) • Apremilast • Dimethyl fumarate	The target population is adults for whom systemic non-biologic treatment or phototherapy is not an option. Infliximab is not considered a direct comparator since it is indicated for patients with very severe psoriasis only. Nevertheless, infliximab is included in the network meta-analysis to strengthen the network; it is also included in the economic model for completeness. Best supportive care (BSC) is not included as a direct comparator since many active treatment options are now available. As such, patients receive BSC as last resort in clinical practice after having switched from one treatment to another when their treatment loses efficacy, or the treatment becomes contraindicated or not tolerated.

Outcomes	• Severity of psoriasis • Psoriasis symptoms, such as itch, and symptoms on the following areas: face, scalp, nails and joints, and other difficult-to-treat areas including the hands, feet and genitals • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects of treatment • Health-related quality of life	• Severity of psoriasis • Psoriasis symptoms, such as itch, and symptoms on the following areas: face, scalp, nails and joints, and other difficult-to-treat areas including the hands, feet and genitals • Response rate • Duration of response • Time to relapse • Adverse effects of treatment • Health-related quality of life	Relapse rate was not included as an outcome in the clinical trials. However, time to relapse was assessed in the clinical trials and the results are reported in B2. Mortality was not included as people with psoriasis are not expected to die earlier than the general population. It was also not collected in the pivotal studies due to the short-term nature of psoriasis trials. Impact on mortality is explored in a scenario analysis.
Subgroups to be considered	• Previous use of phototherapy and systemic non-biological therapy • Previous use of biological therapy • Severity of psoriasis (moderate, severe)	In the clinical trials, the efficacy was analysed by the following pre-specified subgroups: • Previous use of phototherapy and systemic non-biological therapy • Previous use of biological therapy • Severity of psoriasis by baseline PASI and sPGA scores	N/A

Abbreviations: BSA = body surface area; BSC = best supportive care; DLQI = Dermatology Life Quality Index; IL = interleukin; NHS = National Health Service; N/A = not applicable; PASI = Psoriasis Area Severity Index; sPGA = static physician global assessment; TNF = tumour necrosis factor.

B.1.2 Description of the technology being evaluated

Deucravacitinib is a first-in-class, once daily oral small molecule that selectively inhibits TYK2 with an allosteric mechanism of action (MOA) (see section B.1.2.2) that is unique and distinct from other JAK inhibitors as described in more detail below (see section B.1.2.1).[1-5]

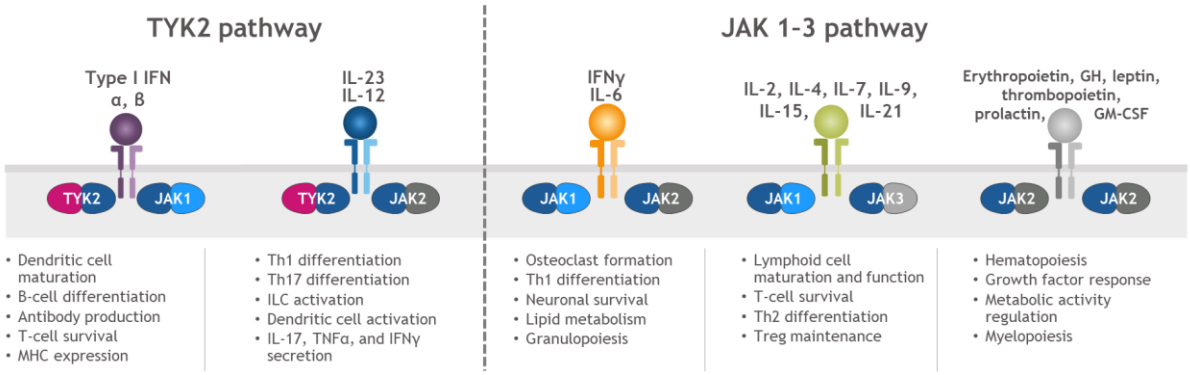
B.1.2.1 Pathophysiology and involvement of TYK-2 in psoriasis

The inflammatory response in psoriasis is driven by T cells and mediated by multiple cytokines, namely the type I interferons (IFN) and IL-23/IL-17 signalling cascades.

The JAK signal transducer and activator of transcription (JAK-STAT) pathway participates in the pathophysiology of psoriasis as well as other autoimmune diseases such as psoriatic arthritis and inflammatory bowel disease. There are four JAK proteins involved in the JAK-STAT pathway: JAK1, JAK2, JAK3, and TYK2.[6, 7] Once activated, these JAKs mediate signalling for a multitude of cytokines, leading to a cascade that causes a proinflammatory response.[6, 8] Specifically, the JAKs activated by type I IFN signalling are JAK1 and TYK2, while those activated by IL-23 signalling are JAK2 and TYK2 (see Figure B.1.1).[6, 7]

Activation of IL-23, type I IFN and the JAK-STAT pathway leads to secretion of IL-17, tumour necrosis factor α (TNFα), IL-26, and IL-29.[8, 9] Activation of IL-17 cytokines in turn increase expression of proinflammatory cytokines, colony-stimulating factors, and chemokines.[9] This ultimately produces an inflammatory response leading to psoriatic plaques.[6, 8]

Figure B.1.1. Selective TYK2 inhibition and cytokine responses



Abbreviations: GH = growth hormone; GM-CSF = granulocyte macrophage colony-stimulating factor; IFN = interferon; IL = interleukin; ILC = innate lymphoid cell; JAK = Janus kinase; MHC = major histocompatibility complex; Th = T helper; TNF = tumour necrosis factor; Treg = regulatory T cell; TYK = tyrosine kinase.
Source: Adapted from Baker et al., 2018;[10] Burke et al., 2019;[11] Wrobleski et al., 2019[12]

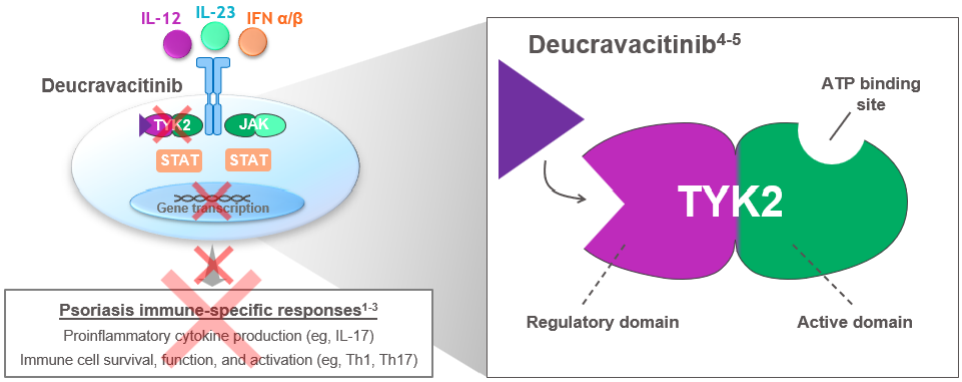
B.1.2.2 Mechanism of action and differentiation from JAK inhibitors

Deucravacitinib is a small molecule that selectively inhibits the TYK2 enzyme.[13] All currently approved small-molecule JAK 1,2 3 inhibitors exert their effect by binding to the ATP binding site of the active (or kinase) domain of the JAK protein, blocking downstream phosphorylation.[1, 14] Deucravacitinib is distinct because it binds to the regulatory (or pseudo-kinase) domain of TYK2, stabilising an inhibitory interaction between the regulatory and the active domains of the enzyme (see Figure B.1.2.)[13] Allosteric inhibition is a form of non-competitive inhibition. Instead of directly competing with the substrate (e.g., ATP) for access to the target's site, deucravacitinib instead binds outside the active site and locks TYK2 in an inactive state. This resulting allosteric inhibition of TYK2 reduces the downstream signalling

of IL-23, IL-12, and type I IFN receptors.[13] The high degree of selectivity of deucravacitinib for TYK2 reduces the potential for off-target and pan-JAK effects seen with other kinase inhibitors.[11, 13, 15]

Although TYK2 is a member of the JAK family, TYK2-dependent receptors are distinct from JAK-dependent receptors, suggesting that targeting TYK2 would have a different therapeutic response compared with targeting JAK1-3.[1] At physiologically relevant concentrations, deucravacitinib demonstrated >100-fold greater selectivity for pathways mediated by TYK2 in comparison with pathways mediated by JAK1 and JAK3 and >2,000-fold selectivity for TYK2 versus pathways mediated by JAK2.[11, 12, 16, 17] As a result, deucravacitinib does not inhibit pathways that are mediated only by JAK1,2,3, including those involved in hematopoiesis, myelopoiesis, granulopoiesis, metabolic activity regulation, and lipid metabolism.

Figure B.1.2. Mechanism of action of deucravacitinib



Abbreviations: ATP = adenosine triphosphate; IL = interleukin; INF = interferon; JAK = Janus kinase; Th = T helper; TYK = tyrosine kinase.
1. Hawkes et al., 2017.[8] 2. Baker et al., 2018.[10] 3. Ghoreschi et al., 2009.[18] 4. Papp et al., 2018.[1] 5. Morris et al., 2018.[14]

B.1.2.3 Description of the technology being appraised

A description of deucravacitinib is presented in Table B.1.1.2. The draft summary of product characteristics (SmPC) is presented in confidence in Appendix C. The European and UK public assessment reports of deucravacitinib are not yet available and will be shared with NICE upon receipt.

Table B.1.1.2. Technology being evaluated

UK approved name and brand name	Deucravacitinib (Brand name not yet available)
Mechanism of action	Deucravacitinib is a selective TYK2 enzyme inhibitor which binds to the pseudo-kinase domain on TYK2 and selectively blocks the TYK2 enzyme targeting specific cytokine pathways (see section B.1.2.2.)
Marketing authorisation/CE mark status	• CHMP positive opinion anticipated in [redacted] • EMA marketing authorisation anticipated in [redacted] • MHRA (GB) marketing authorisation anticipated in [redacted]
Indications and any restriction(s) as described in the SmPC	Deucravacitinib is anticipated to be indicated for [redacted] 13

Method of administration and dosage	The recommended dose is 6 mg taken orally once-daily with or without food. [redacted] Treatment with deucravacitinib should be initiated by clinicians experienced in the diagnosis and treatment of psoriasis. The patient's response to treatment should be evaluated on a regular basis. No dose adjustment is required in patients with renal impairment (including ESRD patients on dialysis), patients with mild or moderate hepatic impairment and elderly patients aged 65 years and older.[13]
Additional tests or investigations	None.
List price and average cost of a course of treatment	The list price of a pack of 28 tablets is [redacted].
Patient access scheme (if applicable)	A simple discount patient access scheme (PAS) discount has been approved providing a PAS price of [redacted] per pack.

Abbreviations: ATP = adenosine triphosphate; CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; ESRD = end-stage renal disease; GB = Great Britain; MHRA = Medicines and Healthcare products Regulatory Agency; TYK = tyrosine kinase.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease description and presentation

Plaque psoriasis is a chronic, immune-mediated, inflammatory skin disease with associated multi system comorbidities.[19, 20] It cannot be cured and typically follows a relapsing and remitting course, often requiring lifelong management.[21]

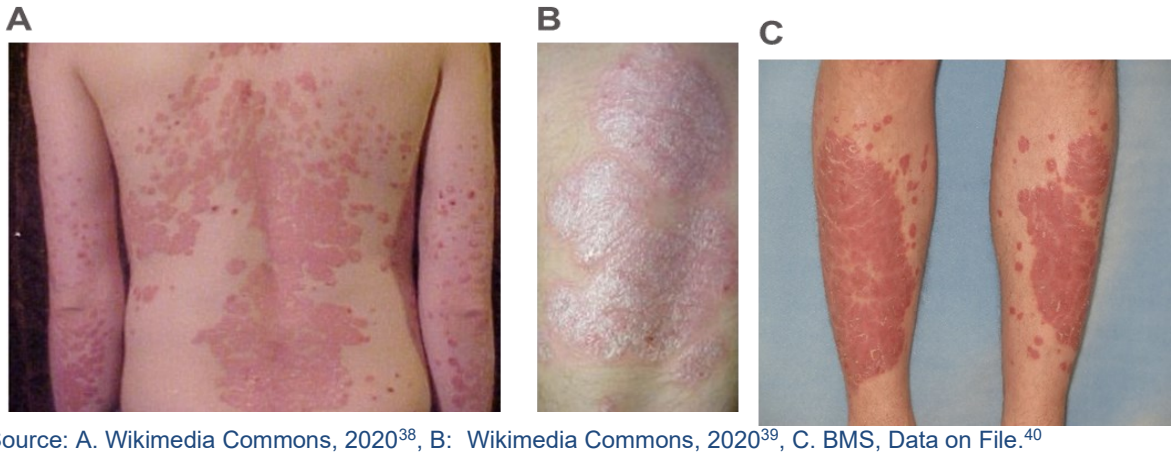
Plaque psoriasis (also known as psoriasis vulgaris) is the most common form and is characterised by well demarcated red scaly plaques that vary in their extent from isolated patches to widespread involvement.[17, 22-26] It typically presents on knees, elbows, and scalp, but it can present anywhere on the body (see Figure B.1.3).[27, 28] Some of the most reported symptoms that vary in severity are scaling of the skin, itching, skin pain, bleeding, skin cracking and dry skin.[29, 30] Nail and scalp psoriasis are common and problematic presentations in psoriasis.[28, 31] Nail psoriasis can include pitting, onycholysis, subungual hyperkeratosis and nail discoloration.[32] Scalp psoriasis poses challenges to treatment, in part because it is difficult to reach the scalp for topical treatments.[31]

The prevalence of psoriasis is between 1.3% and 2.2% in the UK.[33] Approximately 90% of people with psoriasis have plaque psoriasis, and approximately 41% of those have moderate-to-severe disease (34% moderate, 7% severe) in England. This equates to a projection of approximately 289,453 adults with moderate-to-severe plaque psoriasis in England in 2023.[34, 35]

Psoriasis presents at any age but is more commonly seen in adults compared with children.[36] Males and females are affected equally.[36] Studies have observed a bimodal distribution of the

onset of psoriasis, with the first peak ranging from 15–22 years of age, and the second peak ranging from 55–60 years of age.[19, 22, 37]

Figure B.1.3. Presentation of psoriatic lesions on the (A) back, (B) arm, and (C) legs



Source: A. Wikimedia Commons, 2020[38], B: Wikimedia Commons, 2020[39], C. BMS, Data on File.[40]

B.1.3.2 Diagnosis and grading

Psoriasis is diagnosed clinically, and rarely requires a skin biopsy for diagnostic confirmation.[28, 41] The severity of disease can vary over a patient's lifetime.[42]

The NICE guideline for psoriasis assessment and management (NICE clinical guidelines [CG] 153) recommends that all suspected cases of psoriasis should be assessed for disease severity, the impact of disease on physical, psychological, and social wellbeing, the presence of psoriatic arthritis (PsA) and other comorbidities.[20] In the specialist setting, the severity of psoriasis is assessed using the Psoriasis Area Severity Index (PASI) scoring system but clinicians also assess the impact of psoriasis on physical, psychological and social wellbeing using the Dermatology Life Quality Index (DLQI) (see section B.2.3.2).[20] Patients with severe psoriasis (defined as PASI ≥10 and DLQI >10) and for whom systemic non-biologic treatment or phototherapy is not an option because of lack of response, contraindication or not being tolerated are eligible to receive biologic treatments or apremilast or dimethyl fumarate.

The British Association of Dermatologists (BAD) guidelines also use failure of previous systemic treatment (methotrexate, ciclosporin) to base their severity grading on alongside DLQI, body surface area (BSA), and PASI scores and the involvement of high-impact and difficult-to-treat sites. As such, the following criteria apply for guiding treatment decisions to prescribe biologics:[43]

- DLQI scores >10, or clinical signs and symptoms of depression or anxiety
- Extensive psoriasis defined as a BSA >10% or PASI ≥10
- The psoriasis is severe at localised sites and associated with significant functional impairment and/or high levels of distress (e.g., nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals)

NICE and BAD guidelines mention several assessment tools to aid diagnosis and to determine disease severity and the impact of psoriasis on health-related quality of life (HRQoL), and

when to start treating patients with biologics. In Table B.2.4 the most used disease-specific assessment instruments for psoriasis are described.

B.1.3.3 Burden of disease

Impact on patients

Patients with moderate-to-severe plaque psoriasis often suffer from various comorbidities associated with the disease.[44] For example, a non-interventional retrospective study conducted by BMS and based on the Discover database in the UK (DISCOVER study) found that the majority of patients with psoriasis had comorbidities [redacted]. The most common comorbidities associated with psoriasis were mental health disorders (affecting [redacted] of patients), hypertension [redacted], cardiovascular disease [redacted], diabetes [redacted] and asthma [redacted].[45] There is evidence to suggest that having psoriasis increases a patient's risk of malignancy and cancer-related mortality.[46, 47] Mortality risk in patients with psoriasis also increases with disease severity.[48] In a prospective cohort study of 8,760 adults with psoriasis and 87,600 controls in the UK, patients with severe psoriasis (BSA >10%) had an increased risk of mortality (hazard ratio [HR] = 1.79) versus controls.[49] The observed reduction in life expectancy is estimated to range from 3.5 to 4.4 years in those who have severe psoriasis ($p<0.001$).[50]

According to quantitative research, patients with psoriasis report significantly worse HRQoL than the general population.[51] Psoriasis can have a significant impact on mental health and well-being, which is often inadequately recognised and managed by clinicians.[52] A UK cohort study using data from Clinical Practice Research Datalink (CPRD) found that patients with psoriasis showed an elevated risk of developing depression (HR = 1,39; 95% confidence interval [CI]: 1.37, 1.41), anxiety (HR = 1.31; 95% CI: 1.29, 1.34), and suicidality (HR = 1.44; 95% CI: 1.32, 1.57) compared to the general population, and this risk increased with disease severity.[53] Also, chronic itch, one of the most common and distressing symptoms of psoriasis, creates a high burden on HRQoL for patients with inflammatory dermatoses.[54] Real-world data indicate that in patients with psoriasis, the presence of itch versus no itch had a negative impact on Short Form (SF)-12 mental and physical scores, DLQI scores, and EuroQol 5-Dimensions (EQ-5D) scores ($p<0.01$ for all comparisons).[55] Furthermore, the impact on HRQoL worsens with itch severity.[55]

The anatomical location and visibility of psoriatic plaques (e.g., scalp, face, hands, nails) can also have a significant impact on HRQoL. The visible nature of disfiguring psoriatic plaques can lead to social stigmatisation, with those affected reporting exclusion from normal social environments such as schools, workplaces, and swimming pools. Psoriasis can also negatively impact people's relationships. As a result, patients with plaque psoriasis might avoid social activities and commonly report experiencing loneliness, isolation, feelings of being unattractive and frustration.[19] In a large multinational survey, 84% of people with psoriasis reported discrimination or humiliation, 43% reported effects on their relationships, and 54% reported effects on work life due to psoriasis.[56]

Impact on society and NHS

Patients with moderate-to-severe psoriasis treated with non-biologics incur greater health-related resource use (HRCU) costs compared to those treated with biologics[57, 58] In the

DISCOVER study, primary and secondary care medical records from patients with psoriasis who discontinued a biologic between April 2016 and August 2019 were analysed 12 months before and 12 months after discontinuation [redacted].[45] During the 12 months before stopping, patients with psoriasis had a mean of [redacted] inpatient admissions. months after discontinuation. Although patients were admitted to the hospital more frequently before discontinuation of biologic, length of inpatient bed days per patient year was higher after discontinuing the treatment [redacted]. After discontinuation of a biologic, the mean number of secondary care visits increased [redacted] compared to before discontinuation [redacted]. The total costs (cost year: 2020) for secondary care per patient were highest post discontinuation versus before in both secondary care [redacted] versus [redacted] and primary care setting [redacted], including patients with no visit.[45]

Similar to the DISCOVER study, another retrospective observational study from the UK assessed health-related resource use (HCRU) and related costs in patients with moderate-to-severe plaque psoriasis receiving biologics versus non-biologics.[59] Patients not receiving biologics had an average of 6.5 days ([SE]: 2.0) of inpatient admissions and 3.2 (SE: 0.1) outpatient visits within 12 months. Associated mean costs (cost year: 2010) for inpatient and outpatient visits were £1,887.7 (SE: 578.4) and £232.1 (SE: 8.0), respectively. The total costs (cost year: 2010) per patient were highest in patients not receiving biologics versus biologics (£2,956.7 [SE: 758.8] versus £1,274.3 [SE: 240.2])

Employed patients with psoriasis in the UK suffer from losses in work productivity (e.g., mean loss of 26 days [SD: 21.9] in one year), which account for significant indirect costs.[60, 61] In patients with moderate-to-severe psoriasis the mean percentage of lost work hours ranges between 18-30%. This corresponds to a potential productivity loss of £3,000 per patient per year in the UK, equating to almost £4 billion of indirect costs due to psoriasis per year.[61]

A key cost driver in the management of psoriasis is treatment switching (section B.1.3.4). Treatment switching and discontinuation are commonplace in psoriasis. The key reasons for this are a lack of initial response (primary failure) or loss of response (secondary failure) after starting therapy or poor tolerability. As current therapies do not always result in durable responses, patients can experience multiple therapy changes over the course of their disease.[62]

Impact of COVID-19 pandemic

Dermatology is a high-volume outpatient specialty under significant pressure, resulting from a combination of increased incidence and prevalence of skin disease with challenges resulting from secondary care and dermatology workforce shortages across the multidisciplinary team.[63] In addition, the pressures upon the NHS have undoubtedly increased during the COVID-19 pandemic.[64] As a result, there are backlogs of outpatient appointments, diagnostics, treatments, and surgery across dermatology services. The BAD noted that these backlogs could lead to poor patient outcomes, more acute hospital admissions, and an increased need for expensive therapies.[64] In response, the NHS refocused its 2022/23 priorities and systems are now asked to make the most effective use of the resources available to get above pre-pandemic levels of productivity.[65]

B.1.3.4 Unmet need

Starting a patient on a biologic is a multi-step process and a clinical expert has estimated that there is often a delay of around 6 weeks in patients receiving treatment from when it is first initiated. Often contributing to the delay in patients receiving treatment is the time required to complete the recommended pre-treatment screening examinations. These include baseline blood tests, viral and tuberculosis infection screening (blood test and chest x-ray) and any necessary pre-treatment vaccinations.

Furthermore, there can be delays in delivering the biologic to the patient once it has been prescribed. The mode of administration of biologics is mostly by subcutaneous injection and the current options for administration include the hospital setting and at home via the homecare system with associated injection training by homecare nursing staff. Both options can incur lengthy setup timeframes, an administrative burden and other costly healthcare resource utilisation. Drug administration costs are meaningful in the UK with biologics administered in a hospital setting being more expensive than those administered via homecare system funded by the NHS or by manufacturers distributing the biologic (ranging from £4,224 to £7,463 in hospital and £693 to £3,445 for homecare, over a two-year period). The burden of homecare cost could soon solely lie with the NHS as there has been investigations that the NHS could be funding the home delivery of biologics rather than drug manufacturers. [66]

Patients started on biologics require ongoing monitoring. The BAD recommend that patients should have regular monitoring blood tests at three to four months after starting treatment and six-monthly thereafter or as often as clinically indicated, to include full blood count, renal and liver function tests. These monitoring examinations create additional touchpoints in primary and secondary care, contributing to the HCRU and overall system burden.[67] Deucravacitinib offers the advantage of being an oral treatment requiring no dose titration, no special storage conditions and fewer pre-treatment screening and ongoing blood monitoring tests than biologics. Furthermore, it can potentially be started on the day it is prescribed, adding to its convenience and may help to decrease backlogs in dermatology services.

Biologics offer patients a treatment option with rapid onset of action and high efficacy but can lose response over time, in part attributed to the formation of anti-drug antibodies, a characteristic of biologics referred to as immunogenicity. Treatment switching is an additional complexity which might also contribute to the delays in patients receiving care, thereby increasing cost and resource use overall. The clinical uncertainty of when the patient will start a new prescribed biologic is another complication and can potentially put the patient at risk of disease flare-up during the run-in switching period. As a small molecule medication, it is anticipated that deucravacitinib will not develop immunogenicity and it therefore presents patients with an option for a treatment with good durability and less need for switching. This durability is well supported by data from the two global Phase 3 trials and long-term extension studies detailed in clinical effectiveness (see section B.2.6.3).

Self-administering treatment by subcutaneous injection can be unappealing to some patients. In the Multinational Assessment of Psoriasis and PsA (MAPP) study, 202 patients (52%) currently receiving a biologic or having used one in the past described their treatment as burdensome; 66 patients (31%) currently using a biologic found it burdensome due to the fear, anxiety or inconvenience such as physical preparation for self-injection (e.g., icing and premedicating) of injections.[67]

After the conventional systemic treatments (methotrexate, acitretin and ciclosporin), oral small molecule therapy options are limited to apremilast and dimethyl fumarate. To date, no orally administered biologics are available for moderate-to-severe plaque psoriasis. The prospect of deucravacitinib as a new treatment option that may be as efficacious as some biologics, but with the convenience and ease of oral administration, is likely to be welcomed by both clinicians and patients. Having a convenient treatment option, with oral administration and less necessity for primary or secondary care touchpoints is especially important during and after the COVID-19 pandemic. The COVID-19 rapid guideline highlights options for delivering treatments during the pandemic prioritising route of administration or mode of delivery that could make hospital attendance less likely.[68]

B.1.3.5 Treatment pathway and anticipated position of deucravacitinib

Current treatments for psoriasis are life-long and not curative but are aimed at reducing disease burden, alleviating symptoms, and improving HRQoL.[69]

NICE guidelines

The NICE guideline on assessment and management of psoriasis was published in 2012 and updated in 2017.[20] The psoriasis NICE Pathway was issued in 2012 and updated in 2021.[70]

Moreover, NICE published several technology appraisal (TA) reports. An overview of these TAs is provided in Table B.1.1.3.

Table B.1.1.3. Overview of NICE TAs

Technology appraisal	Therapy class	Recommended population	Stopping rule
Bimekizumab (2021), TA 723[71]	IL 17-inhibitor	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and phototherapy)	16 weeks
Risankizumab (2019), TA 596[72]	IL 23-inhibitor	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and phototherapy)	16 weeks
Tildrakizumab (2019), TA 575[73]	IL-23 inhibitor	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and phototherapy)	12/28 weeks*
Certolizumab pegol (2019), TA 574[74]	Anti TNF-α	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and phototherapy)	16 weeks
Guselkumab (2018),TA 521[75]	IL-23 inhibitor	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and PUVA)	16 weeks
Brodalumab (2018), TA 511[76]	IL-17 inhibitor	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and PUVA)	12 weeks

Technology appraisal	Therapy class	Recommended population	Stopping rule
Dimethyl fumarate (2017), TA 475[77]	Non-biologic systemic treatment	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and PUVA)	16 weeks
Ixekizumab (2017), TA 442[78]	IL-17 inhibitor	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and PUVA)	12 weeks
Apremilast [rapid review of TA 368] (2016), TA 419[79]	Non-biologic systemic treatment	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and PUVA)	16 weeks
Secukinumab (2015), TA 350[80]	IL-17 inhibitor	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and PUVA)	12 weeks
Ustekinumab (2009), TA 180[81]	IL-12 and IL-23 inhibitor	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and PUVA)	16 weeks
Adalimumab of (2008), TA 146[82]	Anti TNF-α	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and PUVA)	16 weeks
Infliximab of (2008), TA 134[83]	Anti TNF-α	Severe plaque psoriasis defined as PASI ≥20 and DLQI >18 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate or PUVA)	10 weeks
Etanercept & efalizumab (2006), TA 103[84]	Anti TNF-α	Severe plaque psoriasis defined as PASI ≥10 and DLQI >10 and if no response/contraindication/ intolerance to other systemic treatments (incl. ciclosporin, methotrexate and PUVA)	12 weeks

*The NICE recommendation on tildrakizumab specifies that treatment with tildrakizumab should be considered to stop between weeks 12 and 28, if there has not been ≥50% reduction in the PASI score compared to start of treatment; at 28 weeks tildrakizumab should be stopped if the psoriasis has not responded adequately, i.e., 75% reduction in the PASI score (PASI 75) from when treatment started, or a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.
Abbreviations: DLQI = Dermatology Life Quality Index; IL = interleukin; PASI = Psoriasis Area and Severity Index; PUVA = psoralen plus ultraviolet A; TA = technology appraisal; TNF = tumour necrosis factor.

Recent NICE TAs (from 2018) recommend to also consider costs in the treatment choice and to choose the least expensive among the range of suitable treatments including the availability of biosimilar products.[75]

BAD guidelines

In 2020, the BAD published a rapid update to their 2017 guideline on the use of biologics.[43] This guideline provides evidence-based recommendations on the use of biologics targeting TNF (adalimumab, etanercept, certolizumab pegol, infliximab), IL-12/23 (ustekinumab), IL-17 inhibitorsA (ixekizumab, secukinumab, brodalumab), IL-23A (risankizumab), and IL-23P19 (guselkumab, tildrakizumab) for the treatment of psoriasis.[43] Where relevant, this guidance

applies to biosimilars, subject to recommendations given within the BAD position statement and the EMA guidelines.[85, 86]

The BAD guidelines recommend the use of biologics if methotrexate and/or ciclosporin have failed, are not tolerated or are contraindicated or if the disease has a large impact on physical, psychological or social functioning (see section B.1.3.2).[43]

An important change in the 2020 update is that any licensed biologic can be offered to a patient who is eligible to receive a biologic, unlike the previous (2017) guidelines which recommended ustekinumab, adalimumab, and secukinumab as first-line biologics. This means that no specific treatment sequences are recommended in the current BAD guidelines. The choice of biologic should be tailored to the patient's individual needs.[43] If a patient does not respond to the biologic of first choice (first-line biologic), treatment switching to any other biologic can be offered, as adequate.[43] To gain insight into the clinical practice of psoriasis management with biologics in the UK, a clinical expert was consulted (as part of an advisory board). The expert stated that the use and treatment sequences of biologics vary largely across hospitals in the UK, depending on whether clinicians are rapid adopters of new treatments.

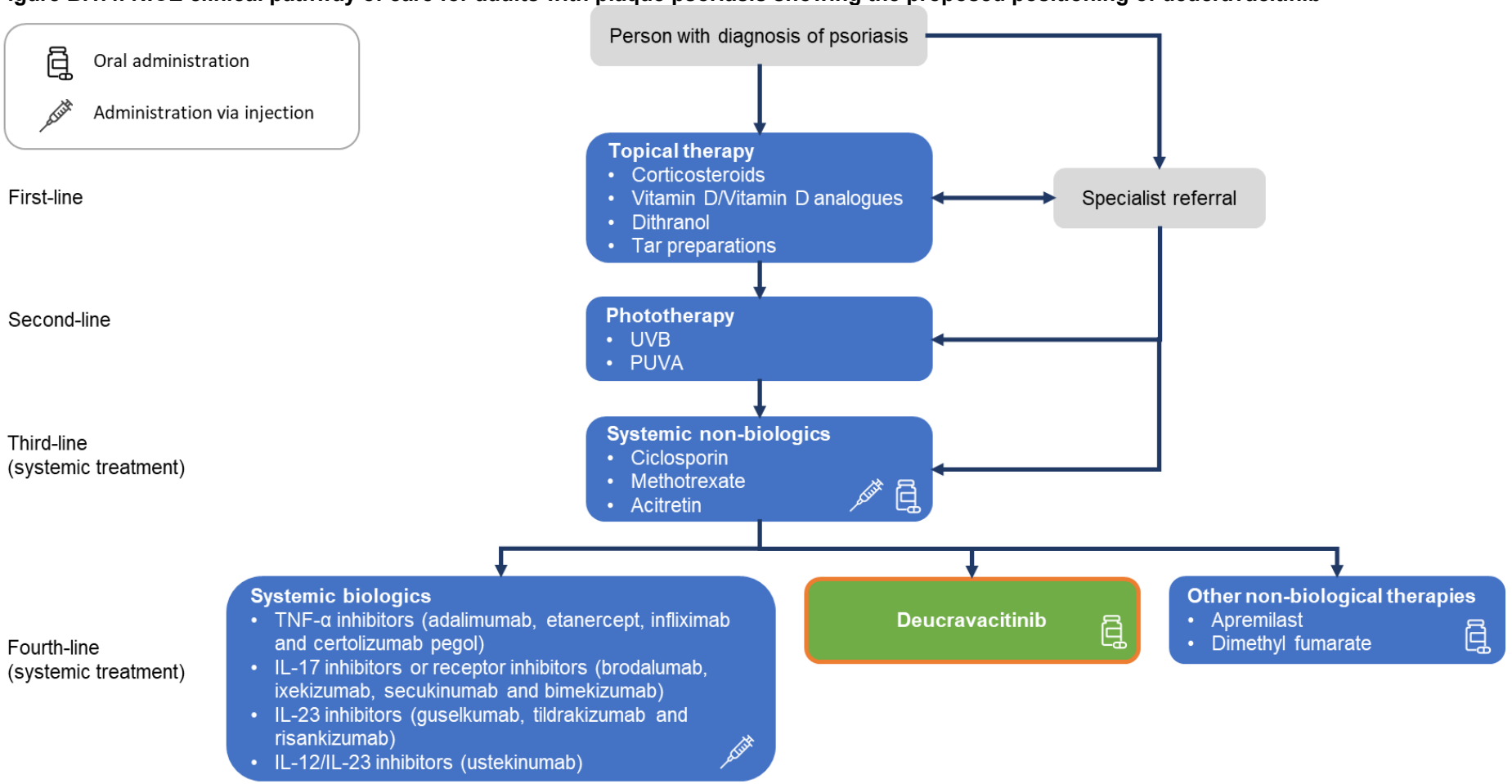
Plaque psoriasis that has not responded to topical therapy (first line), phototherapy (second line) or non-biologic systemic treatments (third line) can be treated in fourth line with a range of biologics as described in Table B.1.1.3. Oral therapy options, also recommended at fourth line, are limited to non-biologics such as the anti-inflammatory dimethyl fumarate and the phosphodiesterase type-4 inhibitor apremilast.[87, 88]

Positioning of deucravacitinib in the current psoriasis landscape

The current armamentarium of approved therapies for the treatment of moderate-to-severe plaque psoriasis provides a range of treatment options. Despite this, there remains an unmet need for a well-tolerated and effective oral treatment alternative with a different mechanism of action. Since the COVID-19 pandemic, patients are even more in need of an option that allows them to be treated remotely, requiring fewer hospital visits, and for which the treatment response is well maintained. Deucravacitinib, as a novel TYK2 oral agent, provides an alternative to existing treatment options that may be as efficacious as some biologics, but with the convenience and ease of oral administration helping to improve patient's satisfaction.

It is proposed that deucravacitinib is positioned as an alternative to current injectable biologics or other systemic oral non-biologics (see Figure B.1.4).

Figure B.1.4. NICE clinical pathway of care for adults with plaque psoriasis showing the proposed positioning of deucravacitinib



Abreviations: IL = interleukin; PUVA = psoralen plus ultraviolet A; TNF: tumour necrosis factor; UVB = ultraviolet B.
Note: Methotrexate administration may be parenteral. All biologics are administered by subcutaneous injection, except infliximab which is administered as an intravenous infusion.
Source. Adapted from the NICE pathway for psoriasis.[70]

B.1.4 Equality considerations

There are two relevant equality considerations that need to be acknowledged, as previously reported in NICE guidance for moderate-to-severe plaque psoriasis. Firstly, when using the PASI scoring system, it is necessary to consider the patient's skin type as disease severity may be underestimated in darker skin colours.[20, 74] Secondly, when using the DLQI questionnaire, the age of the patient as well as any physical, visual, or cognitive impairments, and any language or communication issues need to be considered.[20, 74] In both cases, adjustments should be made in the assessment as necessary.

B.2 Clinical effectiveness

Overview of clinical studies

- The clinical efficacy and safety of deucravacitinib in adults with moderate-to-severe plaque psoriasis was assessed in two Phase 3, international, randomised, double-blind, placebo-controlled (through Week 16) and active comparator (apremilast) controlled (through Week 24), 52-week studies (POETYK-PSO-1, n=666 and POETYK-PSO-2, n=1,020). In POETYK-PSO-1 (see Figure B.2.1): patients initially randomised to deucravacitinib and placebo switched to deucravacitinib at Week 16 and continued treatment through Week 52, while patients initially randomised to apremilast who did not achieve PASI 50 response at Week 24 switched to deucravacitinib through Week 52; patients who did achieve PASI 50 response remained on apremilast, through Week 52. POETYK-PSO-2 study design was identical to POETYK-PSO-1 until 24 weeks (see Figure B.2.2) and there was a randomised withdrawal and retreatment period between 24-52 weeks to assess the maintenance of response and time to relapse or loss of response of deucravacitinib
- On completion of POETYK-PSO-1 and POETYK-PSO-2 patients could enter the ongoing open-label, long-term extension study, POETYK-PSO-LTE
- POETYK-PSO-1 and POETYK-PSO-2 (n=1,686, including [redacted] patients in the UK) were pooled to assess short- to mid-term efficacy (Weeks 16 and 24) and long-term safety (Week 0 to 52)

Short- to mid-term clinical efficacy

- Pooled efficacy results were consistent with the individual studies. In the pooled analysis, [redacted] the co-primary efficacy outcomes (PASI 75 and sPGA 0/1) and multiple key secondary efficacy and patient-reported outcomes, compared to placebo and apremilast:
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
- In the pooled analysis and individual studies, the co-primary outcomes, PASI 75 and sPGA 0/1 response, were higher at Week 24 than at Week 16, indicating that assessment at Week 16 could be premature. In line with deucravacitinib's draft SmPC, this may suggest that [redacted] is a more appropriate timepoint for clinicians to assess treatment response in patients

Long-term durability and maintenance of response

- In the individual studies, deucravacitinib response was [redacted] and continued over the longer-term [redacted], demonstrated by interim data from POETYK-PSO-LTE. Deucravacitinib response also persisted in patients that stopped treatment at week 24, as measured in the randomised withdrawal arm of POETYK-PSO-2

Safety

- Deucravacitinib was well-tolerated, with a low proportion of discontinuations due to adverse events. Results from the pooled analysis demonstrated that the safety profile of deucravacitinib was comparable to apremilast. Importantly, [redacted]

[redacted]. Pooled safety results were consistent with the individual studies

- No new previously unreported safety signals for deucravacitinib were observed during the 52-week trial period, nor have these been found in the extension study (POETYK-PSO-LTE; database lock safety: 1 October 2021)

Network meta-analysis

- In a network meta-analysis deucravacitinib was [redacted] In the longer-term, it also showed to [redacted]
- In a network meta-analysis better reflecting likely usage of deucravacitinib and tildrakizumab in clinical practice, results showed [redacted]; deucravacitinib was also [redacted]

Conclusion

- Deucravacitinib demonstrated a robust efficacy profile. Results from the Phase 3 trials confirm that patients with moderate-to-severe psoriasis treated with deucravacitinib achieved treat-to-target absolute PASI outcomes that were superior to placebo and apremilast. Deucravacitinib was also [redacted] Deucravacitinib was efficacious [redacted], and responses demonstrated durable efficacy. Clinical responses [redacted] It also was shown to improve [redacted] of patients compared to both apremilast and placebo
- In a network meta-analysis reflecting clinical practice response assessment, deucravacitinib was [redacted]
- The safety profile was comparable to apremilast with a low proportion of discontinuations due to adverse events. No new previously unreported safety signals were observed in the extension study
- Deucravacitinib has the potential to become a treatment of choice and new standard of care for patients who require systemic therapy for their moderate to severe plaque psoriasis that provides patients the convenience of a once-daily oral dose with no need for routine laboratory monitoring.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify and summarise the available randomised controlled trial (RCT) evidence for treatments for moderate-to-severe plaque psoriasis. The literature search was performed on 11 October 2021. Full details of the methodology and the results of the SLR are provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Three phase 3 RCTs provided evidence for the efficacy and safety of deucravacitinib: two completed pivotal phase 3 studies, POETYK-PSO-1 (IM011046) and POETYK-PSO-2

(IM011047), and one ongoing, phase 3b long-term extension (LTE) study, POETYK-PSO-LTE (IM011075). The expected completion date for POETYK-PSO-LTE is 2026.[89]

Of these three RCTs, POETYK-PSO-1 was identified by the SLR. The other pivotal phase 3 study, POETYK-PSO-2, and the long-term extension study, POETYK-PSO-LTE, were identified by the manufacturer.

The entry criteria of POETYK-PSO-1 and POETYK-PSO-2 were identical.[90] The two study populations were similar in almost all aspects including study design until Week 24, with the only major difference being Asian ethnicity due to the geographic locations of the study sites (POETYK-PSO-1: n=121, 18.2% versus POETYK-PSO-2: n=44, 4.3%).[90-92] These similarities allowed the short- to mid-term (Week 16 and Week 24) efficacy and safety data to be pooled (naïve pooling) across POETYK-PSO-1 and POETYK-PSO-2 for an integrated analysis of the efficacy of deucravacitinib in patients with moderate-to-severe plaque psoriasis.

The purpose of the pooled analysis was to estimate the efficacy of treatment with deucravacitinib versus placebo and apremilast with added precision obtained by pooling the data from both individual studies. Another objective of pooling the efficacy data was to demonstrate the consistency of treatment effect for the co-primary outcomes across various subgroups of intrinsic and extrinsic variables.[93]

POETYK-PSO-1, POETYK-PSO-2 and the pooled analysis are the primary sources of evidence for this submission and the economic model, detailed in section B.3.3.1 and section B.3.4. [redacted][94] The POETYK-PSO-LTE data provides additional, long-term evidence of the efficacy of deucravacitinib and is included in section B.2.1 to B.2.6. However, as all patients were switched to deucravacitinib when entering POETYK-LTE, no relative efficacy can be drawn from this study, it was therefore not used to inform the economic model.[95]

The methodology of POETYK-PSO-1 and POETYK-PSO-2, and results for the pooled analysis and interim results from POETYK-PSO-LTE are provided in the following sections. The individual study results for POETYK-PSO-1 and POETYK-PSO-2 are provided in Appendix N.

An overview of POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE is provided in Table B.2.1.

Table B.2.1. Clinical effectiveness evidence

Study	IM011046 (POETYK-PSO-1; NCT03624127)	IM011047 (POETYK-PSO-2; NCT03611751)	IM011075 (POETYK-PSO-LTE; NCT04036435)
Study design	Phase 3, 52-week, international, multicentre, randomised, double-blind, placebo- and active comparator-controlled	Phase 3, 52-week, international, multicentre, randomised, double-blind, placebo- and active comparator-controlled, with a randomised withdrawal and retreatment phase (Week 24–52)	Ongoing, phase 3b, open-label, single-arm, international, multicentre (only interim data available)
Population	Adult patients with moderate-to-severe plaque psoriasis (PASI ≥12, sPGA ≥3 and BSA ≥10%)	Adult patients with moderate-to-severe plaque psoriasis (PASI ≥12, sPGA ≥3 and BSA ≥10%)	Adult patients with moderate-to-severe plaque psoriasis (PASI ≥12, sPGA ≥3 and BSA ≥10%) who completed POETYK-PSO-1 and POETYK-PSO-2
Intervention(s)	Deucravacitinib 6 mg QD (N=332)	Deucravacitinib 6 mg QD (N=511)	Deucravacitinib 6 mg QD (N=1,221)
Comparator(s)	Placebo (N=166) and apremilast 30 mg BID (N=168)	Placebo (N=255) and apremilast 30 mg BID (N=254)	N/A
Indicate if study supports application for marketing	Yes	Yes	Yes
Indicate if study used in the economic model	Yes (pooled with POETYK-PSO-2)	Yes (pooled with POETYK-PSO-1)	No
Rationale if study not used in model	N/A	N/A	POETYK-PSO-LTE data was not included in the economic model because no relative efficacy could be drawn as all patients received deucravacitinib (see section B.3.3.2)
Reported outcomes specified in the decision problem (outcomes marked in bold are used in the model)	• severity of psoriasis: PASI, sPGA • psoriasis symptoms: variations of the PASI adapted for nail (PGA-F), scalp scores (ss)-PGA • **response rate:** PASI 50, **PASI 75**, PASI 90 and PASI 100 • duration of response: response rates at different timepoints e.g. 16, 24 and 52 weeks • time to relapse • adverse effects of treatment: treatment-emergent adverse events (AEs), deaths, serious adverse events, discontinuations due to AEs, and **AEs of interest** • health-related quality of life: **EQ-5D-3L**, DLQI 0/1		

Study	IM011046 (POETYK-PSO-1; NCT03624127)	IM011047 (POETYK-PSO-2; NCT03611751)	IM011075 (POETYK-PSO-LTE; NCT04036435)

All other reported outcomes	• Change from baseline and percent change from baseline in:
	  ○ PASI
	  ○ BSA
	  ○ BSA x sPGA
	  ○ PSSI
	  ○ mNAPSI
	• mNAPSI response
	• Health-related quality of life: PSSD, SF-36, HADS, PGI-C, PGI-S		

Abbreviations: BID = twice daily; BSA = body surface area; DLQI = dermatology life quality index; HADS = hospital anxiety and depression scale; HRQoL = health-related quality of life; mNAPSI = modified Nail Psoriasis Severity Index; PGA-F = Physician's Global Assessment of Fingernail Psoriasis; PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; PSSD = Psoriasis Symptoms and Signs Diary; PSSI = Psoriasis Scalp Severity Index; QD = once daily; LTE = long-term extension; SF-36 = 36-item short-form; sPGA = Static Physicians Global Assessment; ss-PGA = scalp-specific Physicians Global Assessment.
Source: POETYK-PSO-1 CSR, BMS Data on File;[91] POETYK-PSO-2 CSR, BMS Data on File;[92] POETYK-PSO-LTE CSR, BMS Data on File[94]; Warren et al, 2022[96]

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

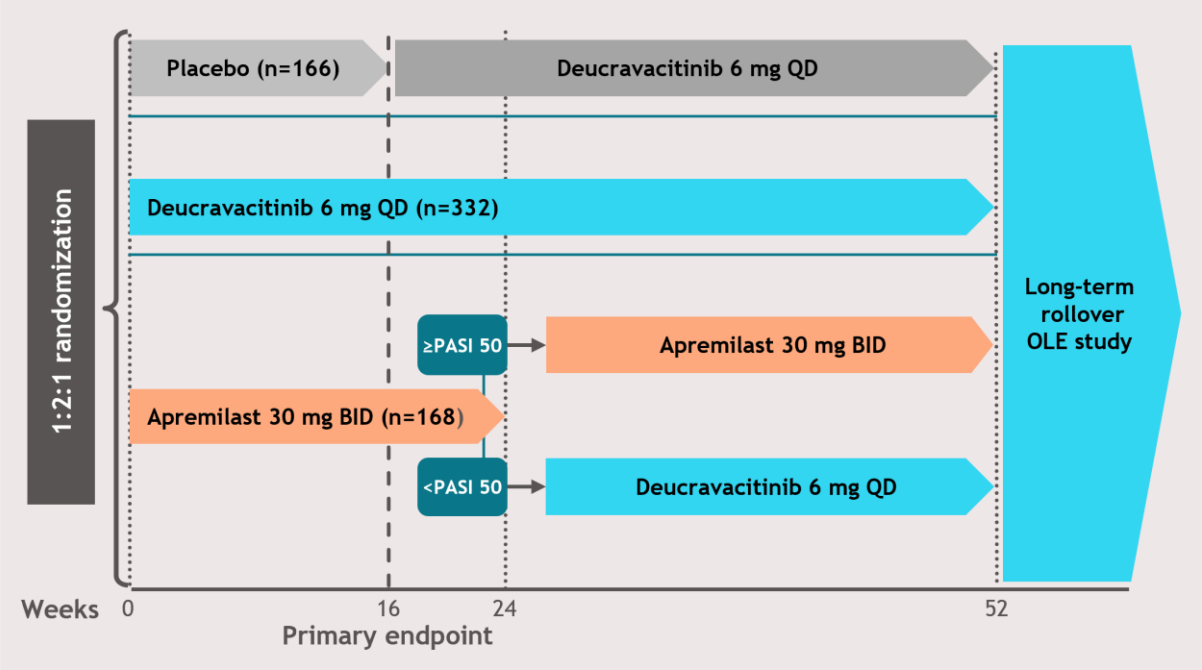
B.2.3.1 Study design: POETYK-PSO-1 and POETYK-PSO-2

POETYK-PSO-1 and POETYK-PSO-2 were 52-week, international, multicentre, randomised, double-blind, placebo- and active comparator (apremilast)-controlled phase 3 studies. Both studies evaluated the efficacy and safety of deucravacitinib 6 mg once daily (QD) in patients with moderate-to-severe plaque psoriasis (defined as PASI ≥12, static sPGA ≥3, and BSA involvement ≥10%) who were candidates for phototherapy or systemic therapy for their psoriasis.[90-92]

The study designs are presented in Figure B.2.1 and Figure B.2.2. Both studies consisted of the following periods: screening; initial, maintenance and open-label treatment and safety follow-up. They were identical until the end of the initial period (Week 24).

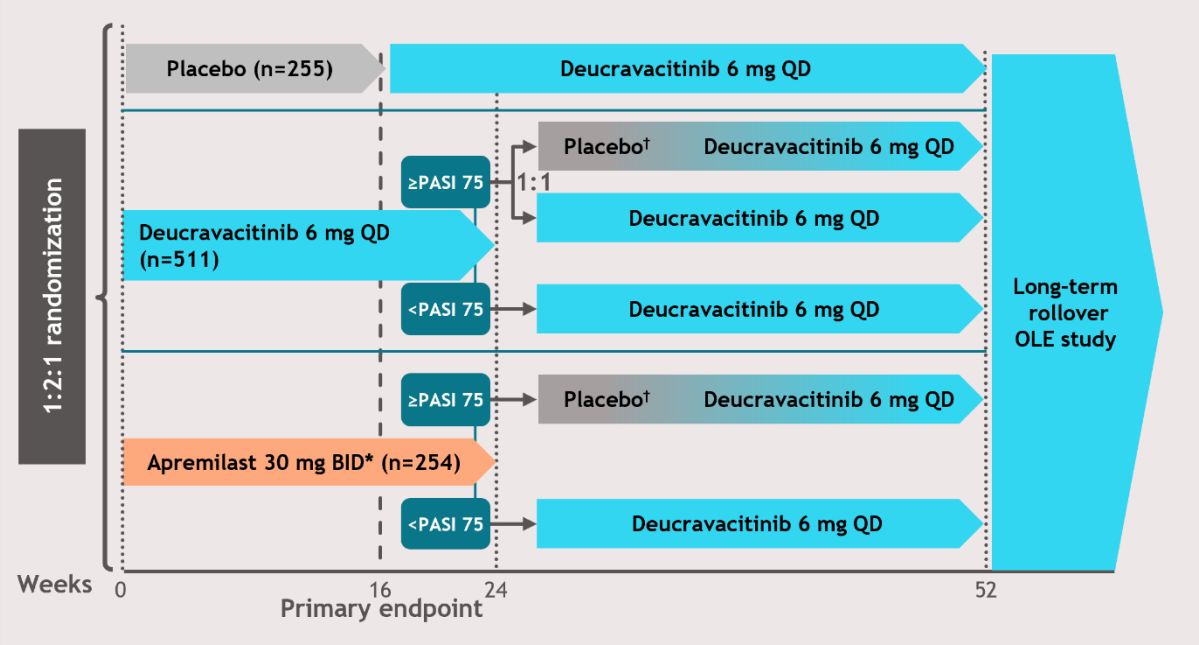
POETYK-PSO-2 had a randomised withdrawal and retreatment period between Week 24-52 to assess the durability and maintenance of response and time to relapse or loss of effect of deucravacitinib.[91, 92]

Figure B.2.1. Study design, POETYK-PSO-1



Abbreviations: BID = twice daily; OLE = open-label extension; PASI = Psoriasis Area Severity Index; QD = once daily.
* Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
Source: Armstrong et al. 2021;[90] POETYK-PSO-1 CSR, BMS Data on File[91]

Figure B.2.2. Study design, POETYK-PSO-2



Abbreviations: BID = twice daily; OLE = open-label extension; PASI = Psoriasis Area Severity Index; QD = once daily.
* Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
† Upon relapse (≥50% loss of Week 24 PASI percent improvement from baseline), patients were switched to deucravacitinib 6 mg QD.
Source: Armstrong et al. 2021;[90] POETYK-PSO-2 CSR, BMS Data on File[92]

In both studies, efficacy and safety assessments such as physical exams, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations were completed at select visits during the study. Patients were monitored for AEs throughout the study. Additional blood samples were collected for biomarker and pharmacokinetic (PK) analyses.[91, 92] According to the draft SmPC, treatment with deucravacitinib [redacted] It is therefore anticipated that deucravacitinib will require little or no monitoring from when the patient has started treatment. This was further supported by a clinical expert (consulted as part of an advisory board).

Week 0–16: placebo-controlled Period

In both studies, patients were randomised in a blinded manner in a 2:1:1 ratio to deucravacitinib 6 mg QD, placebo, or apremilast 30 mg twice daily (BID), respectively.[91, 92] Randomisation was stratified by:[90]

- Geographic region: POETYK-PSO-1; United States [US], Japan, China, and Rest of World (ROW); POETYK-PSO-2; US and ROW
- Previous biologic use: for psoriasis, PsA or other inflammatory diseases only; yes/no
- Body weight: ≥90 kg and <90 kg; body weight stratum was not applied in Japan or China for POETYK-PSO-1

Week 16–24

In both studies, patients randomised to placebo at baseline switched to deucravacitinib at Week 16 and remained on deucravacitinib until at least Week 24. Patients randomised to deucravacitinib or apremilast at baseline continued the same treatment regimen through Week 24.[91, 92]

Week 24-52: POETYK-PSO-1 maintenance period

In POETYK-PSO-1 at Week 24, patients randomised to[90, 91]:

- Apremilast at baseline who did not achieve PASI 50 response were switched in a blinded manner to deucravacitinib through Week 52, while patients achieving PASI 50 response continued apremilast through Week 52
- Deucravacitinib at baseline continued treatment through Week 52
- Placebo at baseline and switched to deucravacitinib at Week 16 continued deucravacitinib through Week 52

At Week 52, eligible patients entered POETYK-PSO-LTE.[90, 91]

Week 24-52: POETYK-PSO-2 maintenance period and randomised withdrawal

In POETYK-PSO-2 at Week 24, patients randomised to[90, 92]:

- Deucravacitinib at baseline, who did not achieve PASI 75 response continued deucravacitinib through Week 52, while patients achieving PASI 75 response, were re-randomised to either deucravacitinib or placebo
    - If patients switched to placebo experienced a relapse (defined as ≥50% loss of Week 24 PASI percent improvement from baseline) they were switched back to deucravacitinib through Week 52
- Apremilast at baseline, who did not achieve PASI 75 response were switched to deucravacitinib, while patients achieving PASI 75 response were switched to placebo through Week 52
    - If patients switched to placebo experienced a relapse (defined as ≥50% loss of Week 24 PASI percent improvement from baseline) they were switched to deucravacitinib through Week 52
- Placebo at baseline, who were switched to deucravacitinib at Week 16 remained on deucravacitinib through Week 52

At Week 52 eligible patients entered POETYK-PSO-LTE as in POETYK-PSO-1,.[90, 94]

Follow-up period: safety

In both studies, all patients who did not enter POETYK-PSO-LTE (see section B.2.3.2) had a 4-week safety follow-up visit. Patients who discontinued treatment early were followed up for adverse events until Week 52.[91, 92]

B.2.3.2 Study design: POETYK-PSO-LTE

POETYK-PSO-LTE is an ongoing multi-year, multicentre, open-label, phase 3b study. The study evaluates the long-term safety, tolerability, and efficacy of deucravacitinib 6 mg QD in patients with moderate-to-severe plaque psoriasis (defined as PASI ≥12, sPGA ≥3, and BSA involvement ≥10%) who were previously enrolled in the parent studies (POETYK-PSO-1 and POETYK-PSO-2). The duration of study participation for patients is expected to be 240 weeks, with 30 additional days for safety follow-up. [redacted][94]

Baseline study data for POETYK-PSO-LTE were based on the last visit of the parent study. Among the 1,286 patients who completed the POETYK-PSO-1 and POETYK-PSO-2 parent trials, 1,221 patients enrolled in the POETYK-PSO-LTE study (see Table B.2.2). A total of [redacted] of patients had received deucravacitinib for at least [redacted] and [redacted], respectively [redacted].[93] The study is ongoing. [redacted]

Table B.2.2. POETYK-PSO-LTE study groups by last treatment in the parent study

Groups (stratification by last treatment in parent study)	Last treatment in parent study	Treatment in POETYK-PSO-LTE study	N
Deucravacitinib → deucravacitinib (from POETYK-PSO-1 and POETYK-PSO-2)	Deucravacitinib	Deucravacitinib	[redacted]
Placebo → deucravacitinib (all from POETYK-PSO-2)	Placebo	Deucravacitinib	[redacted]
Apremilast → deucravacitinib (all from POETYK-PSO-1)	Apremilast	Deucravacitinib	[redacted]
Total	**All patients**		**1,221**

Abbreviations: N = number of patients evaluable; QD = once daily.
Source: Summary of Clinical Efficacy, BMS Data on File[93]

[redacted][94]

B.2.3.3 Study methodology: POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE

A summary of POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE study methodology is provided in Table B.2.3.

Table B.2.3. Summary of study methodology, POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE

STUDY	POETYK-PSO-1[97]	POETYK-PSO-2[98]	POETYK-PSO-LTE[89]
Locations	154 sites in 11 countries (Canada, China, Germany, Japan, Poland, Russia, South Korea, Spain, Taiwan, UK [redacted], and the US)	191 sites in 15 countries (Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, New Zealand, Poland, Puerto Rico, Spain, Sweden, UK [redacted], and the US)	264 sites in 19 countries (Australia, Canada, China, Czech Republic, Finland, France, Germany, Hungary, Israel, Japan, Korea, New Zealand, Poland, Russian Federation, Spain, Sweden, Taiwan, United Kingdom [redacted], and the US)
Study design	Phase 3, 52-week, randomised, double-blind, placebo- and active comparator-controlled	Phase 3, 52-week, randomised, double-blind, placebo- and active comparator-controlled, with a randomised withdrawal and retreatment period, Week 24–52	Phase 3b, multi-year, multicentre, open-label study
Primary study objective	To assess whether the efficacy of deucravacitinib is superior to placebo at Week 16 in patients with moderate-to-severe plaque psoriasis		To characterise the safety and efficacy of long-term use of deucravacitinib in subjects with moderate-to-severe plaque psoriasis
Key inclusion criteria	• Adults (≥18 years) diagnosed with stable plaque psoriasis for ≥6 months (defined as no morphology changes or significant flares of disease activity in the opinion of the investigator) • Deemed by the investigator to be a candidate for phototherapy or systemic therapy • PASI ≥12, sPGA ≥3 and BSA ≥10% at Screening Visit and Day 1		
Key exclusion criteria	• No other forms of psoriasis, other immune-mediated conditions requiring current systemic immunosuppressant treatment • No history of HIV or hepatitis B or C or TB infection (latent or active) • No history of lack of response to agents with target in same pathway		
Study treatments	• Deucravacitinib 6 mg QD • Placebo • Apremilast 30 mg BID	• Deucravacitinib 6 mg QD • Placebo • Apremilast 30 mg BID	• Deucravacitinib 6 mg QD
Blinding	Treatments were blinded to patients, investigators and other study personnel. The active and placebo tablets for deucravacitinib were identical in appearance to each other, and the active and placebo tablets for apremilast were identical in appearance to each other. All tablets were supplied in blister cards or bottles with each daily dose made-up of the appropriate combination of active and/or placebo tablets to provide the correct treatment.		POETYK-PSO-LTE is an open-label study, but patients, investigators and other study personnel remained blinded to parent study treatment assignments.
Concomitant medication	• [redacted] • [redacted]		

STUDY	POETYK-PSO-1[97]	POETYK-PSO-2[98]	POETYK-PSO-LTE[89]
	[redacted]		
Prohibited and/or restricted medication	[redacted]		
Co-primary outcomes (see Table B.2.4 for outcome definitions)	Proportion of patients at Week 16 with: • sPGA 0/1 response • PASI 75 response		• AEs • Serious AEs

Key secondary outcomes (see Table B.2.4 for outcome definitions)	**Versus placebo** Proportion of patients at Week 16 with: • PASI 90 • ss-PGA 0/1 • sPGA 0 • PASI 100 • PSSD symptom score 0 • DLQI 0/1[b] • PGA-F 0/1 **Versus apremilast** Proportion of patients at Week 16 with: • sPGA 0/1 • PASI 75 • PASI 90 • ss-PGA 0/1 • sPGA 0 • PSSD symptom score 0 Change from baseline in PSSD symptom score at Week 16 Proportion of patients at Week 24 with: • sPGA 0/1 • PASI 75 • PASI 90 • sPGA 0/1 • PASI 75 • PASI 90 Proportion of patients at Week 52 with: • sPGA 0/1 • PASI 75 • PASI 90	**Versus placebo** Proportion of patients at Week 16 with: • PASI 90 • ss-PGA 0/1 • sPGA 0 • PASI 100 • PSSD symptom score 0 • DLQI 0/1[c] • PGA-F 0/1 Time to relapse until Week 52 in Week 24 PASI 75 responders[c] **Versus apremilast** Proportion of patients at Week 16 with: • sPGA 0/1 • PASI 75 • PASI 90 • ss-PGA 0/1 • sPGA 0 • PSSD symptom score 0 Change from baseline in PSSD symptom score 0 at Week 16 Proportion of patients at Week 24 with: • sPGA 0/1 • PASI 75 • PASI 90	• sPGA 0/1 response • PASI 75 response

STUDY	POETYK-PSO-1[97]	POETYK-PSO-2[98]	POETYK-PSO-LTE[89]
Other efficacy and health-related quality of life (HRQoL) outcomes	• Time to relapse • PASI 100 • BSA • PSSI • mNAPSI • Health-related quality of life: EQ-5D-3L, EQ-5D-3L VAS, SF-36, HADS, PGI-C, PGI-S		• BSA • PASI 90 • PASI 100
Pre-planned subgroups	**sPGA 0/1 and PASI 75 at Week 16:** • Geographic region • Country • Sex • Age group • Body weight • Ethnicity • Baseline sPGA score • Baseline PASI score • Baseline BSA involvement • Duration of disease (years) • Age at disease onset (years) • Prior biologic use • Prior systemic treatment for psoriasis • Prior phototherapy use		N/A

Abbreviations: AE = adverse event; BID = twice daily; BSA = body surface area; DLQI = Dermatology Life Quality Index; HADS = hospital anxiety and depression scale; HIV = human immunodeficiency virus; IRT = interactive response technology; mNAPSI = modified Nail Psoriasis; PASI = Psoriasis Area and Severity Index; PGA-F = Physician's Global Assessment-Fingernail; PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; PSSD = Psoriasis Symptoms and Signs Diary; PSSI = Psoriasis Scalp Severity Index QD = once daily; SAE = serious adverse event; SF-36 = 36-item short-form; sPGA = static Physician's Global Assessment; ss-PGA = scalp severity Physician's Global Assessment; TB = tuberculosis; UK = United Kingdom; US = United States; VAS = visual analogue scale.
[a]Previous experience with certain treatments (biologics, systemic conventional therapies, phototherapy, or topical therapy) was permitted, but not within specified timeframes prior to starting the study, or at any time during the study.
[b]Ranked as per hierarchical order of testing
[c]Ex-US hierarchy only.

Source: POETYK-PSO-1 CSR, BMS Data on File;[91] POETYK-PSO-2 CSR, BMS Data on File;[92] POETYK-PSO-LTE CSR, BMS Data on File;[94] POETYK-PSO-1 Study Protocol, BMS Data on File;[99] POETYK-PSO-2 Study Protocol, BMS Data on File[100]

Outcome descriptions and definitions

A summary of outcome descriptions and definitions is provided in Table B.2.4.

Table B.2.4. Summary of outcome definitions in POETYK-PSO-1 and POETYK-PSO-2

Category	Outcome	Description	Definition
Co-primary efficacy outcome	sPGA 0/1	5-point scale of an average assessment of all psoriasis lesions based on erythema, scaling, and induration. The sPGA measure was used to determine psoriasis severity at a single point in time (without taking into account the baseline disease condition) as clear (0), almost clear (1), mild (2), moderate (3), or severe (4).	sPGA 0/1 response is defined as sPGA score of 0 or 1 in patients with ≥2-point improvement from baseline.
	PASI 75	Measure of the average redness, thickness, and scaliness of psoriasis skin lesions (each graded on a 0-4 scale), weighted by the area of involvement (head, arms, trunk to groin, and legs to top of buttocks). PASI produces a numeric score that can range from 0 to 72, with higher PASI scores denoting more severe disease activity.	PASI 75 response is defined as ≥75% improvement from baseline in PASI score.
Secondary outcomes	PASI 90, 100	As described above.	PASI 90 and 100 response is defined as ≥90% and ≥100% improvement from baseline in the PASI score, respectively.
	ss-PGA 0/1	For patients with scalp involvement at baseline, scalp lesions were evaluated in terms of the clinical signs of redness, thickness, and scaliness and were scored on the following 5-point ss-PGA scale: 0 = absence of disease, 1 = very mild disease, 2 = mild disease, 3 = moderate disease, and 4 = severe disease.	ss-PGA 0/1 response is defined as ss-PGA score of 0 or 1 in patients with ≥2-point improvement from baseline and a baseline ss-PGA score ≥3.
	sPGA 0	As described above.	sPGA 0 is defined as sPGA score of 0.
	PSSD 0	11-item patient-reported instrument used to assess the severity of symptoms and patient-observed signs commonly associated with plaque psoriasis. PSSD assessed the severity of five symptoms (itch, pain, stinging, burning, and skin tightness) as collected in eDiaries by patients. The severity of each item was rated from 0 (absent) to 10 (worst imaginable). The PSSD symptom score is the average of the scores of the five symptom questions multiplied by 10, and a PSSD symptom score of 0 indicates an absence of symptoms.	PSSD symptom score 0 response is defined as PSSD score of 0 among patients with baseline PSSD symptom score ≥1.

Category	Outcome	Description	Definition
	DLQI 0/1	Patient-reported quality-of-life (QoL) index consisting of 10 questions concerning symptoms and feelings, daily activities, leisure, work, school, personal relationships, and treatment during the last week. Each question was scored on a 0 to 3 scale by a tick box: 0 - "not at all", 1 - "a little", 2 - "a lot", or 3 - "very much". The scores were summed and ranged from 0 (no impairment of QoL) to 30 (maximum impairment). A DLQI score of 0/1 indicates no effect at all on a patient's life.	DLQI 0/1 response is defined as DLQI score of 0 or 1 in patients with baseline DLQI score ≥2.
	PGA-F	In patients with psoriatic fingernail involvement at baseline, the overall condition of the fingernails was rated on a 5-point scale (0 = clear, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe) to assess severity and subsequent improvement.	PGA-F 0/1 response is defined as PGA-F score of 0 or 1 in patients with ≥2-point improvement from baseline and a baseline PGA-F score ≥3.
	Time to relapse	PASI scores after Week 24 were used to determine whether PASI 75 responders at Week 24 had relapsed after Week 24 (study POETYK-PSO-2 only). Time to relapse was only measured until 32 weeks (224 days) after Week 24; if relapse was found after the follow-up resulting from the delayed visits, it was censored at Day 224.	≥50% loss of Week 24 PASI percent improvement from baseline in Week 24 deucravacitinib PASI 75 responders after switching to placebo through Week 52.
Other outcomes	BSA	Estimated using the handprint method with the size of a patient's handprint (including finger and thumb) representing 1% of the BSA involved.	Total BSA (100%) broken-down by body region was as follows: head and neck = 10% (10 handprints), upper extremities = 20% (20 handprints), trunk including axillae and groin = 30% (30 handprints), and lower extremities including buttocks = 40% (40 handprints).
	EQ-5D-3L/EQ-5D 3L VAS	The questionnaire includes 2 components: a descriptive system and a VAS. EQ-5D-3L: Using a system of five health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and three levels (1 = no problems, 2 = some/moderate problems, and 3 = extreme problems) for each dimension, it provides a utility for a total of 243 health states.	A population-based utility can be attached to each health state from the EQ-5D-3L to inform economic assessments of interventions. Overall scores range from 0–1 where 0 = health equivalent to death and 1 = perfect health. VAS allows respondents to rate their own current health on a 100-point scale ranging from "best imaginable" to "worst imaginable".

Abbreviations: BSA = body surface area; DLQI = Dermatology Life Quality Index; EQ-5D-3L = EuroQol 5-Dimensions 3-Level; PASI = Psoriasis Area and Severity Index; PGA-F = Physician's Global Assessment-Fingernail; PSSD = Psoriasis Symptoms and Signs Diary; sPGA = static Physician's Global Assessment; ss-PGA = scalp severity Physician's Global Assessment; VAS = Visual Analogue Scale.
Source: Armstrong et al. 2021;[90] Summary of Clinical Efficacy, BMS Data on File.[93]

Patient disposition

Pooled analysis POETYK-PSO-1 and POETYK-PSO-2

Across POETYK-PSO-1 and POETYK-PSO-2, a total of 1,686 patients (including [redacted] patients in the UK) were randomised to receive deucravacitinib (843 patients), placebo (421 patients) and apremilast (422 patients) and were included in the Full Analysis Set (FAS) for the efficacy analysis. [redacted].[93] A consort diagram of patient disposition for the pooled analysis (Week 0–24) is provided in Appendix D. The disposition of patients up to Week 24 was generally consistent across treatment groups, within and across the studies.[93] Due to the differences in study designs after Week 24, the details of patient disposition in the individual studies during Week 24–52 are provided separately in Appendix D.

POETYK-PSO-LTE

[redacted] of patients were ongoing in the study. Of the 1,221 patients who continued POETYK-PSO-LTE, [redacted] patients reached Week 48 and [redacted] patients reached Week 60. The median duration of exposure to deucravacitinib in POETYK-PSO-LTE was [redacted][93] Note that patients in POETYK-PSO-LTE could have received deucravacitinib for [redacted] in POETYK-PSO-1 and POETYK-PSO-2 prior to enrolling POETYK-PSO-LTE (see section B.2.3.1).[94] A table outlining the patient disposition for POETYK-PSO-LTE is provided in Appendix D.

Patient baseline characteristics

Pooled analysis POETYK-PSO-1 and POETYK-PSO-2

A summary of baseline characteristics for the pooled analysis is provided in Table B.2.5. For the individual pivotal studies, these are outlined in Appendix M. The baseline characteristics of patients were generally well balanced in the pooled analysis and were consistent with those in the individual studies.[93] Prior psoriasis treatment experience was generally consistent across POETYK-PSO-1 and POETYK-PSO-2, as well as across its treatment groups.[93] In POETYK-PSO-1, a slightly greater proportion of subjects had prior systemic biologic use compared with POETYK-PSO-2; in POETYK-PSO-2, a slightly greater proportion of subjects were naive to prior systemic treatment compared with POETYK-PSO-1, which may be attributed to regional distribution of the POETYK-PSO-1 and POETYK-PSO-2 study populations. When comparing POETYK trials (pooled analysis, see Table B.2.5) with other studies in psoriasis from the last decade, proportions of patients with prior systemic biologic experience were similar (range for majority of studies: 10-40%; see Appendix D, section 1.3). Trial populations were also similar with regards to disease severity at baseline (mean PASI score: 17-25 in most trials) and disease duration (11-23 years in most trials). The mean body weight of patients across psoriasis trials ranged from 80 and 100 kg in most studies. Regarding race, most trials include White patients as the highest proportion of their cohort. The patients in POETYK trials were therefore considered to be in line with other psoriasis trials, supporting generalisability of POETYK patients to adult patients in the UK with moderate to severe plaque psoriasis. This was also confirmed by a clinical expert.

Table B.2.5. Baseline characteristics (pooled analysis POETYK-PSO-1 and POETYK-PSO-2)

Parameter	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)	Total (N=1,686)
Age, years, mean (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg, mean (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)				
White	[redacted]	[redacted]	[redacted]	[redacted]
Black or AA	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration, years, mean	[redacted]	[redacted]	[redacted]	[redacted]
sPGA score, n (%)				
3 = moderate	[redacted]	[redacted]	[redacted]	[redacted]
4 = severe	[redacted]	[redacted]	[redacted]	[redacted]
PASI, mean	[redacted]	[redacted]	[redacted]	[redacted]
BSA, mean	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic treatment use, n (%)				
Naïve to prior systemic treatment[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic treatment use[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic biologic use[b], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior phototherapy use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AA = African American; BSA = body surface area; max = maximum; min = minimum; n = number of patients in the category; N = number of patients evaluable; PASI = Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment.

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

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

Source: Summary of Clinical Efficacy, BMS Data on File.[93]

POETYK-PSO-LTE

The baseline demographics and disease characteristics of POETYK-PSO-LTE are based on the baseline values in POETYK-PSO-1 and POETYK-PSO-2 and are provided in Table B.2.6.

Table B.2.6. Baseline demographics and disease characteristics (POETYK-PSO-LTE)

Characteristic	Stratification by last treatment received			Total (n = 1,221)
	Deucravacitinib to deucravacitinib (n=944)	Placebo to deucravacitinib (n=80)	Apremilast to deucravacitinib (n=197)	
Age, years, mean (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg, mean (min, max)				
Baseline in parent studies	[redacted]	[redacted]	[redacted]	[redacted]
Last visit in parent studies	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)				
White	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration, years, mean (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
sPGA, n (%)				
Baseline in parent studies				
3 = moderate	[redacted]	[redacted]	[redacted]	[redacted]
4 = severe	[redacted]	[redacted]	[redacted]	[redacted]
Last visit in parent studies				
3 = moderate	[redacted]	[redacted]	[redacted]	[redacted]
4 = severe	[redacted]	[redacted]	[redacted]	[redacted]
PASI, mean (min, max)				
Baseline in parent studies	[redacted]	[redacted]	[redacted]	[redacted]
Last visit in parent studies	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: min = minimum; max = maximum; n = number of patients in the category; N = number of patients evaluable; PASI = Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

B.2.3.4 Expert opinion

An advisory board was held on 7 July 2021 and was attended by five dermatology experts, one general practitioner and two health economists. The objectives of the meeting are outlined below, in conjunction with the discussion results.

Identification and selection

The panel of experts was chosen by the company to represent a spectrum of dermatology expert opinions from a range of different backgrounds and perspectives. These included 'thought leader' dermatologists from UK secondary and tertiary care centres with research backgrounds, dermatologists with extensive experience in the clinical management of patients with psoriasis and prescribing advanced treatments, and a GP with a special interest in dermatology and experience in patient pathways. The health economists were chosen based on their experience and knowledge of NICE. The experts also represented a good geographical spread within England and Wales.

Results

Meeting objective 1: To gain insights and opinion on currently available deucravacitinib data
• Phase 2 and phase 3 data for deucravacitinib are [redacted], particularly for an oral treatment, as shown by a significant improvement in PASI and sPGA response compared with placebo and apremilast at Week 16 and Week 24. • The overall safety profile looks [redacted] and different to that of the [redacted].
Meeting objective 2 & 3: To identify unmet needs and treatment gaps in psoriasis and to identify psoriasis patient types who would benefit most from deucravacitinib, in the context of the current UK treatment algorithm and patient expectations of treatment
• Psoriasis patients with the most substantial unmet need currently encompass patients with [redacted] • The key barriers to treating these patients are: o NICE guidelines: the disease severity threshold for using systemic biologics in psoriasis patients set by NICE is relatively high, compared with other dermatological conditions such as hidradenitis suppurativa or eczema, which limits their use in patients with lower PASI scores (<10). o Practical, social and logistical factors, such as issues with transporting medication to more rural areas or access issues to specialist clinics. o GP education, time, resource, funding, and communication between primary and secondary care are all challenges to successfully implementing shared care. • Deucravacitinib should be available for [redacted] There is an unmet need for treating patients early, preferably in primary care. Disease duration has an impact on response rate and can prevent comorbid conditions.
Meeting objective 4: To identify the key considerations for treatment decision-making with systemic treatments
• While overall psoriasis clearance should be the focus, advisers believe that there is some value in assessing efficacy on nail, scalp or genital psoriasis to show that difficult-to-treat areas are considered, as these are often of more concern to patients because they are visible. Additionally, key considerations should include: o Comorbidities including obesity, PsA and depression. o Understanding which PASI scores may be best suited to specific treatments, including accounting for low PASI score patients with high DLQI. o The COVID-19 pandemic has affected the way in which many patients are managed, and there are possible advantages to using treatments without the need for regular follow-up appointments and monitoring. o Speed of onset of action is vital for a select group of patients.

Meeting objective 5: To gather insights on positioning of deucravacitinib compared with other systemic therapies
• The oral route of administration was seen as [redacted] by several advisers, as there are currently a [redacted] Specifically, oral administration can be [redacted] • Advisers suggested two versions of the sequencing scenarios that may align more closely with clinical practice: [redacted] • It was unclear to the advisers where [redacted]
Meeting objective 6: To gather opinions on different positioning strategies and the impact of cost-effectiveness on each, and key insights surrounding key modelling-based questions
See section B.3.14

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis populations in POETYK-PSO-1 and POETYK-PSO-2

The analysis populations for the phase 3 studies are outlined in Table B.2.7. Analysis sets in POETYK-PSO-1 and POETYK-PSO-2 included the FAS analysed as a primary population for the efficacy analyses (individual and pooled), andthe 'as-treated' population which was used for the safety analyses.[91, 92]

Table B.2.7. Analysis populations in the individual POETYK-PSO-1 and POETYK-PSO-2 studies

Analysis Population	Deucravacitinib	Placebo	Apremilast	Total
Full Analysis Set	All patients who were randomised following intent-to-treat principal			
POETYK-PSO-1 (N)	332	166	168	666
POETYK-PSO-2 (N)	511	255	254	1,020
Per Protocol Set	A subset of the Full Analysis Set of patients who were compliant with study treatment and who did not have any relevant protocol deviations that may have impacted the co-primary efficacy outcome assessments			
POETYK-PSO-1 (N)	[redacted]	[redacted]	[redacted]	[redacted]
POETYK-PSO-2 (N)	[redacted]	[redacted]	[redacted]	[redacted]
As-treated population (safety)	All randomised patients who took at least one dose of study treatment			
POETYK-PSO-1 (N)	[redacted]	[redacted]	[redacted]	[redacted]
POETYK-PSO-2 (N)	[redacted]	[redacted]	[redacted]	[redacted]
Biomarker population	All randomised patients who took at least one dose of study treatment and had at least one post-treatment biomarker measurement			
POETYK-PSO-1 (N)	[redacted]	[redacted]	[redacted]	[redacted]
POETYK-PSO-2 (N)	[redacted]	[redacted]	[redacted]	[redacted]
PK population	All randomised patients who took at least one dose of deucravacitinib and had any available concentration data			

Analysis Population	Deucravacitinib	Placebo	Apremilast	Total
POETYK-PSO-1 (N)	[redacted]	[redacted]	[redacted]	[redacted]
POETYK-PSO-2 (N)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PK = pharmacokinetic; n = number of patients in the category; N = number of patients evaluable.
Source: POETYK-PSO-1 CSR, BMS Data on File[91]; POETYK-PSO-2 CSR, BMS Data on File.[92]

B.2.4.2 Statistical analysis

For pooled analysis, the statistical methodology applied was identical to that used in the individual studies (see Table B.2.8).[99, 100] Estimates of treatment differences and odd ratios are provided along with 95% CIs.[99, 100] Statistically significant" refers to p-values ≤0.025 for treatment comparisons that were subject to multiplicity adjustment in the pre-defined hierarchical testing scheme in the individual studies. The term "nominally significant" refers to p-values ≤0.05 for treatment comparisons that were not subject to multiplicity adjustment, either because the treatment comparison was not controlled for Type I error (i.e. not included in hierarchical testing) or because the treatment comparison was a post-hoc analysis.[93, 99, 100]

For POETYK-PSO-LTE ([redacted]; see section B.2.3.2) no formal statistical testing was conducted. No imputation methods were applied.[94]

Table B.2.8. Summary of statistical analyses (individual POETYK-PSO-1 and POETYK-PSO-2 studies)

Statistical analysis
Co-primary outcomes sPGA 0/1 and PASI 75 • Tests of significance of deucravacitinib 6 mg QD versus placebo at Week 16 for the co-primary outcomes were 2-sided with a significance level of 0.05 (primary family) • The analysis model for the co-primary efficacy outcomes at Week 16, used stratified Cochran-Mantel-Haenszel tests stratified by the factors used for randomisation to compare the response rates of deucravacitinib to placebo for the FAS • If expected cell counts were not sufficient for each strata level, then strata levels were combined for the analysis. The odds ratio (ratio of odds in the deucravacitinib group to the odds in placebo group) and the corresponding 2-sided 95% CIs were provided • If significant for both co-primary outcomes, testing would proceed for the secondary family of key secondary outcomes **Key secondary outcomes** • A hierarchical testing method was used for the testing of key secondary outcomes • Alpha-controlled testing could proceed to the next key secondary outcome only if the null hypothesis was rejected at Type 1 error = 0.025 • If an outcome failed at any step, then all subsequent comparisons in that testing branch were considered descriptive Two separate hierarchies were provided: one for US submissions and one for Ex-US submissions (the hierarchy ranking is provided in Table B.2.3)
Sample size, power calculation
• Sample size considerations were based on providing exposure in sufficient numbers of patients for the deucravacitinib 6 mg QD arm in both studies **POETYK-PSO-1**

• A total sample size of 600 patients randomised in a blinded manner in a 2:1:1 ratio to deucravacitinib 6 mg QD, apremilast 30 mg BID, and placebo respectively (300 patients initially to deucravacitinib 6 mg QD and 150 patients randomised each to placebo and apremilast) provided adequate power to compare deucravacitinib 6 mg QD with placebo for each co-primary efficacy outcome (proportion of patients with sPGA 0/1 and PASI 75 at Week 16) • Assuming a 2-sided chi-square test with an α = 0.05 and expected response rates of 60% and 10% for deucravacitinib and placebo, respectively, this study had >99% power to test superiority of deucravacitinib to placebo for each of the co-primary efficacy outcomes
POETYK-PSO-2 • A total sample size of 1,000 patients randomised in a blinded manner in a 2:1:1 ratio to deucravacitinib 6 mg QD, apremilast 30 mg BID, and placebo respectively (500 patients initially to deucravacitinib 6 mg QD and 250 patients randomised each to placebo and apremilast) provided adequate power to compare deucravacitinib 6 mg QD with placebo for each co-primary efficacy outcome (proportion of patients with sPGA 0/1 and PASI 75 at Week 16) • Assuming a 2-sided chi-square test with an α = 0.05 and expected response rates of 60% and 35% for deucravacitinib and apremilast, respectively, this study had >99% power to test superiority of deucravacitinib to apremilast for each of the co-primary efficacy outcomes
Data management, patient withdrawals
Missing data and discontinuations • Non-responder imputation (NRI) was used for co-primary and secondary efficacy binary outcomes for patients who discontinued treatment or study prior to timepoint of comparison or had missing outcome data for any reason at timepoint of comparison, hence there was an implicit composite estimate and analysis strategy in place • For continuous key secondary outcomes, a modified baseline observation carried forward approach was used for missing data

Abbreviations: BID = twice daily; CI = confidence interval; FAS Full Analysis Set; IRT = interactive response technology; LS = least-squares; NRI = non-responder imputation; QD = once daily; PASI = Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment; US = United States.
Source: POETYK-PSO-1 Study Protocol, BMS Data on File[99]; POETYK-PSO-2 Study Protocol, BMS Data on File.[100]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The quality assessments of POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE are provided in Appendix D. POETYK trials were well-designed trials with appropriate randomization and concealment of treatment allocation. The groups in the trials were similar at the outset of the study in terms of prognostic factors and there were no unexpected imbalances in drop-outs between groups. All planned outcomes were reported.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Overview

POETYK-PSO-1 and POETYK-PSO-2 both achieved their co-primary efficacy endpoints demonstrating robust clinical response (PASI 75 and sPGA 0/1 response at Week 16) in patients with moderate-to-severe plaque psoriasis, including superiority to apremilast.[91, 92] Interim results from the subsequent extension study (POETYK-PSO-LTE; [redacted]) suggest that deucravacitinib [redacted], with primary endpoints covering safety endpoints only (see section B.2.10).[94]

Table B.2.9 outline the sections in which the clinical effectiveness results of the relevant trials are presented in more detail.

Table B.2.9. Overview of outcomes presented

Outcomes	Section
Short- (Week 16) and mid-term (Week 24) pooled efficacy data of the co-primary and related outcomes	Section B.2.6.2
Long-term efficacy data on maintenance and durability of response (Week 24 through Week 52) from the individual studies (POETYK-PSO-1 and POETYK-PSO-2)	Section B.2.6.3
Short- (Week 16) and mid-term (Week 24) pooled efficacy data of difficult-to-treat regions	Section B.2.6.4
Short- (Week 16) and mid-term (Week 24) pooled health-related quality of life data	Section B.2.6.5
Interim efficacy results from POETYK-PSO-LTE ([redacted])	Section B.2.6.6

B.2.6.2 Short- and mid-term pooled efficacy: co-primary and related outcomes

PASI-related efficacy outcomes

In the pooled analysis, a greater proportion of deucravacitinib-treated patients achieved PASI 75 response and the [redacted] compared with placebo at Week 16, and compared with apremilast at Week 16 and Week 24 [redacted] (see Figure B.2.3 and Table B.2.10).[93] Comparison to placebo at Week 24 was not possible given that no patients received placebo at 24 weeks (see trial design in section B.2.3). These results indicate that patients on deucravacitinib benefitted from clinically meaningful improvements in their psoriasis compared to the placebo and apremilast groups. The trends observed in the pooled analysis were consistent with those observed in the individual studies and are outlined in detail in Appendix N.[93]

Figure B.2.3. PASI 75 response by treatment group Week 1–24 (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS)

Abbreviations: FAS = Full analysis Set; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

Table B.2.10. Results of PASI-related outcomes (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS)

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
PASI 75 at Week 16, n (%)[a]			
Difference (95% CI)			
Odds ratio (95% CI)			
p-value[b]			
PASI 75 at Week 24, n (%)		-	
Difference (95% CI)		-	
Odds ratio (95% CI)		-	
p-value[b]		-	
PASI 90 at Week 16, n (%)			
Difference (95% CI)			
Odds ratio (95% CI)			
p-value[b]			
PASI 90 at Week 24, n (%)		-	
Difference (95% CI)		-	
Odds ratio (95% CI)		-	
p-value[b]		-	
PASI 100 at Week 16, n (%)			

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
PASI 100 at Week 24, n (%)	[redacted]	-	[redacted]
Difference (95% CI)		-	[redacted]
Odds ratio (95% CI)		-	[redacted]
p-value[b]		-	[redacted]

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; n = number of patients in the category; N = number of patients evaluable; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index.
[a] Co-primary efficacy outcome in the individual studies.
[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

sPGA-related efficacy outcomes

In the pooled analysis, a greater proportion of deucravacitinib-treated patients achieved sPGA 0/1 (clear/almost clear) [redacted] compared with placebo at Week 16, and compared with apremilast at Week 16 and Week 24 [redacted] (see Figure B.2.4 and

Table B.2.11).[93] Similarly to PASI 75, comparison to placebo at Week 24 was not possible given that no patients received placebo at 24 weeks (see trial design in section B.2.3). The trends observed in the pooled analysis were consistent with those observed in the individual studies and are outlined in detail in Appendix N.[91, 92]

Figure B.2.4. sPGA 0/1 response by treatment group Week 1–24 (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS)

Abbreviations: FAS = Full analysis Set; NRI = non-responder imputation; sPGA = static Physician's Global Assessment.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

Table B.2.11. Results sPGA-related outcomes (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS)

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
sPGA 0/1 at Week 16, n (%)[a]	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
sPGA 0/1 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
sPGA 0 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
sPGA 0 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; n = number of patients in the category; N = number of patients evaluable; NRI = non-responder imputation; sPGA = static Physician's Global Assessment.
[a] Co-primary efficacy outcomes in the individual studies.
[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

Relevance of timepoints in response assessment

In POETYK-PSO-1 and POETYK-PSO-2 both the PASI 75 response and sPGA 0/1 score were better at Week 24 than at Week 16 for deucravacitinib, indicating that assessment at Week 16 might be premature.[93] This is due to the relatively slower onset of response of deucravacitinib (see section B.2.6.3) which BMS postulates is due to the mechanism of action of selective inhibition of TYK2 resulting in the delayed downstream downregulation of IL-23 and IL-17. BMS therefore suggests that it would be more appropriate to assess the efficacy of deucravacitinib at Week 24. In clinical practice, it would be unreasonable to switch a patient from a treatment that is working; such a switch is likely to have a negative impact on the patient, increases healthcare resource use and ultimately reduces the future potential options

for treatment. Assessment at Week [redacted] is also consistent with the deucravacitinib draft SmPC that states: [redacted][13]

For context, a similar situation presented itself in the tildrakizumab reSURFACE studies where PASI 75 response was statistically significantly higher at Week 28 compared with Week 12.[73] The tildrakizumab marketing authorisation states that if there is no response after 28 weeks of treatment, stopping tildrakizumab should be considered.[13] In the NICE appraisal of tildrakizumab (TA575), the clinical expert advised that assessment at 12 weeks would be premature, and they would prefer to minimise the risk of a patient switching from a potentially effective treatment and it would be more appropriate to assess response at Week 28.[73] As such, the company suggested an assessment time point for deucravacitinib at 24 weeks.

B.2.6.3 Long-term maintenance and durability of response through Week 52

A consistent increase in PASI 75 and sPGA 0/1 response rates from Week 1 to Week 24 was observed, as reported for the pooled analysis in section B.2.6.2 and individual trials in Appendix N. Specifically, in POETYK-PSO-1, PASI 75 response in patients initially randomised to receive deucravacitinib at baseline was [redacted] at week 16 and continued to increase to week 24 ([redacted]; see Figure B.2.6).

Deucravacitinib demonstrated durable efficacy from week 24 through to week 52. For the patients who achieved PASI 75 at 24 weeks, this PASI 75 response was maintained or increased through to week 52 in [redacted] and [redacted] of patients in POETYK PSO-1 and POETYK PSO-2, respectively [91, 92] (see Table B.2.12 and Figure B.2.5.)[93] Similar trends were seen for sPGA 0/1 response, with [redacted] and [redacted] patients maintaining their response from week 24 through to week 52 in POETYK PSO-1 and POETYK PSO-2, respectively.

Table B.2.12. Maintenance of response at Week 52 among Week 24 responders NRI

Efficacy endpoint at Week 52	POETYK-PSO-1	POETYK-PSO-2
PASI 75 Responders, n (%)	[redacted]	[redacted]
PASI 90 Responders, n (%)	[redacted]	[redacted]
PASI 100 Responders, n (%)	[redacted]	[redacted]
sPGA 0/1 Responders, n (%)	[redacted]	[redacted]

Abbreviations: NR = not reported; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index.
Source: POETYK-PSO-1 CSR, BMS Data on File[91]; POETYK-PSO-2 CSR, BMS Data on File [92]

Figure B.2.5. PASI 75 response: among Week 24 PASI 75 responders NRI (POETYK-PSO-2)

Abbreviations: CI = confidence interval; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

Among patients who switched from apremilast to deucravacitinib at Week 24, [redacted] through to Week 52 and reached [redacted] Among patients who switched from placebo to deucravacitinib at week 16, similar rates of PASI 75 responses were also reached at week 52 (see Figure B.2.6). Results from POETYK-PSO-2 were consistent with POETYK-PSO-1.[93]

Figure B.2.6. PASI 75 response: Week 1 through Week 52 NRI (POETYK-PSO-1)

Abbreviations: APR = apremilast; DEUC = deucravacitinib; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index; PBO = placebo.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

Longer-term maintenance of response was demonstrated by interim data ([redacted]) from POETYK-PSO-LTE (see section B.2.6.6).

Persistence of PASI 75 and sPGA 0/1 response off treatment was measured in the randomised withdrawal arm of the POETYK-PSO-2 (see Table B.2.13).[92] Of patients who had a PASI 75 response to deucravacitinib at week 24 who then discontinued treatment, [redacted] maintained a PASI 75 response at Week 52 (see Figure B.2.5). Notably, some patients who lost response later recovered response by Week 52.

After scheduled discontinuation of deucravacitinib at week 24, the median time to drop below PASI 75 response was [redacted]. By comparison, the median time to loss of PASI 75 response in those who discontinued apremilast at 24 weeks [redacted].[93] Median time to relapse for the deucravacitinib group (defined as >50% loss of week 24 PASI percent improvement from baseline) [redacted] (see Figure B.2.5 and Table B.2.13).

Table B.2.13. Time to first loss of PASI 75 and sPGA 0/1 response (POETYK-PSO-2)

Efficacy endpoint	Deucravacitinib → deucravacitinib (maintenance group) n = 145	Deucravacitinib → placebo (withdrawal group) n = 150	Apremilast → placebo N=95
Subjects who lost **PASI 75** response, n (%)	[redacted]	[redacted]	[redacted]
Median time (95% CI) to loss (days)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Subjects who lost **sPGA 0/1** response, n (%)	[redacted]	[redacted]	[redacted]
Median time (95% CI) to loss (days)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Subjects who relapsed, n (%)	[redacted]	[redacted]	[redacted]
Median time (95% CI) to relapse (days)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]

[a]Median time loss cannot be calculated as < 50% of subjects had response loss through Week 52.
p-value was obtained using a stratified Cochran-Mantel-Haenszel test. Nominally significant p-value is designated using italicised type.
Abbreviations: CI = confidence interval; N/A = Not available; PASI = Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

B.2.6.4 Short- and mid-term pooled efficacy: difficult-to-treat regions

Scalp psoriasis

In the pooled analysis, [redacted] (absence of disease/very mild disease) [redacted] at Week 16 [redacted] (see Table B.2.14).[93] The trends observed in the pooled analysis were consistent with those observed in the individual studies.[91, 92] These results suggest that the [redacted]

[redacted] (see section B.2.3.4).

Table B.2.14. Results ss-PGA at Week 16 and Week 24 (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS)

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
Baseline, n[a]	[redacted]	[redacted]	[redacted]
ss-PGA 0/1 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
ss-PGA 0/1 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; n = number of patients in the category; N = number of patients evaluable; NRI = non-responder imputation; ss-PGA = scalp severity Physician's Global Assessment.
[a] Number of patients with a baseline ss-PGA score ≥3.
[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

Fingernail psoriasis

In the pooled analysis, among patients with moderate-to-severe fingernail psoriasis at baseline (PGA-F ≥3), [redacted] (see Table B.2.15).[93] The trends observed in the pooled analysis were consistent with those observed in the individual studies.[91, 92] These results suggest that [redacted] This outcome was further supported to be of importance [redacted] (see section B.2.3.4).

Table B.2.15. Results PGA-F at Week 16 and Week 24 (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS)

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
Baseline, n[a]	[redacted]	[redacted]	[redacted]
PGA-F 0/1 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
PGA-F 0/1 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; n = number of patients in the category; N = number of patients evaluable; NRI = non-responder imputation; PGA-F = Physician's Global Assessment-Fingernail.
[a] Number of patients with a baseline PGA-F score ≥3.
[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

B.2.6.5 Short- and mid-term health-related quality of life

PSSD

In the pooled analysis, [redacted] compared with placebo [redacted] and compared with apremilast at Week 16 ([redacted]) and at Week 24 ([redacted]) (see Table B.2.16).[93, 101, 102] Deucravacitinib [redacted] compared with placebo and apremilast at Week 16 and 24 [redacted][93, 101, 102] The trends observed in the pooled analysis were consistent with those observed in the individual studies and are outlined in detail in Appendix N.[91, 92]

The daily symptoms of psoriasis (e.g., itching, pain and burning) can have a substantial negative impact on the HRQoL of patients with moderate-to-severe plaque psoriasis. [redacted] that are of concern to patients (itching, pain, stinging, burning, and skin tightness) compared with placebo and apremilast measured by the PSSD symptom score.[93, 101, 102] The greatest symptom improvement was consistently observed for the itch domain with deucravacitinib treatment.[93, 101, 102]

Table B.2.16. Results PSSD-related outcomes (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS), for PSSD symptom score 0 and ANCOVA/(mBOCF) for change from baseline PSSD

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
Baseline, n[a]	[redacted]	[redacted]	[redacted]
PSSD symptom score 0 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[c]		[redacted]	[redacted]
PSSD symptom score 0 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[c]		[redacted]	[redacted]
Baseline, n[b]	[redacted]	[redacted]	[redacted]
Mean at baseline (SD)	[redacted]	[redacted]	[redacted]
Change from baseline in PSSD symptom score at Week 16			
Adjusted mean change from baseline (SE) at Week 16	[redacted]	[redacted]	[redacted]

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
Adjusted mean difference (95% CI)		[redacted]	[redacted]
p-value[c]		[redacted]	[redacted]
Change from baseline in PSSD symptom score at Week 24			
Adjusted mean change from baseline (SE) at Week 24	[redacted]	[redacted]	[redacted]
Adjusted mean difference (95% CI)		[redacted]	[redacted]
p-value[c]		[redacted]	[redacted]

Abbreviations: ANCOVA = analysis of covariance; baseline = baseline; CI = confidence interval; mBOCF = modified baseline observation carried forward; n = number of patients in the category; N = number of patients evaluable; NRI = non-responder imputation; PSSD = Psoriasis Symptoms and Signs Diary; SD = standard deviation; SE = standard error.
[a] = PSSD symptom score ≥1.
[b] = Number of patients with PSSD symptom score at baseline with ≥ 1 score post baseline.
[c] = p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

DLQI

The mean DLQI score at baseline across the treatment groups was [redacted], which represents a [redacted][93] Deucravacitinib achieved [redacted] in the impact of psoriasis on HRQoL at Week 16 (DLQI 0/1). Specifically, in the pooled analysis [redacted] achieved a DLQI 0/1 score (no effect at all on patient's HRQoL) compared with placebo and apremilast at Week 16 ([redacted]) (see Table B.2.17).[93] The trends observed in the pooled analysis were consistent with those observed in the individual studies and are outlined in detail in Appendix N.[91, 92]

Table B.2.17. Results DLQI 0/1 (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS)

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
Baseline, n[a]	[redacted]	[redacted]	[redacted]
DLQI 0/1 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]

Abbreviations: CI = confidence interval; DLQI = Dermatology Life Quality Index; FAS = Full Analysis Set; n = number of patients in the category; N = number of patients evaluable; NRI = non-responder imputation.
[a] Number of patients with baseline DLQI score ≥2.
[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

EQ-5D-3L/EQ-5D-3L VAS

In the pooled analysis, the adjusted mean change from baseline in the EQ-5D-3L VAS score [redacted] compared with placebo at Week 16 ([redacted], and compared with apremilast at Week 16 ([redacted] and at Week 24 ([redacted]) (see Table B.2.18).[93] The trends observed in the pooled analysis were generally consistent with those observed in the individual studies and are outlined in detail in Appendix N.[91, 92]

Mean change from baseline in EQ-5D-3L was not included in the pooled analysis. In the individual studies [redacted] in the mean change from baseline in EQ-5D-3L was observed with [redacted] compared with placebo ([redacted]) and apremilast ([redacted]).

Table B.2.18. Results EQ-5D-3L VAS at Week 16 and Week 24 (pooled POETYK-PSO-1 and POETYK-PSO-2) – ANCOVA/(mBOCF)

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
Baseline, n[a]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]
Adjusted mean change from baseline at Week 16 (SE)	[redacted]	[redacted]	[redacted]
Adjusted mean difference (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
Adjusted mean change from baseline at Week 24 (SE)	[redacted]	[redacted]	[redacted]
Adjusted mean difference (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-3L VAS = EuroQol 5-Dimensions 3-Level Visual Analogue Scale; mBOCF = modified baseline observation carried forward; n = number of patients in the category; N = number of patients evaluable; SD = standard deviation; SE = standard error.
[a] Number of patients with an EQ-5D-3L VAS score at baseline and with ≥1 score post baseline.
[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

B.2.6.6 Interim results of POETYK-PSO-LTE

Data for key efficacy outcomes were available from Week 0 (in the parent study, POETYK-PSO-1 and POETYK-PSO-2) [redacted]. As the study is ongoing, many patients have not reached assessment timepoints [redacted]. Therefore, data for [redacted] are provided in the following sections. Overall, the results from the long-term extension study, POETYK-PSO-LTE, support the key findings from the [redacted] (POETYK-PSO-1 and POETYK-PSO-2, as outlined in sections B.2.6.2) and demonstrate [redacted] of treatment with deucravacitinib [redacted][93] Results from [redacted]

PASI

The PASI 75 responses for patients in the "deucravacitinib to deucravacitinib" group were [redacted] in POETYK-PSO-LTE (see Figure B.2.7 and Table B.2.19), [redacted] results seen through [redacted] in the pooled analysis (see section B.2.6.3).[93]

Patients in the "placebo to deucravacitinib" group [redacted] and a response [redacted] of patients in the "deucravacitinib to deucravacitinib" group [redacted]. Similarly, PASI 75 responses [redacted] among patients in the "apremilast to deucravacitinib" group.[93] Additionally, the [redacted] and [redacted] response rates in the total population were [redacted] from Week [redacted] and [redacted] respectively) through Week [redacted] and [redacted] respectively) and Week [redacted] and [redacted], respectively).[93]

Figure B.2.7. PASI 75 response[a,b] over time (POETYK-PSO-LTE)

Abbreviations: DEUC-DEUC = deucravacitinib: deucravacitinib; PBO-DEUC = placebo: deucravacitinib; APR-DEUC = apremilast: deucravacitinib; PASI = Psoriasis Area and Severity Index.

[a] ≥75% improvement from baseline in the PASI score

[redacted] Note: [redacted] discontinued the treatment [redacted] (database lock efficacy: [redacted])

Source: Summary of Clinical Efficacy, BMS Data on File.[93]

Table B.2.19. PASI 75 response[a] over time (POETYK-PSO-LTE)

Group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deucravacitinib → deucravacitinib, (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo → deucravacitinib, (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast → deucravacitinib, (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total, (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: n = number of patients in the category; N = number of patients evaluable; PASI = Psoriasis Area and Severity Index.

[a] ≥75% improvement from baseline in the PASI score.

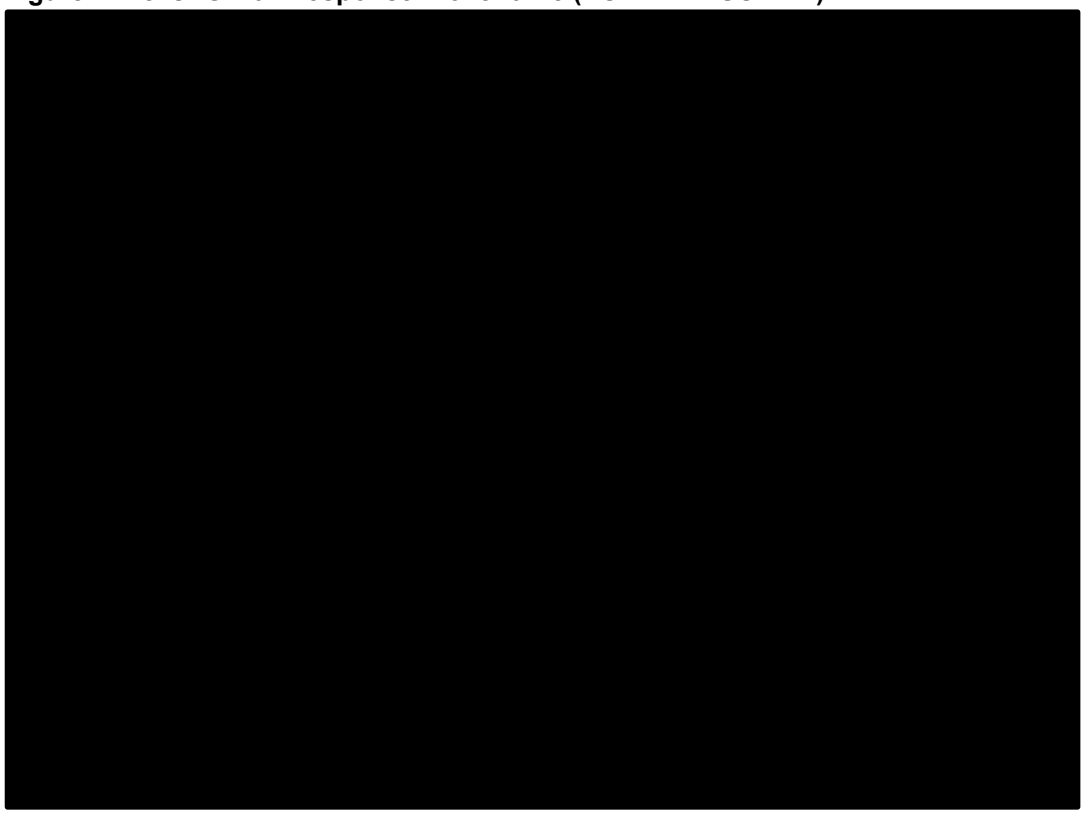
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

sPGA 0/1

The sPGA 0/1 responses in the "deucravacitinib to deucravacitinib" group [redacted] (see Figure B.2.8 and Table B.2.20)

[redacted] seen through Week 52 in the pooled analysis (see section B.2.6.3). Patients in the "placebo to deucravacitinib" [redacted] as early as [redacted] and had a response [redacted] in the "deucravacitinib to deucravacitinib" group [redacted]. Similarly, sPGA 0/1 response was [redacted] among patients in the "apremilast to deucravacitinib" group.[93]

Figure B.2.8. sPGA 0/1 response[a,b] over time (POETYK-PSO-LTE)



Abbreviations: DEUC-DEUC = deucravacitinib: deucravacitinib; PBO-DEUC = placebo: deucravacitinib; APR-DEUC = apremilast: deucravacitinib; sPGA = static Physician's Global Assessment.
[a] Score of 0/1 in patients with ≥2-point improvement from baseline.
[redacted] Note: (database lock efficacy: [redacted])
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

Table B.2.20. sPGA 0/1 response[a] over time (POETYK-PSO-LTE)

Group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deucravacitinib → deucravacitinib, (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo → deucravacitinib, (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast → deucravacitinib, (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total, (n/N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: n = number of patients in the category; N = number of patients evaluable; sPGA = static Physician's Global Assessment.
[a] Score of 0/1 in patients with ≥2-point improvement from baseline.
Source: Summary of Clinical Efficacy, BMS Data on File.[93]

B.2.6.7 POETYK trials efficacy conclusions

At 16 and 24 weeks, deucravacitinib demonstrated a robust efficacy profile, including superiority to and maintenance of response versus placebo and apremilast in the pooled analysis of two Phase 3 trials (POETYK-PSO-1 and POETYK-PSO-2) in patients with moderate-to-severe psoriasis. Specifically, a significantly greater number of patients treated with deucravacitinib achieved PASI 75, PASI 90, PASI 100 responses at 16 and 24 weeks compared with patients in the placebo groups in the pooled analysis. The efficacy of deucravacitinib [redacted] and [redacted] In a long-term extension study ([redacted]), deucravacitinib efficacy was maintained. Deucravacitinib response also persisted in patients that stopped treatment at week 24, as measured in the randomised withdrawal arm of POETYK-PSO-2.

[redacted] reached a state in which psoriasis in difficult-to-treat regions (scalp and fingernails) was absent or very mild than patients treated with apremilast and placebo. Similarly, health-related quality of life, as measured by PSSD, DLQI and EQ-5D-3L, was [redacted].

In the pooled analysis of POETYK-PSO-1 and POETYK-PSO-2, short- and mid-term results (Week 16 and Week 24) were consistent with those of the individual studies.[91-93]

B.2.7 Subgroup analysis

The efficacy of deucravacitinib in subpopulations was evaluated using PASI 75 and sPGA 0/1 response at Week 16. Specifically, subgroup analyses were conducted using the POETYK-PSO-1 and POETYK-PSO-2 pooled data. Forest plots are provided in Appendix E for deucravacitinib compared with placebo and apremilast for the following pre-specified subgroups:

- Baseline demographic factors (age, sex, ethnicity, body weight, body mass index [BMI], and geographic region)
- Baseline disease characteristics (PASI score, sPGA score, BSA involvement and duration of disease)
- Prior psoriasis therapies (systemic use [yes/no], topical use [yes/no], prior phototherapy use [yes/no], prior systemic non-biologic use [yes/no], prior systemic biologic use [yes/no], as well as the number of prior biologics used), in line with the NICE scope

The summaries and analyses were based on the FAS population using NRI analyses for missing data.

For each of the pre-specified subgroups, the pooled subgroup analyses [redacted] results of the overall pooled population, thus supporting the robustness of the efficacy data.[93]

Overall, the analyses found that [redacted] for the pooled subgroup analyses of PASI 75 and sPGA 0/1 responses at Week 16 where there were sufficient numbers of patients across the treatment groups for [redacted].[93] In particular, the treatment effect [redacted] observed irrespective of prior systemic use, prior

biologic use, as well as the number of prior biologics used and prior phototherapy. The pooled subgroup results are consistent with the individual study results from POETYK-PSO-1 and POETYK-PSO-2.[91, 92]

B.2.8 Meta-analysis

A network meta-analysis (NMA) was conducted and is described in section B.2.9. Additionally, a naïve comparison of the POETYK trials was conducted, see section B.2.6. This was conducted on the basis that the entry criteria of POETYK-PSO-1 and POETYK-PSO-2 were identical.[90] The two study populations were similar in almost all aspects including study design until Week 24, with the only major difference being Asian ethnicity due to the geographic locations of the study sites (POETYK-PSO-1: n=121, 18.2% versus POETYK-PSO-2: n=44, 4.3%).[90-92] These similarities allowed the short- to mid-term (Week 16 and Week 24) efficacy and safety data to be pooled (naïve pooling) across POETYK-PSO-1 and POETYK-PSO-2 for an integrated analysis of the efficacy of deucravacitinib in patients with moderate-to-severe plaque psoriasis.

B.2.9 Indirect and mixed treatment comparisons

Two head-to-head trials of deucravacitinib compared to apremilast and placebo as well as a pooled analysis of both trials have been conducted (see section B.2.3). To compare the relative efficacy of deucravacitinib versus the other relevant comparators specified in the decision problem, a network consisting of placebo-controlled trials was created. The results of the NMA feed into the economic model described in section B.3. Full details of the methodology applied is described in Appendix D.

B.2.9.1 Summary of trials included in the NMA

An SLR was conducted on 11 October 2021 to identify clinical efficacy evidence for deucravacitinib and other relevant comparators. The interventions considered in the SLR are detailed in Table B.2.21. Assumptions regarding dosing schedule of each of these treatments are specified in the Appendix D, section 1.3.1. Note that the interventions considered reflect a global scope which is broader than that relevant in standard UK clinical practice for moderate-to-severe patients for whom systemic non-biologic treatment or phototherapy is not an option because of lack of response, contraindication or are not tolerated. (see section B.1.3). Results of mirikizumab, piclidonoson, methotrexate, ciclosporin and acitretin are therefore not considered in the NMA results. A detailed overview of the search strategy and the criteria for study selection for the NMA can be found in Appendix D, sections 1.1.2 and 1.1.3.1.

A total of 84 unique RCTs reported in 251 publications (including 132 pooled analyses) were identified in the SLR (see Appendix D, section 1.2).

Table B.2.21. Interventions considered in the NMA

Class	Interventions
TYK2	• Deucravacitinib
TNFα inhibitors	• Certolizumab • Adalimumab • Etanercept • Infliximab

Class	Interventions
IL-17 family or receptor inhibitors	• Brodalumab • Ixekizumab • Secukinumab • Bimekizumab • Mirikizumab[a]
IL-23 inhibitors	• Risankizumab • Tildrakizumab • Guselkumab
IL-12/IL-23 inhibitors	• Ustekinumab
ADORA3 antagonists	• Piclidonoson[a]
Systemic non-biologics	• Apremilast • Methotrexate[a] • Ciclosporin[a] • Dimethyl fumarate • Acitretin[a]

[a]While these treatments were considered in the NMA, they are not considered for the NMA results as they reflect a broader scope than relevant in standard UK clinical practice.
ADORA3 = Adenosine A3 receptor; IL = interleukin; TNFα = tumour necrosis factor-alpha; TYK2 = tyrosine kinase 2 inhibitor

Size of trials

Among the 84trials, nine were phase II, four were phase II/III, 60 were phase III, and four were phase IV. For the remainder, trial phase was not reported. Within the quality assessment, the majority of trials were rated to have an overall low risk of bias (43%) or some concerns (41%), with missing outcome data and deviations from intended interventions being the main reasons for downrating (see Appendix D, section 1.3.5 for details).

Inclusion criteria

Despite the absence of a formal consensus for a definition of mild, moderate-to-severe plaque psoriasis, most trials defined moderate-to-severe plaque psoriasis as having a PASI score ≥12 and involving at least 10% of BSA, several trials also defined a PGA score of more than three.

Outcomes

The included trials reported the relevant study endpoints 50%, 75%, 90% and 100% PASI responses (see section B.1.3.2). PASI is considered as the gold standard measure of psoriasis severity (as used to define adequate response in NICE CG153 and technology appraisals in psoriasis) and the most common disease severity measure used in clinical studies therefore was selected as the outcome measure for the NMA at four percentage levels (PASI 50, 75, 90, and 100).[103]

Timepoints

Primary endpoints were most commonly assessed at 12 weeks (48 studies) or 16 weeks (30 studies). Additional primary endpoint assessment timeframes included 10 weeks (three studies) and 14 weeks (one study), as well as later time points on three occasions (24 weeks [two studies] and 28 weeks [one study]). Furthermore, some studies reported additional assessments between weeks 24 and 28 and between Week 44 and Week 60.

Prior biologic exposure

Exposure to prior biologic treatment varied across the studies, ranging from 0 to 60%; however, the majority of studies reported exposure to previous biologic treatment from 10% to 40%. The POETYK PSO-1 and POETYK PSO-2 trials reported proportions of patients previously receiving biologic therapies ranging from 31.1% to 39.3%, similar to the majority of the studies.

NMA analyses

Multinomial (probit) NMAs on multinomial categories of 50%, 75%, 90% and 100% PASI responses were conducted at three different timepoint:

- Analysis 1: short-term (10-16 weeks) PASI responses for all treatments
- Analysis 2: mid-term (24-28 weeks) PASI responses for all treatments
- Analysis 3: long-term (44-60 weeks) PASI responses for all treatments

In the subsequent sections, forest plots for all PASI outcomes of the short-term analysis are reported since it included the highest number of studies. Forest plots of the mid- and long-term analyses can be found in Appendix D, section 1.7.

B.2.9.2 NMA methods

The NMA was conducted using a multinomial model approach on multinomial categories of 50%, 75%, 90%, and 100% PASI responses, to allow models to 'borrow strength' across PASI responses by filling data gaps of missing data through the dependence between the PASI thresholds. Fixed and random effect models were fitted. In line with NICE guidelines[104] and common practice for NMAs in psoriasis,[71, 74, 76] models were adjusted for baseline risk as relative effects of drugs in autoimmune diseases often depend on baseline risk, i.e. the placebo rate and relative effect of a treatment versus placebo are likely related. The baseline-risk adjustment first takes into consideration the placebo rates of each individual study and then applies a correction factor (anchor rate). The anchor rate for the baseline risk-adjusted analysis is based on a treat-through analysis using the 10–16-week placebo data across all timepoints. This was necessary to ensure the use of placebo data that are similar across trials, protect the integrity of the transitivity assumption that underlies NMA (i.e., that a common treatment arm can serve to facilitate the integration of evidence across comparators) and enable a connected network to be designed that includes most active treatments of interest. The treat-through scenario is limited to only patients who remained on their initial treatment assigned at randomisation through 52 weeks.

Additionally, a random effect was added to parameter z of the model (REZ model) allowing treatments to vary around a common mean in efficacy across PASI cut-offs, thus enabling treatments to have different efficacies and rankings for various levels of PASI. Non informative priors were used for all non-random effects (RE) parameters.

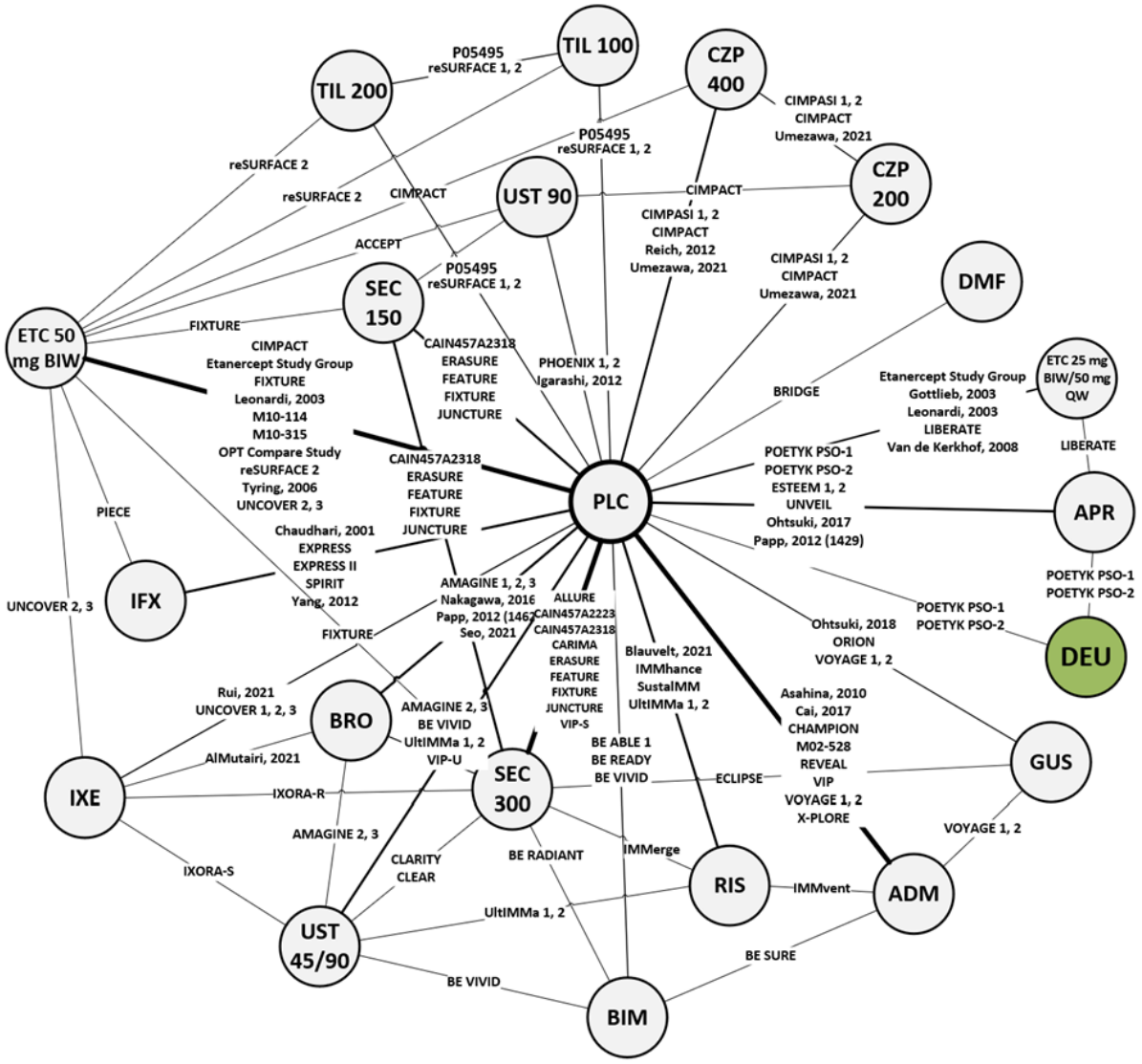
The NMA was carried out using Markov chain Monte-Carlo simulations with 100,000 burn-in iterations and 100,000 iterations for parameter estimation. Convergence was confirmed by Brooks-Gelman-Rubin plots as well as the ratios of Monte Carlo error to the SDs of the posteriors. Full details of the methodology applied can be found in Appendix D, section 1.3.4.

B.2.9.3 NMA results

Figure B.2.9 illustrates the network diagram of all included trials for the short-term analysis. Note that for the mid- and long-term analyses, studies were restricted as only patients who remained on the treatment to which they were initially randomised were included, resulting in studies being further excluded. See associated network diagrams, along with full details of the methodology of the NMA, in Appendix D, section 1.7 and section 1.3.4.

Details of the model selection for each of the time points are presented in Appendix D, section 1.7. For PASI responses at all timepoints, the baseline risk-adjusted model (REZ) was chosen, based on clinical expert recommendations and significance of the coefficient associated with adjustment on baseline risk.

Figure B.2.9. Network diagram for all studies included in the NMA (short-term; 10-16 weeks)



Abbreviations: ADM = adalimumab; APR = apremilast; BIM = bimekizumab; BIW = twice weekly; BRO = brodalumab; CZP = certolizumab pegol; DEU = deucravacitinib; DMF = dimethyl fumarate; ETC = etanercept; GUS = guselkumab; IFX = infliximab; IXE = ixekizumab; PLC = placebo; Q2W = every two weeks; QW = once weekly; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab

Short-term (10-16 weeks) results

The model results for the short-term (10-16 weeks) analysis, presented in forest plots (seeFigure B.2.10 to Figure B.2.13) indicated that for [redacted], deucravacitinib was:

[redacted]

Figure B.2.10. Forest plot for multinomial REZ, adjusted, random-effects model PASI 50 Odds Ratios (short-term)

Abbreviations: ADM = adalimumab; APR = apremilast; BIM = bimekizumab; BIW = twice weekly; BRO = brodalumab; CrI = credible interval; CZP = certolizumab pegol; DEU = deucravacitinib; DMF = dimethyl fumarate; ETC = etanercept; GUS = guselkumab; IFX = infliximab; IL = interleukin; IXE = ixekizumab; PLC = placebo; Q2W = every two weeks; QW = once weekly; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; TNF = tumour necrosis factor; UST = ustekinumab

Figure B.2.11. Forest plot for multinomial REZ, adjusted, random-effects model PASI 75 Odds Ratios (short-term)

Abbreviations: ADM = adalimumab; APR = apremilast; BIM = bimekizumab; BIW = twice weekly; BRO = brodalumab; CrI = credible interval; CZP = certolizumab pegol; DEU = deucravacitinib; DMF = dimethyl fumarate; ETC = etanercept; GUS = guselkumab; IFX = infliximab; IL = interleukin; IXE = ixekizumab; PLC = placebo; Q2W = every two weeks; QW = once weekly; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; TNF = tumour necrosis factor; UST = ustekinumab

Figure B.2.12. Forest plot for multinomial REZ, adjusted, random-effects model PASI 90 Odds Ratios (short-term)

Abbreviations: ADM = adalimumab; APR = apremilast; BIM = bimekizumab; BIW = twice weekly; BRO = brodalumab; CrI = credible interval; CZP = certolizumab pegol; DEU = deucravacitinib; DMF = dimethyl fumarate; ETC = etanercept; GUS = guselkumab; IFX = infliximab; IL = interleukin; IXE = ixekizumab; PLC = placebo; Q2W = every two weeks; QW = once weekly; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; TNF = tumour necrosis factor; UST = ustekinumab

Figure B.2.13. Forest plot for multinomial REZ, adjusted, random-effects model PASI 100 Odds Ratios (short-term)

Abbreviations: ADM = adalimumab; APR = apremilast; BIM = bimekizumab; BIW = twice weekly; BRO = brodalumab; CrI = credible interval; CZP = certolizumab pegol; DEU = deucravacitinib; DMF = dimethyl fumarate; ETC = etanercept; GUS = guselkumab; IFX = infliximab; IL = interleukin; IXE = ixekizumab; PLC = placebo; Q2W = every two weeks; QW = once weekly; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; TNF = tumour necrosis factor; UST = ustekinumab

The model results for the mid- (24-28 weeks) and long-term (44-60 weeks) analysis are summarised bellowed. Associated forest plots are outlined in Appendix D, section 1.7.

Mid-term (24-28 weeks) results

The mid-term analysis results (see Appendix D, section 1.7) indicated that , deucravacitinib was:

[redacted]

Long-term (44-60 weeks) results

The long-term analysis results (see Appendix D, section 1.7) indicated that [redacted], deucravacitinib was:

[redacted]

[redacted]

B.2.9.4 Subgroup analyses

Two subgroup analyses of the short-term (10-16 weeks) NMA were conducted and are outlined below.

Bio-naïve

Twenty-seven trials contributed data to the subgroup analysis for PASI 75 responses among bio-naïve patients. The network diagram and model selection for the bio-naïve subgroup analysis are outlined in Appendix D, section 1.8. Bimekizumab, risankizumab, guselkumab and dimethyl fumarate could not be included in this analysis as no data were available on the biologic naïve subpopulation. The results were consistent with the analyses on the entire patient population at 10-16 weeks. The only difference was that [redacted]

Figure B.2.14. Forest plot for multinomial REZ, adjusted, random-effects model PASI 75 Odds Ratios (bio-naïve)

Abbreviations: ADM = adalimumab; APR = apremilast; BIW = twice weekly; BRO = brodalumab; CrI = credible interval; CZP = certolizumab pegol; DEU = deucravacitinib; ETC = etanercept; IFX = infliximab; IL = interleukin; IXE = ixekizumab; PLC = placebo; Q2W = every two weeks; QW = once weekly; SEC = secukinumab; TIL = tildrakizumab; TNF = tumour necrosis factor; UST = ustekinumab

Biologic experienced

The subgroup analysis of the biologic experienced population was not viable. Eleven trials reported data for PASI 75 responses among patients previously treated with biologic agents and were analysed using a binomial approach. Convergence and lack of precision issues were experienced in the baseline-adjusted models, and there was little difference in terms of DIC and total residual deviance between the fixed effects (FE) and RE models. Any subsequently derived estimates of response probabilities would be very imprecise, making the interpretations in terms of relative effects hazardous. Alternative approaches to analysing the data are not likely to reduce the imprecision and uncertainties. As such, no subgroup results for biologic experienced patients could be reported. The network diagram and model fit of the analysis is reported in Appendix D, section 1.8.

B.2.9.5 Sensitivity analyses

The following sensitivity analyses were conducted:

- Sensitivity analysis (SA) 1: Both deucravacitinib and tildrakizumab were assessed at a later timepoint. Specifically, deucravacitinib was assessed at [redacted] (see section B.2.6.2.3) and tildrakizumab at 28 weeks. This is in line with tildrakizumab's SmPC

and guidance by NICE.[49,100] For all other comparators, clinical assessment occurred between 10 and 16 weeks (short-term).[92, 93, 95-105] SA 1 is considered to be more reflective of clinical practice and is therefore used in the cost-effectiveness model.

- SA 2: Similar to SA 1, deucravacitinib is assessed at [redacted], while tildrakizumab is assessed as per timepoints in the short-term (10-16 weeks) analysis, at 12 weeks. This is in line with NICE guidance of tildrakizumab,[73] which recommends assessment of response at both 12 and 28 weeks and stopping of treatment between 12 and 28 weeks if there has not been at least a 50% reduction in the PASI score from when treatment started.
- SA 3: The same analysis as SA 1 was conducted, using a binomial model.

Further details regarding the network diagram and model selection of each of the SAs are presented in Appendix D, section 1.9.

Sensitivity analyses results

SA 1: Results showed [redacted] across all PASI responses compared to the short-term (10-16 week) analysis, except for the comparisons with [redacted] which were slightly more in favour of [redacted] (see Appendix D, section 1.9). Compared to the short-term analysis, deucravacitinib was still [redacted] than placebo, apremilast, dimethyl fumarate (similar trend is seen for PASI 50, 90 and 100). In SA1, deucravacitinib was significantly more [redacted] and there were no [redacted] Deucravacitinib was [redacted] than other biologics, including [redacted]

SA 2: Results were very similar to SA1 with the exception that [redacted]

SA 3: Results were [redacted]

A more detailed description of SA results, including forest plots are presented in Appendix D, section 1.9.

B.2.9.6 Inconsistencies between the direct and indirect evidence

The findings from the mid- (24-28 weeks) and long-term (44-60 weeks) analyses were consistent with the findings from the short-term (10-16 weeks) analysis for deucravacitinib versus placebo and apremilast, [redacted] for PASI 75 response (and all other levels of PASI, see Appendix, section 1.7). Similar findings were also reported for the [redacted], as well as all [redacted]. These findings are in line with the findings from POETYK-PSO-1 and POETYK-PSO-2 (see section B.2.6), for both the individual and pooled analyses.

No direct evidence of deucravacitinib versus any of the other comparators considered in the submission is available.

B.2.9.7 Conclusion

The NMA compared the relative efficacy, as defined by PASI response rates, of deucravacitinib versus the other relevant comparators specified in the decision problem at short- (10-16 weeks), mid- (24-28 weeks) and long-term (44-60 weeks) timepoints. The analyses found that deucravacitinib was associated with [redacted] other available oral systemic non-biologic treatments (apremilast and dimethyl fumarate) at all timepoints. Deucravacitinib also showed [redacted] weekly at all timepoints.

The NMA results showed that [redacted] to the other TNFα-inhibitors (adalimumab and infliximab) and other more recent second-generation biologics (such as IL-12/23 inhibitor ustekinumab and IL-23 inhibitor tildrakizumab and IL-17 inhibitor secukinumab) as there [redacted]. This highlights the maintenance of response of deucravacitinib (described in section B.2.6.3) by which, [redacted], point estimates of the odd ratios [redacted]. This could also be attributed to the possible [redacted].

Subgroup and sensitivity analyses [redacted].

- Specifically, subgroup analyses for [redacted] showed results were [redacted].
- The two sensitivity analyses (SA1 and 2) investigating alternative PASI assessment timepoints for tildrakizumab and deucravacitinib, and in line with their likely use in clinical practice (tildrakizumab's TA recommends assessment of response at both 12 and 28 weeks and deucravacitinib's appropriate time to measure response is [redacted] as per draft SmPC, see section B.2.6.1); all other comparators' assessment remained between 10 and 16 weeks. Results showed a [redacted] compared to the short-term (10-16 week) analysis. In particular when [redacted] (28 weeks, see SA1), deucravacitinib was [redacted]. However, it showed results more in favour of [redacted]. Interestingly, when considering the earlier timepoint at which tildrakizumab can be stopped (12 weeks, see SA 2), [redacted].

  SA1 is used in the base case of the cost effectiveness model; SA2 is used in a sensitivity analysis.

B.2.10 Adverse reactions

B.2.10.1 Overview

Data from POETYK-PSO-1 and POETYK-PSO-2 suggest that deucravacitinib 6 mg QD was well-tolerated and had low discontinuation rates due to AEs.[91, 92, 105] No new safety signals for

deucravacitinib were observed during the 52-week trial periods.[90-92, 105] Interim results from the subsequent extension study (POETYK-PSO-LTE; (database lock safety: 1 October 2021) suggest a safety profile consistent with that of POETYK-PSO-1 and POETYK-PSO-2, with low rates of discontinuation due to AEs and severe AEs and no additional safety signals.[96, 105]

Integrated clinical safety data were investigated in two separate data pools (see Table B.2.22):

- The Controlled Safety Pool comprised POETYK-PSO-1 and POETYK-PSO-2 and is the main basis for the evaluation of safety of deucravacitinib for the licensed indication. Safety results from the pooled POETYK-PSO-1 and POETYK-PSO-2 are presented in section B.2.10.2 and individual studies are presented in Appendix F
- The Phase 3 Safety Pool comprised patients treated with deucravacitinib from POETYK-PSO-1 and POETYK-PSO-2 and interim data from POETYK-PSO-LTE (database lock safety: 1 October 2021)[96] to provide additional person-years (p-y) of exposure. Only patients who completed POETYK-PSO-1 and POETYK-PSO-2 and entered POETYK-PSO-LTE were included in the Phase 3 Safety Pool. Safety results from the Phase 3 Safety Pool are presented in Appendix F.

The type and frequency of AEs was similar between the Controlled Safety Pool and the Phase 3 Safety Pool.

Table B.2.22. Deucravacitinib safety pools

Data pool	Studies in data pools	Duration	Patients, N
Controlled safety pool	POETYK-PSO-1 POETYK-PSO-2	1 year (Weeks 0–52)	1,364
Phase 3 safety pool	POETYK-PSO-1 POETYK-PSO-2 POETYK-PSO-LTE[a]	2 years (Median duration of exposure: 97 weeks)	1,519

[a] Interim data (database lock safety: 1 October 2021).[96]
Source: Warren et al. 2022;[96] Summary of Clinical Safety, BMS Data on File.[105]

B.2.10.2 Controlled Safety Pool

Safety results from the Controlled Safety Pool are presented based on the full study duration of POETYK-PSO-1 and POETYK-PSO-2 (Week 0–52). Results for the initial, placebo-controlled period (Week 0–16), are provided in Appendix F and are in line with the findings from the full study duration.

Throughout this section, deucravacitinib safety results are reported using the exposure-adjusted incidence rate (EAIR) per 100 person-years (p-y). The EAIR reflects the number of patients with a particular AE divided by the total exposure time among patients in the respective treatment group at risk of an initial occurrence of the event. This accounts for the differences in duration of exposure beyond Week 16. Specifically, the deucravacitinib exposure time was shorter for patients initially randomised to placebo or apremilast, compared to deucravacitinib. The EAIR allows for the combination of these observations into one succinct value

A total of 1,364 patients were treated with ≥1 dose of deucravacitinib, 666 patients received ≥1 dose of placebo, and 422 patients received ≥1 dose of apremilast. A summary of deucravacitinib treatment exposure is provided in Table B.2.23.[105] These form the basis of the EAIR calculations.

Table B.2.23. Summary of deucravacitinib treatment exposure[a] of the Controlled Safety Pool (pooled POETYK-PSO-1 and POETYK-PSO-2)

Parameter	Deucravacitinib N=1,364
≥1 dose (%)	1,364 (100.0)
Continuous exposure[b]	
≥16 weeks of continuous exposure (%)	[redacted]
≥26 weeks of continuous exposure (%)	[redacted]
≥52 weeks of continuous exposure (%)[96]	503 (36.9)
Total exposure	
≥52 weeks of total exposure (%)	[redacted]
≥78 weeks of total exposure (%)	[redacted]
≥104 weeks of total exposure (%)	[redacted]
Total exposure in person-years[c]	[redacted]

Abbreviations: N = number of patients evaluable.
[a] Frequency of exposure in weeks is a cumulative frequency.
[b] Continuous exposure is based on the longest exposure of deucravacitinib.
[c] Total exposure in patient-years is calculated as the sum of exposure from all patients divided by 365.25.
Source: Summary of Clinical Safety, BMS Data on File.[105]

Summary of adverse events

AEs [redacted] in the deucravacitinib group were comparable with the apremilast group. The following sections and Table B.2.24 provide further details on AEs. The trends observed are in line with the findings for the placebo-controlled period (Week 0-16), see Appendix F.

AEs leading to treatment discontinuation were lower for the deucravacitinib group than the apremilast group (deucravacitinib: n=43 [3.2%]; apremilast n=26 [6.2%]; Table B.2.24).[105] In the deucravacitinib group, [redacted][105]

Few deaths occurred during the treatment period. In the placebo-controlled period (Week 0–16), three deaths occurred, one in each group; there was one additional death in the deucravacitinib group between Week 16 and Week 52. None of the deaths were considered treatment-related by the investigator.[105]

Table B.2.24. Overall safety summary for the Deucravacitinib Exposure Period (Week 0–52) in the Controlled Safety Pool – as-treated population

AE category	Deucravacitinib (N=1,364)		Placebo (N=666)		Apremilast (N=422)	
	n (%)	100 IR/P-Y	n (%)	100 IR/P-Y	n (%)	100 IR/P-Y
AEs	995 (72.9)	229.2	347 (52.1)	217.4	299 (70.9)	281.1
Drug-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	55 (4.0)	5.7	14 (2.1)	5.7	9 (2.1)	4.0
Discontinued due to AEs	43 (3.2)	4.4	23 (3.5)	9.3	26 (6.2)	11.6
Deaths	2 (0.1)	0.2	1 (0.2)	0.4	1 (0.2)	0.4

Abbreviations: AEs = adverse events, 100 IR/P-Y = incidence rate per 100 person-years of exposure; n = number of patients in the category; N = number of patients evaluable; N/A = not available; SAEs = serious adverse events.
Source: Armstrong et al. 2021;[90] Summary of Clinical Safety, BMS Data on File.[105]

Adverse events

The most commonly reported AEs in the deucravacitinib group were nasopharyngitis, upper respiratory tract infection (URTI), headache and diarrhoea (see Table B.2.25)[105]. Headache, diarrhoea, and nausea were more common in the apremilast group than the deucravacitinib group.[105] During the initial placebo-controlled period (Week 0-16) similar AEs rates were reported between deucravacitinib and placebo groups (see Appendix F).

Table B.2.25. Most common AEs (≥2% of patients in any treatment group) in the Deucravacitinib Exposure Period (Week 0–52) in the Controlled Safety Pool – as-treated population

AE category	Deucravacitinib (N=1,364)		Placebo (N=666)		Apremilast (N=422)	
	n (%)	100 IR/P-Y	n (%)	100 IR/P-Y	n (%)	100 IR/P-Y
Patients with most common AEs	995 (72.9)	229.2	347 (52.1)	[redacted]	299 (70.9)	[redacted]
Nasopharyngitis	229 (16.8)	26.1	54 (8.1)	[redacted]	54 (12.8)	[redacted]
URTI	124 (9.1)	13.4	33 (5.0)	[redacted]	27 (6.4)	[redacted]
Headache	80 (5.9)	8.5	21 (3.2)	[redacted]	53 (12.6)	[redacted]
Diarrhoea	69 (5.1)	7.3	28 (4.2)	[redacted]	54 (12.8)	[redacted]
Arthralgia	55 (4.0)	5.7	[redacted]	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood CPK increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VURI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psoriasis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acne	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Folliculitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	20 (1.5)	2.1	10 (1.5)	[redacted]	47 (11.1)	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AEs = adverse events, CPK = creatinine phosphokinase; IR = incidence rate/100 person-years; n = number of patients in the category; N = number of patients evaluable; SAEs = serious adverse events; URTI = upper respiratory tract infection; UTI = urinary tract infection; URTI = upper respiratory tract infection; VURI = vital upper respiratory tract infection.
Source: Warren et al. 2022;[96] Armstrong et al. 2021;[90] Summary of Clinical Safety, BMS Data on File.[105]

Serious adverse events

The majority of serious AEs (SAE; ≥2 patients in any treatment group) [redacted] in the deucravacitinib group; SAEs that occurred [redacted] (see Table B.2.26).[105]

Table B.2.26. SAEs (≥2 patients in any treatment group) in the Deucravacitinib Exposure Period (Week 0–52) in the Controlled Safety Pool – as-treated population

AE category	Deucravacitinib (N=1,364)		Placebo (N=666)		Apremilast (N=422)	
	n (%)	100 IR/P-Y	n (%)	100 IR/P-Y	n (%)	100 IR/P-Y
Patients with an SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cholecystitis acute	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pericarditis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 100 IR/P-Y = incidence rate per 100 person-years of exposure; n = number of patients in the category; N = number of patients evaluable; SAEs = serious adverse events.
Source: Summary of Clinical Safety, BMS Data on File.[105]

Adverse events of interest

Adverse events of interest (AEIs) were skin events, infections, malignancies, major adverse cardiovascular events, thromboembolic events, and suicidality. With the exception of skin events, the incidence of these events with deucravacitinib was infrequent, generally comparable to placebo and apremilast, and similar to background rates (see section B.3.3.2). There was no evidence of increased risk for any of these events with longer-term deucravacitinib use from the Phase 3 pool safety (see Appendix F).[90, 105]

The most common skin AEIs were acne and folliculitis. None of the skin AEIs were severe or serious, and the rate of discontinuations due to skin events remained low.[90, 105]

B.2.10.3 Phase 3 Safety Pool

Overall, the 2-year safety profile of deucravacitinib was consistent with the controlled safety pool (Weeks 0—52), and there were no emerging safety signals profile from POETYK-LTE. The most common AEs continued to be nasopharyngitis, upper respiratory tract infection, diarrhoea, arthralgia, headache, and COVID-19 infection. An additional 8 deaths were reported in the POETYK-LTE; 6 of these deaths were due to COVID-19 (comparable to rates in the general population during the pandemic), 1 was attributed to a ruptured thoracic aortic aneurysm, and 1 was due to an unknown cause.

Safety results from the Phase 3 Safety Pool are presented in Appendix F.

B.2.10.4 Safety conclusion

The safety profile of deucravacitinib in patients with moderate-to-severe plaque psoriasis over a period of up to 52 weeks was comparable with that reported over shorter time periods.[105]

Results from the pooled analysis (POETYK-PSO-1 and POETYK-PSO-2) demonstrated that the safety profile of deucravacitinib was comparable to apremilast. Importantly, AEIs were [redacted] (see also B.3.3.2).[105]

No new previously unreported safety signals for deucravacitinib were observed during the 52-week trial period. The 2-year safety profile from POETYK-LTE was consistent with the controlled safety pool (Weeks 0—52) (see Appendix F).

B.2.11 Ongoing studies

Currently, three clinical trials investigating the effectiveness of deucravacitinib in patients with moderate-to-severe plaque psoriasis are ongoing:

- POETYK-PSO-LTE (see section B.2.6.6): this study is ongoing and open to participants in any of the parent POETYK-PSO trials. Results as of database lock from [redacted] (efficacy) and October 2021 (safety) are presented in this submission.
- Two regional phase 3 studies from which data are not yet available:
    - POETYK-PSO-3 (NCT04167462):[106] a double-blind, placebo-controlled, 52-week study being conducted in China, Singapore, South Korea, and Taiwan
    - POETYK-PSO-4 (NCT03924427):[107] a single-arm, open-label study being conducted in Japan

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Findings from the clinical evidence

The clinical efficacy and safety of deucravacitinib has been demonstrated in the POETYK-PSO-1 and POETYK-PSO-2 studies, with both studies successfully meeting their co-primary outcomes (PASI 75 and sPGA 0/1). These findings along with the interim results of the phase 3b long-term extension study, POETYK-PSO-LTE ([redacted]) were further confirmed by expert opinion (see section B.2.3.4).

Baseline demographic and disease characteristics were well balanced across the three treatment groups (deucravacitinib, placebo and apremilast) in the pooled analysis and included a broad population of patients with moderate-to-severe plaque psoriasis. Baseline demographic and disease characteristics were also similar to other trials in psoriasis (see section B.2.3.3). This was supported by expert opinion.

Overall, the study population was consistent with that in the decision problem (see section B.1.1), was considered generalisable to the UK NHS patients and represents the anticipated population that deucravacitinib will be prescribed to in clinical practice.[13]

Short- to mid-term clinical efficacy

In the pooled analysis set of POETYK-PSO-1 and POETYK-PSO-2, deucravacitinib was superior versus placebo and apremilast at Week 16 ([redacted]) and versus

apremilast at Week 24 ([redacted]), meeting the co-primary outcomes for these studies (PASI 75 and sPGA 0/1) as well as the [redacted]. The trends observed in the pooled analysis were consistent with those observed in the individual studies.[91, 92] Subgroup analyses found that [redacted].

The trials showed that assessment at Week 16 might be premature with both PASI 75 response and sPGA 0/1 score scoring better at Week 24 than at Week 16 for deucravacitinib.[93] This is reflected in the draft SmPC which stipulates that [redacted][13] Therefore, [redacted] is the appropriate timepoint to measure response of deucravacitinib. This was also supported by a clinical expert.

Long-term durability and maintenance of response

In POETYK-PSO-1 and POETYK-PSO-2, deucravacitinib demonstrated durability and maintenance of response through [redacted]. Consistent increases in clinical responses to Week 24, as measured by PASI 75 and sPGA 0/1 response, [redacted]. Persistence of those responses while off treatment was measured in the randomised withdrawal arm of the POETYK-PSO-2 from Week 24 to 52. Long-term durability and maintenance of response was confirmed by interim data ([redacted] from POETYK-PSO-LTE). In the psoriasis treatment landscape, where some treatments are seen to lose effect over time, the durability exhibited by deucravacitinib in the data to date may be appealing to both patients and clinicians.

Short-to mid-term efficacy (other key secondary outcomes and patient-reported outcomes)

In both the pooled analysis set and individual studies, a greater proportion of deucravacitinib-treated patients than apremilast-treated patients achieved:

- [redacted] in difficult-to-treat regions as measured by ss-PGA and PGA-F
- [redacted] in symptom burden, including itch, the most bothersome symptom for patients, as measured by PSSD
- [redacted], as measured by DLQI, EQ-5D-3L and EQ-5D-3L VAS

Safety

Expert opinion suggested that safety outcomes of deucravacitinib looked promising with no unexpected signals of concern (see section B.2.3.4). Overall, deucravacitinib was well-tolerated, with a low rate of discontinuations due to AEs. The safety profile of deucravacitinib in patients with moderate-to-severe plaque psoriasis over a period of up to 52 weeks was comparable with that reported over shorter time periods and is consistent with the mechanism of action of deucravacatinib.

Results from the pooled analysis demonstrated that the safety profile of deucravacitinib was comparable to apremilast. Importantly, AEIs were [redacted] (see also section B.3.3.2).

No new previously unreported safety signals for deucravacitinib were observed during the 52-week trial period, nor were these found in the extension study (POETYK-PSO-LTE).

Network meta-analysis

A network meta-analysis found that at the short-term (10-16 weeks) timepoint, deucravacitinib was significantly more efficacious than [redacted] and that, on the [redacted] with adalimumab and some more recent second-generation biologics [redacted]. [redacted] This is attributed to the [redacted]

When considering timepoints better reflective of clinical practice (deucravacitinib at [redacted] tildrakizumab at 12 or 28 weeks, all other treatments between 10 to 16 weeks), results showed [redacted] for deucravacitinib for most comparisons. In particular when tildrakizumab's later timepoint was considered (28 weeks, see SA1), [redacted]. This analysis was slightly more in favour of [redacted] Interestingly, when considering the earlier timepoint at which tildrakizumab can be stopped (12 weeks, see SA 2), deucravacitinib showed [redacted]

Conclusion

Results from the trials confirm that patients with moderate-to-severe psoriasis treated with deucravacitinib achieved clinically meaningful and treat-to-target absolute PASI outcomes that were superior to placebo and apremilast. Deucravacitinib was also [redacted], demonstrating [redacted]. Clinical responses [redacted] and were maintained in patients who receive deucravacitinib through Week 52. It also was shown to [redacted] of patients compared to both apremilast and placebo

In a network meta-analysis, deucravacitinib was [redacted], it also showed to be [redacted] adalimumab and some more recent second-generation biologics due to its [redacted]. In a network meta-analysis better reflecting likely usage of deucravacitinib and tildrakizumab in clinical practice, deucravacitinib [redacted] than apremilast, dimethyl fumarate and etanercept, and was [redacted]

Deucravacitinib was also shown to provides meaningful health benefits to patients with moderate-to-severe psoriasis. Its safety profile was comparable to apremilast with a low proportion of discontinuations due to adverse events. No new previously unreported safety signals were observed in the extension study

Given that deucravacitinib is administered as a once daily oral tablet, patients and clinicians will benefit from the convenience of a once daily oral tablet and it is straightforward initiation of treatment and its ongoing use after initial prescription by a physician in the clinical setting.

It is anticipated that deucravacitinib may become an oral treatment of choice for patients with moderate-to-severe plaque psoriasis

B.2.12.2 Strengths and limitations of the clinical evidence base

Overall, the clinical data for deucravacitinib (POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE) are highly relevant to the NICE decision problem and provides an appropriate evidence base for the assessment of its clinical- and cost-effectiveness in the treatment of moderate-to-severe plaque psoriasis.

The three studies provide comparative evidence for deucravacitinib versus placebo and apremilast. The active comparator, apremilast, is the most commonly used third-line oral treatment in the UK for adults with moderate-to-severe plaque psoriasis, and thus a relevant direct comparator.[34] All three studies were well-designed, with appropriate randomisation methods applied where applicable, following appropriate double-blinding procedures, and adequate concealment of treatment allocation. The key clinical outcomes assessed in the three trials directly measure health benefits relevant to the patient and are clinically meaningful and highly relevant to the UK clinical practice. The data from the POETYK-PSO-1 and POETYK-PSO-2 studies are sufficiently mature (52 weeks) to demonstrate the efficacy and safety of deucravacitinib for the treatment of moderate-to-severe plaque psoriasis. The data are complemented by interim data from the ongoing POETYK-PSO-LTE study of the long-term durability and maintenance of deucravacitinib response ([redacted]).

The POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE clinical programme included a population of patients with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy. The study population was consistent with the population considered in the decision problem and considered generalisable to the UK NHS population (n=[redacted] UK patients were enrolled).[13]

Data from the overall clinical programme demonstrated that deucravacitinib is an effective and safe treatment option for patients with moderate-to-severe plaque psoriasis, including pre-specified subgroups as also confirmed by expert opinion (see section B.2.3.4). The following limitations relating to the clinical evidence based were identified:

- Both POETYK-PSO-1 and POETYK-PSO-2 include a placebo-controlled period of 16 weeks. As a result, no long-term clinical efficacy and safety in comparison to placebo could be assessed. In terms of safety outcomes, EAIRs were used to allow for comparison despite the differences in duration of exposure beyond Week 16. Apremilast was included in the full study duration (52 weeks) in POETYK-PSO-1.
- Treatment discontinuation poses a potential challenge for comparison as treatment arms may become unbalanced, resulting in the introduction of bias. In POETYK-PSO-1 and POETYK-PSO-2, discontinuation rates were low and reasons for discontinuation were similar. Therefore, it was considered that treatment discontinuation was unlikely to impact outcomes.
- The lack of direct comparison with active comparators, other than apremilast, as per the decision problem. To address this limitation, an NMA was conducted to allow comparisons with relevant comparators in the decision problem. The NMA approach was in line with the methodology suggested by the NICE DSU. The NMA found that skin clearance rates achieved with deucravacitinib were better than systemic non-biologics and comparable to those achieved with some first-generation biologics.

- In the NMA, the anchor rate (i.e., placebo response) for the baseline risk-adjusted analysis is based on the 10–16-week placebo data across all timepoints.
- In the NMA, the treat-through scenario is limited to only patients who remained on their initial treatment assigned at randomization through one year. This may not align with true clinical practice as patients may cycle on and off different treatments over time, and also limits the evidence network such that trials with re-randomization and/or switches to other active treatments become ineligible for inclusion in the NMA.

B.3 Cost effectiveness

Cost-effectiveness analysis

- A Markov sequence model was created to compare the cost-effectiveness of deucravacitinib in patients with moderate-to-severe plaque psoriasis to the relevant comparators in this submission. A lifetime horizon was used, and the model takes the perspective of the National Health Service (NHS) and Personal Social Services (PSS). The model structure is in line with previous NICE appraisals for moderate-to-severe plaque psoriasis.
- The base case analysis used the pooled population of the two pivotal phase III deucravacitinib trials: POETYK-PSO-1 and POETYK-PSO-2, which was in line with the decision problem. Treatment efficacy was based on PASI response rates which were informed by an NMA. Treatment response at PASI 75 was used as the clinically significant threshold for adequate treatment response. The response rates used in the model were based on an induction period of 24 weeks for deucravacitinib. Other clinical outcomes included in the analysis were adverse events, utilities and disutility associated with severe infections.
- Treatment sequences were based on market share data and expert opinion. Cost outcomes of the model were informed by drug acquisition (including PAS price for deucravacitinib) and administration costs, monitoring costs, costs related to adverse events, costs associated with best supportive care and non-responder costs.

Base case results

- Base case results used an NMA with treatment response measured at timepoints expected to reflect clinical practice. Specifically, deucravacitinib response was assessed at [redacted] and tildrakizumab at 28 weeks.
- The economic analysis showed that deucravacitinib is cost-effective when evaluated against all relevant comparators in the decision problem for the treatment [redacted]
- The deucravacitinib sequence was associated with a positive iNHB when evaluated against all comparator sequences and dominated the apremilast, DMF and etanercept sequences.

Sensitivity analysis

- The probabilistic sensitivity analysis produced ICURs similar to the deterministic results, supporting the base case conclusions of deucravacitinib being a cost-effective treatment and indicated model stability. Three separate deterministic sensitivity analyses were undertaken comparing the deucravacitinib sequences to the apremilast, adalimumab and brodalumab sequences. The top drivers for each analysis were found to be the treatment discontinuation rate, PASI 75 response for deucravacitinib and the utility value associated with PASI 100 respectively.
- A range of scenarios were explored, and results demonstrated that the deucravacitinib sequence was cost-effective against all comparator sequences in each scenario at a WTP threshold of £20,000/QALY.

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify cost-effectiveness studies relevant to the decision problem. The searches were performed on 31 May 2021 and updated on 21 December 2021. The SLR

found 84 economic evaluations (66 full publications, 18 conference abstracts) and 67 HTA (including 14 NICE TAs) reports of relevance. The detailed SLR methodology and results can be found in Appendix G.

The outputs from the SLR indicated there have been no previous studies examining the cost-effectiveness of deucravacitinib and therefore a *de novo* health economic analysis was conducted.

B.3.2 Economic analysis

B.3.2.1 Patient population

The anticipated marketing authorisation indication for deucravacitinib as stated in B.1.3 is [redacted]. The submission focuses on a narrower population within the marketing authorisation, that is adult patients with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option. This is limited to those patients who have a baseline PASI score ≥10 and a DLQI score >10 and have previously failed, or are contraindicated to, conventional systemic therapies.

The population in the economic model is reflective of those from the pooled POETYK PSO-1 and POETYK PSO-2 clinical trials (see sections B.2.4.2 and B.2.5.1) which included adult patients with baseline PASI ≥12, sPGA ≥3, BSA ≥10% and no requirement for DLQI for those who are candidates for systemic therapy and phototherapy. Baseline characteristics i.e., mean age at model start, mean patient weight, and proportion of male patients were pooled together using the data from the individual POETYK-PSO-1 and POETYK-PSO-2 trials (weighted by the number of patients in each trial).

B.3.2.2 Model structure

A Markov sequence model with a lifetime horizon was constructed to examine the cost-effectiveness of deucravacitinib in moderate-to-severe psoriasis. In line with the findings from the economic SLR (Appendix G.1.2), the model structure is based on the core framework of Markov models used in previous NICE technology appraisals (TAs) in psoriasis. The initial induction phase is based on the structure of the York model published as part of the etanercept & efalizumab NICE submission in 2006 (TA103). Since 2006, more treatments have become available in the psoriasis disease area, thereby increasing choice of treatment for patients. This has resulted in patients being able to receive multiple treatment lines before they reach best supportive care (BSC). To account for this and in line with previous TAs (TA475, TA419, TA575, TA521, TA442, TA511, TA574), treatment sequencing has been used in this model to reflect clinical practice.

The model consists of several mutually exclusive health states. Psoriasis treatments are characterised by an initial induction phase, at the end of which response to treatment is assessed and followed by a maintenance phase.

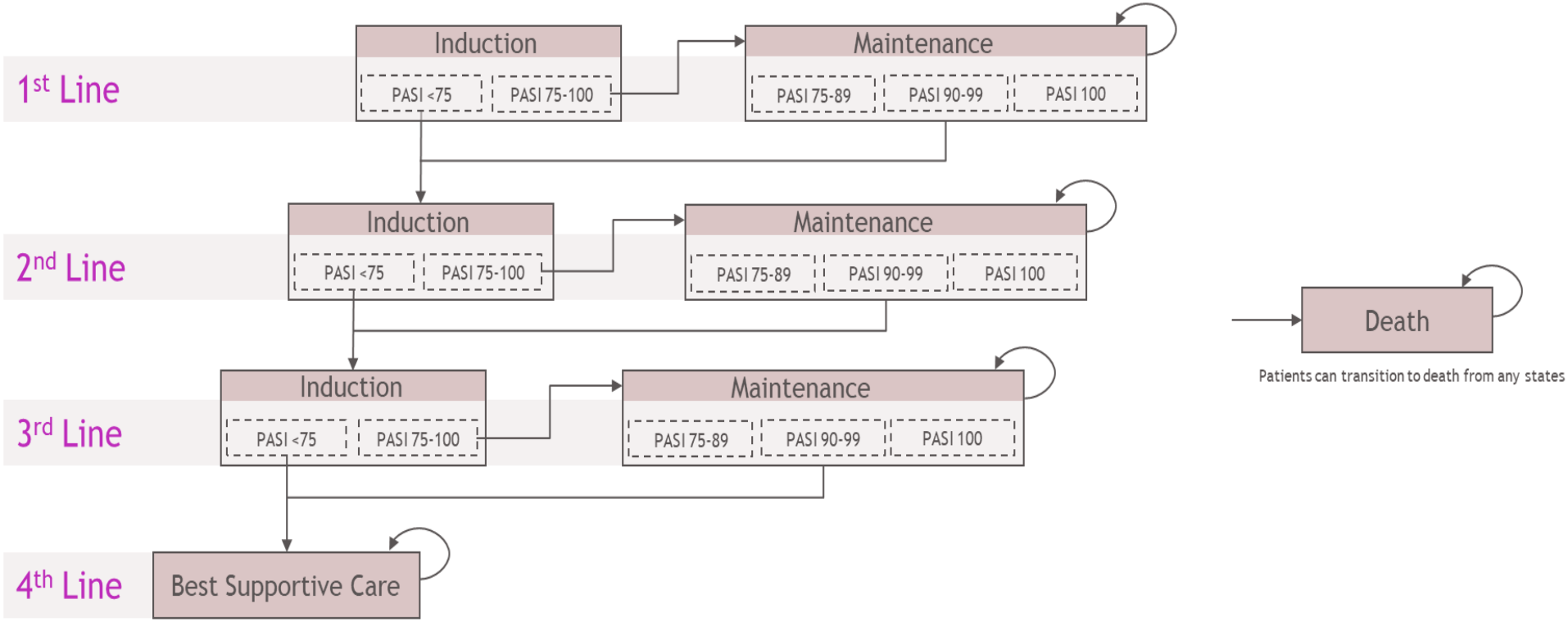
Figure B.3.1 shows the generalised model framework including the following four health states and the transition pathways between them. Within each health state prior to death, patients are distributed according to their PASI response at the end of the induction period; the level of PASI response determines the health effects accrued by patients in the model. The PASI

categories used in this model align with those in TA511. Note these ranges are mutually exclusive and collectively exhaustive:

- PASI <50
- PASI 50-74
- PASI 75-89
- PASI 90-99
- PASI 100

Based on prior NICE submissions (TA442, TA475, TA511, TA574, TA575) and expert advice, it was assumed that patients retain the same PASI response until they exit the health state.

Figure B.3.1. Generalised model framework



Abbreviations: PASI = psoriasis area severity index.

Induction phase

In line with previous appraisals, the induction phase was used to establish response to treatment. During the induction phase, patients start a new treatment and remain on it until response is assessed at a specific timepoint. The duration of the induction phase is based on the recommended timing of response assessment for each treatment as defined from their NICE guidance (Table B.3.1). For deucravacitinib, assessment of response was modelled at [redacted] after treatment initiation, in line with the recommendations in the draft SmPC which states that [redacted] of treatment, see section B.1.3.

At the end of the induction phase, patients are categorised according to treatment response:

- The responders move into the maintenance phase of the same treatment. Response to treatment was defined as achieving PASI75 response; this is the outcome used in the majority of psoriasis clinical trials and has been accepted by NICE as the marker of treatment response used in clinical practice (see section B.3.3.1)
- The non-responders (<PASI75 response) moved into the induction phase of the next line of treatment (in the sequence - see section B.3.2.3)

It was assumed that all patients remain on treatment until their response was assessed at the end of induction phase except for those who died during the induction phase. This assumption is in line with prior TAs (see Table B.3.2).

Table B.3.1. Duration of induction phase per treatment

Treatment	Induction period (weeks)	Source
Deucravacitinib	[redacted]	Draft SmPC (see section B.1.3)
Adalimumab	16	TA511
Apremilast	16	TA511
Bimekizumab	16	TA723
Brodalumab	12	TA511
Certolizumab pegol	16	TA574
Dimethyl fumarate	16	TA475
Etanercept	12	TA511
Guselkumab	16	TA575
Infliximab	10	TA511
Ixekizumab	12	TA511
Risankizumab	16	TA596
Secukinumab	12	TA511
Tildrakizumab	28/12*	TA575
Ustekinumab	16	TA511

*28-week induction period in base case, 12-week induction period in scenario analysis.
Abbreviations: TA = technology appraisal.

Maintenance phase

Patients who enter the maintenance phase are assumed to remain on the same treatment as they were in the induction phase. Patients remain in the maintenance phase of a given treatment until they die or discontinue treatment for any reason such as no longer responding to treatment, adverse events, or patient or physician choice. During this time, they remain in the same PASI health state. Once the patients discontinue, they move to the induction phase of the next treatment within the sequence.

Best supportive care

Once patients discontinue the last active treatment in a sequence in the model, they move to the BSC health state. In the model, BSC is defined as a basket of non-systemic treatments (see section B.3.5.2) that patients are assumed to remain on until death. In line with previous NICE submissions (e.g., TA511), patients in the BSC health state are distributed across the five PASI response categories and response is based on the placebo arm from the NMA; patients on BSC remain in the same PASI response health state until death.

Death

Patients can transition to the death health state at any time during the model. This is based on age-adjusted all-cause mortality. Although there is evidence to suggest that patients with psoriasis may have a higher mortality risk than people without psoriasis (see section B.1.4.7.2), this has not been modelled in the base case in line with previous appraisals. Death is an absorbing health state, meaning that once patients enter the death state they remain there until the end of the model. For simplicity, the arrows showing possible transitions to death are not shown in Figure B.3.1.

B.3.2.3 Model characteristics

Table B.3.2 provides an overview of the key features of the economic model compared with the models presented in previous NICE technology appraisals of other treatments for moderate-to-severe psoriasis.

Table B.3.2. Features of the economic analysis

Model attribute	Previous NICE appraisals	Chosen values/settings	Justification & sensitivity analysis
Model approach *(section B.3.2.2)*	• Decision tree & Markov: TA103, TA134, TA180, TA350 • Markov sequence model : TA419, TA442, TA475, TA511, TA574, TA575 • Cost-comparison analysis : TA521, TA596	Markov sequence model	Previous NICE submissions and expert opinion.
Time horizon *(section B.3.2.2)*	• 5 years: TA521 • 10 years: TA103, TA134, TA146, TA180, TA350, TA419, TA475, TA596 • 40 years: TA511 • Lifetime : TA442, TA574, TA575	Lifetime horizon	Consistent with the NICE reference case.[108] ○ Alternative time horizon examined in scenario analysis.
Discounting *(section B.3.2.2)*	• As per NICE guidance for all previous TAs	3.5% for costs and effects	Consistent with the NICE reference case.[108]
Cycle length *(section B.3.2.2)*	• 2 weeks/ 14 days : TA475, TA511, TA574 • 4 weeks/28 days/1 month: TA419, TA442 • 3 months: TA180 • 14 weeks: TA575 • 12 months/1 year : TA103, TA134, TA146, TA350 • Not applicable: TA521, TA596	2 weeks	Captures induction phase length for all comparator treatments. Half-cycle correction is not applied since the cycle length is sufficiently short to capture changes in costs and effects.
Treatment discontinuation (annual rate) *(section B.3.3.2)*	• 20% for all responders: TA103, TA134, TA180, TA350, TA419, TA442, TA475, TA521, TA574, TA596 • 18.7% for all responders: TA511, TA575	16.4% for all responders	BAD Biologic Interventions Register (BADBIR) (2020)[95] as this is the most recent UK real-world evidence source available. ○ Alternative discontinuation rates examined in scenario analyses.
Treatment waning *(section B.3.3.2)*	• All previous appraisals assumed treatment effect to be maintained with ongoing treatment • All previous appraisals assumed treatment efficacy to be the same regardless of line of treatment:	No treatment waning effect modelled	In line with all previous appraisals. ○ Treatment waning is examined in a scenario analysis.
Source of utilities *(section B.3.4.5)*	• Pivotal clinical trials: TA103, TA134, TA350, TA419, TA442, TA511, TA574, TA575	Pooled EQ-5D data from POETYK trials and TA350 and TA511	Crude pooling used to mitigate the impact of ceiling effect resulting from high baseline utility in POETYK trials.

Model attribute	Previous NICE appraisals	Chosen values/settings	Justification & sensitivity analysis
	• Previous NICE submission: TA134, TA180, TA475 • Not applicable: TA521, TA596		○ Alternative utilities examined in scenario analyses.
Source(s) of resource use (section B.3.5)	• Woolacott et al. (2006): TA103, TA134, TA146, TA180 • British Association of Dermatologists (BAD) guidelines: TA180, TA511 • NICE Clinical Guideline 153: TA350, TA419, TA442, TA475, TA521, TA575 • Fonia et al. (2010): TA475 • Not stated: TA574, TA596	BAD guidelines and TA511 to inform monitoring resource use, Fonia et al. (2010) to inform BSC and non-responder costs	TA511 contains most comparators included in this model, and resource use included was accepted by NICE. Previous NICE appraisals used BAD guidelines, and this has been accepted by NICE. ○ Alternative source for BSC costs examined in scenario analysis.
Source(s) of unit costs (section B.3.5)	• Drug costs: BNF: TA103, TA134, TA146, TA180, TA350, TA419, TA475, TA574, TA575 • Drug costs: Monthly Index of Medical Specialties: TA442, TA511, TA521, TA596 • Other unit costs: NHS Reference costs & PSSRU: TA103, TA134, TA146, TA180, TA350, TA419, TA442, TA475, TA511, TA521, TA574, TA575, TA596	Drug costs: BNF[109] Other unit costs: 2020-2021 NHS Reference costs[110], PSSRU[111]	Consistent with the NICE reference case.[108]
Adverse events (sections B.3.4.4 & B.3.5.5)	• Only costs considered: TA350 • Costs and disutility considered: TA511 • Not considered: TA103, TA134, TA146, TA180, TA419, TA442, TA475, TA521, TA574, TA575, TA596	Impact of serious infections, impact of NMSC and impact of malignancies other than NMSC in terms of costs and disutilities will be considered in the base case	In line with TA511[112].
Mortality (section B.3.3.4)	• All-cause mortality: TA350, TA442, TA475, TA574, TA575, TA596 • All-cause mortality with impact of psoriasis: TA511 • Not considered: TA103, TA134, TA146, TA180, TA419	All-cause mortality, not treatment dependent	In line with previous NICE submissions and expert opinion. ○ Impact of psoriasis on mortality examined in scenario analysis.

Abbreviations: NICE = National Institute for Health and Care Excellence; BADBIR = British Association of Dermatologists Biologic and Immunomodulators Register; NHS = National Health Service; PSSRU = Personal Social Services Research Unit; BNF = British National Formulary; TA103 – etanercept; TA134 – infliximab; TA146 – adalimumab; TA180 – ustekinumab; TA350 – secukinumab; TA419 – apremilast; TA442 – Ixekizumab; TA475 - dimethyl fumarate; TA511 – brodalumab; TA521 – guselkumab; TA574 – certolizumab pegol; TA575 – tildrakizumab; TA596 – risankizumab; TA723 – bimekizumab

B.3.2.4 Intervention technology and comparators

Intervention

Deucravacitinib is the intervention of interest. The dose is 6 milligrams (mg) once daily.

Comparators

The comparators considered in the base case analysis are those that are recommended by NICE and BAD guidelines (see section B1.4.9.1) for patients with moderate-to-severe psoriasis who have not responded to conventional systemic therapies. Although infliximab is recommended for very severe patients only, it was included as a comparator for completeness, in line with TA511 (see table B.1.1 in section B.1.2). An overview of all 14 comparators considered in the model is provided in Table B.3.3 below. Please note information on dosing and mode of administration for these treatments is provided in section B.3.5.

Table B.3.3. Comparators included in the base case

Class	Comparator
Systemic non-biologics	Apremilast (TA419) Dimethyl fumarate (DMF) (TA475)
TNF-α inhibitors	Adalimumab (TA146) Certolizumab pegol (TA574) Etanercept (TA103) Infliximab (TA134)
IL-17 inhibitors	Bimekizumab (TA723) Brodalumab (TA511) Ixekizumab (TA442) Secukinumab (TA350)
IL-23 inhibitors	Guselkumab (TA521) Risankizumab(TA596) Tildrakizumab (TA575)
IL-12/IL-23 inhibitors	Ustekinumab (TA180)

Abbreviations: TNF-α = tumour necrosis factor alpha; IL-17 = interleukin-17 family or receptor; IL-23 = interleukin-23; IL-12/IL-23 = interleukin-12/interleukin-23.

B.3.2.5 Treatment sequences

As per NICE treatment guidelines[20] and BAD guidelines,[43] patients can receive multiple lines of active treatment therapy before they move on to BSC. To model this, the following assumptions were made:

- The model allowed for three lines of active therapy followed by BSC, in line with TA419, TA442, TA475, TA511, TA574, TA575.
- Each of the 14 comparators occupies the first treatment in each sequence (see Table B.3.4 below). This is to ensure that all comparators are compared against deucravacitinib.

- The second and third line of treatment is fixed to allow a meaningful comparison across sequences. UK clinical experts indicated that clinical practice varies across hospitals. Therefore, BMS developed a sequence algorithm based on market share data and clinical insight (from a market research study): the second-line therapy is secukinumab which is the most prescribed second-line option in the UK (as per December 2021 IQVIA DermoTrak data[113]) and the third-line therapy is risankizumab. Risankizumab is used after secukinumab because it has a different mechanism of action and is seen as a highly effective option that clinicians prescribe when previous therapies have failed, as reported in a market research study[115]. It was considered an appropriate third-line option within the sequence that would be used before reaching the best supportive health state. When secukinumab and risankizumab were used as first-line, ustekinumab replaced them in the sequence (see Table B.3.4 below)

Table B.3.4. Base case comparator sequences

Sequence number	1st line	2nd line	3rd line	4th line
1	Deucravacitinib	Secukinumab	Risankizumab	BSC
2	Apremilast	Secukinumab	Risankizumab	BSC
3	Dimethyl fumarate	Secukinumab	Risankizumab	BSC
4	Adalimumab	Secukinumab	Risankizumab	BSC
5	Bimekizumab	Secukinumab	Risankizumab	BSC
6	Brodalumab	Secukinumab	Risankizumab	BSC
7	Certolizumab pegol	Secukinumab	Risankizumab	BSC
8	Etanercept	Secukinumab	Risankizumab	BSC
9	Guselkumab	Secukinumab	Risankizumab	BSC
10	Infliximab	Secukinumab	Risankizumab	BSC
11	Ixekizumab	Secukinumab	Risankizumab	BSC
12	Risankizumab	Secukinumab	Ustekinumab	BSC
13	Secukinumab	Ustekinumab	Risankizumab	BSC
14	Tildrakizumab	Secukinumab	Risankizumab	BSC
15	Ustekinumab	Secukinumab	Risankizumab	BSC

Abbreviations: BSC = best supportive care.

Since UK clinical experts indicated that clinical practice varies across hospitals, a scenario analysis investigated sequences modelled in previous TAs (TA511 and TA575) which were based on the 2017 BAD guidelines. This sequence considered ustekinumab in second line and secukinumab in third line. Additionally, a scenario analysis was run in which each

comparator was compared directly to deucravacitinib as part of a one treatment sequence, i.e. after discontinuation from the first treatment in the sequence, patients move straight to BSC.

B.3.3 Clinical parameters and variables

For the base case analysis, PASI response, treatment related adverse events and transition probabilities (using discontinuation rates) were used to inform the clinical parameters of the model.

B.3.3.1 Treatment effectiveness

The effectiveness for each treatment is based on the relative change in PASI from baseline to the end of the induction phase. PASI change was categorised into five groups: percentage change of <50, change of ≥50, change of ≥75, change of ≥90 and change of 100. The proportion of patients achieving the change in PASI scores was obtained from the NMA (described in section B.2.9). The base case determines response to treatment by PASI 75, in line with all previous cost-effectiveness models in moderate-to-severe psoriasis as it is linked to the definition of adequate response in NICE guidance.

As described previously, during the induction phase, patients were assumed to remain on treatment unless death occurred. The proportions of patients achieving each PASI response level (PASI 50, PASI 75, PASI 90, PASI 100) at the end of the induction phase for each treatment are derived from the NMA (see Table B.3.5). PASI response rates are assumed to increase linearly during the induction phase.

- Patients who had a change in PASI of ≥ 75 at the end of the induction phase were defined as responders and assumed to continue on the same treatment to the maintenance phase, with response being maintained until discontinuation (see section B.3.2.2).
- Patients who had a PASI change of < 75 at the end of the induction phase were defined as non-responder and assumed to move to the induction period of the subsequent treatment in the sequence (see section B.3.2.2).

For BSC, the response rates derived from the placebo arm of the NMA were used. This approach is in line with recent NICE appraisals e.g., TA511.

Table B.3.5. Proportion of patients achieving each level of PASI response at the end of the induction phase derived from NMA

Treatment	Induction phase duration (weeks)	PASI ≥ 50	PASI ≥ 75	PASI ≥ 90	PASI 100
Deucravacitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	16	[redacted]	[redacted]	[redacted]	[redacted]
Apremilast	16	[redacted]	[redacted]	[redacted]	[redacted]
Bimekizumab	16	[redacted]	[redacted]	[redacted]	[redacted]
Brodalumab	12	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	16	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	16	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Induction phase duration (weeks)	PASI ≥ 50	PASI ≥ 75	PASI ≥ 90	PASI 100
Etanercept	12	[redacted]	[redacted]	[redacted]	[redacted]
Guselkumab	16	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	14	[redacted]	[redacted]	[redacted]	[redacted]
Ixekizumab	12	[redacted]	[redacted]	[redacted]	[redacted]
Risankizumab	16	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	12	[redacted]	[redacted]	[redacted]	[redacted]
Tildrakizumab	28*	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab	16	[redacted]	[redacted]	[redacted]	[redacted]
BSC	N/A	[redacted]	[redacted]	[redacted]	[redacted]

*For tildrakizumab, a 28-week induction period was modelled in the base case and a 12-week induction period was explored in a scenario analysis.
Abbreviations: BSC = best supportive care; PASI = Psoriasis Area Severity Index.

B.3.3.2 Treatment discontinuation

All-cause discontinuation was considered in the maintenance phase. Since in the POETYK trials, the deucravacitinib arm is treat-through (that is, patients continued to receive deucravacitinib regardless of their response), discontinuation rate was not reflective of clinical practice and therefore not used to inform the model. Evidence on long-term discontinuation was also not available for the comparator trials, and in line with previously accepted NICE submissions (TA442, TA475, TA521, TA574, TA575, TA596), a common annual discontinuation rate was applied to all treatments using real world data. Specifically, an annual probability of discontinuation of 14.3% was applied for all treatments which was based on a study of the BADBIR registry by Yiu et al.[95]

The Yiu et al (2020) study assessed the relative drug survival of adalimumab, ustekinumab and secukinumab in patients with psoriasis. The annual discontinuation rate was calculated using the survival functions at years 1 and 2 for all treatments in the Yiu et al (2020) study stratified by reason for drug discontinuation. Participants who discontinued due to ineffectiveness in year 1 were not considered to avoid double counting of the discontinuation due to lack of response at the end of the induction phase, in line with TA511. The annual discontinuation after years 1 and 2 was obtained by calculating the weighted average. of treatment discontinuation for both years. This 14.3% (1,571/10,973) annual discontinuation rate was transformed into a constant discontinuation rate of 0.59% per 2-week model cycle as per the below formula and was applied to all patients in the maintenance phase of an active treatment.

$$Pcycle = 1 - e^{\left(-\left(\frac{-\ln(1-Pannual)}{weeks\ per\ year}\right) x\ cycle\ length\right)}$$

Three scenarios were explored to assess the impact of discontinuation rates on the analysis:

- A discontinuation rate which includes only adalimumab from Yiu et al. (2020), as this was the most prevalent treatment in BADBIR.
- A discontinuation rate which uses older data from BADBIR,[115] including data for adalimumab, etanercept, infliximab and ustekinumab, as per TA511 and TA575
- Treatment-specific discontinuation rates as per Table B.3.6. It should be noted that the discontinuation rate applied to deucravacitinib (assumed similar to guselkumab at 9% based on deucravacitinib working partly using the IL-23 pathway) was found in line with the one from the POETYK pooled which found that, among patients treated with deucravacitinib who achieved PASI 75 at week 16 and continued to maintain response through to 52 weeks, [redacted] discontinued treatment. This analysis was a post-hoc analysis and did not impute for non-responders.

Table B.3.6. Treatment-specific discontinuation rates

Treatment	Discontinuation rate	Source	Justification
Deucravacitinib	9%	Assumed same as guselkumab	Expert opinion, based on mechanism of action (works partly using the IL-23 pathway)
Adalimumab	16.4%	Yiu et al. (2020)	Best available evidence from BADBIR registry
Apremilast	31%	Sbidian et al. (2019)[116]	Best available evidence from BADBIR registry
Bimekizumab	12.8%	Assumed same as secukinumab	Expert opinion, based on common discontinuation rate for IL17 class
Brodalumab	12.8%	Assumed same as secukinumab	Expert opinion, based on common discontinuation rate for IL17 class
Certolizumab pegol	16.4%	Assumed same as adalimumab	Expert opinion, based on common discontinuation rate for TNF-α class
Dimethyl fumarate	31%	Assumed same as apremilast	Expert opinion, based on lack of data available for DMF
Etanercept	16.4%	Assumed same as adalimumab	Expert opinion, based on common discontinuation rate for TNF-α class
Guselkumab	9%	Gene 2 clinic FC20[95]	Best available evidence from BADBIR registry
Infliximab	16.4%	Assumed same as adalimumab	Expert opinion, based on common discontinuation rate for TNF-α class
Ixekizumab	24%	Gene 2 clinic FC20[95]	Best available evidence from BADBIR registry
Risankizumab	9%	Assumed same as guselkumab	Expert opinion, based on common discontinuation rate for IL-23 class
Secukinumab	12.8%	Yiu et al. (2020)	Best available evidence from BADBIR registry
Tildrakizumab	9%	Assumed same as guselkumab	Expert opinion, based on common discontinuation rate for IL-23 class
Ustekinumab	10.9%	Yiu et al. (2020)	Best available evidence from BADBIR registry

Abbreviations: TNF-α = Tumour necrosis factor alpha; IL-17 = Interleukin-17 family or receptor; IL-23 = Interleukin-23.

Furthermore, the model provides the option to apply a waning efficacy to subsequent treatments. A study by Gniadecki et al. (2015) of patients in the DERMBIO prospective registry found that patients who have been previously treated with a biologic therapy have a shorter drug survival than patients who were biologic treatment naïve[117]. This only applies to active

treatments and not BSC. Based on this study, it is plausible that patients who have already failed on one or more systemic treatments experience a higher discontinuation rate on subsequent treatments. However, this waning effect is only modelled in a scenario, consistent with prior NICE appraisals (TA575, TA596 & TA574) where treatment effect is assumed to be maintained with ongoing treatment regardless of exposure to prior therapies.[118-120] A hazard ratio of 1.24 derived from the Gniadecki et al. (2015) study is explored in a scenario analysis.

B.3.3.3 Adverse events

The model base case considered the cost of treatment of severe infections, non-melanoma skin cancer (NMSC), and malignancies other than NMSC. These adverse events are included because they are serious adverse events requiring hospitalisation, in line with TA350 and TA442.

For deucravacitinib, apremilast and BSC, rates for these adverse events were taken from the pooled POETYK PSO-1 and POETYK PSO-2 trial data,[105] and for the comparators, these were taken from published literature as described in Table B.3.7.

Table B.3.7. Adverse event rates per treatment

Treatment	Severe infections	Non-melanoma skin cancer (NMSC)	Malignancies other than NMSC	Source(s)
Deucravacitinib	[redacted]	[redacted]	[redacted]	POETYK PSO-1 & POETYK PSO-2 pooled data
Adalimumab	5.190%	0.970%	0.980%	Dixon et al. (2006) (severe infection)[121], SmPC (NMSC and other malignancies)
Apremilast	[redacted]	[redacted]	[redacted]	POETYK PSO-1 & POETYK PSO-2 pooled data
Bimekizumab	1.266%	0.000%	0.253%	Reich et al. (2021)[122]
Brodalumab	1.150%	0.000%	0.000%	Lebwhol et al. (2015)[123]
Certolizumab pegol	5.520%	0.500%	0.000%	Rates for all AEs assumed same as infliximab
Dimethyl fumarate	3.575%	0.000%	0.000%	SmPC
Etanercept	5.130%	3.540%	0.043%	Dixon et al. (2006) (severe infection)[121], Enbrel product information (NMSC and other malignancies)
Guselkumab	0.608%	0.608%	0.608%	Blauvelt et al. (2017)[124]
Infliximab	5.520%	0.500%	0.000%	Dixon et al. (2006) (severe infection)[121], Reich et al. (2015)[125] (NMSC and other malignancies)
Ixekizumab	1.900%	0.700%	0.400%	Gordon et al. (2016)[126]

Treatment	Severe infections	Non-melanoma skin cancer (NMSC)	Malignancies other than NMSC	Source(s)
Risankizumab	0.650%	0.000%	0.300%	Gordon et al. (2018)[127]
Secukinumab	1.500%	0.000%	0.000%	SmPC (severe infection), Rates for NMSC and other malignancies assumed same as brodalumab
Tildrakizumab	0.230%	0.100%	0.110%	Reich et al. (2019)[128]
Ustekinumab	2.000%	0.490%	0.480%	SmPC

Abbreviations: AE = adverse event; NMSC = non-melanoma skin cancer; SmPC= Summary of product characteristics.

The impact of adverse events on health-related quality-of-life (HRQoL) is discussed in section B.3.4.4.

B.3.3.4 Mortality

Age- and gender-dependent all-cause mortality rates from the ONS National Life Tables for England and Wales (2018-2020) were used in the model.[129] Mortality was applied in the model based on a weighted average of the gender-specific mortality rates according to the proportion of males in the POETYK PSO-1 and POETYK PSO-2 trials.[91] A scenario analysis was performed using an increased risk of mortality (HR = 1.79) based on a prospective cohort study of 8,760 adults with severe psoriasis (BSA of >10%) and 87,600 controls in the UK. [49] Overall, the choice of treatment was assumed to have no impact on the mortality rate. This approach is aligned with previous submissions.

B.3.4 Measurement and valuation of health effects

In line with the NICE reference case, health effects were expressed in terms of QALYs, which account for both life expectancy and health-related quality of life. The model assumed the following when accruing health effects:

- The health effects for each sequence are determined by the change in utility from baseline (or utility gain) for each of the PASI response categories (PASI < 50, PASI 50-74, PASI 75-89, PASI 90-99, PASI 100) that patients occupy throughout the model
- Utility gains are applied to patients according to their health states (based on PASI responses), thus patients in different sequences will accrue utility based on the efficacy of the treatments in each sequence
- The utility associated with achieving a certain PASI response is the same regardless of treatment. The model assumes that the utility of patients receiving BSC defaults back to the baseline utility (as per TA575).

PASI response was accrued linearly during the induction phase of treatment, so utilities are also accrued linearly in the induction phase

B.3.4.1 Health-related quality-of-life data from clinical trials

EQ-5D-3L data collected in both POETYK trials to inform health-related quality-of-life were valued using the Dolan algorithm[130] and values obtained from both trials were pooled to generate utility values for each PASI category. EQ-5D data was collected during patients visits at weeks 0, 4, 8, 12, and 16.

Linear regression models were used to estimate the average health utility within subgroups defined by level of PASI response. For each trial, linear regression was used with the Week 16 EQ-5D-3L health utility score (or change from baseline to Week 16) as the dependent variable with the following fixed effects in a series of models. The model adjusting for baseline EQ-5D score and PASI response at Week 16 was considered the best statistical fit. There was no imputation of missing data. For more details regarding model selection, please refer to appendix H.1.3.

Because the subpopulation with baseline DLQI >10 represent the patients seen in clinical practice with severe psoriasis in England and Wales, EQ-5D scores were analysed for this subpopulation. The change in EQ-5D score from baseline to week 16 was calculated for each patient, pooled across treatment arms and stratified by the level of PASI response. Summary of health utility scores derived from the pooled POETYK trials with baseline DLQI >10 are reported in Table B.3.8.

A summary utility table is presented in appendix H.1.3.2 for the ITT population.

Table B.3.8. Summary of health utility score derived from the pooled POETYK trial in patients with a baseline DLQI >10

	Pooled POETYK trials		POETK PSO-1		POETYK PSO-2	
	Change from baseline (SE)	Adjusted mean	Change from baseline (SE)	Adjusted mean	Change from baseline (SE)	Adjusted mean
Baseline	[redacted]		[redacted]		[redacted]	
PASI<50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 50-74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 75-89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 90-99	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PASI 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PASI = Psoriasis Area Severity Index; SE = standard error.

It is important to note that the mean utility for patients with baseline DLQI >10 with a week 16 PASI response of 90 or better is higher than the general population utility for an UK age-matched population with mean age of 46.[119] Furthermore, in comparison to the utilities that are reported in previous TAs, the POETYK utilities are considerably higher. This is due to the difference in baseline utility values, which is higher in the POETYK studies versus the comparator trials (ranging between 0.521 and 0.642, see Table B.3.10) causing a ceiling effect on the extent to which utilities could increase from baseline in improved health states. This results in the utility gains among different PASI categories in POETYK to be smaller than for

comparators. It is unclear why the POETYK baseline utilities are not within the range of comparator trials' baseline utilities. One key consideration was to assess if there were differences in trial populations between studies. It appears there is no important difference and the key trial population characteristics are similar across studies (such as mean PASI score and prior use of biologics, see Section B.2.3.3). However, it should be noted that among the few published trial utilities (only TA350, TA511 and TA575, see Table B.3.9), the data compared are from the subgroups of individuals with DLQI>10 which causes difficulties in identifying systematic differences between the trials. In the absence of detailed information on the baseline characteristics across the studies for the DLQI>10 population, it is difficult to determine the reason for these differences.

Considering the above, the (pooled) POETYK trial utility values are not used in the base case but explored in a scenario analysis. Section B.3.4.5 discusses the base case utilities.

B.3.4.2 Mapping

No mapping was performed since utility values were derived from EQ-5D data from the POETYK PSO-1 and POETYK PSO-2 trials and previous NICE appraisals.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify relevant HRQoL studies. The searches were performed on 31 May 2021 and updated on 21 December 2021. The SLR identified 290 publications of which 263 were full-text articles and 27 were conference abstracts. Of the studies identified, 37 studies (24 non-randomized and 13 randomized) reported health utilities using the EQ-5D. The detailed SLR methodology and results can be found in Appendix H.

B.3.4.4 Health-related quality-of-life for adverse events

The available evidence on the effect of adverse events on health-related quality of life for psoriasis patients is sparse. The only previous NICE submission to incorporate adverse event disutility is TA511. A one-off utility multiplier of 0.986 was applied for severe infections, which was based on a rheumatoid arthritis study by Diamantopoulos et al. (2014), which was itself based on a study of pneumococcal bacteraemia by Sisk et al. (1997).[131, 132] The multiplier was calculated based on a utility for pneumonia and adjusting it for the expected duration of the event along with baseline age and gender of the Sisk et al. (1997) cohort. For use in this model, the multiplier was converted into a disutility of 0.014 per event, applied for the first cycle of receiving the treatment the severe infection is associated with.

No evidence was identified for the effect and duration of the effect of non-melanoma skin cancer or other malignancies on QALY loss. Since these adverse events are conditions that are expected to persist over a long period of time and significantly impact health-related quality of life, their impact on QALYs is assumed to be captured by the health state utility values. In addition, these events are likely to exceed the duration of treatment with any given therapy, makes their addition to the economic model complex.

In the base case, the duration of the effect of adverse events on QALY loss is equal for all treatments regardless of mode of administration. Furthermore, the utility decrement is only applied during the first cycle in the model.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The high baseline utility in the POETYK trials (see Section B.3.4.1) results in a ceiling effect on the utility values generated for PASI response. To mitigate the impact of this ceiling effect and better reflect clinical practice, a new set of utility data was derived via a crude pooling approach where the pooled POETYK trials and utility values sourced from prior TAs were pooled weighted by the sample size for each study, as described in NICE DSU12.[133] In order to limit heterogeneity and prevent potential bias, suitable TAs to include in the pooling were selected based on the following criteria:

- Availability in the public domain
- Baseline utility value reported
- Similar PASI response categories to the POETYK trials
- Utility values based on pivotal trials
- Utility values for patients' baseline PASI ≥ 12 and stratified by DLQI>10 and, in line with the POETYK trials' utilities

Table B.3.9 gives an overview of prior TAs' baseline utility and how the comparator trial compared to the POETYK trials (when utility was generated from trial) and shows that TA511 and TA350 and their respective clinical trials are the only TAs suitable for inclusion. It should be noted that the utilities reported in TA575 were not included as these were criticized by the ERG and were subsequently adjusted and redacted in the clarification responses.[119]

Table B.3.10 presents the utility values associated with each trial used to derive the utilities for the base case. TA350 combined PASI 90-99 and PASI 100 and as such it was assumed that PASI 90-99 and PASI 100 were associated with the same utility value. The utility values used in the cost-effectiveness analysis are summarised in Table B.3.11. Since no uncertainty information was reported for utilities in TA511 and TA350, the standard errors (SE) in the pooled analysis were assumed to be 20% of the respective mean utility values.

Table B.3.9. Inclusion and exclusion of TAs for crude pooling of utility values

NICE TA	Report baseline utility value?	Similar PASI categories to POETYK trials?	Utility estimates based on respective pivotal trials?	Contain trial utility values for patients with a DLQI>10 and baseline PASI ≥ 12?
TA103 (Etanercept)	No	Yes	Yes (DLQI measurements mapped to EQ-5D-3L)	Not reported
TA134 (Infliximab)	No	Yes	No	N/A
TA146 (Adalimumab)	No	Yes	Yes (EQ-5D-3L)	Trial population included PASI≥12, utility values stratified by DLQI>10
TA180 (Ustekinumab)	No	Yes	Yes (DLQI measurements mapped to EQ-5D-3L)	Trial population included PASI≥12 utility values stratified by DLQI≥10

NICE TA	Report baseline utility value?	Similar PASI categories to POETYK trials?	Utility estimates based on respective pivotal trials?	Contain trial utility values for patients with a DLQI>10 and baseline PASI ≥ 12?
TA350 (Secukinumab)	**Yes (0.642)**	**Yes**	**Yes (EQ-5D-3L)**	**Trial population included PASI≥12, utility values stratified by baseline DLQI**
TA419 (Apremilast)	Yes (0.800)	No	No	N/A
TA442 (Ixekizumab)	No	Yes	Yes (EQ-5D-5L)	Trial population included PASI≥12, utility values stratified by DLQI>10
TA475 (Dimethyl fumarate)	Yes (0.700)	Yes	No	N/A
TA511 (Brodalumab)	Yes (0.521)	Yes	Yes (EQ-5D-3L)	Trial population included PASI≥12, utility values stratified by DLQI>10
TA521 (Guselkumab)	N/A*	N/A*	N/A*	N/A*
TA574 (Certolizumab Pegol)	Redacted	Yes	Yes (EQ-5D-3L)	Trial population included PASI≥12, no inclusion criteria relating to DLQI score
TA575 (Tildrakizumab)	**Yes (0.610)**	**Yes**	**Yes (EQ-5D-3L)**	**Trial population included PASI≥12, utility values stratified by DLQI>10**
TA596 (Risankizumab)	N/A*	N/A*	N/A*	N/A*
TA723 (Bimekizumab)	N/A*	N/A*	N/A*	N/A*

*N/A: no utility values reported as submissions were based on a cost-minimisation model.
Abbreviations: DLQI = Dermatology Life Quality Index; N/A = not applicable; PASI = Psoriasis Area Severity Index; TA = technology appraisal.

Table B.3.10. Utility values used to pool the POETYK trial derived utilities with TA511 and TA350

Change from baseline	POETYK pooled trials N=858	Utilities reported in TA511 (AMAGINE-1) N=401	Utilities reported in TA350 (FIXTURE, ERASURE, JUNCTURE, FEATURE, SCULPTURE) N=3,231
Baseline	[redacted]	0.521	0.642
PASI <50	[redacted]	0.016	0.109
PASI 50-74	[redacted]	0.190	0.193
PASI 75-89	[redacted]	0.295	0.226
PASI 90-99	[redacted]	0.355	0.264
PASI 100	[redacted]	0.368	0.264

Abbreviations: PASI = Psoriasis Area Severity Index; TA = technology appraisal.

Table B.3.11. Summary of utility values for cost-effectiveness analysis

State	Utility value		Reference in submission (section and page number)	Justification
	Mean	SE		
Baseline	[redacted]	[redacted]	B.3.4.5	Based on pooled data from POETYK trials and relevant TAs to mitigate the impact of the ceiling effect and better reflect clinical reality
PASI <50	[redacted]	[redacted]		
PASI 50-74	[redacted]	[redacted]		
PASI 75-89	[redacted]	[redacted]		
PASI 90-99	[redacted]	[redacted]		
PASI 100	[redacted]	[redacted]		
Disutility associated with severe infections	0.014	-	B.3.4.4	Used in previous TA511. Multiplier from TA511 converted to a disutility

Abbreviations: PASI = Psoriasis Area Severity Index.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify cost and healthcare resource use data relevant to the decision problem. The searches were performed on 31 May 2021 and updated on 21 December 2021. In total, 66 publications were included. Of these, 58 were full-text articles and 8 were conference abstracts. The detailed SLR methodology and results can be found in Appendix H.

Costs for drug acquisition, drug administration, treatment monitoring, BSC, non-response, and management of adverse events were considered in the model. When possible, unit costs were obtained from the 2019-2020 NHS reference costs, the British National Formulary (BNF) online 2021, and the Personal Social Services Research Unit (PSSRU).[109-111] BSC and non-responder costs were sourced from literature.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

Drug acquisition costs were calculated as a function of unit costs and dosing schedules for each comparator included in the model. The recommended dose of deucravacitinib is 6mg orally once a day as per the draft SmPC. The list price for a pack of 28 tablets for deucravacitinib 6mg is [redacted]. The acquisition cost of deucravacitinib is based on the Patient Access Scheme (PAS) of [redacted] per pack.

Unit costs for all comparators were retrieved from the BNF and dosing schedules were retrieved from the SmPC of each comparator.[109] The base case includes list prices of all comparators regardless of any confidential PAS. For certolizumab pegol, a complex non-confidential PAS is reported where the first 12 weeks of treatment are free of charge,[118] this has been taken into account in the base case analysis. Unit costs of biosimilars were applied for adalimumab, etanercept, and infliximab in the base case.

An overview of the unit costs, dosing schedules and mode of administration is presented in Table B.3.12. The calculated units required, total costs, and costs per cycle for the induction

and maintenance phases are presented in Abbreviations: mg = milligrams; SC = subcutaneous; IV = intravenous.

Table B.3.13.

Table B.3.12. Unit costs and dosing schedule

Treatment	Unit costs			Dosing schedule	Mode of administration
	Pack size (units)	Strength per unit (mg)	Pack cost		
Deucravacitinib	28	6	[redacted]	6mg once daily	Oral
Adalimumab (biosimilar)	2	40	£633.60	80mg at week 0, 40mg every 2 weeks from week 1	SC
Apremilast (titration pack)[a]	1	690	£265.18	Titration pack (14 days) then 30mg twice daily	Oral
Apremilast	56	30	£550.00	After titration pack, 30mg twice daily	Oral
Bimekizumab	2	160	£2,443.00	320mg every 4 weeks for 5 doses (at weeks 0,4,8,12 and 16), followed by maintenance 320mg every 8 weeks	SC
Brodalumab	2	210	£1,280.00	210mg at week 0, 1, 2, then every 2 weeks	SC
Certolizumab pegol[b]	2	200	£715.00	400mg at week 0, 2, 4, then 200mg every 2 weeks	SC
Dimethyl fumarate	42	30	£89.04	30mg once daily for 1 week then increase by 30mg once a week for 3 weeks, then increase by 120mg once a week for 5 weeks (max dose 720mg once a day).	Oral
Etanercept (biosimilar)	4	50	£643.50	50mg once per week. Unit price for etanercept 50mg is the same as 2x25mg.	SC
Guselkumab	1	100	£2,250.00	100mg at week 0, 4, then every 8 weeks	SC
Infliximab (biosimilar)	1	100	£377.66	5mg/kg at week 0, 2, 6, then every 8 weeks. Mean weight of 90.7kg used based on pooled POETYK trials.	IV
Ixekizumab	1	80	£1,125.00	160mg at week 0, 80mg every 2 weeks	SC
Risankizumab	2	75	£3,326.09	150mg at week 0, 4, 16	SC
Secukinumab	1	300	£1,218.78	300mg at weeks 0, 1, 2, 3, 4, then every 4 weeks	SC
Tildrakizumab[c]	2	100	£3,241.00	100mg (if <90kg) or 200mg (if weight ≥90kg) at weeks 0, 4, then every 12 weeks	SC
Ustekinumab[c]	1	45	£2,147.00	45mg (if <100kg) or 90mg (if >100kg) at week 0, 4, then every 12 weeks	SC

[a]The apremilast titration pack covers the first 14 days of treatment.
[b]For certolizumab pegol, a complex non-confidential PAS has been applied, where the first 12 weeks of treatment are free of charge.
[c]For tildrakizumab and ustekinumab, the distribution of patients below and above the threshold weight was based on the body weight distribution of the patients from the pooled POETYK trials assuming that body weight was normally distributed. This resulted in 48.0% of patients weighing less than 90kg and 75.2% weighing less than 100kg.
Abbreviations: mg = milligrams; SC = subcutaneous; IV = intravenous.

Table B.3.13. Treatment acquisition costs during induction and maintenance phases

Treatment	Total units required	Induction phase			Maintenance phase		
		Cost per 2-week cycle	Total cost	Annual units required	Cost per 2-week cycle	Total cost from end of induction phase to end of year 1	Annual cost for subsequent year
Deucravacitinib	168	[redacted]	[redacted]	365.25	[redacted]	[redacted]	[redacted]
Adalimumab (biosimilar)	10	£396.00	£3,168.00	26.09	£316.80	£5,730.69	£8,265.09
Apremilast	196[a]	£273.77	£2,190.18	730.50	£275.00	£4,974.55	£7,174.55
Bimekizumab	10	£1,526.88	£12,215.00	13.04	£610.75	£11,048.03	£15,934.03
Brodalumab	8	£853.33	£5,120.00	26.09	£640.00	£12,857.14	£16,697.14
Certolizumab pegol	12	£89.38[b]	£715[b]	26.09	£357.50	£6,466.92	£9,326.92
Dimethyl fumarate	1,806	£478.59	£3,828.72	8,766.00	£712.32	£12,885.36	£18,583.92
Etanercept (biosimilar)	12	£321.75	£1,930.50	52.18	£321.75	£6,463.73	£8,394.23
Guselkumab	3	£843.75	£6,750.00	6.52	£562.50	£10,175.22	£14,675.22
Infliximab (biosimilar)	14	£1,027.54	£5,137.68	29.58	£428.14	£9,029.17	£11,169.87
Ixekizumab	8	£1,500.00	£9,000.00	13.04	£562.50	£11,300.22	£14,675.22
Risankizumab	6	£1,247.28	£9,978.27	8.70	£554.35	£10,027.77	£14,462.55
Secukinumab	7	£1,421.91	£8,531.46	13.04	£609.39	£12,242.21	£15,898.55
Tildrakizumab	4	£416.64	£5,832.99	6.61	£410.50	£4,962.65	£10,709.64
Ustekinumab	3	£805.13	£6,441.00	4.35	£357.83	£6,472.95	£9,335.62

[a]In addition to the titration pack, which covers the first 14 days (16 weeks=112 days, minus 14 leads to 98 days. 98 * 2 doses per day leads to 196 units required in addition to the titration pack).
[b]For certolizumab pegol, a complex non-confidential PAS has been applied, where the first 12 weeks of treatment are free of charge.

Treatment administration costs

Treatment administration costs were applied depending on the route of administration for each treatment (see Table B.3.14). It was assumed that the cost of training patients to self-administer subcutaneous (SC) injection required three hours of general practitioner nurse (sourced from the PSSRU[111] as per TA442) and was applied only once at the start of SC self-injection. On the other hand, the unit cost of infliximab was applied as intravenous (IV) infusion at each administration and was sourced from the NHS Reference Costs.[110] The drug administration costs are summarized in Table B.3.14.

Table B.3.14. Drug administration costs

Route of administration	Unit cost per administration	Total cost and frequency	Source
Oral	£0.00	£0.00	TA442, TA475, TA511
IV	£121.00	£121.00 applied for each IV administration	2019-2020 NHS Reference Costs, total unit cost of a dermatology outpatient appointment[110]
SC self-injection	£0.00	£126.00 applied at start of treatment	PSSRU, unit costs of health and social care 2021, Nurse (GP practice), wage cost per hour (3 hours)[111]

Abbreviations: IV = intravenous; SC = subcutaneous; PSSRU = personal social services research unit; NHS = National Health Service.

Monitoring Costs

The required monitoring activities and monitoring resource use were based on TA511 and include physician visits, full blood counts, urea and electrolyte tests, and liver function tests.[112] This was based on the 2009 BAD guideline for biologic therapies for psoriasis.[134] The following was taken into consideration when basing monitoring resource use on TA511:

- Recommended monitoring activities presented in the updated 2020 BAD guidelines[43] are consistent with the 2009 BAD guidelines (used in TA511).
- Other TAs such as TA442, TA475 and TA575 use slightly different units of monitoring resource use with these being based on NICE CG153.[103]
- TA596 and TA723 assumed similar monitoring requirements for SC as previous TAs e.g., TA511.
- Infliximab is associated with additional monitoring resource use compared to the other treatments, because of its route of administration. This is in line with other TAs, e.g. TA511.

In this submission, a conservative approach has been taken where deucravacitinib was assumed to incur the same amount of resource use as its comparators. Although deucravacitinib requires little to no monitoring given its mode of administration (as per draft SmPC, see section B.2.3.1), it is a new treatment with a new mechanism of action whereby clinicians may request initial monitoring for caution. This has been taken into consideration given the critique in TA419 (apremilast) by NICE and clinical experts on monitoring resource use.

Monitoring resource use, unit costs and total costs for the induction and maintenance phases are presented in Table B.3.15.

Table B.3.15. Resource use and unit costs for treatment monitoring activities

Resource	Unit cost (£)	Service/code	Resource use		Total cost		References
			Induction phase	Maintenance phase	Induction phase	Maintenance phase	
Physician visit	£121.01	Outpatient Attendance - Dermatology	2 for all treatments except infliximab which is 3	2	£142.02 for all treatments, £163.03 for infliximab	£142.02	2019-2020 NHS Reference Costs[110]
Full blood count	£2.53	DAPS05	2 for all treatments except infliximab which is 3	2	£5.06 for all treatments, £7.59 for infliximab	£5.06	2019-2020 NHS Reference Costs[110]
Urea & electrolyte	£1.20	DAPS04	2 for all treatments except infliximab which is 3	2	£2.40 for all treatments, £3.60 for infliximab	£2.40	2019-2020 NHS Reference Costs[110]
Liver function test	£1.20	DAPS04	2 for all treatments except infliximab which is 3	2	£2.40 for all treatments, £3.60 for infliximab	£2.40	2019-2020 NHS Reference Costs[110]

B.3.5.2 Best Supportive Care Costs

A total cost encompassing the healthcare resource use of patients on BSC was applied for each model cycle once patients discontinue the last active treatment in the sequence. In previous NICE HTA appraisals, the costs from the Fonia et al (2010)[59] publication has been used to inform the cost estimates for BSC. However, the use of this publication has been criticised by the NICE committee in many instances for being outdated, especially as it included patients with more severe psoriasis and therefore potentially not being generalisable to other care settings and that the treatment paradigm in psoriasis has changed over the years. In particular, this was raised in TA575 [73] where NICE highlighted the need for further research to investigate costs associated with BSC and resource use, including the frequency and length of hospitalisation and their associated costs. In response to this recommendation, BMS have conducted a non-interventional retrospective longitudinal cohort study (DISCOVER) to quantify the cost of BSC once a patient has discontinued biologic therapy as discussed in section B.1.3.3.[45] As opposed to the Fonia study, DISCOVER focuses on the costs before and after biologic treatment has stopped for patients, the latter being in line with the place of BSC in the model. From the DISCOVER study, the mean total costs associated with secondary care visits per patient in the 12 months post discontinuation of biologic treatment (including patients with no visits) was used to inform the costs for BSC in the base case.[45] These costs informing BSC are those associated with inpatient admissions, outpatient visits, critical care admissions, accident and emergency (A&E) visits, day case admission and phototherapy.

Cost estimates for BSC reported in Fonia et al (2010) were explored in a scenario analysis. The costs informing BSC are those associated with inpatient admissions, outpatient visits, intensive care unit admissions, high dependency unit admissions, A&E visits, day ward admissions and phototherapy. These were adjusted for inflation to 2021 prices using the health component of the Consumer Price Index from the ONS.[135]

The BSC costs are presented in Table B.3.16.

Table B.3.16. Best Supportive Care costs

Cost item	Annual cost	Cost per 2-week cycle	Source
Secondary healthcare use 12 months post-biologic discontinuation	[redacted]	[redacted]	DISCOVER (BMS data on file)[45]
Secondary healthcare use 12 months before initiating on a biologic	£4,074.39	£156.17	Fonia et al. (2010)[59]

B.3.5.3 Non-responder Costs

In line with previous NICE submissions, non-responder costs are applied during the induction period of the next active therapy; patients who fail an active treatment and switch to BSC do not incur additional non-responder costs, since the components of non-responder costs are included in those of BSC. The annual cost of non-response was converted into a cost per 2-week cycle, which was applied in each cycle of the induction phase of the next active treatment in the sequence.

Non-responder costs represent the additional healthcare costs incurred by patients who fail to respond to an active treatment. This was informed by the mean total costs from the

DISCOVER cohort study associated with secondary care visits per patient in the 12 months pre-discontinuation of biologics (including patients with no visits).[45]

Previous NICE submissions such as TA442 derived non-responder costs from the cost incurred 12 months before a patient begins a biologic treatment minus outpatient visits from Fonia et al. (2010). This value was inflated to 2021 prices using the Consumer Price Index from ONS and was explored in a scenario analysis.[59, 135, 136]

The non-responder costs are outlined in Table B.3.17.

Table B.3.17. Non-responder costs

Cost item	Annual cost	Cost per 2-week cycle	Source
12 months pre-biologic discontinuation	[redacted]	[redacted]	DISCOVER (BMS data on file)[45]
Medical service cost (excluding outpatient care)	£3,754.55	£143.91	Fonia et al. (2010)

B.3.5.4 Health-state unit costs and resource use

The costs associated with each PASI response category are listed in Table B.3.18. This is a summary of the information stated above but categorised to the costs associated with patients achieving different possible PASI response categories. Drug acquisition, drug administration, monitoring, and BSC costs are incurred in every health state, whereas non-responder costs are only incurred in the PASI response categories that are not sufficient for response to treatment (PASI <50 and PASI 50-74).

Table B.3.18. Unit costs associated with patients achieving each PASI response states in the economic model

State	Cost item	Value	Source
Patients achieving the following PASI response states: PASI <50 PASI 50-74 PASI 75-89 PASI 90-99 PASI 100	**Drug acquisition**		
	Deucravacitinib (PAS price)	[redacted] per pack	BMS
	Adalimumab	£704.28 per pack	BNF[109]
	Adalimumab (biosimilar)	£633.60 per pack	
	Apremilast: titration pack	£265.18 per pack	
	Apremilast	£550.00 per pack	
	Bimekizumab	£2,443.00 per pack	
	Brodalumab	£1,280.00 per pack	
	Certolizumab pegol	£715.00 per pack	
	Dimethyl fumarate	£89.04 per pack	
	Etanercept	£715.00 per pack	
	Etanercept (biosimilar)	£643.50 (bs)	

State	Cost item	Value	Source
	Guselkumab	£2,250 per pack	
	Infliximab	£419.62 per pack	
	Infliximab (biosimilar)	£377.66 per pack	
	Ixekizumab	£1,125.00 per pack	
	Risankizumab	£3,326.09 per pack	
	Secukinumab	£1.218.78 per pack	
	Tildrakizumab	£3,241.00 per pack	
	Ustekinumab	£2,147.00 per pack	
	Drug administration		
	Oral	N/A	
	IV	£121 per administration	2019-2020 NHS Reference Costs total unit cost of a dermatology outpatient appointment[110]
	Subcutaneous self-injection	£42.00 per nurse hour (total of 3 hours per active treatment given by subcutaneous self-injection)	PSSRU, Unit Costs of Health and Social Care 2021, Nurse (GP practice), wage cost per hour[111]
	Monitoring		
	Physician visit	£121.01 per visit	2019-2020 NHS Reference Costs, Outpatient Attendance – Dermatology[110]
	Full blood count	£2.53 per test	2019-2020 NHS Reference Costs, DAPS05 (Haematology)[110]
	Urea & electrolyte	£1.20 per test	2019-20120 NHS Reference Costs, DAPS04 (Clinical biochemistry)[110]
	Liver function test	£1.20 per test	2019-2020 NHS Reference Costs, DAPS04 (Clinical biochemistry)[110]
	BSC		
	Inpatient admissions and outpatient care	[redacted] per year	DISCOVER[45]
	Non-responder		

State	Cost item	Value	Source
Patients achieving the following PASI response states: PASI <50 PASI 50-74	Medical service cost (excluding outpatient care)	[redacted] per year	DISCOVER[45]

Abbreviations: PASI = Psoriasis Area Severity Index; BNF = British National Formulary; NHS = National Health Service; PSSRU= personal social services research unit; IV = intravenous; SC= subcutaneous

B.3.5.5 Adverse event unit costs and resource use

Adverse event costs are presented in Table B.3.19 and were obtained from the 2019-2020 NHS Reference Costs for severe infections.[110] Costs for severe infections were an average of the costs for six types of infection: sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection, and urinary tract infection. The costs for NMSC were based on inpatient costs for the disease, and costs for malignancies other than NMSC were based on average inpatient costs for lymphoma and melanoma. This costing approach is in line with TA442. The total adverse event costs associated with each treatment are applied during the first cycle that a patient is on that treatment.

Table B.3.19. AE resource use and unit costs

AE	Resources	Unit cost	Source
Severe infections	Weighted average of hospital costs for 6 types of severe infections (sepsis, tuberculosis, pneumonia, skin and soft tissue infection, bone and joint infection, urinary tract infection)	£ 2,315.71	2019-2020 NHS Reference Costs, WJ06A-F, DZ14F-J, DZ23H-N, JD07A-D, HD25D-H, LA04H-S[110]
Non-melanoma skin cancer (NMSC)	Hospital costs for NMSC	£2,868.21	2019-2020 NHS Reference Costs, JC41Z[110]
Malignancies other than NMSC	Weighted average of hospital costs for lymphoma and melanoma	£ 2,678.86	2019-2020 NHS Reference Costs, SA31A-F, JC41Z[110]

Abbreviations: AE = adverse event; NHS = National Health Service; NMSC = Non-melanoma skin cancer

B.3.5.6 Miscellaneous unit costs and resource use

No other healthcare resources were modelled in the analysis.

B.3.6 Severity

Given the QALY shortfall is not expected to reach 12 QALYs for the population under consideration, this population does not meet the criteria for a severity weight.

B.3.7 Uncertainty

There are no concerns regarding the quality of the evidence presented in this submission since:

- the prevalence of moderate-to-severe psoriasis is considerable in England (see section B1),
- the evidence for deucravacitinib in this submission is based on two robust RCTs (see section B.2.4), and

- numerous previous TAs have been published in this disease area, and the modelling approach and data sources used in this submission broadly align with these submissions.

B.3.8 Managed access proposal

Not applicable.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

Table B.3.20: Summary of parameters used in the base case economic analysis

Parameter category	Parameter	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings	Discount rate (costs)	3.5%	N/A	B.3.2
	Discount rate (effects)	3.5%	N/A	
Patient characteristics	Age (years)	[redacted]	[redacted]	B.3.2
	Females	[redacted]	[redacted]	
	Average weight (kg)	[redacted]	[redacted]	
Response rates: deucravacitinib	PASI 50	[redacted]	[redacted]	B.3.3
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: adalimumab	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: apremilast	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: brodalumab	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	

Parameter category	Parameter	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	PASI 100	[redacted]	[redacted]	
Response rates: certolizumab pegol	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: etanercept	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: guselkumab	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: infliximab	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: ixekizumab	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: risankizumab	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
	PASI 50	[redacted]	[redacted]	

Parameter category	Parameter	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Response rates: secukinumab	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: tildrakizumab	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: ustekinumab	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: DMF	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: bimekizumab	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Response rates: BSC	PASI 50	[redacted]	[redacted]	
	PASI 75	[redacted]	[redacted]	
	PASI 90	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Discontinuation	Annual probability of discontinuation	14.3%	SE: 2.9%* (beta)	B.3.2
Change in utility from baseline	Baseline	[redacted]	[redacted]	B.3.4
	PASI <50	[redacted]	[redacted]	

Parameter category	Parameter	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	PASI 50-74	[redacted]	[redacted]	
	PASI 75-89	[redacted]	[redacted]	
	PASI 90-99	[redacted]	[redacted]	
	PASI 100	[redacted]	[redacted]	
Disutility for severe infections		0.014	SE: 0.003* (beta)	
Drug acquisition costs (per pack)	Deucravacitinib	[redacted]	N/A	B.3.5
	Adalimumab (bs)	£633.60	N/A	
	Apremilast: titration pack	£265.18	N/A	
	Apremilast	£550.00	N/A	
	Bimekizumab	£2,443.00	N/A	
	Brodalumab	£1,280.00	N/A	
	Certolizumab pegol	£715.00	N/A	
	Dimethyl fumarate	£89.04	N/A	
	Etanercept (bs)	£643.50	N/A	
	Guselkumab	£2,250	N/A	
	Infliximab (bs)	£377.66	N/A	
	Ixekizumab	£1,125.00	N/A	
	Risankizumab	£3,326.09	N/A	
	Secukinumab	£1.218.78	N/A	
	Tildrakizumab	£3,241.00	N/A	
	Ustekinumab	£2,147.00	N/A	
Drug administration unit costs by mode of administration	Oral	£0.00	SE: £0* (gamma)	B.3.5
	IV	£121.00	SE: £24.20* (gamma)	
	SC	£126.00	SE: £25.20* (gamma)	
BSC costs (per year)		[redacted]	[redacted]	B.3.5
Non-responder costs		[redacted]	[redacted]	B.3.5

Parameter category	Parameter	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Monitoring unit costs	Physician visit	£121.01	SE: £24.20* (gamma)	B.3.5
	Full blood count	£2.53	SE: £0.51* (gamma)	
	Urea & electrolyte	£1.20	SE: £0.24* (gamma)	
	Liver function test	£1.20	SE: £0.24* (gamma)	
Monitoring use in induction phase: physician visit, full blood count, urea & electrolyte liver function test	All treatments except infliximab	2	SE: 0.4* (gamma)	B.3.5
	Infliximab	3	SE: 0.6* (gamma)	
Monitoring resource use in maintenance phase: physician visit, full blood count, urea & electrolyte, liver function test	All treatments	2	SE: 0.4* (gamma)	B.3.5
AE unit costs	Severe infections	£2,315.71	SE: £463.14* (gamma)	B.3.5
	NMSC	£2,868.21	SE: £573.64* (gamma)	
	Malignancies other than NMSC	£2,678.86	SE: £535.77* (gamma)	
AE rates: severe infections	Deucravacitinib	[redacted]	[redacted]	B.3.3
	Adalimumab	0.05	SE: 0.010* (gamma)	
	Apremilast	[redacted]	[redacted]	
	Bimekizumab	0.01	SE: 0.003* (gamma)	
	Brodalumab	0.01	SE: 0.002* (gamma)	
	Certolizumab pegol	0.06	SE: 0.011* (gamma)	
	Dimethyl fumarate	0.04	SE: 0.007* (gamma)	
	Etanercept	0.05	SE: 0.010* (gamma)	
	Guselkumab	0.01	SE: 0.001* (gamma)	
	Infliximab	0.06	SE: 0.011* (gamma)	
	Ixekizumab	0.02	SE: 0.004* (gamma)	
	Risankizumab	0.01	SE: 0.001* (gamma)	

Parameter category	Parameter	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Secukinumab	0.02	SE: 0.003* (gamma)	
	Tildrakizumab	0.00	SE: 0.000* (gamma)	
	Ustekinumab	0.02	SE: 0.004* (gamma)	
AE rates: NMSC	Deucravacitinib	[redacted]	[redacted]	B.3.3
	Adalimumab	0.01	SE: 0.002* (gamma)	
	Apremilast	[redacted]	[redacted]	
	Bimekizumab	0.00	SE: 0.000* (gamma)	
	Brodalumab	0.00	SE: 0.000* (gamma)	
	Certolizumab pegol	0.01	SE: 0.001* (gamma)	
	Dimethyl fumarate	0.00	SE: 0.000* (gamma)	
	Etanercept	0.04	SE: 0.007* (gamma)	
	Guselkumab	0.01	SE: 0.001* (gamma)	
	Infliximab	0.01	SE: 0.001* (gamma)	
	Ixekizumab	0.01	SE: 0.001* (gamma)	
	Risankizumab	0.00	SE: 0.000* (gamma)	
	Secukinumab	0.00	SE: 0.000* (gamma)	
	Tildrakizumab	0.00	SE: 0.000* (gamma)	
	Ustekinumab	0.00	SE: 0.001* (gamma)	
AE rates: malignancies other than NMSC	Deucravacitinib	[redacted]	[redacted]	B.3.3
	Adalimumab	0.01	SE: 0.002* (gamma)	
	Apremilast	[redacted]	[redacted]	
	Bimekizumab	0.00	SE: 0.001* (gamma)	
	Brodalumab	0.00	SE: 0.000* (gamma)	
	Certolizumab pegol	0.00	SE: 0.000* (gamma)	
	Dimethyl fumarate	0.00	SE: 0.000* (gamma)	
	Etanercept	0.00	SE: 0.000* (gamma)	

Parameter category	Parameter	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Guselkumab	0.01	SE: 0.001* (gamma)	
	Infliximab	0.00	SE: 0.000* (gamma)	
	Ixekizumab	0.00	SE: 0.001* (gamma)	
	Risankizumab	0.00	SE: 0.001* (gamma)	
	Secukinumab	0.00	SE: 0.000* (gamma)	
	Tildrakizumab	0.00	SE: 0.000* (gamma)	
	Ustekinumab	0.00	SE: 0.001* (gamma)	
AE duration: oral (weeks)	Severe infections	1	SE: 0.2* (gamma)	B.3.4
	NMSC	N/A	N/A	
	Malignancies other than NMSC	N/A	N/A	
AE duration: IV (weeks)	Severe infections	1	SE: 0.2* (gamma)	B.3.4
	NMSC	N/A	N/A	
	Malignancies other than NMSC	N/A	N/A	
AE duration: SC (weeks)	Severe infections	1	SE: 0.2* (gamma)	B.3.4
	NMSC	N/A	N/A	
	Malignancies other than NMSC	N/A	N/A	

*SE is assumed 20% of the mean value.
Abbreviations: PASI = Psoriasis Area Severity Index; SE = standard error; CI = confidence interval; IV = intravenous; SC = subcutaneous; AE = adverse event; NMSC = non-melanoma skin cancer; BSC = best supportive care; BS = biosimilar.

B.3.9.2 Assumptions

Table B.3.21. Assumptions made in the base case of the economic analysis

Parameter	Assumption	Consistent with prior NICE TAs?	Justification
Model structure			
Time horizon	Lifetime horizon	Yes	A lifetime horizon was used to capture all relevant costs and health effects of sequences composed of several treatments.
PASI response within health states	Patients retain the same PASI response until they exit the health state (for any reason)	Yes	In absence of long-term data on PASI response after the induction phase of treatment, changes in PASI response are assumed to be sufficiently captured by changing health states.
Discontinuation during the induction phase	Patients remain on treatment until response assessment at the end of the induction phase, and discontinuation at the end of the induction phase is based only on efficacy	Yes	This is based on treatment protocols and the best available evidence on discontinuation at the end of the induction phase.
Discontinuation during the maintenance phase	A single all-cause discontinuation is applied every model cycle regardless of treatment	Yes	Long-term treatment-specific discontinuation data is sparse, especially for oral therapies. Using a single all-cause discontinuation rate eliminates any bias that considering different sources of evidence may have introduced.
Comparators and sequences			
Adherence to treatment protocol	100% adherence	Yes	In the absence of evidence showing reason to employ lower adherence rates, full adherence to treatment protocol is assumed for all treatments.
Costs			
AE costs	AE costs for severe infections, NMSC, and malignancies other than NMSC are included	Yes, either in base case or scenario analysis	These AEs are reported for most comparator treatments, these AEs are associated with

Parameter	Assumption	Consistent with prior NICE TAs?	Justification
			significant healthcare resource use, and the costs could be estimated.
Drug administration	Training costs for subcutaneous self-injection are only applied to the first treatment given by that mode of administration in a sequence	Unclear (not stated in previous NICE submissions)	While previous NICE submissions have included training costs for treatments given via subcutaneous self-injection, none mention whether this cost is applied for each treatment or only for the first treatment given via this route. It is assumed that patients only require this training once and that they can apply this knowledge to any future treatments given via this route.
Health effects			
PASI response on BSC	Patients in the BSC health state are distributed across the five PASI response health states based on placebo responses from the NMA; patients on BSC remain in the same PASI response health state until death	Yes	Since patients on BSC are not receiving any systemic treatments, the placebo arm of the NMA is the best estimate of PASI response for these patients.
Accrual of health effects during the induction phase	During the induction phase, patients are assumed to accrue health effects (utility) in a linear fashion. In the model, this is implemented by applying 0.5 of the full health effects achieved at the end of the induction phase to patients in each cycle of the induction phase	Unknown	Mixed approaches to the accrual of health effects have been taken in previous NICE submissions, but none have explicitly mentioned applying a linear accrual of health effects. Since the accrual of zero health effect is not representative of the patient's experience, linear accruals is a realistic approach to representing the actual health effects accrued during this period.

Abbreviations: PASI = Psoriasis Area Severity Index; AE = adverse event; BSC = best supportive care; NICE = National Institute of Health and Care Excellence; NMA = network meta-analysis.

B.3.10 Base-case analysis

B.3.10.1 Base case methods

In the base case, sensitivity analysis 1 of the NMA was used (see section B.2.9.5); it considered treatment response at different timepoints and specific for each treatment:

- Deucravacitinib response was assessed at [redacted] as it is considered the most appropriate timepoint for several reasons. The draft SmPC states: [redacted]. This is illustrated by trends seen in POETYK-PSO-1 and POETYK-PSO-2 in which both the PASI 75 and sPGA 0/1 responses were better at Week 24 than at week 16 for deucravacitinib, indicating that assessment at week 16 might be premature.[94] This slower onset of response is mainly due deucravacitinib's mechanism of action of selective inhibition of TYK2 resulting in the delayed downstream downregulation of IL-23 and IL-17. In clinical practice, it would be unreasonable to switch a patient from a treatment that is working.
- Tildrakizumab response was assessed at 28 weeks in line with its NICE guidance
- All other comparators were assessed at 10-16 weeks in line with their NICE guidance

Since there is no difference in life years (LY) gained, the incremental costs per LY are not reported. Disaggregated costs and clinical outcomes are presented in appendix J for the deucravacitinib sequence versus the comparator sequences.

A summary of the incremental cost-effectiveness results is presented in Table B.3.22; it reports deterministic and probabilistic incremental cost-utility ratios (ICURs) for the deucravacitinib sequence compared to each comparator sequence. A pairwise comparison of the incremental net health benefits (iNHB) of deucravacitinib sequence compared to each comparator sequence is also reported, in line with recent NICE manual on developing guidelines. The manual highlights the additional information that iNHB can provide in case the differences in costs or QALYs between comparators are small and the technology provides less health benefit at lower costs. In the calculations of the iNHB, a WTP threshold of £30,000 per QALY gained was assumed. If an intervention has an iNHB >0 at £30,000 per QALY, it is considered to be cost-effective.

Results include PAS price for deucravacitinib, non-confidential complex PAS for certolizumab pegol and list price for other comparators. These does not include the confidential PAS for several comparators (apremilast, brodalumab, bimekizumab, guselkumab, ixekizumab, risankinumab, secukinumab, tildrakizumab).

B.3.10.2 Base-case results

Table B.3.22 presents deterministic, probabilistic ICURs and iNHB for the deucravacitinib sequence compared to each comparator sequence.

The deucravacitinib sequence was found to be cost-effective versus all the comparator sequences. The deucravacitinib sequence dominated the apremilast, DMF and etanercept sequences. When compared with the other sequences, the deucravacitinib sequence was less costly but was associated with less QALYs resulting in deucravacitinib saving more than £20,000 for every QALY foregone for each comparison. Consequently, the deucravacitinib sequence is associated with a positive iNHB compared to all comparator sequences. The comparison versus the adalimumab and certolizumab sequences resulted in the smallest iNHB, as these comparisons yielded the lowest cost per QALYs foregone. The largest iNHB was observed versus the bimekizumab, brodalumab, ixekizumab, guselkumab, and DMF sequences.

Table B.3.22. Base case results - Incremental results

Sequence*	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Deterministic ICUR	Probabilistic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	**19.71**	[redacted]	**-**	**-**	**-**	**-**		**-**
APR- SEC-RIS	182,471	19.71	[redacted]	[redacted]	-	[redacted]	Dominant (-£10,442)	Dominant (-£13,067)	0.406
DMF- SEC-RIS	205,321	19.71	[redacted]	[redacted]	-	[redacted]	Dominant (-£102,566)	Dominant (-£109,744)	1.120
ADA- SEC-RIS	185,882	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£81,945 per QALY foregone)	SW quadrant (£80,333 per QALY foregone)	0.138
BIM- SEC-RIS	231,685	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£147,986 per QALY foregone)	SW quadrant (£153,171 per QALY foregone)	1.391
BRO- SEC-RIS	226,855	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£165,585 per QALY foregone)	SW quadrant (£170,778 per QALY foregone)	1.297
CER- SEC-RIS	187,333	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£86,238 per QALY foregone)	SW quadrant (£87,222 per QALY foregone)	0.174
ETA- SEC-RIS	185,111	19.71	[redacted]	[redacted]	-	[redacted]	Dominant (-£22,462)	Dominant (-£25,684)	0.450
GUS- SEC-RIS	218,046	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£146,246 per QALY foregone)	SW quadrant (£149,928 per QALY foregone)	1.026
INF- SEC-RIS	204,866	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£136,463 per QALY foregone)	SW quadrant (£140,153 per QALY foregone)	0.664
IXE- SEC-RIS	222,521	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£139,387 per QALY foregone)	SW quadrant (£142,823 per QALY foregone)	1.130

Sequence*	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Deterministic ICUR	Probabilistic ICUR	iNHB (deucravacitinib versus comparator)
RIS- SEC-UST	200,372	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£186,809 per QALY foregone)	SW quadrant (£193,676 per QALY foregone)	0.589
SEC- UST-RIS	198,251	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£177,667 per QALY foregone)	SW quadrant (£183,562 per QALY foregone)	0.524
TIL- SEC-RIS	195,721	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£111,904 per QALY foregone)	SW quadrant (£114,168 per QALY foregone)	0.400
UST- SEC-RIS	193,022	19.71	[redacted]	[redacted]	-	[redacted]	SW quadrant (£139,667 per QALY foregone)	SW quadrant (£140,232 per QALY foregone)	0.358

*Please note all sequences have BSC as fourth-line treatment.
Abbreviations: LY = life years; QALY = quality adjusted life years; ICUR = incremental cost utility ratio; iNHB = incremental net health benefit; SW = Southwest; DEU = deucravacitinib; APR = apremilast; DMF= dimethyl fumarate; ADA = adalimumab; BIM = bimekizumab; BRO = brodalumab; CER = certolizumab pegol; ETA = etanercept; GUS = guselkumab; INF = infliximab; IXE = ixekizumab; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab.

B.3.11 Exploring uncertainty

The major source of structural uncertainty is related to the simplifying assumption that patients will receive only three lines of treatment before moving to BSC. This assumption has been applied in all recent TAs but is not in line with clinical practice in England and Wales. However, extending the number of sequences is not anticipated to have a meaningful impact on cost-effectiveness estimates since the additional lines of treatment would need to be similar for each sequence under evaluation. All uncertainties that can be included in this analysis have been captured in either the deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA) or the scenario analyses. For the sensitivity analyses, each model parameter was specified a certain distribution, where the mean of the distribution is equal to the point estimate. The standard error of the distribution was set according to any distributional information provided in the original source. If no distributional information was available, the standard error was assumed to be 20% of the mean.

B.3.11.1 Probabilistic sensitivity analysis

One thousand simulations were performed for the PSA, which gives a distribution of incremental results, and consequently, an idea of the overall uncertainty surrounding cost-effectiveness results. Using the NMB approach, the probability of each treatment to be cost-effective at different levels of Willingness-To-Pay (WTP) per QALY is presented in the cost-effectiveness acceptability curve (CEAC).

The model allows for a maximum of 13 sequences to be explored and therefore the PSA can only run 13 sequences simultaneously. To accommodate this, the first PSA was conducted with the exclusion of bimekizumab (as this has recently been approved and use in practice would be less than more established therapies) and infliximab (this is not commonly used in practice due to its indication being for severe disease only). The second PSA included deucravacitinib, bimekizumab and infliximab only.

The cost-effectiveness plane for the deucravacitinib sequence versus the comparator sequences is presented in Figure B.3.2 and Figure B.3.4. The PSA presented in Figure B.3.2 and Figure B.3.4 confirms the deterministic results.

The CEAC presented in Figure B.3.3 shows that the deucravacitinib sequence had the highest probability of being cost-effective over a range of WTP thresholds between £0 and £60,000/QALY. Up until approximately £29,000/QALY the deucravacitinib sequence had a 100% probability of being cost-effective. Similar findings are shown in Figure B.3.5 with the CEAC for the deucravacitinib, bimekizumab and infliximab sequences. The PSA shows that up until approximately £29,000/QALY the deucravacitinib sequence had a 100% probability of being cost-effective. As the WTP increases, the probability of the infliximab sequence being cost-effective started to increase, but deucravacitinib still had a probability of being cost-effective of approximately 99% at a WTP of £30,000/QALY. An overview of the PSA outcomes is presented in Table B.3.23.

Figure B.3.2. Cost-effectiveness plane - deucravacitinib sequence versus comparator sequences (excluding the bimekizumab and infliximab sequences)

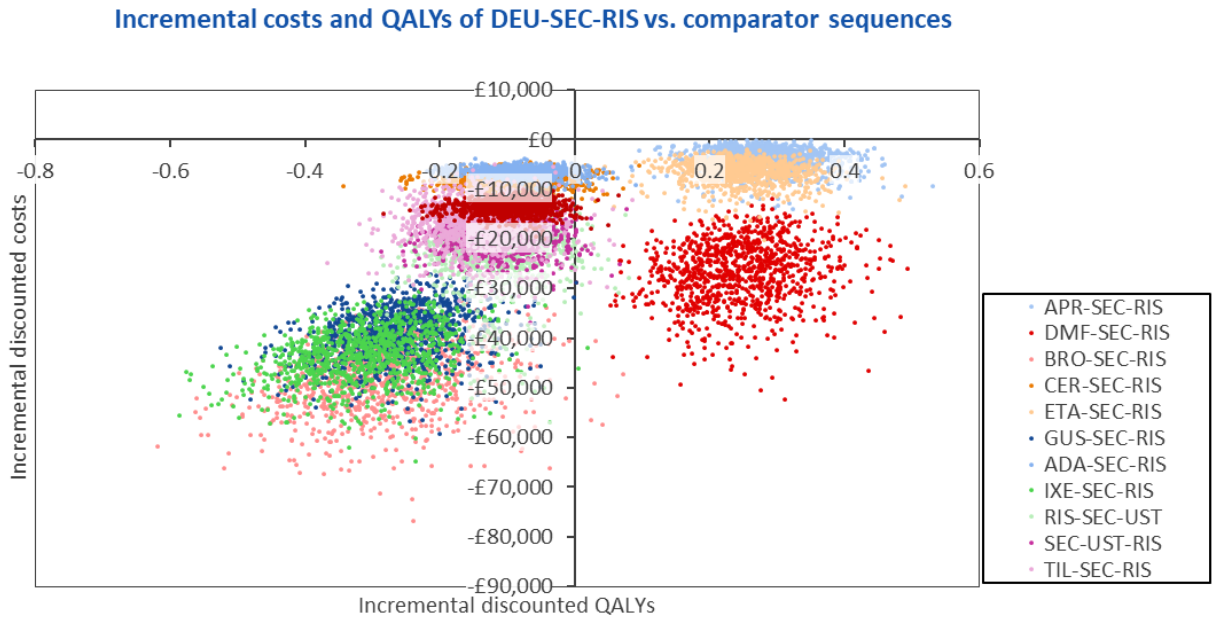


Figure B.3.3. Cost-effectiveness acceptability curve - deucravacitinib sequence versus comparator sequences (excluding the bimekizumab and infliximab sequences)

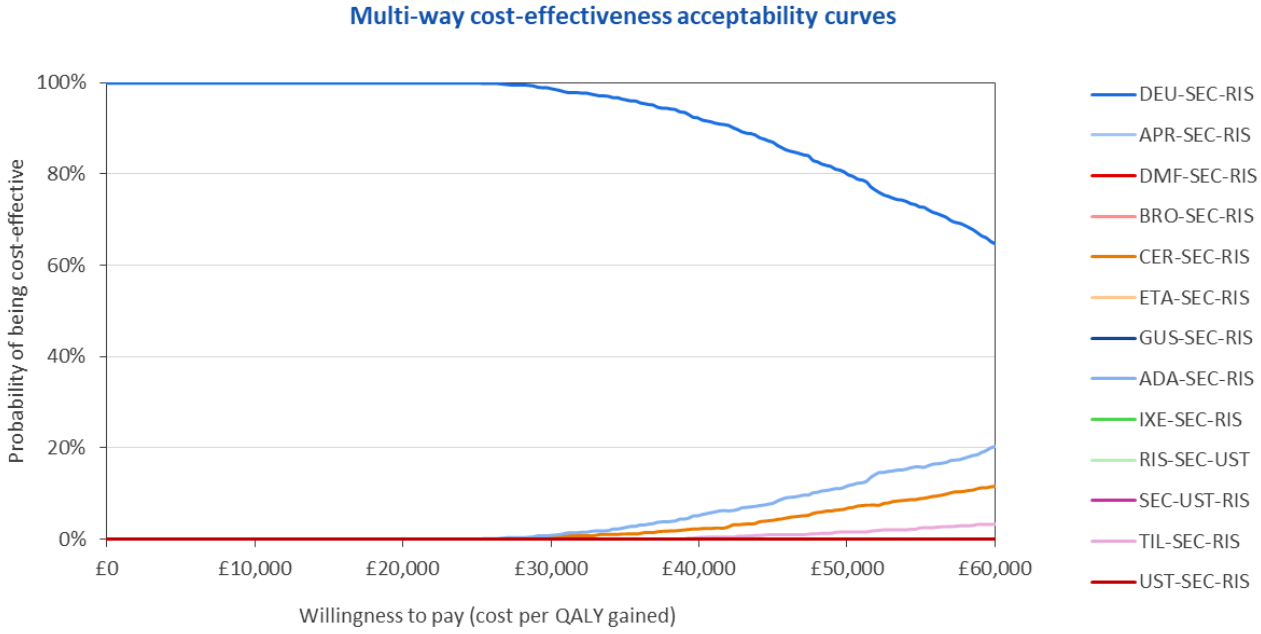


Figure B.3.4. Cost-effectiveness plane - deucravacitinib sequence versus the bimekizumab and infliximab sequences

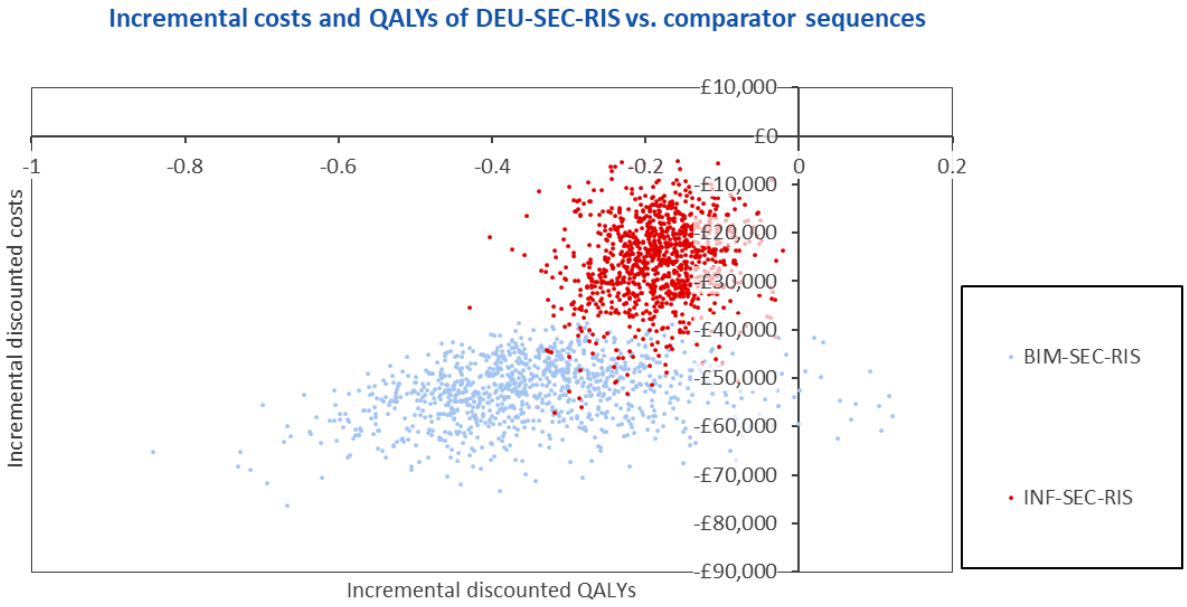


Figure B.3.5. Cost-effectiveness acceptability curve - deucravacitinib sequence versus bimekizumab and infliximab sequences

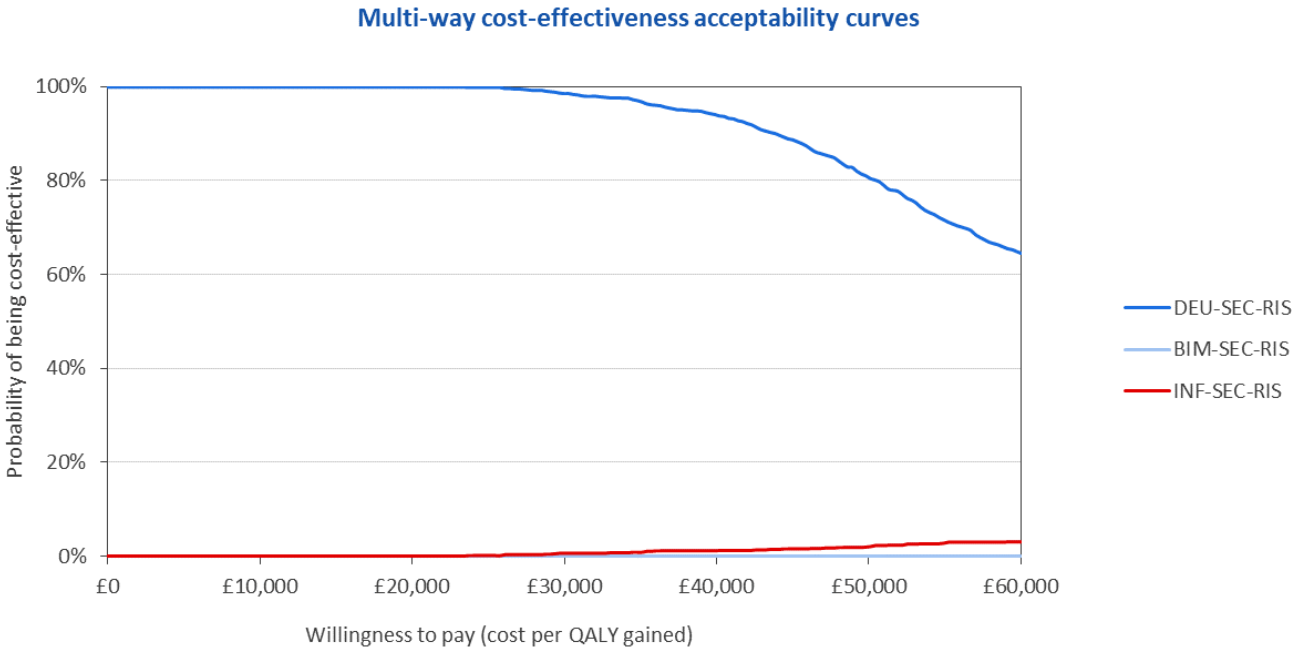


Table B.3.23. Overview of the probabilistic incremental results of the PSA

Sequence*	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICUR
DEU-SEC-RIS	[redacted]	[redacted]	-	-	-
APR- SEC-RIS	£181,795	[redacted]	[redacted]	[redacted]	Dominant (-£13,067)
DMF- SEC-RIS	£204,932	[redacted]	[redacted]	[redacted]	Dominant (-£109,744)
ADA- SEC-RIS	£184,511	[redacted]	[redacted]	[redacted]	SW quadrant (£80,333 per QALY foregone)
BIM- SEC-RIS	£231,304	[redacted]	[redacted]	[redacted]	SW quadrant (£153,171 per QALY foregone)
BRO- SEC-RIS	£225,862	[redacted]	[redacted]	[redacted]	SW quadrant (£170,778 per QALY foregone)
CER- SEC-RIS	£185,999	[redacted]	[redacted]	[redacted]	SW quadrant (£87,222 per QALY foregone)
ETA- SEC-RIS	£184,382	[redacted]	[redacted]	[redacted]	Dominant (-£25,684)
GUS- SEC-RIS	£216,927	[redacted]	[redacted]	[redacted]	SW quadrant (£149,928 per QALY foregone)
INF- SEC-RIS	£204,377	[redacted]	[redacted]	[redacted]	SW quadrant (£140,153 per QALY foregone)
IXE- SEC-RIS	£221,323	[redacted]	[redacted]	[redacted]	SW quadrant (£142,823 per QALY foregone)
RIS- SEC-UST	£199,756	[redacted]	[redacted]	[redacted]	SW quadrant (£193,676 per QALY foregone)
SEC- UST-RIS	£197,484	[redacted]	[redacted]	[redacted]	SW quadrant (£183,562 per QALY foregone)
TIL- SEC-RIS	£194,374	[redacted]	[redacted]	[redacted]	SW quadrant (£114,168 per QALY foregone)
UST- SEC-RIS	£191,681	[redacted]	[redacted]	[redacted]	SW quadrant (£140,232 per QALY foregone)

Abbreviations: QALY = quality adjusted life years; ICUR = incremental cost utility ratio; DEU = deucravacitinib; APR = apremilast; DMF= dimethyl fumarate; ADA = adalimumab; BIM = bimekizumab; BRO = brodalumab; CER = certolizumab pegol; ETA = etanercept; GUS = guselkumab; INF = infliximab; IXE = ixekizumab; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab.

B.3.11.2 Deterministic sensitivity analysis

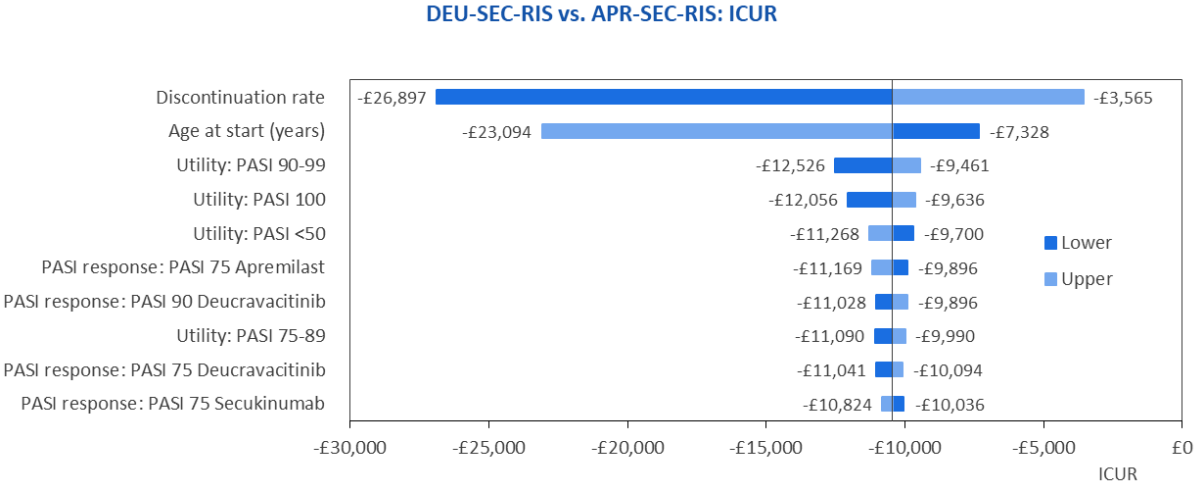
Due to the large number of comparator sequences, only three separate deterministic sensitivity analyses (DSAs) were undertaken comparing the deucravacitinib sequence with the apremilast, adalimumab and brodalumab sequences. The apremilast sequence was chosen as one of the comparators for the DSA as it was the active comparator in the POETYK trials. The DSA versus the adalimumab sequence was conducted to represent the TNF-α class of treatments (based on UK clinician advice and market share research that adalimumab is the most common treatment in this patient population). The DSA versus the brodalumab sequence was conducted to represent the IL class of treatments.

Results from the DSA for the deucravacitinib sequence versus the apremilast sequence are presented below in Figure B.3.8 and tabulated in appendix J.1.1.2. The parameter with the greatest impact on the ICUR was the treatment discontinuation rate. Other key drivers included the age at model start and utility associated with PASI 90-99. Figure B.3.6 shows that the top three parameters with the greatest impact on incremental costs were the discontinuation rate, age at model start and the PASI 75 response for deucravacitinib. The top three parameters with the greatest impact on incremental QALYs were the PASI 75 response for deucravacitinib, age at model start and the utility associated with PASI 90-99 (as shown in Figure B.3.7). It should be noted that the deucravacitinib sequence dominated the apremilast sequence in all cases.

Figure B.3.6. DSA tornado diagram - deucravacitinib versus apremilast sequence (incremental costs)

Figure B.3.7. DSA tornado diagram - deucravacitinib versus apremilast sequence (incremental QALYs)

Figure B.3.8. DSA tornado diagram - deucravacitinib versus apremilast sequence (ICUR)

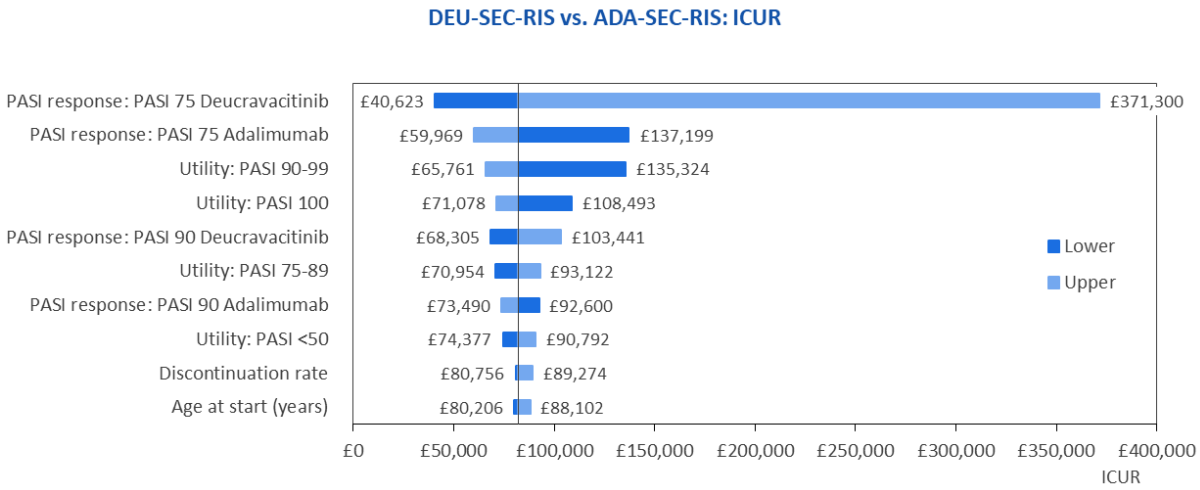


Results from the DSA for the deucravacitinib sequence versus the adalimumab sequence are presented below in Figure B.3.11 and tabulated in appendix J.1.1.2. The parameter with the greatest impact on the ICUR was the PASI 75 response for deucravacitinib. Other key drivers were the PASI 75 response for adalimumab and the utility associated with PASI 90-99. Figure B.3.9 shows that the top three parameters with the greatest impact on incremental costs were the discontinuation rate, the PASI 75 response for deucravacitinib and the age at model start. The top three parameters with the greatest impact on incremental QALYs were the PASI 75 response for deucravacitinib, the PASI 75 response for adalimumab and the utility associated with PASI 90-99 (as shown in Figure B.3.10). It should be noted that the deucravacitinib sequence was cost-effective compared to the adalimumab sequence in all cases.

Figure B.3.9. DSA tornado diagram - deucravacitinib versus adalimumab sequence (incremental costs)

Figure B.3.10. DSA tornado diagram - deucravacitinib versus adalimumab sequence (incremental QALYs)

Figure B.3.11. DSA tornado diagram - deucravacitinib versus adalimumab sequence (ICUR)



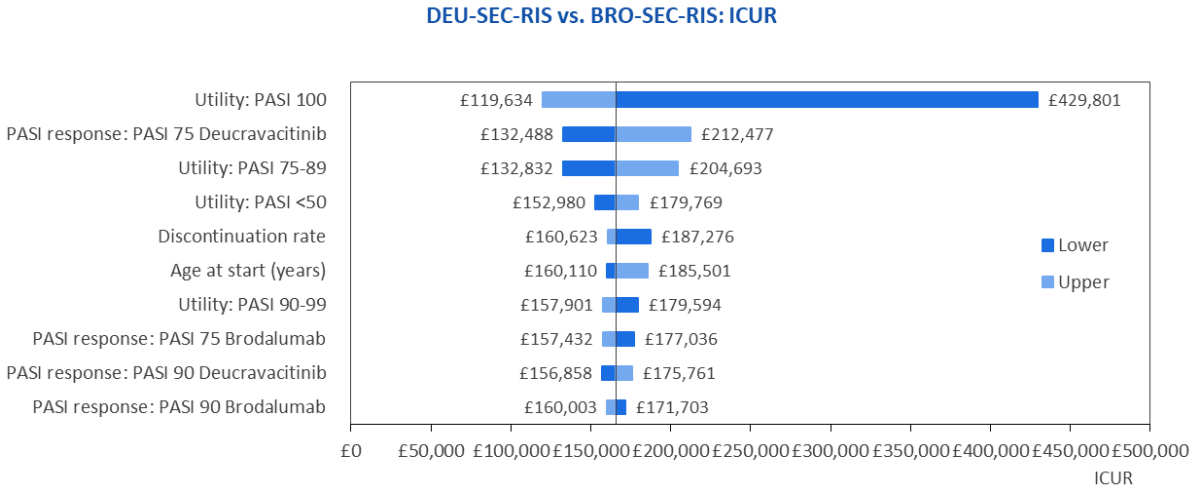
Results from the DSA for the deucravacitinib sequence versus the brodalumab sequence are presented below in **Figure B.3.14** and tabulated in appendix J.1.1.2. The parameter with the greatest impact on the ICUR was the utility value associated with PASI 100. Other key drivers included the PASI 75 response for deucravacitinib and the utility value associated with PASI 75-89. Figure B.3.12 shows that the top three parameters with the greatest impact on incremental costs were the discontinuation rate, age at model start and the PASI 75 response for brodalumab. The top three parameters with the greatest impact on incremental QALYs were the utility value associated with PASI 100, the PASI 75 response for deucravacitinib and the utility value associated with PASI 75-89 (as shown in Figure B.3.13). It should be noted that the deucravacitinib sequence remained cost-effective compared to the brodalumab sequence in all cases.

Figure B.3.12. DSA tornado diagram - deucravacitinib versus brodalumab sequence (incremental costs)

Figure B.3.13. DSA tornado diagram - deucravacitinib versus brodalumab sequence (incremental QALYs)

[redacted]

Figure B.3.14. DSA tornado diagram - deucravacitinib versus brodalumab sequence (ICUR)



B.3.11.3 Scenario analysis

Structural uncertainty was explored by generating results using alternative assumptions for key input parameters, all other settings and inputs as per base case remained the same.

An overview of the findings for each scenario is detailed below. The detailed results for each scenario are presented in appendix J.1.1.3. A summary table of the impact each scenario has on the cost-effectiveness of the deucravacitinib sequence against all comparator sequences considered can be found in Table B.3.24.

Scenario 1: Earlier timepoint for assessing tildrakizumab response (12 weeks)

Table B.5.58 in appendix J presents the outcomes of scenario 1 where the NMA used in the model is reflective of a 12-week induction period for tildrakizumab (24-week for deucravacitinib and 10-16 week for all comparators); this is the earliest timepoint when treatment can be stopped as per NICE guidance (as per SA2 of the NMA). Results were similar to that of the base case where the deucravacitinib sequence dominated the apremilast, DMF and etanercept sequences. When compared with the other sequences, the deucravacitinib

sequence was less costly but was associated with less QALYs, with deucravacitinib saving more than £20,000 for every QALY foregone. The incremental QALYs between deucravacitinib and tildrakizumab was smaller in this scenario than compared to the base case. As per the base case results, the deucravacitinib sequence was cost-effective against all treatment sequences.

Scenario 2: Earlier induction period for deucravacitinib (16 week) and tildrakizumab (12 week)

Table B.5.59 in appendix J reports the outcomes of scenario 2 where the NMA used in the model is reflective of a 16-week induction period for deucravacitinib and a 10–16-week induction period for all comparators (as per analysis 1 of the NMA). As a result of the deucravacitinib sequence generating slightly less QALYs, the QALY differences between the deucravacitinib sequence and the apremilast, DMF and etanercept sequences were smaller than in the base case, whereas the QALY differences between the deucravacitinib sequence and the other comparator sequences were larger. Despite the slightly lower efficacy for deucravacitinib in this scenario, the deucravacitinib sequence remained cost-effective against all treatment sequences with deucravacitinib dominating the apremilast, DMF and etanercept sequences and saving more than £20,000 for every QALY foregone versus all other comparators.

Scenario 3: Long-term response data for all treatments (40–60-week)

Table B.5.60 in appendix J presents the outcomes of scenario 3 where the NMA used in the model is reflective of a 52-week induction period for deucravacitinib and a 40-60-week induction period for all other comparators, as per analysis 3 of the NMA. This scenario aimed at assessing impact of long-term response on the ICUR. It showed there are less comparator sequences as not all comparator treatments have longer term efficacy data publicly available. Thus, the certolizumab, DMF, etanercept and tildrakizumab sequences were omitted from this analysis. The results vary from the base case analysis as in this scenario the deucravacitinib sequence dominated the apremilast, adalimumab and infliximab treatment sequences. This is due to deucravacitinib being more efficacious than these comparators when long-term response data was used. Compared to the other treatment sequences, the deucravacitinib sequence saved more than £20,000 for every QALY foregone. Overall, the deucravacitinib sequence is cost-effective against all treatment sequences considered.

Scenario 4: Using sequences modelled in previous TAs

A scenario was conducted where treatment sequences were based on the sequences presented in the brodalumab NICE submission[112] and BAD guidelines 2017[137] (see section B.2.2.5). The total costs and QALYs accrued with each of the sequences were lower than those accrued in the base case analysis (see results in Table B.5.61 in appendix J). This was mainly due to the outcomes of the NMA showing ustekinumab to have lower PASI response rates than risankizumab. The deucravacitinib sequence remained cost-effective when compared against all comparator sequences.

Scenario 5: Single treatment comparison

A scenario was undertaken whereby all treatments were compared in a pairwise manner. In this scenario patients who discontinued their first line treatment move to BSC. The outcomes

from scenario 5 are presented in Table B.5.62 (in appendix J). As patients in this scenario move straight to BSC after discontinuation, each treatment sequence accrued fewer total costs and QALYs than the base case analysis. The deucravacitinib sequence was dominant versus the DMF sequence and the ICURs versus the apremilast and etanercept sequences were below £20,000/QALY (£10,682/QALY and £3,255/QALY respectively). When compared to the other sequences, the deucravacitinib sequence saved more than £20,000 for every QALY foregone.

Scenario 6: Treatment discontinuation based on adalimumab discontinuation data from BADBIR 2020, in Yiu et al. (2020)

Table B.5.63 (in appendix J) presents the outcomes of scenario 6 where the discontinuation rate from the BADBIR 2020 study[95] was only based on patients who received adalimumab (since it was the most prevalent treatment in BADBIR, see section B.3.3.2). Results showed that the total costs and QALYs for each sequence are lower in this scenario than in the base case. This is expected as the discontinuation rate per cycle is higher than the rate used in the base case analysis, resulting in more patients discontinuing treatment and moving to the next line of treatment. Despite the changes in total costs and QALYs, results for this scenario were in line with the results from the base case analysis.

Scenario 7: Treatment discontinuation based on BADBIR 2015[115]

Table B.5.64 (in appendix J) presents the outcomes of scenario 7 based on BADBIR 2015 discontinuation rates used in previous TAs (see section B.3.3.2). As the discontinuation rate was higher than the discontinuation rate used in the base case analysis, less patients remain on treatment resulting in the total costs and QALYs for each sequence in this scenario being lower than the base case results. In line with the base case, the outcomes of this scenario showed that the deucravacitinib sequence remains cost-effective when compared against all comparator sequences.

Scenario 8: Treatment-specific discontinuation rates

Using treatment-specific discontinuation rates resulted in outcomes that varied considerably from the base case results (see Table B.5.65 in appendix J). The deucravacitinib sequence dominated the apremilast, DMF, adalimumab, certolizumab, etanercept, infliximab and ixekizumab sequences. This is due to deucravacitinib having a lower discontinuation rate than the treatment sequences it dominates. Compared to the other treatment sequences, the deucravacitinib sequence saved more than £20,000 for every QALY foregone.

Scenario 9: Treatment waning

Scenario 9 applied a HR of 1.24 from Gniadecki[117] to the probabilities of PASI response of the second and third-line treatments in the treatment sequences when patients had previously received a biologic (see results in Table B.5.66 in appendix J). This resulted in lower total costs and QALYs for each treatment sequence compared to the base case analysis. This is due to the second and third-line biologics in the treatment sequences being less efficacious than in the base case, leading to a reduction in patients achieving adequate response to treatment, consequently resulting in treatment discontinuation. This resulted in lower ICUR values. Although the ICURs were lower, the deucravacitinib sequence was cost-effective when evaluated against all comparator sequences. The apremilast, DMF and etanercept

sequences were dominated by deucravacitinib and the deucravacitinib sequence saved more than £20,000 for every QALY foregone when compared against the other sequences.

Scenario 10: Utilities based on pooled POETYK trials

When the pooled POETYK-PSO trial utilities were used, the total QALYs associated with each treatment sequence were higher than in the base case resulting in higher ICUR values (see results in Table B.5.67 in appendix J). This is due to the POETYK-PSO trial utilities being higher than the base case utilities leading to all utilities associated with each of the PASI ranges being higher in this scenario (see section B.3.4.1). However, results were in line with the base case results with the deucravacitinib sequence remaining cost-effective when compared to all treatment sequences.

Scenario 11: Utilities based on TA350 (secukinumab) submission

The utility values reported in TA350[80] are pooled values from the secukinumab pivotal clinical trials (see section B.3.4.5). In this scenario, the total QALYs accrued with each treatment sequence was lower than in the base case analysis resulting in lower ICUR values (see results in Table B.5.68 in appendix J). This is due to the utilities based on TA350 being lower than the base case utility values for all PASI categories. However, the deucravacitinib sequence remained cost-effective against all treatments, dominating the apremilast, DMF and etanercept sequences and saving more than £20,000 per QALY foregone against the other treatment sequences.

Scenario 12: Utilities based on TA511 (brodalumab) submission

The utility values reported in TA511[76] are pooled values from the brodalumab pivotal clinical trials (see section B.3.4.5). Similar to scenario 11, the total QALYs accrued with each treatment sequence was lower than in the base case analysis resulting in lower ICUR values, as the utilities in TA511 were lower than the base case utility values for all PASI categories (see results in Table B.5.69 in appendix J). In line with scenario 11, the outcomes of this scenario show that the deucravacitinib sequence remained cost-effective when compared against all comparator sequences.

Scenario 13: Psoriasis-related mortality

A HR of 1.79 was applied to the all-cause mortality rate which was based on a prospective cohort study of adults with severe psoriasis.[49] In this scenario, there was a reduction in the total LYs gained for each treatment sequence due to the assumption that there is a higher rate of mortality for patients with psoriasis (see results in Table B.5.70 in appendix J). Consequently, there was a reduction in total costs and QALYs as less patients were assumed to be alive and receive treatment. However, the deucravacitinib sequence continued to dominate the apremilast, DMF and etanercept sequences and saved more than £20,000 per QALY foregone compared to the other sequences.

Scenario 14: 10-year time horizon

Results of scenario 14 are presented in Table B.5.71 (in appendix J) and show that with a shorter time horizon, less costs, LYs and QALYs were accrued and the ICUR values were higher compared to the ICURs reported in the base case analysis. Regardless of the shorter time horizon, the deucravacitinib sequence dominated the apremilast, DMF and etanercept

sequences and saved more than £20,000 for every QALY foregone when compared to the other sequences.

Scenario 15: BSC and non-responder costs informed from Fonia et al, 2010

A scenario has been conducted where costs for both BSC and non-responders were informed from the Fonia et al (2010)[59] publication. Results of scenario 15 are presented in Table B.5.72. Compared to the base case analysis, the total costs associated with each treatment sequence were higher due to the BSC costs from Fonia et al (2010) being higher than the DISCOVER study[45] costs used for the base case analysis (see results in Table B.5.67 in appendix J). The results showed the ICUR values were slightly lower than the base case analysis, however the deucravacitinib sequence remained cost-effective when evaluated against all comparator sequences.

Table B.3.24. Summary of the impact each scenario has on the cost-effectiveness of the deucravacitinib sequence vs all comparator sequences

Base case and scenarios	Input modified *vs base case (BC)*	Impact on ICER vs APR/ DMF/ ETA compared to base case	Impact on ICER vs other biologics compared to base case	DEU sequence cost-effective vs comparator sequences?
Base case	-	**Dominant**	**SW quadrant**	**Yes**
Scenario 1	TIL response measured at 12 weeks *BC: TIL response measured at 28 weeks*	Similar	• vs TIL: ICUR increased by approximately £543,000 • vs all others: ICURs remained similar	Yes
Scenario 2	DEU response measured at 16 weeks and TIL at 12 weeks *BC: DEU response measured at 24 weeks, TIL at 28 weeks*	Similar with an increase in ICUR values	• vs TIL: ICUR increased by approximately £27,000 • vs all others: ICUR values decreased substantially	Yes
Scenario 3	Long-term response data for all treatments *BC: DEU response measured at 24 weeks, TIL at 28 weeks, all other comparators between 10 to 16 weeks*	Similar for APR and DMF sequences with an increase in ICUR values. No long- term data for ETA available.	• DEU sequence dominated INF sequence • Where long-term data was available for other biologics, ICURs increased	Yes
Scenario 4	Using treatment sequences modelled in previous Tas *BC: Sequence: 1L>SEC>RISA*	Similar with a decrease in ICUR values	• vs CER, SEC and TIL there is an increase in ICUR values • vs all other sequences there is a decrease in ICUR values	Yes
Scenario 5	Single treatment comparison *BC: sequences comparison*	• DEU sequence no longer dominates APR and ETA sequences. For both comparisons, the ICUR< £10,000 per QALY gained. • DEU sequences remains to dominate DMF sequence however there is a decrease in ICUR value	• vs all sequences: decrease in ICUR values	Yes
Scenario 6	Treatment discontinuation based on ADA discontinuation data from BADBIR 2020, in Yiu et al. (2020).	Similar with a decrease in ICUR values	• vs INF and UST there is an increase in ICUR values • vs all other sequences there is a decrease in ICUR values	Yes

Base case and scenarios	Input modified *vs base case (BC)*	Impact on ICER vs APR/ DMF/ ETA compared to base case	Impact on ICER vs other biologics compared to base case	DEU sequence cost-effective vs comparator sequences?
	BC: common treatment discontinuation based on all treatments from BADBIR 2020			
Scenario 7	Treatment discontinuation based on BADBIR 2015. *BC: common treatment discontinuation based on all treatments from BADBIR 2020*	Similar with a decrease in ICUR values	• Vs ADA, INF and UST: increase in ICUR values • Vs all other sequences: decrease in ICUR values	Yes
Scenario 8	Treatment specific discontinuation rates *BC: common treatment discontinuation based on all treatments from BADBIR 2020*	Similar with the ICURs increasing for APR and ETA and decreasing for DMF	• DEU sequence dominated ADA, CER, ETA, INF and IXE sequences. • vs all other sequences: increase in ICUR values	Yes
Scenario 9	Treatment waning *BC: no treatment waning*	Similar with a decrease in ICUR values	• vs all sequences: decrease in ICUR values	Yes
Scenario 10	Utilities based on pooled POETYK trials *BC: utilities fromTA511 and TA350 pooled POETYK*	Similar with an increase in ICUR values	• vs all sequences: decrease in ICUR values	Yes
Scenario 11	Utilities based on TA350 (SEC) *BC: utilities fromTA511 and TA350 pooled POETYK*	Similar	• Similar vs all sequences with an increase in ICUR values	Yes
Scenario 12	Utilities based on TA511 (BRO) *BC: utilities from TA511 and TA350 pooled POETYK*	Similar with a decrease in ICUR values	• vs all sequences: decrease in ICUR values	Yes
Scenario 13	Including psoriasis-related mortality *BC: all-cause mortality*	Similar with an increase in ICUR values	• vs all sequences: increase in ICUR values	Yes
Scenario 14	Using a 10-year time horizon *BC: Lifetime horizon*	There is a substantial increase in ICUR values	• vs all sequences: substantial increase in ICUR values	Yes

Base case and scenarios	Input modified *vs base case (BC)*	Impact on ICER vs APR/ DMF/ ETA compared to base case	Impact on ICER vs other biologics compared to base case	DEU sequence cost-effective vs comparator sequences?
Scenario 15	BSC and non-responder costs informed by Fonia et al, 2010 *BC: BSC costs and non-responder costs sourced from DISCOVER*	Similar with an increase in ICUR values	• similar vs all sequences with a decrease in ICUR values	Yes

Abbreviations: ADA = adalimumab; APR = apremilast; BC = base case; BRO = brodalumab; BSC = best supportive care; CER = certolizumab pegol; DEU = deucravacitinib; DMF= dimethyl fumarate; ETA = etanercept; ICUR = incremental cost utility ratio; INF = infliximab; SEC = secukinumab; TA = technology appraisal; TIL = tildrakizumab; UST = ustekinumab; SW = south-west

B.3.12 Subgroup analysis

The results of the subgroup analyses presented in section B.2.8 show that the pooled POETYK results are consistent with the individual results from the POETYK PSO-1 and POETYK PSO-2 trials. Furthermore, deucravacitinib was significantly more efficacious than apremilast and placebo regardless of disease severity and prior use of biologics in the POETYK trials. As such, no investigation of cost-effectiveness according to subgroups was performed.

B.3.13 Benefits not captured in the QALY calculation

There are additional benefits in introducing deucravacitinib as a treatment option for patients with moderate-to-severe plaque psoriasis, which have not been captured in the QALY.

- Unlike most other therapies in this disease setting, deucravacitinib is administered orally, providing a more convenient treatment option for patients that are averse to injectable treatments. This is reinforced by the MAPP study discussed in section B.1.3.8 where it was found that 52% of patients that had received or were receiving a biologic therapy found their treatment burdensome with 31% of these patients citing the main reason to be the fears, anxiety and inconvenience of the injectable treatments.[67] BMS conducted market research with health care professionals to identify patient preferences to systemic treatments for patients with moderate-to-severe psoriasis. It was found that approximately 26% of patients request/have preference for an oral treatment and 19% of patients are hesitant to use injectables.
- In addition to this, NHS England provide guidelines that advise switching patients from intravenous medications to oral therapies to avoid patients being exposed to COVID-19.[138] Although these are guidelines specific to patients with cancer, this could be generalisable to patients with other diseases as it reduces the number of patients entering hospitals and being exposed. Similarly, the NICE COVID-19 rapid guideline highlights options for delivering treatment during the pandemic and values the route of administration or mode of delivery that could make hospital attendance less likely.
- Although there are effective biologics in this disease setting, specialist initiation is required, and pre-treatment screening investigations are needed such as blood tests including viral and TB infection screens (blood test and chest x-ray) and pre-treatment vaccinations. Once all assessments have been cleared, logistical issues such as homecare deliveries can arise, and it was estimated by a clinical expert that there is often around 6-week delay in patients receiving treatment from when it was first initiated. This can create costly healthcare resource utilisation and can be a burden on the NHS as discussed in section B.1.3.8. Deucravacitinib's oral mode of administration and less need for pre-treatment screening and ongoing monitoring as supported by the draft SmPC may reduce the resource use and delayed treatment initiation associated with psoriasis care.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Internal validation

The internal validity of the economic model was examined by two modelling experts not involved in this study to identify potential programming errors within the model itself. A series of stress tests involving both extreme values and equal values across treatment arms were run in which the model input parameters were varied to examine whether the results updated as expected. Any tests that led to unexpected outcomes were examined in more detail and remedied wherever applicable. One comment was that the model's file size is large, but it was recognized that this was due to the short cycle length in combination with the number of sequences modelled. A potential solution could be to use VBA macros, however, this would make the model less transparent and therefore the VBA functionality was not incorporated.

External validation

The model was validated for its suitability for the UK by two health economists different to the developer of the original model. The following aspects were validated: model structure and model settings. The key inputs and assumptions used in the model were validated by two UK clinical experts, to ensure they reflect clinical practice in England and Wales. The following factors were considered when selecting and approaching the experts: representation of different background and perspectives in dermatology, representation of varied geographical areas in England and Wales, and knowledge of the NICE process). After approaching all the clinical experts of interest, a total of two clinicians participated. Potential conflict of interest from each expert was not sought.

The participating clinicians were sent a formal invitation to attend the meeting and were given pre-reading material to familiarise themselves with the meeting objectives and discussion topics. The pre-reading material consisted of a slide-deck generated in Microsoft PowerPoint which detailed the background of deucravacitinib and its pivotal clinical trials, outcomes of the POETYK-PSO-1 and POETYK-PSO-2 clinical trials and the NMA, and the proposed model structure and model inputs to be discussed and the assumptions/rationale around these.

The expert meeting was held via video call on Microsoft Teams and the two clinical experts were interviewed with their cameras on. Information was elicited via a range of open and closed questions relating to the modelling assumptions and topics in the pre-reading material. Where clinicians were unfamiliar with a term or concept this was clarified with further information. Questions were asked relating to the following topics: NMA, timing of response assessment, treatment sequences, treatment discontinuation, efficacy of biologics in subsequent treatment lines, resource use relating to monitoring, costs relating to BSC and safety/AEs. Where possible and relevant, the information provided by the clinical experts were incorporated into the model.

The only areas where it was believed that the model inputs could vary depending on clinician's preference was the treatment sequencing: the clinical experts mentioned this varies by hospital and as such it is difficult to define a commonly used second- and third-line treatments in the sequence to represent the national use. This has been explored in a scenario analysis.

When the sequences were changed, there was some variation in the ICURs, but the conclusions were in line with the base case analysis.

B.3.15 Interpretation and conclusions of economic evidence

This economic evaluation considered patients with moderate-to-severe plaque psoriasis, which reflects the population of the POETYK trials and reflects the population included in the decision problem.

The results of the economic evaluation are generalisable to clinical practice in England and Wales, for the following reasons:

- The structure of the economic model is consistent with previous submissions to NICE in this indication.
- The population of the POETYK PSO-1 and POETYK PSO-2 trials are considered to be reflective of the patient population in England and Wales.
- Unit costs have been sourced from relevant, well-established UK sources (e.g., NHS Reference Costs, PSSRU, BNF).
- The approach adopted takes into account feedback from the ERGs and Appraisal Committees in previous NICE psoriasis appraisals.
- The model structure and inputs have been validated by UK-based clinical and health economic experts.

Strengths of the analysis

Strengths of the economic evaluation include that the efficacy of deucravacitinib within the model was based directly on data from high quality RCTs and that resource use was estimated from UK data. In addition, the main source of efficacy data was a comprehensive NMA that connects a number of large-scale RCTs, which was conducted according to NICE DSU best practice recommendations.[139] In addition, the PASI 75 endpoint used to define response is a key endpoint in psoriasis according to clinical guidelines and clinical expert opinion. The model structure allowed for accurate tracking of this outcome during the assessment period, and also includes the use of PASI 100, representing complete skin clearance, as a distinct response level. Furthermore, the cost estimates for BSC and non-responders in this economic evaluation were informed by the DISCOVER study.[45] With the cost estimates from the Fonia et al. (2010)[59] publication being criticised in previous NICE appraisals, further research has been encouraged in this area by NICE to reduce the uncertainties surrounding BSC cost estimates. The DISCOVER[45] study is a recent, representative, and robust source of evidence and hence minimises a key source of uncertainty in the analysis. The model allowed for variable induction periods to align with NICE TAs guidance and used a 40-year time horizon, a period long enough to capture any differences between sequenced comparators.

Limitations of the analysis

A limitation of the analysis is the lack of long-term data for clinical outcomes. The discontinuation rate in the model was based on data from the UK BADBIR registry; however, no suitable data are available to assess discontinuation rates over longer periods. In addition, during maintenance therapy patients are assumed to maintain the same level of PASI

response they achieved during induction, until discontinuation. This approach is consistent with all prior TAs in psoriasis, and data from the POETYK trials demonstrate stable levels of response up to 52 weeks. However, longer-term evidence for this assumption is lacking.

The mean utility in the POETYK trials for patients with baseline DLQI >10 with a week 16 PASI response of 90 or better is higher than the general population utility for an UK age-matched population. To mitigate the impact of the resulting ceiling effect and better reflect clinical reality, the base-case analysis used a new set of utility data which were derived via a crude pooling approach using data from the POETYK trials and prior TAs.

Conclusion

This economic analysis shows that deucravacitinib is a cost-effective treatment relative to the comparators in the decision problem for the treatment of adult patients with moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. However, these results exclude the confidential PAS for several comparators (apremilast, brodalumab, bimekizumab, guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab).

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HTAI PCIG project:

Summary of Information for Patients (SIP):

International SIP template

Introduction for patient organisations:

Background:

Understanding the experiences of patients, their families and carers, is becoming widely recognised as an important component in any Health Technology Assessment (HTA). Patients and patient organisations can help to provide this information through their engagement with the HTA process, and it is now becoming standard practice for HTA bodies to request input during the assessment process. It is therefore important that relevant patient representative have an informed and appropriate understanding of the new medicine under review to optimise their input.

Why should I use a SIP?

This *Summary of Information for Patients (SIP)* is a supporting document that has been developed to provide you with relevant background information about the new medicine under review. We hope it will help you / your organisation to structure a response to the HTA body, and comment on where you see the new medicine adding most value to the patient community. Production of the SIP has been in response to patient organisations requesting this information. However, using the SIP template is optional.

The information within this template has been provided by the pharmaceutical company that is developing the new medicine, and sent to you by your HTA agency assessing the new medicine. This has been reviewed by the HTA body to ensure that the content is not commercial in any way.

It is important that the information included within this template is used as background reading to inform and support your input into the ongoing HTA assessment. Patient groups are requested to kindly not copy statements directly into their responses when providing input into the HTA review.

To help you navigate the SIP it has been divided into four sections:

- **SECTION 1: Submission summary.** This includes a summary about the new medicine, the pharmaceutical company that makes it and the HTA body undertaking the assessment of the new medicine.

- **SECTION 2: Current landscape.** This section has details about the condition, how it is diagnosed and currently treated. Patient-based evidence about the condition may be included here to help set the scene as to where the new medicine will potentially fit in and provide benefit to patients.

- **SECTION 3: The new medicine.** This is where all of the details about the new medicine can be found, such as how it works, how it is given or taken, and its key attributes.

- **SECTION 4: Further information, glossary and references.**

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the guidance included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers.

1a) Executive summary: In only a few sentences please provide a top-level summary to describe the new medicine. Please outline the main patient population it is proposed to treat:

Deucravacitinib is a new type of small molecule. It targets the body's immune system to encourage it to stop the inflammation caused by psoriasis. Deucravacitinib is an alternative to existing treatment options that may be as efficacious as some biologics, but with the convenience and ease of oral administration for patients by being an oral tablet that is taken once a day.

1b) Name of new medicine (generic and brand name):

Deucravacitinib (Brand name not yet available).

1c) Authorisation: Please provide marketing authorisation information and link to the regulatory agency approval:

A marketing authorisation application has been filed for deucravacitinib for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. This has not yet been approved. Please refer to submission Document B section B.1.2.3.

1d) Name, address and contact details of SIP author at the pharmaceutical company making the submission. Please provide this for patients/patient groups should they require additional information. In some countries, this section may be removed depending on local compliance regulations:

• Company name and address: Bristol-Myers Squibb, Unit 2 Uxbridge Business Park Sanderson Road, Uxbridge UB8 1DH • Representative name and title: Aminata Thiam, Senior Manager HEOR • Representative contact details (email/phone): aminata.thiam@bms.com

1e) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the new medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Psoriasis Association: grant of £1,500 for corporate membership (2022)

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation may wish to add country-level information where needed to provide local country-level context.

Please focus this submission on the **target indication** rather than sub-groups, as this could distract from the focus of the SIP and the HTA review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition

Please provide a few sentences to describe the main condition that the new medicine is planned to treat. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available.
Plaque psoriasis is a chronic, immune-mediated, inflammatory condition which causes symptoms on the skin and sometimes other parts of the body.[1, 2] It cannot be cured and typically follows a relapsing and remitting course, often requiring lifelong management.[3] Plaque psoriasis (also known as psoriasis vulgaris) is the most common form and is characterised by well demarcated red scaly plaques that vary in their extent from isolated patches to widespread coverage.[4-9] It typically presents on knees, elbows, and scalp, but it can present anywhere on the body.[10, 11] Some of the most reported symptoms that vary in severity are scaling of the skin, itching, skin pain, bleeding, skin cracking and dry skin.[12, 13] Nail and scalp psoriasis are common and problematic presentations in psoriasis.[11, 14] Nail psoriasis can include pitting, fungal growth under the nail, subungual hyperkeratosis, which means a chalky substance under the nail and nail discoloration.[15] Scalp psoriasis poses challenges to treatment, as it is difficult to reach the scalp for topical treatments.[14] The prevalence of psoriasis is between 1.3% and 2.2% in the UK.[16] Approximately 90% of people with psoriasis have plaque psoriasis, and approximately 41% of those have moderate-to-severe disease (34% moderate, 7% severe) in England and Wales. This equates to a projection of approximately 280,438 adults with moderate-to-severe plaque psoriasis in England in 2023.[17, 18]

2b) Diagnosis of the condition (in relation to the new medicine being evaluated)

If relevant to the new medicine submission, please briefly explain how the condition is diagnosed and how this impacts patients:
This is not applicable to deucravacitinib, as psoriasis will already have been diagnosed prior to initiating treatment.

2c) Current treatment options:

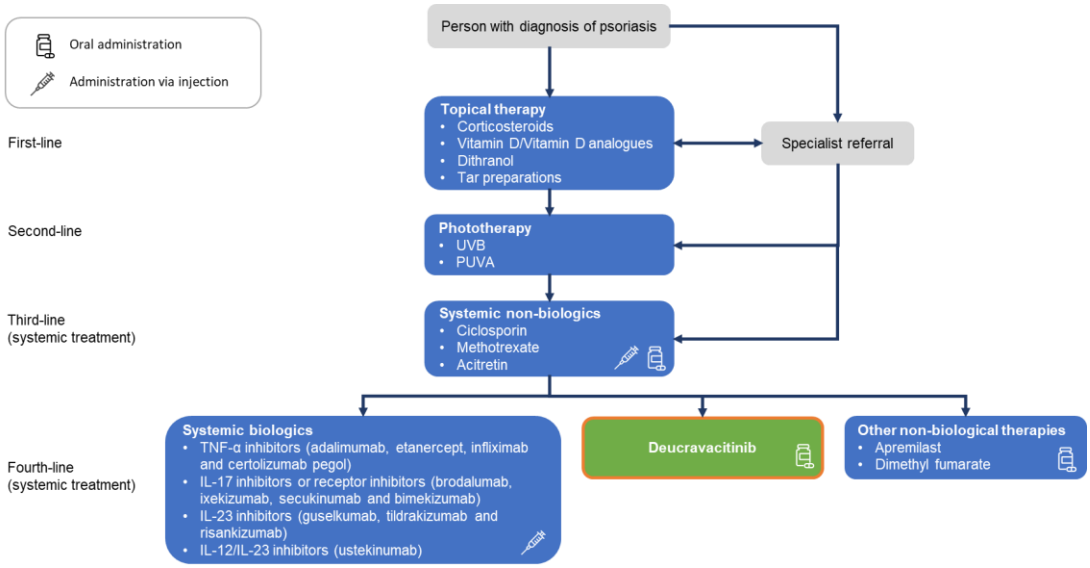
The purpose of this section is to set the scene on how the condition is currently managed:
• What is considered the standard of care for this condition? Please give emphasis to the specific setting and condition being considered by the HTA body in this review
• Please also consider:
  ○ Are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are
  ○ What are the short- and long-term implications of using current medicines?
• Please reference current treatment guidelines where needed

- Please conclude by stating how you feel the new medicine will potentially address the unmet needs of patients

Figure 1 presents the current clinical pathway of care based on the available treatment guidelines for patients with moderate-to-severe plaque psoriasis in England, and the proposed placement for deucravacitinib within the fourth line setting within the treatment pathway. Patients with severe psoriasis (defined as PASI ≥10 and DLQI >10 by NICE clinical guidelines 153) and for whom second-line phototherapy or third-line systemic non-biologic treatment is not an option because of lack of response, contraindication or not being tolerated can be treated in the fourth line with a range of biologics. Oral therapy options, also recommended at the fourth line, are limited to non-biologics such as the anti-inflammatory dimethyl fumarate and the phosphodiesterase type-4 inhibitor apremilast.[19, 20]

Deucravacitinib, a novel oral treatment that targets tyrosine kinase 2 (TYK2), provides an alternative to existing fourth line treatment options but with the convenience and ease of oral administration for patients.

Figure 1. NICE clinical pathway of care for adults with plaque psoriasis showing the proposed positioning of deucravacitinib



Abbreviations: IL = interleukin; PUVA = psoralen plus ultraviolet A; TNF: tumour necrosis factor; UVB = ultraviolet B.
Note: Methotrexate administration may be parenteral. All biologics are administered by subcutaneous injection, except infliximab which is administered as an intravenous infusion.
Source. Adapted from the NICE pathway for psoriasis.[21]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might include outputs from patient preference studies, when conducted in order to show what matters most to patients and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE evidence that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Any such evidence included in the SIP should be formally referenced wherever possible.

Patients with psoriasis have reported significantly worse health-related quality of life (HRQoL) than the general population,[22] and psoriasis can have a significant impact on mental health and well-being, which is often inadequately recognised and managed by clinicians.[23] The anatomical location and visibility of psoriatic plaques (e.g., scalp, face, hands, nails) can also have a significant

impact on HRQoL.[1] The visible nature of disfiguring psoriatic plaques can lead to social stigmatisation, with those affected reporting exclusion from normal social environments such as schools, workplaces, and swimming pools. Psoriasis can also negatively impact people's relationships. This is seen for example, in people with psoriasis on their genitals. As a result, patients with plaque psoriasis might avoid social activities and commonly report experiencing loneliness, isolation, feelings of being unattractive, and frustration.[1]

Patient HRQoL in psoriasis has been reported in several studies:

- A UK cohort study using data from Clinical Practice Research Datalink (CPRD) found that patients with psoriasis showed an elevated risk of developing depression, anxiety, and suicidality compared to the general population, and this risk increased with disease severity.[24]
- A real-world study of multiple countries including the UK (the Growth for Knowledge [GfK] study) indicated that in patients with psoriasis, the presence of itch versus no itch had a negative impact on multiple HRQoL measures, which worsened with itch severity.[25]
- In a large multinational survey, 84% of people with psoriasis reported discrimination or humiliation, 43% reported effects on their relationships, and 54% reported effects on work life due to psoriasis.[26]

SECTION 3: The new medicine

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used if they will help to convey information more clearly.

3a) How does the new medicine work?

What are the important features of this medicine? Please outline as clearly as possible important details relating to the mechanism of action and how the medicine interacts with the body that you consider relevant to patient groups. Where possible, please describe how you feel the new medicine is innovative or novel, and how this might be important to patients and their communities.
Deucravacitinib blocks the activity of TYK2, an enzyme in the immune system that triggers chemical 'messengers' to send signals to other cells to cause inflammation in the body. Examples of these chemical 'messengers' include interleukin (IL)-23, IL-12, and type I interferon. By only blocking a specific region of TYK2, deucravacitinib reduces the trigger of inflammatory chemical messengers, without affecting other important pathways/functions in the body.

3b) Combinations with other medicines

Is the new medicine intended to be used in combination with any other medicines? • Yes? / No? If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination medicine, please ensure the sections on efficacy (3d), QoL (3e) and safety/side effects (3f) focus on data that relate to the combination, rather than the individual medicine.**
No

3c) Administration and dosing

How and where is the new medicine given or taken? Please include the amount and how often the medicine should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers. How does this differ to existing treatments?

The recommended dose of deucravacitinib is 6 mg taken orally once-daily with or without food. No dose titration is required which means that the same dose is used during the entire treatment with deucravacitinib.

Most other treatments are taken as an injection under the skin or as an infusion into the bloodstream. Other oral treatments include apremilast and dimethyl fumarate. The recommended dose of apremilast is 30 mg taken orally twice daily, approximately 12 hours apart, with no food restrictions. Apremilast requires dose titration, which means that a smaller dose is taken on the first day and is gradually increased over 6 days to the target dose of 30 mg twice daily. Dimethyl fumarate also requires a dose titration up to a maximum total daily dose of 720 mg per day and its frequency of administration varies between 1 to 3 times a day until reaching the maximum dose

Deucravacitinib would provide another oral treatment option for patients, where the majority of available treatments are injections. It is taken once a day and does not require dose titration.

3d) Efficacy

Efficacy is the measure of how well a medicine works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the new medicine is at treating the main condition outlined in section 2a. If there are data available, please also describe how it is different to other medicines available outlined in section 2c?

The primary outcomes of the phase 3 trials, POETYK-PSO-1 and POETYK-PSO-2, were the proportion of patients achieving a Psoriasis Area and Severity Index (PASI) 75 response (which indicates that a patient has had at least a 75% improvement in skin symptoms since the start of the study) and a static Physician's Global Assessment score (sPGA) of 0 or 1 (which indicates clear skin or almost clear skin, respectively) after 16 weeks of treatment with deucravacitinib.[32]

The PASI 75 response in POETYK PSO-1 and POETYK PSO-2 was as follows (see section B.2.6.3 and Appendix N of Document B):

- At Week 16, 58.4% and 53% of patients receiving deucravacitinib achieved a PASI 75 response, respectively, compared with 12.7% and 9.4% receiving placebo and 35.1% and 39.8% receiving apremilast.
- At Week 24, 69.3% and 59.3% of patients receiving deucravacitinib achieved a PASI 75 response, respectively, compared with 38.1% and 37.8% receiving apremilast.

Among patients who achieved PASI 75 response at Week 24 with deucravacitinib and continued treatment with deucravacitinib, 81.3% and 80.4%, respectively, maintained a PASI 75 response at Week 52.

The sPGA 0/1 response in POETYK PSO-1 and POETYK PSO-2 was as follows (see Appendix N of Document B):[32]

- At Week 16, 53.6% and 43.5% of patients receiving deucravacitinib achieved an sPGA 0/1 response, respectively, compared with 7.2% and 8.6% receiving placebo and 32.1% and 33.9% receiving apremilast.
- At Week 24, 58.7% and 49.8% of patients receiving deucravacitinib achieved an sPGA 0/1 response, respectively, compared with 31.0% and 29.5% receiving apremilast.

These results show that, in both trials, deucravacitinib was more efficacious than placebo and apremilast for the two primary outcomes.

In a type of analysis called an indirect treatment comparison, which allows treatments from different clinical trials to be compared, deucravacitinib was more efficacious than dimethyl fumarate and etanercept and comparable to adalimumab, ustekinumab and tildrakizumab. Details of this analysis are included in Document B section B.2.9.

3e) Quality of life impact of the new medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the new drug profile, for instance research to understand the trade-offs and willingness to accept benefit/risk by patients. Please include all references as required.

The daily symptoms of psoriasis, such as itching, pain and burning, can have a substantial negative impact on the HRQoL of patients with moderate-to-severe plaque psoriasis.[1, 22, 23]

In the POETYK-PSO-1 and POETYK-PSO-2 trials, outcomes reported by patients (PROs) were recorded using various measurements. One of these is the EuroQol-5D (EQ-5D), a questionnaire capturing aspects around mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In each trial, patients receiving deucravacitinib reported an improved EQ-5D score compared to patients receiving apremilast or placebo.

Another PRO measured was the Psoriasis Symptoms and Signs Score (PSSD) symptom score, which records psoriasis symptoms that are of concern to patients (itching, pain, stinging, burning, and skin tightness). Across both trials, deucravacitinib-treated patients achieved a greater improvement compared with placebo and apremilast in the PSSD symptom score (across itching, pain, stinging, burning, and skin tightness), with the greatest improvement in itch.[33-35]

Another PRO measured in the deucravacitinib trials was the Dermatology Life Quality Index (DLQI), which is commonly used for skin conditions. In each of the two trials, more patients receiving deucravacitinib reported a DLQI score of 0 or 1, which means that psoriasis no longer had an effect on their life, than patients receiving apremilast or placebo.[32]

Further details on PRO can be found in section B.2.2 of Document B.

3f) Safety of the new medicine and side effects

When a regulatory or HTA body makes a decision about a new medicine, it will pay close attention to the benefits of the medicine in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this medicine, and include benefit/risk assessment details where possible. This will support patient group reviewers to consider the potential overall benefits and side effects that the new medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen and how they could potentially be managed. Where appropriate and relevant to patients, please also highlight risk reduction comparisons with other treatments.

Where it will add value or context for patient readers please included references to the Summary of Product Characteristics from regulatory agencies etc.

Deucravacitinib was well-tolerated and had a similar safety profile in both the POETYK-PSO-1 and POETYK-PSO-2 trials.[32] Details on safety profile can be found in section B.2.10 of Document B.

At Week 16, 2.9% of patients on placebo, 1.8% of patients on deucravacitinib and 1.2% patients on apremilast experienced serious adverse events (SAEs) across both studies. The most common adverse events (AEs; occurring in at least 5% of patients) with deucravacitinib treatment at Week 16 were nasopharyngitis (common cold) and upper respiratory tract infection with low rates of headache, diarrhoea, and nausea. At Week 16, 3.8% of patients on placebo, 2.4% of patients on deucravacitinib and 5.2% of patients on apremilast experienced AEs leading to discontinuation of treatment.[32]

Over 52 weeks, across both trials, when SAEs were adjusted for length of exposure (exposure adjusted incidence per 100 patient-years [EAIR]) the result were 5.7 with placebo, 5.7 with deucravacitinib and 4.0 with apremilast. In the same timeframe, EAIRs for AEs leading to discontinuation were 9.4 with placebo, 4.4 with deucravacitinib and 11.6 with apremilast. No new safety signals were observed during Weeks 16 through 52.[32]

Across both trials, rates of malignancy, major adverse cardiovascular events, venous thromboembolism and serious infections were low and generally consistent across active treatment groups (deucravacitinib and apremilast). No clinically meaningful changes were observed in multiple laboratory parameters (including anaemia, blood cells, lipids and liver enzymes) over 52 weeks.[32]

3g) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the new medicine. Please provide a top-level summary for each, such as title, location, patient group size, completion dates etc.

Three phase 3 randomized-controlled trials (RCTs) provide evidence for the efficacy and safety of deucravacitinib in moderate-to-severe plaque psoriasis: two completed pivotal phase 3 studies, POETYK-PSO-1 (IM011046) and POETYK-PSO-2 (IM011047), and one ongoing, phase 3b long-term extension (LTE) study, POETYK-PSO-LTE (IM011075). Table 1 presents a summary of these three RCTs which is further discussed in the section B.2.3.3 of the submission

Table 1. Phase 3 clinical studies of deucravacitinib in moderate-to-severe plaque psoriasis

Study	**POETYK-PSO-1; NCT03624127**	**POETYK-PSO-2; NCT03611751**	**POETYK-PSO-LTE; NCT04036435**
Locations	154 sites in 11 countries (Canada, China, Germany, Japan, Poland, Russia, South Korea, Spain, Taiwan, UK, and the US)	191 sites in 15 countries (Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, New Zealand, Poland, Puerto Rico, Spain, Sweden, UK, and the US)	264 sites in 19 countries (Australia, Canada, China, Czech Republic, Finland, France, Germany, Hungary, Israel, Japan, Korea, New Zealand, Poland, Russian Federation, Spain, Sweden, Taiwan, United Kingdom, and the US)
Population	Adult patients with moderate-to-severe plaque psoriasis	Adult patients with moderate-to-severe plaque psoriasis	Adult patients with moderate-to-severe plaque psoriasis who completed POETYK-PSO-1 and POETYK-PSO-2
Key inclusion criteria	• Adults (≥18 years) diagnosed with stable plaque psoriasis for ≥6 months (defined as no morphology changes or significant flares of disease activity in the opinion of the investigator) • Deemed by the investigator to be a candidate for phototherapy or systemic therapy • PASI ≥12, sPGA ≥3 and BSA ≥10% at Screening Visit and Day 1		
Key exclusion criteria	• No other forms of psoriasis, other immune-mediated conditions requiring current systemic immunosuppressant treatment • No history of HIV or hepatitis B or C or TB infection (latent or active) • No history of lack of response to agents with target in same pathway		
Intervention (and number of people receiving intervention)	Deucravacitinib 6 mg once daily (N=332)	Deucravacitinib 6 mg once daily (N=511)	Deucravacitinib 6 mg once daily (N=1,221)

Comparator(s) (and number of people receiving comparators)	Placebo (N=166) and apremilast 30 mg twice daily after dose titration (N=168)	Placebo (N=255) and apremilast 30 mg twice daily after dose titration (N=254)	Not applicable
Primary study objective	To assess whether the efficacy of deucravacitinib is superior to placebo at Week 16 in patients with moderate-to-severe plaque psoriasis	To assess whether the efficacy of deucravacitinib is superior to placebo at Week 16 in patients with moderate-to-severe plaque psoriasis	To characterise the safety and efficacy of long-term use of deucravacitinib in patients with moderate-to-severe plaque psoriasis
Completion date	September 2020	November 2020	July 2026 (estimated)

BSA = body surface area; CSR = clinical study report; HIV = human immunodeficiency virus; PASI = Psoriasis Area and Severity Index; sPGA = Static Physicians Global Assessment; TB = tuberculosis.

3h) Summary of key benefits to patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the new medicine for patients, caregivers and their communities when compared with current medicines
- Please outline any data from the clinical trials listed above that support this
- This should inform any relevant cost or value considerations in the following section (3j)

There are few oral treatments available for psoriasis and there is an unmet need for more efficacious and well-tolerated oral treatments with durable response. Deucravacitinib is a new treatment option that may be as efficacious as some biologics, but with the convenience and ease of oral administration. It offers less necessity for primary or secondary care touchpoints which is especially important during and after the COVID-19 pandemic. Deucravacitinib has also shown durability and maintenance of response, as well as benefits in health-related quality of life. Additionally, deucravacitinib is a well-tolerated treatment option with low rates of adverse events reported in clinical trials.[32] Finally, deucravacitinib has the potential to be started earlier than biologics and is associated with no dose titration and little to no monitoring at start and during treatment.

3i) Value and economic considerations

Introduction for patient groups:

Health services want to get the most value from their budget and therefore needs to decide whether a new medicine provides good value compared with other medicines. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the medicines already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the HTA appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g. whether you feel these are the relevant endpoints, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or adverse events of the new medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g. travel costs, time-off work)?

Instructions to manufacturer: This is intended as a single-page summary for patient groups and needs to be completed in non-technical language. Focus should be on a summary of the key costs/drivers used in any models, the value afforded by the new medicine, and any financial implications that may be of relevance to patients/patient groups, rather than a detailed health economic justification (cost/QALY, for example).

- What were the important improvements in health from the new medicine compared with the medicines already in use that support its value offering (e.g. longer survival times or reduction in

severity or frequency of symptoms)? Were there important side effect differences between the medicines that support the value of the new medicine? • Would the new medicine lead to any cost implications (positive or negative) for the health service (e.g. number of days in hospital)? • Are there any important differences in the way the new medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g. where it is given or the monitoring that is needed)?
• The economic model used by BMS included 14 comparators • It was designed to include the main benefits of deucravacitinib, which are cheapest associated costs vs most comparators and improvements in quality of life vs some comparators, observed in the indirect treatment comparison inclusing PEOTYK trials • Deucravacitinib is administered orally and does not require administration cost. This is similar to only two other available treatments (among 14), and it is not expected to need additional monitoring once treatment is started. Therefore, the way deucravacitinib is expected to be given provide cost savings in treatment administration and resource use and costs savings associated with a lower likelihood of certain adverse events often observed with other treatments that lead to hospitalisation, such as severe infections or certain malignanciea compared to most existing treatments. • Based on these factors, deucravacitinib would be considered to represent value for money and offer a good use of NHS resources as a treatment for adult patients with moderate-to-severe plaque psoriasis. Details of the economic analyses for deucravacitinib are provided in Document B section B.3.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patient groups would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the HTA assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Further information on psoriasis and treatments for psoriasis: • British Skin Foundation: https://knowyourskin.britishskinfoundation.org.uk/condition/psoriasis/ • Psoriasis and Psoriatic Arthritis Alliance: https://www.papaa.org/learn-about-psoriasis-and-psoriatic-arthritis/just-diagnosed/what-is-psoriasis/ • Psoriasis Association: https://www.psoriasis-association.org.uk/about-psoriasis • Psoriasis Help Organisation: http://www.psoriasis-help.co.uk/what-is-psoriasis/plaque-psoriasis/ • NHS Overview of Psoriasis: https://www.nhs.uk/conditions/psoriasis/ • Psoriasis: assessment and management clinical guidelines 153: https://www.nice.org.uk/guidance/cg153/resources/psoriasis-assessment-and-management-pdf-35109629621701 Further information on deucravacitinib trial results: • BMS Press Release: https://news.bms.com/news/corporate-financial/2021/Bristol-Myers-Squibb-Presents-Positive-Data-from-Two-Pivotal-Phase-3-Psoriasis-Studies-Demonstrating-Superiority-of-Deucravacitinib-Compared-to-Placebo-and-Otezla-apremilast/default.aspx Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adverse event (AE): an unexpected medical issue that occurs during treatment with a drug. AEs may be mild, moderate, or severe, and may be caused by something other than the drug given
Anaemia: low levels of red blood cells, which means that not enough oxygen gets to different parts of the body. Symptoms include feeling tired and shortness of breath
Body surface area (BSA): a measurement of the proportion of the skin on the body that is affected by psoriasis
Dermatology Life Quality Index (DLQI): an outcome reported by patients in clinical trials for skin conditions; a low score (0 or 1) indicates that psoriasis no longer has an effect on a person's life
Lipid: another word for "fat." Lipid blood tests are used to help assess a person's cardiovascular health
Liver enzymes: proteins that speed up chemical reactions in the liver and help with functions such as breaking down food and toxins and fighting infection. Liver enzyme tests are used to assess the health of the liver
Major adverse cardiovascular events: refers to adverse events that can occur in the heart and circulatory system, such as heart attacks and stroke
Nasopharyngitis: generally minor inflammation of the nasal cavities and pharynx; also known as the common cold
Plaque psoriasis: the most common form of psoriasis characterised by well demarcated, red, scaly plaques on skin that can be found on any part of the body; also known as psoriasis vulgaris
Psoriasis Area Severity Index (PASI): a measurement of the severity of psoriasis that is commonly used in clinical trials. The term "PASI 75"refers to an improvement in response to treatment of at least 75% from the start of the clinical study
Psoriasis Symptoms and Signs Score (PSSD) symptom score: an outcome reported by patients in clinical trials which records psoriasis symptoms including itching, pain, stinging, burning, and skin tightness
Static Physician's Global Assessment score (sPGA): a measurement of the severity of psoriasis that is commonly used in clinical trials. The lower the score, the less severe the psoriasis. A score of 1 means that the skin is almost clear and a score of 0 means that it is clear
Tyrosine kinase 2 (TYK2): an enzyme (or biological catalyst) in the immune system which triggers chemical "messengers" that signal other cells to cause inflammation
Upper respiratory tract infection: irritation and swelling of the upper airways (nose, sinuses, pharynx, larynx, and large airways), usually with an associated cough

Venous thromboembolism: refers to a blood clot that starts in the veins

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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systemic-non-biological-therapy&path=view%3A/pathways/psoriasis/systemic-non-biological-therapy-for-psoriasis.xml; 2021.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Deucravacitinib for treating moderate to severe plaque psoriasis (ID3859)

Clarification questions

June 2022

File name	Version	Contains confidential information	Date
BMS response to ERG questions	**1.0**	**Yes**	**7 June**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Identification and selection of relevant evidence

A1. Appendix D, Section D.1.3.5. Please clarify how many reviewers conducted the risk of bias assessment of the studies included in the network meta-analysis and whether reviewers worked independently.

Two independent reviewers conducted the risk of bias assessment. Discrepancies between the two reviewers were resolved through discussion and consensus. A third independent reviewer was consulted, as necessary.

A2. Appendix D, Section D.1.5. Please clarify how many reviewers conducted the quality assessment of the POETYK-PSO-1, POETYK-PSO-2, POETYK-PSO-LTE studies using the NICE checklist and whether reviewers worked independently.

The quality assessment of the POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE studies was completed by a single reviewer and validated for accuracy by a second reviewer. Any conflicts were resolved by a third independent reviewer, as necessary.

A3. Appendix F, Section F.1.1.1. The last sentence of the second paragraph is incomplete. Please provide the text for the sentence in full.

Please find the complete sentence as follows: “All SAEs occurred in single subjects with no discernible trend in any specific type of SAE”.[1]

Methodology of clinical effectiveness evidence

A4. Document B, Section B.2.3.1. Randomisation was stratified by body weight: ≥90 kg and <90 kg. Please clarify why the body weight stratum was not applied in Japan or China for POETYK-PSO-1.

The body weight and BMI distribution in psoriasis is different in Japan and China compared with other regions of Western countries.[2] It is expected that most patients enrolled in China

and Japan have a body weight of less than 90 kg, with only a few patients above 90 kg from these countries. Therefore, the body weight stratification was not applied in these countries. In POETYK-PSO-1, [redacted] patients were enrolled in China or Japan and [redacted] had a body weight of less than 90 kg.

Decision problem

A5. Document B, Table B.1.1.1 p11 and Table B.2.1 page 28. The decision problem indicates that the population will be participants with a PASI of 10 or more while the clinical effectiveness evidence for the POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE trials use a population with a PASI of 12 or more. Please comment on this difference and how it may influence the effect sizes of deucravacitinib, apremilast and placebo.

The inclusion criteria of PASI ≥12 to define patients with moderate-to-severe psoriasis is consistent with most of clinical trials in this population. In fact, only nine trials (out of 84) identified from the systematic literature review and included in our network meta-analysis had a PASI inclusion criterion PASI ≥10. The remainder (82%) had an inclusion criterion of PASI ≥12 (see Appendix 4). Similar trends are associated with previous NICE submissions, with the majority of submissions utilising the inclusion criterion of PASI ≥12 to define the eligible patient population in their clinical trials and most of those are recommended in severe psoriasis defined as PASI≥10 in conjunction with DLQI>10. [5-14]

There is currently no formal definition of moderate-to-severe psoriasis.[16,17] The criteria used to define severity for this population for enrolment in POETYK clinical trials have included BSA (≥ 10%), and sPGA/IGA (≥ 3) scores, besides PASI scores.[16,17] Based on the requirement to meet all three severity criteria (BSA, sPGA, PASI) at baseline in the POETYK studies, there would be no patients expected to have PASI <12 (e.g. 10 and 11) in these studies.

On a clinical level, the difference between patients with a PASI of 10 and 12 is very small, as also confirmed by a clinical expert. Nonetheless, it is important to consider how this PASI 10 and 12 gap might impact on the effect sizes of the treatments. Using PASI 75 as an example, a patient with a PASI of 10 would require a 7.5-point reduction to achieve PASI 75, while a patient with a PASI of 12 would require a 9-point reduction to achieve the same PASI outcome. Hence demonstrating that it would require a slightly larger absolute PASI score reduction to yield the same percentage reduction if starting from a higher baseline PASI of PASI ≥12 vs PASI ≥10. It should be noted that this is a theoretical application, and those numbers are expected to vary in clinical practice, although with the same overall trend.

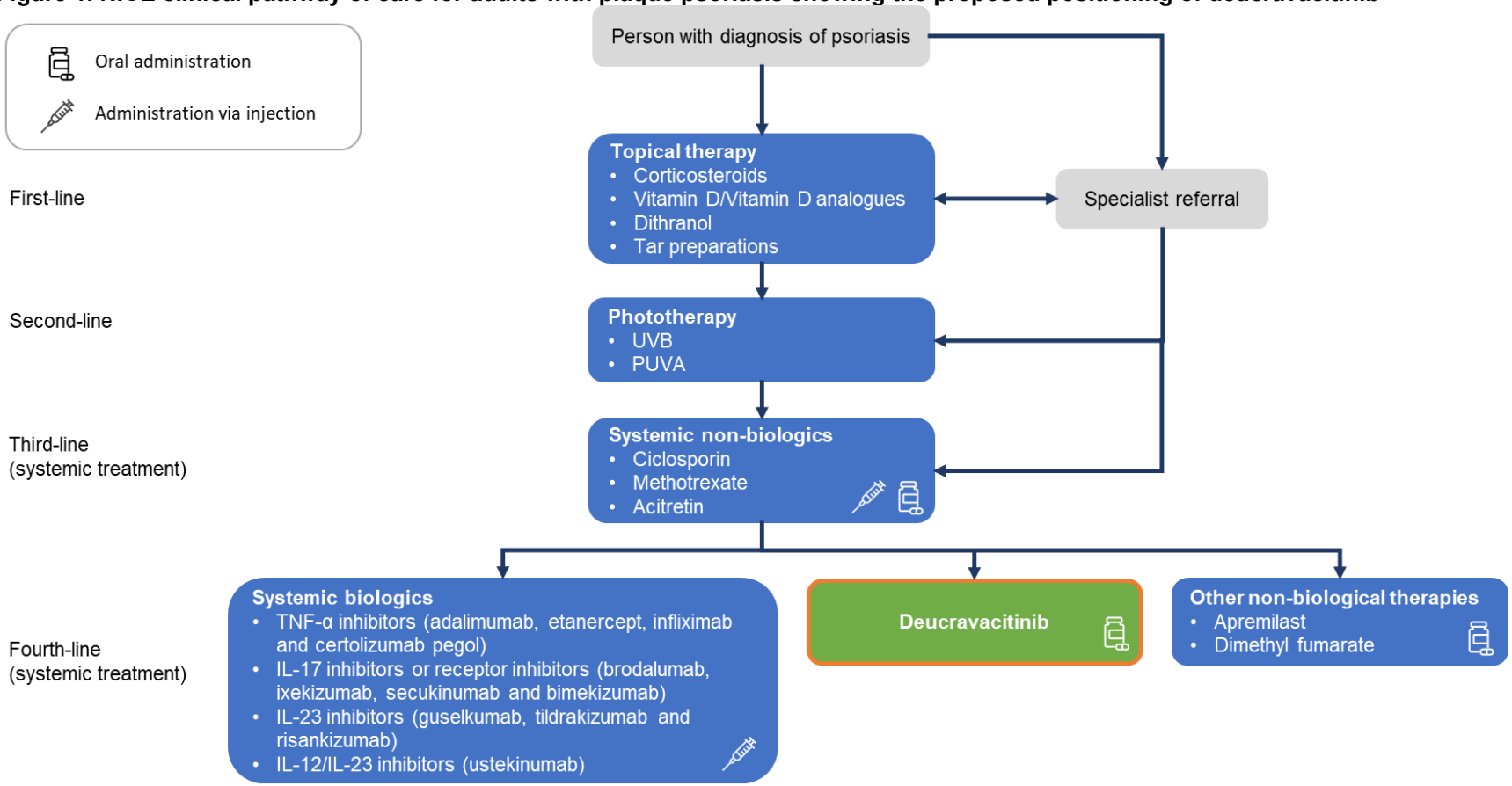
Based on the distribution of the baseline PASI score in the POETYK trials, only [redacted] and [redacted] of patients have been included with PASI ≤ 12 in POETYK-PSO-1 and PSO-2, respectively; and hence, the impact on the effect sizes vs placebo and vs apremilast would be expected to be minimal whether PASI ≥12 or PASI ≥10 were used for enrolment in the POETYK trials.

A6. Document B, Section B.1.1, Table B.1.1.1. In the submission, the population for the decision problem is defined as "*Adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option*", but the chosen comparators appear to be restricted to "*People with severe or very severe psoriasis [defined by a total PASI of 10 or more, and a DLQI of more than 10] for whom systemic non-biological treatment (including methotrexate, ciclosporin and acitretin)*

and phototherapy are inadequately effective, not tolerated or contraindicated". Acknowledging the lack of a definitive definition of what constitutes moderate and severe disease, please clarify if deucravacitinib is considered an option for people who would not otherwise be eligible for the biologics, apremilast or dimethyl fumarate according to the wording of the NICE guidance for these drugs.

The severity of the population described in the decision problem defined as "adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option" is aligned with the severity definition set out in previous NICE appraisals, namely based on PASI and DLQI score, and prior use of, or contraindication to, other systemic treatments and phototherapy. Considering the current treatment pathway of psoriasis patients, the population in the decision problem renders all treatment options which are available after third-line treatment (see Figure 1), i.e. biologics, apremilast, dimethyl fumarate as well as deucravacitinib, eligible for this patient population. Figure 1 shows that deucravacitinib is positioned in the same treatment line as biologics and apremilast/dimethyl fumarate. The chosen comparators in the decision problem align with the treatment options available in this line of treatment.

Figure 1. NICE clinical pathway of care for adults with plaque psoriasis showing the proposed positioning of deucravacitinib



Abbreviations: IL = interleukin; PUVA = psoralen plus ultraviolet A; TNF: tumour necrosis factor; UVB = ultraviolet B.Note: Methotrexate administration may be parenteral. All biologics are administered by subcutaneous injection, except infliximab which is administered as an intravenous infusion.
Source. Adapted from the NICE pathway for psoriasis.[18]

Efficacy results and data synthesis

A7. Document B, Table B.2.13, page 53. The proportion of people (46.6%) who lost sPGA 0/1 response (maintenance group) does not appear to be correct. Please check this and the other proportions shown in the table.

The denominators listed in Document B, Table B.2.13, do not reflect the denominators corresponding to the time to first loss of sPGA 0/1 response. Updated tables are provided in Table 1 and Table 2. Specifically, [redacted] ([redacted] /118) of patients who were PASI 75 responders at Week 24 and continued receiving deucravacitinib, experienced a loss of sPGA 0/1 response at some time after Week 24.

Table 1. Time to first loss of PASI 75 response and relapse rate (POETYK-PSO-2)

Efficacy endpoint	Deucravacitinib → deucravacitinib (maintenance group) n = 145	Deucravacitinib → placebo (withdrawal group) n = 150	Apremilast → placebo N=95
Subjects who lost **PASI 75** response, n (%)	[redacted]	[redacted]	[redacted]
Median time (95% CI) to loss (days)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]
Subjects who **relapsed**, n (%)	[redacted]	[redacted]	[redacted]
Median time (95% CI) to relapse (days)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]

[a]Median time loss cannot be calculated as < 50% of subjects had response loss through Week 52.
p-value was obtained using a stratified Cochran-Mantel-Haenszel test. Nominally significant p-value is designated using italicised type.
Abbreviations: CI = confidence interval; PASI = Psoriasis Area and Severity Index
Source: POETYK-PSO-2 CSR, BMS Data on File[4]

Table 2. Time to first loss of sPGA 0/1 response (POETYK-PSO-2)

Efficacy endpoint	Deucravacitinib → deucravacitinib (maintenance group) n = 118	Deucravacitinib → placebo (withdrawal group) n = 119	Apremilast → placebo N=69
Subjects who lost **sPGA 0/1** response, n (%)	[redacted]	[redacted]	[redacted]
Median time (95% CI) to loss (days)	[redacted]	[redacted]	[redacted]
P-value	[redacted]	[redacted]	[redacted]

[a]Median time loss cannot be calculated as < 50% of subjects had response loss through Week 52.
p-value was obtained using a stratified Cochran-Mantel-Haenszel test. Nominally significant p-value is designated using italicised type.
Abbreviations: CI = confidence interval; sPGA = static Physician's Global Assessment
Source: POETYK-PSO-2 CSR, BMS Data on File[4]

A8. PRIORITY. Document B, Section B.2.9.2, page 63. Please provide the code used to produce all the network meta-analyses along with the relevant input files required for these analyses.

NMA code and data input files for PASI 50, 75, 90 and 100 for the following analyses have been provided (see Appendix 1):

- 10-16 weeks ITT population

    - Multinomial: this corresponds with the main analysis
    - Binomial: this analysis was mistakenly omitted from the submission; please find attached in Appendix 2.
- 24-28 weeks ITT population, multinomial: this corresponds with the main analysis
- 40-44 weeks ITT population, multinomial: this corresponds with the main analysis
- 10-16 weeks subgroup bio-naïve, binomial: this corresponds with the subgroup analysis
- 10-16 weeks subgroup biologic experienced, binomial: this corresponds with the subgroup analysis
- Deucravacitinib [redacted]; tildrakizumab 28 Weeks, other Comparators 10–16 Weeks
    - Multinomial: this corresponds with sensitivity analysis 2
    - Binomial: this corresponds with scenario analysis 3
- Deucravacitinib [redacted], comparators 10–16 weeks, multinomial: this corresponds with sensitivity analysis 1

A9. Document B, Sections B.2.9.2 and B 2.9.3, pages 63-64. There appears to be a contradiction between the sentence *"The treat-through scenario is limited to only patients who remained on their initial treatment assigned at randomisation through 52 weeks"* reported in section B 2.9.2 and the sentence *"Note that for the mid-and long-term analyses, studies were restricted as only patients who remained on the treatment to which they were initially randomised were included, resulting in studies being further excluded"* reported in section B 2.9.3. Please clarify the criteria in terms of adherence to randomised treatment used for the inclusion of trials in the NMA for the short-term, mid-term and long-term analyses?

The criteria for the main analyses (short-, mid- and long-term) are based on study design and treatment allocation (i.e. treatment received by patients) rather than observed adherence to treatment. Due to commonly seen issues in psoriasis trials, such as complex designs (caused by crossovers and re-randomisations) and variations in how patients were allocated to the different treatment arms after completing the induction phase, the mid- and long-term scenarios were defined as treat-through to only include patients who continued to receive the treatment to which they were initially randomised. This approach is consistent with available literature evaluating the long-term efficacy of psoriasis treatments.[19]

Data for the following patient subgroups were not included in the mid- and long-term analyses:

- Any patients who continued active treatment irrespective of achieving PASI 75
- Any patients who were re-randomized to active treatment based on either achieving or not achieving a particular PASI response (e.g., PASI 75)

Finally, trials that did not have any treatment arms meeting the treat-through definitions were excluded in their entirety from the analyses.

A10. Appendix Section D 1.3.2 Table B.5.9 pages 18-46. The study and patient characteristics of the studies included in the NMA show wide variation in the percentage who have received prior biologic therapy. Please comment on the likely

effect of this on the effectiveness of the relevant trial interventions. Please comment on whether these differences were taken into consideration when deciding which trials to include in the network.

Similar to other NMAs,[19,20] prior use of biologics among patients included in the trials analysed varied from 0% to 60%. Therefore, a thorough investigation into the variation in proportions of patients receiving prior biologic therapy was performed during the feasibility assessment.

Based on a review of published literature, there is no consensus on whether prior biologic use is an effect modifier. Some literature[21,22] suggests that prior biologic use may not be an effect modifier, at least for some treatments. A paper from Wade et al. 2020[23] found a different treatment ranking for the probability of achieving 75% improvement in PASI score in studies that consisted of less than 25% of patients with prior biologic therapy when compared to other studies. However, ranking changes were particularly evident for the anti-TNF therapies, certolizumab and infliximab – these drugs ranked higher among patients without previous biologic therapy. The authors explained this response pattern by indicating that most patients who had received previous biologic therapy were likely treated with anti-TNF therapies, which may help explain lower response to anti-TNF drugs among patients who had received previous biologic therapy. A similar relationship between the proportion of patients previously treated with biologics and treatment effects has been replicated in a published NMA, where higher response to anti-TNF therapies was observed among trials with a lower proportion of patients who had received previous biologic therapy.[20]

Therefore, in the presented NMA, previous treatment with biologics was considered a potential effect modifier. While a conservative approach was taken for the main analyses (short-, mid-, long-term) and no studies were excluded based on receipt of prior therapy, two subgroup analyses were conducted, one limited to bio-naive patients and another including only patients who had received prior biologic therapy.

The NMA focused on the bio-naïve population did not demonstrate significant changes in the treatment response across treatments for the probability of achieving 75% improvement in PASI score, regardless of the treatment class. The results suggest that the estimates observed in the current NMA comparing deucravacitinib with other treatments are not substantially impacted by prior biologic exposure, except potentially in the case of certain anti-TNFs (e.g. etanercept).

A subgroup analysis for PASI 75 limited to only patients who had received prior biologic therapy yielded unreliable results due to data limitations. There were only a limited number of studies contributing data to this subgroup analysis (11 total), each of which had small sample sizes in each treatment arm; the NMA therefore yielded very wide credible intervals around the point estimates (Figure 2). The uncertainty around the results of this analysis made the interpretation of relative effects difficult for the majority of comparisons that were feasible.

Figure 2. PASI 75 at 10–16 Weeks – Odds Ratios Between Deucravacitinib and Other Treatments – RE, Unadjusted Binomial NMA – Biologic-experienced Population

Abbreviations: ADM = adalimumab; APR = apremilast; BIW = twice weekly; BRO = brodalumab; CZP = certolizumab pegol; DEU = deucravacitinib; ETC = etanercept; IXE = ixekizumab; PLC = placebo; Q2W = every two weeks; TIL = tildrakizumab; UST = ustekinumab

Section B: Clarification on cost-effectiveness data

Summary of errors rectified and impact on ICURs

Two errors were found in the model which have been rectified. These errors relate to the disutility of serious infections being adjusted for the weeks per year twice and an error in the multiplier used to adjust the utility of BSC (based on placebo response) to reflect baseline utility. A more in-depth explanation is provided in the answers to questions B5 and B6 in which each error is rectified. The error relating to AE disutility has negligible effect on the ICUR results, however the error relating to baseline utility for BSC has a more material impact. As a result, the deterministic base case ICURs have changed and are shown in Table 3. It should be noted that all analyses in this document have been conducted with the cost of deucravacitinib being reflective of the PAS price [redacted] per pack). All analyses undertaken are reflective of the new deterministic base case ICUR apart from the scenarios relating to questions B5 and B6 (this is intentional to show the relative change in ICURs before and after the errors had been rectified).

Table 3. Overview of ICUR results with the two errors identified in the model being rectified

Sequence*	Deterministic base case ICUR with rectified errors
DEU-SEC-RIS	**-**
APR- SEC-RIS	Dominant (-£12,777)
DMF- SEC-RIS	Dominant (-£126,058)
ADA- SEC-RIS	SW quadrant (£93,373 per QALY foregone)
BIM- SEC-RIS	SW quadrant (£172,205 per QALY foregone)
BRO- SEC-RIS	SW quadrant (£191,922 per QALY foregone)
CER- SEC-RIS	SW quadrant (£100,142 per QALY foregone)
ETA- SEC-RIS	Dominant (-£27,666)
GUS- SEC-RIS	SW quadrant (£171,312 per QALY foregone)
INF- SEC-RIS	SW quadrant (£158,850 per QALY foregone)
IXE- SEC-RIS	SW quadrant (£162,486 per QALY foregone)
RIS- SEC-UST	SW quadrant (£212,428 per QALY foregone)
SEC- UST-RIS	SW quadrant (£203,642 per QALY foregone)
TIL- SEC-RIS	SW quadrant (£133,111 per QALY foregone)
UST- SEC-RIS	SW quadrant (£160,393 per QALY foregone)

*Please note all sequences have BSC as fourth-line treatment. Abbreviations: LY = life years; QALY = quality adjusted life years; ICUR = incremental cost utility ratio; iNHB = incremental net health benefit; SW = Southwest; DEU = deucravacitinib; APR = apremilast; DMF= dimethyl fumarate; ADA = adalimumab; BIM = bimekizumab; BRO = brodalumab; CER = certolizumab pegol; ETA = etanercept; GUS = guselkumab; INF = infliximab; IXE = ixekizumab; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab.

Clinical effectiveness inputs

B1. Document B, Section B1.3.4. It is stated that *"The prospect of deucravacitinib as a new treatment option that may be as efficacious as some biologics, but with the convenience and ease of oral administration, is likely to be welcomed by both clinicians and patients."* In Table B.3.2.1, it is further noted that "*In the absence of evidence showing reason to employ lower adherence rates, full adherence to treatment protocol is assumed for all treatments.*" Is there evidence from other contexts to support the assumption that relative adherence to daily oral therapy versus less frequent injections, outside the controlled trial setting, should not affect the generalisability of the comparative response rates obtained from the network meta-analysis?

Firstly, it is important to acknowledge that adherence to a treatment is complex and linked to a multitude of variable factors. These factors include mode of administration but also other variables that are specific to a patient such as severity of disease, prior treatment history, treatment side effect, titration and monitoring, comorbidities and use of other therapies,

healthcare professional interaction and many other elements which affect a patient's adherence to a prescribed treatment.

Due to limited evidence comparing adherence between daily orals and less frequent injectables, differential adherence was not accounted for in the economic model based on mode of administration. This is supported by a Scottish study from Chan et al. (2011), which investigated the treatment adherence of psoriasis patients who attended the dermatology department of a Scottish hospital.[24] The study found adherence rates close to 100% based on Self Assessed Psoriasis Areas and Severity Index (SAPASI) and Dermatology Life Quality Index (DLQI) questionnaires administered to patients (n=43 on oral systemic treatment; n=29 on biologics). The self-reported adherence to biologics was 100% compared to 96% of patients receiving oral therapy.[24] However, this study did not report which biologics and oral systemic therapies were used. Based on the Scottish Intercollegiate Guidelines Network national clinical guideline on diagnosis and management of psoriasis and psoriatic arthritis in adults,[25] it was assumed that systemic treatment encompassed ciclosporin and acitretin, both of which are daily orals. A limitation of these two treatments is that they are subject to titration and laboratory monitoring,[26,27] which naturally adds complexity for patients. Based on this, adherence in general and specifically in relation to the titration recommendations is expected to be affected, with the titration complexity potentially leading to discontinuation. For treatment with deucravacitinib, no titration is required which makes it easier for patients to administer the oral treatment correctly every day. Therefore, and although no formal comparison can be drawn, we assume that adherence rates are similar for daily oral therapies and less frequent injections.

Additionally, clinical experts were consulted concerning treatment adherence. They suggested that patients may be less compliant to an injection at 12-week intervals than a daily oral treatment which is part of the every-day routine and may be taken with other daily oral medications.

Furthermore, it is important to highlight the findings of the pivotal phase 3 trial POETYK-PSO-2 with specific mention of the randomised withdrawal arm and subsequent efficacy results. To evaluate maintenance and durability of response, subjects randomised to deucravacitinib at Week 0 who were PASI 75 responders at week 24 were re-randomised to either continue treatment with deucravacitinib or receive placebo. For those who were re-randomised to placebo at week 24, the median time to loss of sPGA 0/1 response was [redacted], and the median time to loss of PASI 75 response was [redacted]. The effect seen of a sustained response when off treatment has been theorised by BMS and clinical experts consulted to result from the mechanism of action of the drug, which appears to result in a long-lasting effect even after treatment is discontinued. This might be relevant to consider when assessing adherence on treatment in that its overall effect may not be significantly altered by occasional missed doses. By comparison, the effect of a missed or delayed dose of an irregular injectable may be far more marked clinically.

Overall, therefore, given the lack of published data in the real world and the complexities of comparing a range of oral versus injectable treatments, all with different clinical and pharmacological profiles, we are able to justify our assumption of full adherence to all treatments as well as generalisability of the comparative response rates obtained from the network meta-analysis.

B2. Document B, Section B.3.3.2. It is stated that a universal annual discontinuation rate of 14.3%, transformed to a 2-week probability, was employed in the base case and applied to all patients in the maintenance phase of treatment on any drug. A scenario using treatment-specific discontinuation rates was then detailed in Table B.3.6. The annual rate of 9% applied to deucravacitinib, based on expert opinion that deucravacitinib's mechanism of action is similar to that of guselkumab, is substantially lower than the rate applied to the two alternative oral therapies – 31% for apremilast and 31% for dimethyl fumarate. Please further justify your assumptions around discontinuation and clarify if factors other than the drug mechanism of action, such as adverse event rates or mode of administration, were considered in determining the assumptions around the treatment-specific discontinuation rates.

The scenario looking at individual treatment discontinuation rates used data available from the literature complemented with assumptions. Firstly, an error was identified in the derivation of the discontinuation rate for guselkumab from the Gene to clinic publication[28] and the correct rate for guselkumab is 4.5%. This also changes the discontinuation rates for risankizumab and tildrakizumab as these were assumed to be equal to guselkumab. Furthermore, the same error (applying a 2-year rate instead of a 1-year rate) was identified in the derivation for ixekizumab in the Gene to clinic publication with the correct rate for ixekizumab being 12%.

Given the corrected discontinuation rate of 4.5% for guselkumab (now lower than the [redacted] discontinuation rate from POETYK trial data, reported in section B.3.3.2 of the submission), it was deemed more conservative to derive the discontinuation for deucravacitinib in the maintenance phase of POETYK trial data:

- [redacted] patients in the POETYK trials treated with deucravacitinib achieved PASI 75 at week 16 (this analysis was a post-hoc analysis and did not impute for non-responders).
- Out of these [redacted] patients who continued treatment to maintain response through to 52 weeks, [redacted] discontinued treatment. This analysis was a post-hoc analysis and did not impute for non-responders.
- The [redacted] discontinuation rate applies to a period of 36 (52 minus 16) weeks. Hence, the annual discontinuation rate for deucravacitinib was estimated at ([redacted]

The main reasons for discontinuing treatment in psoriasis are lack of initial response (primary failure), loss of response (secondary failure) after starting therapy or poor tolerability. Based on POETYK trials, the difference in discontinuation rates for deucravacitinib versus apremilast is justified due to the following reasons:

- Deucravacitinib demonstrated improved efficacy versus apremilast over all time points (16, 24, and 52 weeks).
- Deucravacitinib had numerically lower rates for headaches (4.5% vs 10.7%), diarrhoea (4.4% vs 11.8%), and nausea (1.7% vs 10.0%) compared with apremilast
- Deucravacitinib was associated with substantially lower incidence of adverse events leading to discontinuation (2.4%) compared to patients in the apremilast arm (5.2%)
- After Week 16, no new safety signals were observed with deucravacitinib, and incidence rates of common adverse events did not change

- The overall safety profile observed in POETYK-PSO-LTE through two years was consistent with that observed in the pivotal Phase 3 trials POETYK PSO-1 and PSO-2

Further to this, studies investigating treatment persistence for apremilast reported large proportions of patients stopping treatment due to adverse events in clinical practice: *"About half of the people had adverse events, including diarrhoea and headache, which were the most commonly reported adverse events; around 20% withdrew from apremilast treatment due to adverse events (headache, digestive disorders and mood change)".*[29,30]

Evidence on treatment discontinuation for dimethyl fumarate (DMF) is scarce. A targeted literature search using PubMed yielded one study describing a European expert consensus on clinical use of DMF in moderate to severe psoriasis.[31] This study reported that DMF was associated with a mild and well-characterised safety profile. It noted that DMF is the most frequently used in Germany and referred to the study by Ismail et al.[32] which investigated drug survival of fumaric acid esters in psoriasis in Germany and showed 4-year drug survival was 60% (64/107) for DMF. There are two important limitations of this study which inhibit its usefulness for the current analysis:

- As the study collected data in the period 2003-2012, it is outdated. Over the recent years, many new treatments have become available in psoriasis, hereby greatly increasing the options for patients with insufficient response to treatment.
- The study does not distinguish between discontinuation due to lack of response and discontinuation due to other reasons. As patients in the economic model will discontinue due to a lack of response in the induction phase, this leads to an overestimation of the discontinuation rate for DMF. Discontinuation data is available for year 1, where the publication reports a discontinuation rate of 61% of which 43% is caused by a lack of response. From figure 3 in the publication, it can be seen that approximately 14% of patients discontinued due to reasons other than discontinuation between 20-48 weeks. Therefore, it was decided to conservatively assume the discontinuation rate of DMF to be equal to that of deucravacitinib.

An updated scenario was run in which discontinuation rates as per Table 4 were used. Outcomes for this scenario are presented in Table 5.

Table 4. Treatment-specific discontinuation rates used in updated scenario

Treatment	Discontinuation rate	Source	Justification
Deucravacitinib	[redacted]	Pooled POETYK trials	Based on pooled POETYK trial discontinuation rate observed in those who are PASI 75 responders and still on treatment between 16 and 52 weeks
Adalimumab	16.4%	Yiu et al. (2020)[33]	Best available evidence from BADBIR registry
Apremilast	31%	Sbidian et al. (2019)[30]	Best available evidence from BADBIR registry
Bimekizumab	12.8%	Assumed same as secukinumab	Expert opinion, based on common discontinuation rate for IL17 class

Brodalumab	12.8%	Assumed same as secukinumab	Expert opinion, based on common discontinuation rate for IL17 class
Certolizumab pegol	16.4%	Assumed same as adalimumab	Expert opinion, based on common discontinuation rate for TNF-α class
Dimethyl fumarate	[redacted]	Assumed same as deucravacitinib	Assumed discontinuation rate similar to deucravacitinib
Etanercept	16.4%	Assumed same as adalimumab	Expert opinion, based on common discontinuation rate for TNF-α class
Guselkumab	4.5%	Gene 2 clinic FC20[28]	Best available evidence from BADBIR registry
Infliximab	16.4%	Assumed same as adalimumab	Expert opinion, based on common discontinuation rate for TNF-α class
Ixekizumab	12%	Gene 2 clinic FC20[28]	Best available evidence from BADBIR registry
Risankizumab	4.5%	Assumed same as guselkumab	Expert opinion, based on common discontinuation rate for IL-23 class
Secukinumab	12.8%	Yiu et al. (2020)[33]	Best available evidence from BADBIR registry
Tildrakizumab	4.5%	Assumed same as guselkumab	Expert opinion, based on common discontinuation rate for IL-23 class
Ustekinumab	10.9%	Yiu et al. (2020)[33]	Best available evidence from BADBIR registry

Table 5. Overview of ICUR results using the updated discontinuation rates (using rectified model)

Sequence*	Original discontinuation scenario analysis ICUR	Updated discontinuation scenario ICUR	Change in ICUR (%)
DEU-SEC-RIS	-	-	-
APR- SEC-RIS	Dominant (-£23,602)	Dominant (-£47,972)	-103.25%
DMF- SEC-RIS	Dominant (-£50,720)	Dominant (-£233,924)	-361.21%
ADA- SEC-RIS	Dominant (-£78,555)	Dominant (-608,777)	-674.97%
BIM- SEC-RIS	SW quadrant (£326,916 per QALY foregone)	SW quadrant (£224,800 per QALY foregone)	31.24%
BRO- SEC-RIS	SW quadrant (£433,557 per QALY foregone)	SW quadrant (£254,980 per QALY foregone)	41.19%
CER- SEC-RIS	Dominant (-£89,744)	Dominant (-£945,542)	-953.59%
ETA- SEC-RIS	Dominant (-£33,116)	Dominant (-£66,525)	-100.88%
GUS- SEC-RIS	SW quadrant (£182,709 per QALY foregone)	SW quadrant (£95,682 per QALY foregone)	47.63%

Sequence*	Original discontinuation scenario analysis ICUR	Updated discontinuation scenario ICUR	Change in ICUR (%)
INF- SEC-RIS	Dominant (-£408,575 per QALY foregone)	SW quadrant (£586,084 per QALY foregone)	N/A**
IXE- SEC-RIS	Dominant (-£244,996 per QALY foregone)	SW quadrant (£193,894 per QALY foregone)	N/A**
RIS- SEC-UST	SW quadrant (£545,654 per QALY foregone)	SW quadrant (£169,959 per QALY foregone)	68.85%
SEC- UST-RIS	SW quadrant (£637,142 per QALY foregone)	SW quadrant (£172,066 per QALY foregone)	72.99%
TIL- SEC-RIS	SW quadrant (£145,314 per QALY foregone)	SW quadrant (£31,685 per QALY foregone)	78.20%
UST- SEC-RIS	SW quadrant (£588,708 per QALY foregone)	SW quadrant (£119,138 per QALY foregone)	79.76%

*Please note all sequences have BSC as fourth-line treatment. . **Since the ICUR "flips" a % change cannot be derived.Abbreviations: LY = life years; QALY = quality adjusted life years; ICUR = incremental cost utility ratio; iNHB = incremental net health benefit; SW = Southwest; DEU = deucravacitinib; APR = apremilast; DMF= dimethyl fumarate; ADA = adalimumab; BIM = bimekizumab; BRO = brodalumab; CER = certolizumab pegol; ETA = etanercept; GUS = guselkumab; INF = infliximab; IXE = ixekizumab; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab.

B3. Document B, Section B.3.3.3, Table B.3.7. Adverse event rates included in the model are presented for each drug. It is further noted in section B.3.3.4., that the utility decrements associated with adverse events are only applied in the first cycle of the model. Please clarify how the event rates in Table B.3.7 have been calculated and what they represent for each comparator (e.g. events per patient-year, first events per patient-year?) If they are event rates per patient-year, why are they applied only in the first cycle of the model, and not on an ongoing basis, with the rates adjusted to the model cycle length?

Adverse events (AEs) have been calculated to represent events per patient-year and were derived from the POETYK PSO trials and published literature. Using the non melanoma skin cancer (NMSC) rate for deucravacitinib as an example, the incident rate per 100 patient years was reported to be 0.7. This was then converted to a rate per patient year by dividing by 100, resulting in an incident rate of 0.007 which was used in the model. The incidence rates for all AEs (severe infections, NMSC and malignancies other than NMSC) were multiplied by their respective cost and disutility (the latter only for severe infections) and applied in the model as a one-off event in the first cycle of a treatment. This simplifying approach is common in economic models and has been accepted in previous NICE HTA submissions, such as in TA633 (ustekinumab for treating moderately to severely active ulcerative colitis) where serious infections were modelled as "one-off events".[34] This was considered a "reasonably simplifying assumption" by the ERG.[34]

Extrapolating AE rates beyond any observed (trial) period would introduce additional uncertainty and is likely not to impact model outcomes. In order to test the impact on the

base case model results a scenario was conducted where the AE rates for all treatments were doubled. Results from this analysis are provided below in Table 6.

Table 6. Overview of ICUR results when AE rates for all treatments are doubled (using rectified model)

Sequence*	Deterministic base case ICUR	Updated AE scenario ICUR	Change in ICUR (%)
DEU-SEC-RIS	-	-	-
APR- SEC-RIS	Dominant (-£12,777)	Dominant (-£12,767)	0.08%
DMF- SEC-RIS	Dominant (-£126,058)	Dominant (-£126,149)	0.07%
ADA- SEC-RIS	SW quadrant (£93,373)	SW quadrant (£94,873)	1.58%
BIM- SEC-RIS	SW quadrant (£172,205 per QALY foregone)	SW quadrant (£172,093 per QALY foregone)	0.07%
BRO- SEC-RIS	SW quadrant (£191,922 per QALY foregone)	SW quadrant (£191,749 per QALY foregone)	0.09%
CER- SEC-RIS	SW quadrant (£100,142)	SW quadrant (£101,053)	0.9%
ETA- SEC-RIS	Dominant (-£27,666)	Dominant (-£28,419)	2.65%
GUS- SEC-RIS	SW quadrant (£171,312 per QALY foregone)	SW quadrant (£171,217 per QALY foregone)	0.06%
INF- SEC-RIS	SW quadrant (£158,850 per QALY foregone)	SW quadrant (£159,294 per QALY foregone)	0.28%
IXE- SEC-RIS	SW quadrant (£162,486 per QALY foregone)	SW quadrant (£162,503 per QALY foregone)	0.01%
RIS- SEC-UST	SW quadrant (£212,428 per QALY foregone)	SW quadrant (£212,287 per QALY foregone)	0.07%
SEC- UST-RIS	SW quadrant (£203,642 per QALY foregone)	SW quadrant (£203,611 per QALY foregone)	0.02%
TIL- SEC-RIS	SW quadrant (£133,111 per QALY foregone)	SW quadrant (£132,646 per QALY foregone)	0.35%
UST- SEC-RIS	SW quadrant (£160,393 per QALY foregone)	SW quadrant (£160,449 per QALY foregone)	0.03%

*Please note all sequences have BSC as fourth-line treatment. Abbreviations: LY = life years; QALY = quality adjusted life years; ICUR = incremental cost utility ratio; iNHB = incremental net health benefit; SW = Southwest; DEU = deucravacitinib; APR = apremilast; DMF= dimethyl fumarate; ADA = adalimumab; BIM = bimekizumab; BRO = brodalumab; CER = certolizumab pegol; ETA = etanercept; GUS = guselkumab; INF = infliximab; IXE = ixekizumab; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab.

Health state utilities

B4. PRIORITY. Document B, Sections B.3.2.3, and B.3.4. It is noted in B.3.2.3 that the patients who revert to best supportive care are distributed across the five PASI

response categories based on the placebo arm response of studies included in the NMA. In Section B.3.4., however, utility of patients receiving the best supportive care defaults back to baseline. Why should this be the case if some response is modelled for BSC?

In the base case analysis of TA575[12], the utility of patients receiving BSC was informed by the utility associated with a PASI <50 response level. The ERG had concerns regarding the validity of this assumption and commented that whilst using a utility based on a response of PASI <50 may be appropriate for patients who receive biological therapies, *"there are significant uncertainties whether these values can be generalised to patients not receiving biological therapies"*. As patients in the BSC health state receive no active therapy, the plausibility of using the utility value associated with a PASI <50 response to inform the utility for BSC was questioned. The ERG therefore considered it more appropriate to set the utility for BSC to be the same as baseline utility and conducted this scenario in their exploratory analysis.

The appropriateness of the utility for BSC being equal to baseline utility was reinforced by a clinical expert in the NICE appraisal committee. This expert advised that "*a patient who switched from an active treatment to best supportive care would revert to their baseline quality of life shortly after switching"*. It was concluded by the committee that the baseline utility was more appropriate to represent health-related quality of life for BSC.

TA575 is the most recent submission that is based on a cost-effectiveness analysis (more recent submissions used cost-minimisation analyses) and therefore the suggestions from the ERG and NICE were reviewed and considered for the deucravacitinib submission. With the ERG showing a preference for BSC utility to be informed by baseline utility, it was considered appropriate for the same methodology to be used in the cost-effectiveness analysis for deucravacitinib.

B5. PRIORITY. Document B, Section B.3.4. and Economic model ("outcomes" worksheet, cells D104 to P104). Related to B4 above, please explain the adjustment (Calcs_Trace_Seq1!$FU$6*(Utilities!$F$25/0.825)) that is made to bring the QALY streams for BSC in line with the assumption that patients on BSC experience baseline utility throughout. It is not clear how the 0.825 is derived and what it represents in this calculation.

The methodology used to adjust for the utility of patients on BSC reverting to baseline is detailed below.

- In each "Calcs_Trace_Seq" sheet, cell Calcs_Trace_Seq1!$FU$6 calculates the total QALYs accrued in the BSC health state by subtracting the QALYs accumulated over all PASI scores for all three active treatments in the sequence (columns FF:FT) from the utilities accumulated over all health states in the model, i.e. the total QALYs accumulated (columns CM:CQ), hereby isolating the QALYs accrued in the BSC health state. Please note that the QALYs from columns CM:CQ are sourced from all health states and that for BSC these are based on the PASI response levels in the placebo arm.
- The sum product of the PASI level responses for the placebo arm and associated utility values for each PASI response level was subsequently calculated to be 0.825. Please note that an error was identified in this calculation and the correct weighted average

was calculated to be 0.759. This leads to updated model outcomes as displayed below in Table 7.

- A correction factor was calculated to adjust the QALYs accrued in the BSC health state to be informed by the baseline utility rather than the placebo responses from the NMA. This correction factor was calculated by dividing the baseline utility value (reference cell "Utilities!$F$25" in the formula above) by the utility based on PASI response from the placebo arm (0.825 as defined above - now updated to 0.759).
- This correction factor was then applied to the total QALYs accrued in the BSC health state to produce the QALYs in the BSC health state that are reflective of patients experiencing baseline utility.
- It should be noted that this approach was used consistently for all treatment sequences.

Table 7. Overview of ICUR results using the updated value for the utility based on PASI response from the placebo arm

Sequence*	Original deterministic base case ICUR	Corrected utility scenario ICUR	Change in ICUR (%)
DEU-SEC-RIS	-	-	-
APR- SEC-RIS	Dominant (-£10,442)	Dominant (-£12,777)	22.36%
DMF- SEC-RIS	Dominant (-£102,568)	Dominant (-£126,058)	22.90%
ADA- SEC-RIS	SW quadrant (£81,936)	SW quadrant (£93,373)	13.96%
BIM- SEC-RIS	SW quadrant (£147,986 per QALY foregone)	SW quadrant (£172,205 per QALY foregone)	16.37%
BRO- SEC-RIS	SW quadrant (£165,586 per QALY foregone)	SW quadrant (£191,922 per QALY foregone)	15.90%
CER- SEC-RIS	SW quadrant (£86,229)	SW quadrant (£100,142)	16.13%
ETA- SEC-RIS	Dominant (-£22,462)	Dominant (-£27,666)	23.17%
GUS- SEC-RIS	SW quadrant (£146,248 per QALY foregone)	SW quadrant (£171,312 per QALY foregone)	17.14%
INF- SEC-RIS	SW quadrant (£136,456 per QALY foregone)	SW quadrant (£158,850 per QALY foregone)	16.41%
IXE- SEC-RIS	SW quadrant (£139,387 per QALY foregone)	SW quadrant (£162,486 per QALY foregone)	16.57%
RIS- SEC-UST	SW quadrant (£186,810 per QALY foregone)	SW quadrant (£212,428 per QALY foregone)	13.71%
SEC- UST-RIS	SW quadrant (£177,667 per QALY foregone)	SW quadrant (£203,642 per QALY foregone)	14.62%

Sequence*	Original deterministic base case ICUR	Corrected utility scenario ICUR	Change in ICUR (%)
TIL- SEC-RIS	SW quadrant (£111,907 per QALY foregone)	SW quadrant (£133,111 per QALY foregone)	18.95%
UST- SEC-RIS	SW quadrant (£139,666 per QALY foregone)	SW quadrant (£160,393 per QALY foregone)	14.84%

*Please note all sequences have BSC as fourth-line treatment. Abbreviations: LY = life years; QALY = quality adjusted life years; ICUR = incremental cost utility ratio; iNHB = incremental net health benefit; SW = Southwest; DEU = deucravacitinib; APR = apremilast; DMF= dimethyl fumarate; ADA = adalimumab; BIM = bimekizumab; BRO = brodalumab; CER = certolizumab pegol; ETA = etanercept; GUS = guselkumab; INF = infliximab; IXE = ixekizumab; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab.

B6. PRIORITY. Document B, Section B.3.4.4, and economic model. The derivation of the QALY losses due to severe adverse events lacks transparency. It is not clear how the multiplier 0.986 for severe infection was calculated from Sisk et al., or what it represents; a utility multiplier or multiplicative adjustment to annual expected QALYs? The size of utility decrement inferred from the multiplier appears implausibly small (-0.014) for a severe infection. The modelled QALY loss per event then appears to be adjusted for the number of weeks in the year twice ("Safety" worksheet, cells N53 to P62, and "Input conversion" worksheet, cells R72 to AD86), leading to almost negligible QALY losses associated with severe infections in the model. Please check and clarify your calculations and assumptions for modelling the QALY losses associated with severe infections and other adverse events.

The multiplier of 0.986 (rounded from 0.9858) is reported in the Diamantopoulos et al, 2014 publication.[35] The authors of the Diamantopoulos publication discuss that, based on a Cochrane safety review conducted, pneumonia was found to be the most common and significant serious infection. Diamantopoulos et al. sourced the utility value for pneumonia from Sisk et al,1997 and adjusted for the following factors:

- expected duration of pneumonia (7 days)
- baseline age and gender of the cohort described in Sisk et al.[36]

From this, Diamantopoulos et al. calculated a utility multiplier of 0.9858.[35]

This value was then used to derive the disutility multiplier used in the deucravacitinib model (1 - 0.968 = 0.014).

The total disutility related to serious infections for each treatment is calculated and modelled in the first cycle when a new treatment is initiated, as per other adverse events within the model. However, as the ERG correctly pointed out, an error has occurred in the model where the utility decrement is adjusted for number of weeks per year twice. The correction of this error leads to negligible differences in model outcomes as shown below in Table 8.

Table 8. Overview of ICUR results once implementation of AE related disutility is corrected

Sequence*	Original deterministic base case ICUR	Corrected AE scenario ICUR	Change in ICUR (%)
DEU-SEC-RIS	-	-	-
APR- SEC-RIS	Dominant (-£12,777)	Dominant (-£12,777)	0.00%

Sequence*	Original deterministic base case ICUR	Corrected AE scenario ICUR	Change in ICUR (%)
DMF- SEC-RIS	Dominant (-£126,054)	Dominant (-£126,058)	0.00%
ADA- SEC-RIS	SW quadrant (£93,385)	SW quadrant (£93,373)	-0.01%
BIM- SEC-RIS	SW quadrant (£172,205 per QALY foregone)	SW quadrant (£172,205 per QALY foregone)	0.00%
BRO- SEC-RIS	SW quadrant (£191,921 per QALY foregone)	SW quadrant (£191,922 per QALY foregone)	0.00%
CER- SEC-RIS	SW quadrant (£100,154)	SW quadrant (£100,142)	-0.01%
ETA- SEC-RIS	Dominant (-£27,665)	Dominant (-£27,666)	0.00%
GUS- SEC-RIS	SW quadrant (£171,310 per QALY foregone)	SW quadrant (£171,312 per QALY foregone)	0.00%
INF- SEC-RIS	SW quadrant (£158,860 per QALY foregone)	SW quadrant (£158,850 per QALY foregone)	-0.01%
IXE- SEC-RIS	SW quadrant (£162,486 per QALY foregone)	SW quadrant (£162,486 per QALY foregone)	0.00%
RIS- SEC-UST	SW quadrant (£212,426 per QALY foregone)	SW quadrant (£212,428 per QALY foregone)	0.00%
SEC- UST-RIS	SW quadrant (£203,643 per QALY foregone)	SW quadrant (£203,642 per QALY foregone)	0.00%
TIL- SEC-RIS	SW quadrant (£133,106 per QALY foregone)	SW quadrant (£133,111 per QALY foregone)	0.00%
UST- SEC-RIS	SW quadrant (£160,394 per QALY foregone)	SW quadrant (£160,393 per QALY foregone)	0.00%

*Please note all sequences have BSC as fourth-line treatment. Abbreviations: LY = life years; QALY = quality adjusted life years; ICUR = incremental cost utility ratio; iNHB = incremental net health benefit; SW = Southwest; DEU = deucravacitinib; APR = apremilast; DMF= dimethyl fumarate; ADA = adalimumab; BIM = bimekizumab; BRO = brodalumab; CER = certolizumab pegol; ETA = etanercept; GUS = guselkumab; INF = infliximab; IXE = ixekizumab; RIS = risankizumab; SEC = secukinumab; TIL = tildrakizumab; UST = ustekinumab.

B7. Document B, Section B.3.4. Please provide further clarification of the regression model and output that were used to derive the values provided in Table B.3.8. Does the model use the change from baseline to 16 weeks as the dependent variable or the actual 16-week EQ-5D score?

A description of the regression models considered, and the associated statistical fits are reported in section H.1.3.1 of the appendices of the company submission. Two sets of linear regression models were used that, due to the adjustment for baseline as a covariate, provided exactly analogous results. One set of models fit the actual EQ-5D health utility score at week 16 as the dependent variable. The second set of models fit the change from baseline to week 16 as the dependent variable. Both sets of models included PASI response category and baseline EQ-5D utility score as fixed effects and were fit using SAS PROC MIXED. Output

from the LSMEANS statement for PASI response category was used to populate Table B.3.8 in the submission. Representative SAS code is provided below.

```
proc mixed data=adhui;
    where avisit = "Week 16" and paramcd eq "&param";
    class &response;
    model &model = &response eq5dbl/alpha=0.05;
    lsmeans &response / cl;
run;

&param – health utility score parameter
&response – PASI response in 4 or 5 categories
&model – aval or chg
```

B8. Document B, Sections B.3.4.1 and B.3.4.5 (Table B.3.10.)**.** There does appear to be a substantial difference in baseline utility between the DLQL >10 subgroup of the POETYK trials and the corresponding subgroups of previous trials informing previous appraisals. While appreciating that you have explored the baseline disparity issue, is there any further insight you can offer as to why this might be the case?

As explained in the submission, it is unclear why the POETYK baseline utilities are not within the range of comparator trials' baseline utilities. No justifying difference was found in trial population characteristics. However, a deeper review of baseline characteristics of POETYK trials and the studies feeding into the utilities reported in TA350 and TA511 was explored. Table 2 in Appendix 3 reports on those. As a remainder, TA350 and TA511 were selected based on the following criteria reported in section B 3.4.5:

- availability of data in the public domain
- baseline utility value reported
- similar PASI response categories to the POETYK trials
- utility values based on pivotal trials
- utility values for patients' baseline PASI ≥ 12 and stratified by DLQI>10 and, in line with the POETYK trials' utilities).

In terms of differences, the FIXTURE trial (one of the 5 trials used to generate TA350 utility) could be seen as outlier with a higher mean PASI score at baseline (ranging 23.2 - 24.1) than the POETYK trials (mean baseline PASI = 20.7-21.8) and the AMAGINE-1 trial (mean baseline PASI = 16.4-19.7) used in TA511. Additionally, the proportion of patients who received prior biologic therapy in FIXTURE was lower than in the POETYK and AMAGINE trials (11-13% in FIXTURE versus 31-39% in the POETYK trials and 45-46% in AMAGINE-1). Furthermore, the proportion of white participants in the POETYK trials was lower (~67%) compared to other trials (~90%; except for ERASURE: 69%). However, because the utility used in TA350 was sourced from FIXTURE as well as 4 other trials (ERASURE, JUNCTURE, FEATURE, SCULPTURE) with similar baseline characteristics than other psoriasis trials (SCULPTURE was not included in the NMA because it is a comparative analysis of different doses of secukinumab and does not include any other comparator or placebo group,) this would compensate for the outlier values observed in FIXTURE. Additionally, both sets of utilities (from TA350 and TA511) have been generated directly from trials using the EQ-5D-3L questionnaire, similar to our submission. Table 2 in Appendix 3 reports on the baseline

characteristics of the following trials POETYK PSO 1, PSO2, AMAGINE-1 (supporting for TA511) and ERASURE, JUNCTURE, FEATURE, FIXTURE SCULPTURE (supporting TA511). Any differences in baseline characteristics that would justify the disparity observed in baseline utility were not identified.

As an exploratory analysis, we conducted the mapping of DLQI of the pooled POETYK to EQ-5D, using the algorithm from Davison et al., 2018[37] (see appendix 5 for the mapped values). Summary of health utility scores derived from the mapped DLQI with baseline DLQI >10 are reported in

Table **9**. The baseline value of the mapped DLQI is lower than the one from EQ-5D, and also more in line with corresponding subgroups of previous psoriasis appraisal (TA350 and TA511). Table 10 presents the outcomes of using the mapped DLQI values. The total QALYs accrued with each treatment sequence were lower than in the base case analysis (using the POETYK pooled utility, see

Table **9**) resulting in lower ICUR values, as the mapped utilities were lower than the base case utility values for all PASI categories. The outcomes show that the deucravacitinib sequence remained cost-effective when compared against all comparator sequences (see results in Table 10).

Table 9. Summary of health utility scores derived from the mapped DLQI with baseline DLQI >10, and other compared values

	Pooled POETYK trials		Pooling of POETYK and other psoriasis trials (used in base case)	Other psoriasis trials	
	Mapped DLQI	EQ-5D		Utilities reported in TA511 (AMAGINE-1)	Utilities reported in TA350 (FIXTURE, ERASURE, JUNCTURE, FEATURE, SCULPTURE)
Baseline	[redacted]	[redacted]	[redacted]	0.521	0.642
PASI<50	[redacted]	[redacted]	[redacted]	0.016	0.109
PASI 50-74	[redacted]	[redacted]	[redacted]	0.190	0.193
PASI 75-89	[redacted]	[redacted]	[redacted]	0.295	0.226
PASI 90-99	[redacted]	[redacted]	[redacted]	0.355	0.264
PASI 100	[redacted]	[redacted]	[redacted]	0.368	0.264

Abbreviations: DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area Severity Index

Table 10. Cost effectiveness outcomes with the mapped DLQI utility (based on rectified model)

Sequence*	Deterministic base case ICUR (using pool of POETYK trial derived utilities with TA511 and TA350)	Updated mapped DLQI scenario ICUR	Change in ICUR (%)
DEU-SEC-RIS	-	-	-
APR- SEC-RIS	Dominant (-£12,777)	Dominant (-£14,611)	12.5%

Sequence*	Deterministic base case ICUR (using pool of POETYK trial derived utilities with TA511 and TA350)	Updated mapped DLQI scenario ICUR	Change in ICUR (%)
DMF- SEC-RIS	Dominant (-£126,058)	Dominant (-£143,121)	11.9%
ADA- SEC-RIS	SW quadrant (£93,373)	SW quadrant (£113,493 per QALY foregone)	17.7%
BIM- SEC-RIS	SW quadrant (£172,205 per QALY foregone)	SW quadrant (£186,390 per QALY foregone)	7.6%
BRO- SEC-RIS	SW quadrant (£191,922 per QALY foregone)	SW quadrant (£203,244 per QALY foregone)	5.6%
CER- SEC-RIS	SW quadrant (£100,142)	SW quadrant (£125,623 per QALY foregone)	20.3%
ETA- SEC-RIS	Dominant (-£27,666)	Dominant (-£31,164)	11.2%
GUS- SEC-RIS	SW quadrant (£171,312 per QALY foregone)	SW quadrant (£192,282 per QALY foregone)	10.9%
INF- SEC-RIS	SW quadrant (£158,850 per QALY foregone)	SW quadrant (£185,994 per QALY foregone)	14.6%
IXE- SEC-RIS	SW quadrant (£162,486 per QALY foregone)	SW quadrant (£178,667 per QALY foregone)	9.1%
RIS- SEC-UST	SW quadrant (£212,428 per QALY foregone)	SW quadrant (£234,052 per QALY foregone)	10.2%
SEC- UST-RIS	SW quadrant (£203,642 per QALY foregone)	SW quadrant (£235,809 per QALY foregone)	15.8%
TIL- SEC-RIS	SW quadrant (£133,111 per QALY foregone)	SW quadrant (£145,184 per QALY foregone)	9.1%
UST- SEC-RIS	SW quadrant (£160,393 per QALY foregone)	SW quadrant (£190,101 per QALY foregone)	15.6%

Health care resource use and costs

B9. Document B, section B.3.5.2. Table B.3.16. An annual cost of £[redacted] is reported for inpatient admission and outpatient care for those on best supportive care following discontinuation of biologics, referencing the DISCOVER study report. Further, in Table 3.16, a value of £4074.39 is offered as an alternative cost of BSC, referencing

Fonia et al 2010. This appears to have been inflated from a 2008 base value of £2,956.70 (model worksheet “Labels and Constants” Cell N63).

Please clarify:

- How the £[redacted] was derived from the DISCOVER study report provided. We are unable to trace it in the report.

  In the DISCOVER report,[38] Supplementary Table 16 (page 60) presents the cost breakdown of the total cost (£[redacted]) used in the model to estimate BSC costs. The costs considered are inclusive of all secondary care use and are based on patients who had discontinued biologic therapy for 12 months (12 months post index). The costs considered include admitted patient care, outpatient visits, critical care (HDU & ITU), A&E, day cases and phototherapy. Please note that the page reference is linked to an updated and final version of the report (dated 2 May 2022) which is shared with this response. It only has minor editorial changes (for example, correction on author name and reference to the DISCOVER database) from the version previously shared with the submission (dated 8 April 2022) but is the final version. (Please note that the cost of £[redacted] can be found on page 62 of the version of the report shared with the submission dated 8 April 2022).

- The exact source of the ONS inflation table (114.1/82.8) used to inflate the 2008 value of £2,956.70 reported by Fonia et al.

  Annual inflation indices relating to the years 2008 to 2021 in Table 23 from the ONS consumer price inflation reference tables were used to inflate the costs reported by Fonia et al.[39] These were derived from the consumer price indices relating to “Health”, (code D7BZ) and according to the table, the inflation indices for 2021 and 2008 are 114.1 and 82.8 respectively.

Similarly for the Non-Responder Costs reported in Table B.3.17, document B, please clarify:

- How the £[redacted] was derived from the DISCOVER study report provided.

  In the DISCOVER report,[38] Supplementary Table 16 (page 60) presents the cost breakdown of the total cost (£[redacted]) used in the model to estimate non-responder costs. The costs considered include admitted patient care, outpatient visits, critical care (HDU & ITU), A&E, day cases and phototherapy based on patients who had not discontinued biologic therapy for 12 months (12 months pre index).

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Deucravacitinib for treating moderate to severe plaque psoriasis [ID3859]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	British Association of Dermatologists
3. Job title or position	Consultant Dermatologists
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training and research of Dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of Dermatology services across all service settings. It is funded by the activities of its Members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	The BAD is a registered charity and owns various companies. The British Association of Dermatologists Biologic Interventions Register (BADBIR) is the national psoriasis biologic and systemic treatment registry (and an NIHR portfolio study) run by the BAD as a non-profit-making limited company. This company receives funding from most manufacturers of biological drugs for psoriasis on the registry to collect pharmacovigilance data. The BAD does not receive any funding from BADBIR.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	• Control of psoriasis with the aim of a 'clear' or 'nearly clear' by Physician's Global Assessment rating • Reducing the impact of the disease on quality of life
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Current guidelines (specifically the published 2020 BAD guidelines on biologic therapies for psoriasis), and prior NICE STAs have defined a minimum clinically significant improvement as: • ≥ 50% reduction in baseline disease severity, e.g. a PASI50 response, or percentage BSA where PASI is not applicable, and • Clinically relevant improvement in physical, psychological or social functioning (e.g. ≥ a 4-point improvement in DLQI score or resolution of low mood)

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – in real-world practice, not all people with psoriasis who fulfil NICE criteria for biologic therapy respond to other NICE-approved biologic therapies; secondary failure is also common (Patterns of biologic therapy use in the management of psoriasis: cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). Br J Dermatol. 2017 May;176(5):1297-1307. doi: 10.1111/bjd.15027. Epub 2017 Mar 20. PubMed PMID:27589476; Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2015 Nov;135(11):2632-2640. doi: 10.1038/jid.2015.208. Epub 2015 Jun 8. PubMed PMID:26053050; Differential Drug Survival of Second-Line Biologic Therapies in Patients with Psoriasis, J Invest Dermatol. 2018 Apr;138(4):775-784. doi: 10.1016/j.jid.2017.09.044. Epub 2017 Dec 6.) **N.B.** Additional reference: Biologics may be less effective in the real world, cf. to trial data due to use of biologic therapies. Comparison of Drug Discontinuation, Effectiveness, and Safety Between Clinical Trial Eligible and Ineligible Patients in BADBIR JAMA Dermatol. 2018 May 1;154(5):581-588. doi: 10.1001/jamadermatol.2018.0183. Use of biologic therapy in the UK is currently limited to those with severe disease as defined by a PASI 10. This excludes use of highly effective biologic therapy (within the licensed indication – i.e. moderate or severe) where the disease is associated with a severe impact on their QoL, physical, social or psychological function. Specifically, people with moderate disease and those with severe disease but of limited extent – i.e. high-impact and difficult-to-treat sites such as the face, hands, feet, flexural/genital sites. People in these two groups will not have a PASI score of 10 but nevertheless will suffer major impact from their disease. Options for these patients are limited if non-biologic systemic therapy is not effective or cannot be tolerated. Newer small molecule drugs (e.g. dimethyl fumarate and apremilast) are not approved by NICE for patients with a PASI <10 either. Therefore, we recommend that NICE CG153 criteria should be used for non-biologic systemic therapy, i.e. psoriasis that cannot be controlled with topical therapy, and: • has a significant impact on physical, psychological or social wellbeing, and • one or more of the following: ○ psoriasis is extensive or

	○ psoriasis is localised and associated with significant functional impairment and/or high levels of distress or ○ phototherapy has been ineffective, cannot be used or has resulted in rapid relapse. Including these indications with the NICE criteria would still be entirely consistent with the licensed indications for these treatments (moderate-to-severe psoriasis).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	With NICE-approved biologic therapies and biosimilars; apremilast; dimethyl fumarate; standard systemic therapies (see NICE CG153).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes – BAD guideline for biologic therapy for psoriasis 2020 https://onlinelibrary.wiley.com/doi/10.1111/bjd.19039 and NICE CG153 www.nice.org.uk/guidance/cg153. Please note the following comments regarding the final scope: ➔ There should be mention of psoriatic arthritis as an important, common co-morbidity and that when present, of the standard systemic therapies used in psoriasis, only methotrexate is helpful for both joints and skin. As previously communicated for more recent biologic STAs for psoriasis, the final scope mentions that *"most treatments reduce the severity of psoriasis flares rather than prevent episodes"* – there is no evidence that any of the treatments are disease-modifying. This would better describe the point being made here (rather than "most treatments reduce the severity….") as many of the new biologic treatments do clear or nearly clear the disease and maintain it in this state.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	Yes – please see NICE CG153. Data from BADBIR national pharmacovigilance registry suggest that most people with psoriasis fulfil stipulated criteria, e.g. PASI mean (SD) = 16.4 (8.3) – please see Demographics and disease characteristics of patients with psoriasis enrolled in the British Association of Dermatologists Biologic Interventions Register. Br J Dermatol. 2015 Aug;173(2):510-8. doi: 10.1111/bjd.13908. Epub 2015 Jul 6. PubMed PMID:25989336.

experience is from outside England.)	**N.B.** Clinical re-audit report based on CG153 standards www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-audits/psoriasis/psoriasis-2017 (July 2018) and https://onlinelibrary.wiley.com/doi/full/10.1111/ced.14286 (May 2020)
9c. What impact would the technology have on the current pathway of care?	An additional option to consider in people with severe psoriasis; another agent with a novel mode of action, i.e. an oral, selective tyrosine kinase 2 (TYK2) inhibitor. More agents within the same 'market' may provide motivation to drive down the NHS price for biological drugs in psoriasis, reducing overall NHS costs. A novel mode of action offers the opportunity to further study and clarify personalised treatment for psoriasis in the future.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes.
10a. How does healthcare resource use differ between the technology and current care?	There would not be any expected differences in health resource use compared to existing NICE-approved agents aside from drug acquisition costs.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment would be required.
11. Do you expect the technology to provide clinically meaningful	Yes.

benefits compared with current care?	
11a. Do you expect the technology to increase length of life more than current care?	N/A.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Potentially yes, by providing an additional treatment option for this major, chronic and debilitating disease. In addition, deucravacitinib has been trialled directly against apremilast. With this greater efficacy, improved health-related quality of life is seen.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No clear evidence of subgroups that would be particularly recommended for deucravacitinib.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use	No additional therapies or monitoring anticipated, ease of use comparable to other therapies. Following inadequate response to standard systemic therapies many patients progress to biologic therapies due to higher efficacy and favourable safety profile, when compared with apremilast (lower efficacy) and dimethyl fumarate (gastrointestinal side effects). An additional, effective oral therapy offers patients choice which may be helpful for individuals who are needle-phobic. Many biologics are self-administered and may also be difficult for some individuals when compared with oral therapies.

or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The published 2020 BAD guidelines recommended biologic therapy for the following people with psoriasis: Offer biologic therapy to people with psoriasis requiring systemic therapy if methotrexate and ciclosporin have failed, are not tolerated or are contraindicated [see National Institute for Health and Care Excellence (NICE) guidelines CG153] and the psoriasis has a large impact on physical, psychological or social functioning [for example, Dermatology Life Quality Index (DLQI) or Children's DLQI > 10 or clinically relevant depressive or anxiety symptoms] and one or more of the following disease severity criteria apply: • the psoriasis is extensive [defined as body surface area (BSA) > 10% or Psoriasis Area and Severity Index (PASI) ≥ 10] • the psoriasis is severe at localized sites and associated with significant functional impairment and/or high levels of distress (for example nail disease or involvement of high-impact and difficult-to-treat sites such as the face, scalp, palms, soles, flexures and genitals). These criteria do extend to additional (small) subsets of people with psoriasis currently not covered by the NICE criteria for biologic therapy and were introduced due the limitations of the PASI disease severity tool (i.e. it is strongly dependent on body surface area affected, and for some people with localised disease at high-impact and difficult-to-treat sites the PASI will not reach 10) and the specific burden (and limited options) for people with disease in both compartments (skin and joint). Generally, therapy is stopped when: • the minimal response criteria (i.e. PASI50 and DLQI≥4 or PASI75 assessed around week 16) are not met, either initially or further down the line (i.e. secondary failure) • adverse effects arise, e.g. development of neurological symptoms suggestive of demyelinating disease, or new/worsening pre-existing heart failure • the risks outweigh the benefits in a) pregnant females or females planning conception and b) people undergoing elective surgery • live vaccines need to be administered.

	No additional testing from what is already recommended for biologics.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No; however, will economic calculations associated with employment be included?
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Targeting the tyrosine kinase 2 (TYK2) is a new treatment approach for psoriasis. Apremilast has been less well adopted due to lower response rates when compared with biologics. Data for deucravacitinib suggest higher response rates which may see it used more widely.
16a. Is the technology a 'step-change' in the management of the condition?	As above – it represents a step-change in the management of people with moderate-to-severe psoriasis.
16b. Does the use of the technology address any particular unmet need of the patient population?	Please see response in Q8 above.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The tolerability and side effects profile based on phase 3 studies are reassuring and unlikely to have a major impact on drug use. The side effects profile is not anticipated to differ from current therapies.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
18a. If not, how could the results be extrapolated to the UK setting?	N/A.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	**The following outcomes were reported in the trials:** PASI100, PASI90, PASI75, sPGA 0/1, (scalp) ss-PGA 0/1, PSSD-Symptoms CFB, DLQI 0/1, PGA-fingernails (PGA-F) 0/1, palmoplantar PGA (pp-PGA) 0/1, serious AEs. PASI90 is very important; PASI75 is important as comparator also to previous biologics. These data require support in conjunction with quality of life assessment. Other outcomes that may not have been reported but are highly relevant include: • **Psoriasis improvement on the face:** Plus, other high-impact and difficult-to-treat sites, i.e. hands and feet, flexural/genital psoriasis. • **Response rate:** Over what time period? It would be important to include longer treatment outcomes. • **Relapse rate:** Over what time period? It would be important to include longer treatment outcomes. • **Adverse effects of treatment:** Infection; separate out adverse effects in the very short term, e.g. during loading doses. • **Health-related quality of life (including dermatology quality of life index [DLQI]):** Include other measures of impact, e.g. on psoriatic arthritis. • **Impact on concomitant psoriatic arthritis**.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See notes above.

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There is very limited information about use of the technology outside clinical trials. It would be extremely important for all people with psoriasis who meet the eligibility criteria to be enrolled in BADBIR when prescribed this agent to ensure capture of high-quality pharmacovigilance data and to allow relevant comparisons with other biologic agents (N.B. around 20,000 patients now registered – please see www.badbir.org). We suggest featuring a future research recommendation in the final guidance, along the lines of that featured in the ustekinumab STA (TA180): "The collection of data on the use of ustekinumab and other biological therapies as part of the British Association of Dermatologists' Biologics Intervention Register (BADBIR)."
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No; however, it is worth pointing to the living systematic review and network meta-analyses by the Cochrane Skin Group: Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No; however, ciclosporin is not recommended for use for >1 year (NICE CG153) and is therefore a less relevant comparator for this STA. Similarly, PUVA is associated with increased risk of skin cancer and can only be used in the shorter term.
21. How do data on real-world experience compare with the trial data?	Not yet available for this technology.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The PASI may underestimate disease severity in people with darker skin (type IV-VI) as redness may be less evidence (a key component of the PASI). DLQI will underestimate the impact in people who are not sexually active, or older (retired) or socially isolated; it does not capture anxiety and depression.
22b. Consider whether these issues are different from issues with current care and why.	These are generic issues.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Important addition, with a novel mode of action • Existing therapies, while effective for many, do not work for *all* those requiring treatment • Comparable adverse effects profile with other systemics for psoriasis • Suitable for patients with multiple comorbidities who may not be suitable for biologics • Those with localised psoriasis in high-impact and difficult-to-treat sites may have severe symptoms and disability despite having a PASI score of <10.

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Single Technology Appraisal

Deucravacitinib for treating moderate to severe plaque psoriasis [ID3859]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Psoriasis and Psoriatic Arthritis Alliance (PAPAA)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	A patient-centred charity that exists to support people affected by psoriasis and psoriatic arthritis. Activities include information both in print and via a comprehensive website. Telephone support offering help, advice and a sign-posting service to other resources is also available. The organisation also supports research via a small grants scheme. Health care professionals continued professional development is promoted and supported with an accredited online training resource (free to NHS staff). There is no formal membership of the organisation, but subscriptions are available to receive a bi-annual journal, all other patient resource and support are free and can be accessed anonymously. Access to the website is also free, with limited sign-up details needed to enter the PAPAA Knowledge Bank and online subscriber's area. Use of social media is also part of the organisation's activities, but with a strict policy of only publishing evidenced-based and reliably sourced content. Funding is via donations, journal subscriptions, online shop sales, fundraising activities and an ethical investment portfolio. No funds are currently accepted from commercial organisations (including the pharmaceutical industry) or third-party agents representing or supporting those sectors.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	No

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information used in this submission has been gathered and based on direct feedback from people affected by psoriasis, and my personal experience of living with psoriasis. PAPAA also has a continuing data gathering process, and since 2014 via the PAPAA survey. All survey data we use is unpublished and for our own internal use to inform our work and direction. Those who identified as having moderate to severe psoriasis in our surveys used for this submission N=578, age range 18-77. The surveys are predominately completed by females (398) male (121) non-disclosed (59), but psoriasis generally affects both men and woman equally. Our surveys are available on our website to complete anonymously and submissions are made from across the UK and elsewhere, for this submission we've only used those who have identified as living in England.

Living with the condition **6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?**	For many people psoriasis can be very mild and not affect them or interfere with their daily lives, but when the condition moves beyond being mild to moderate, and becomes moderate to severe, the experience of living with psoriasis starts to change. The following are quotes from people who have moderate to severe psoriasis and reflect the overall views of what and how the condition affects their education, work, social life and relationships: *"It itches and burns all day. I can't wear what I want because of how uncomfortable it makes me feel"* *"Extremely self-conscious at school. Would cover up"* *"Very difficult with people's lack of knowledge and understanding when other adults would steer their children away from me due to how I looked"* *Having to take time off for Hospital appointments and being admitted for treatment."* *"Whilst I was at college and university it really got me down and caused depression and made it difficult to focus"* *"I work as a paramedic and sometimes have flare-ups especially on hands/ knuckles"* *"All over my body and in my scalp which is the worst"* *"It affected my focus when studying or in class as all I wanted to do was scratch my skin off. Also I was bullied by other kids due to it"* *"Effects my eyes, I have Depression"* *"Psoriasis started when I was 47 after a personal trauma and had breast cancer"* *"I was hospitalised for this several times in the past"*

	"I missed lots of days at school to visit the hospital for treatment." *"I was very bad with psoriasis as a teenager (none now for decades) and I had to phototherapy session which made me miss lessons"* *"I was teased as a child about my knees being constantly scabby"* *"As a musician my arms were covered. Again, uncomfortable changing at venues. Not good if you're a top-class professional musician!"* *"Due to severe palmoplantar on feet and hands it's extremely painful to walk and my hands so sore"* *"Uniform worn makes it v uncomfortable at times. Customers stare or comment on hands is hurtful"* *"It affected my focus when studying or in class as all I wanted to do was scratch my skin off. Also, I was bullied by other kids due to it"* *"I missed lots of days at school to visit the hospital for treatment."* *"The daily itching is painful and distracting. Scalp psoriasis and inside my ears. Ears were always infected. Made listening hard if they had been packed with gauze at hospital. Psoriasis on legs, teased by peers."* *"I was bullied relentlessly at school and a lot of days off due to appointments and treatment."* *"With the pain and constantly feeling uncomfortable because of the burning and itching sensations it affects my moods and is a huge distraction"* *"Can be difficult to dress appropriately and move comfortably."*

	"I constantly want to scratch myself. I also feel like it makes me look dirty to other people, like they think the flakes in my hair is dandruff when it's not sensitive area psoriasis." *"Psoriasis on hands and underneath my feet can make any type of work difficult."* *"The flaking affects my appearance and I'm constantly itching and applying cream."* *"Skin is greatly improved due to biological drug used to treat psoriatic arthritis."* *"Work colleagues and patients continually commented on it which made me uncomfortable. Pain from the plaques cracking made working uncomfortable."* *"Affected work when I had flares and when I had to attend hospital appt's every day for treatments for months on end."* *"Simply trying to concentrate on an email can be tricky when I itch and burn so bad."* *I had to give up caring, I do a less active role now.* *"I've lost all confidence in myself and hate the skin I'm in, making intimacy too painful."* *"I refuse to be intimate with my partner or wear more revealing clothing."* *"Twin beds now, as the plaques were in the bed and my scratching was irritating my partner."* *"I feel unattractive when my skin flares. Do not wish to go out socialising either."* *"My husband has to cream my body for me, sex is a thing of the past."* *"I feel embarrassed to be seen naked; sore cracked skin under breasts and intimate areas."* *"… as a younger person, boys would shy away from me due to my skin."*

	"I don't want to go out and socialise if I can't feel good or comfortable in what I'm wearing." *"I've had days where I've thought I don't care what others think and will show my skin and strangers have come up to me and commented on how disgusting my skin is."* *"I don't want to go out anywhere in case I have to wear something that might show my psoriasis."* *"Red scalp as a child, scratching weeping scalp, equals bullying."* *"Little interest in going out with scabby hands and feet. Wearing anything other than flip flops is difficult."* *"I'm so conscious of what I wear due to flaking."* *I didn't have a social life for years. It limits what clothes I can wear as I always try to hide it* *"Wouldn't go swimming or wear shorts or short sleeves when I was younger."* *"Paranoid about flakes and scratching. Paranoid about skin when out in public."* The key issues raised by those completing our surveys are not only the appearance of psoriasis, but also the impact of the pain, itch and soreness that psoriasis causes and the subsequent effect these have on daily function. Not least work and education but choice of clothing and the restrictions that causes. The psychological affect can be enormous and that affects how people feel and also causes problems with relationships, both those that are new and long-term. Psoriasis can become a lonely disease and leave people feeling inadequate, unloved and alienated.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There is an increased positivity towards newer therapies, but access is often frustrating to patients, with the feeling that they are not being offered the best therapies or are being offered less effective lower costing therapies. There is also a concern that given psoriasis is life-long that once therapies begin to fail that there won't be sufficient alternative treatments going forward.
8. Is there an unmet need for patients with this condition?	The need to have options as therapies begin to fail or stop working is always a fear and will continue to be an unmet need. Choice, accessibility and options are a particular concern of patients with psoriasis.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Adding an alternate targeted therapy is seen as an advantage and complements the existing treatment range, particularly if similar class therapies fail or are inadequate.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	As this technology is not in general use for psoriasis, there doesn't appear to be any obvious disadvantages than other similar class therapies.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who have both psoriasis and psoriatic arthritis might benefit from a therapy that is beneficial in both conditions.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Life-long condition with no cure • Treatments often fail, therefore wide choice needed • Psoriasis causes significant negative impact on quality of life • Relationships, education and work impacted by psoriasis • Psychological impact should not be underestimated

Thank you for your time.

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Deucravacitinib for treating moderate to severe plaque psoriasis [ID3859]

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- Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	Psoriasis Association
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Patient Support Organisation and Charity. The reach of the Psoriasis Association now extends much further than that of the original member. The Psoriasis Association currently has around 2000 members who help to fund the organisation via an annual fee. Other sources of income include fundraising (individuals, legacies and trusts), Gift Aid, investments and unrestricted educational grants from the Pharmaceutical Industry for projects (there is a policy that no more than 15% of the total income of the Psoriasis Association can come from the Pharmaceutical Industry). The Psoriasis Association has three main aims; to provide information advice and support, to raise awareness and to fund and promote research. In addition to traditional members, the Psoriasis Association regularly communicates with, or offers a platform enabling people whose lives are affected by the condition to communicate with one another via online forums on their own websites (~17,500 registered users), and Social Media (~7,200 registered users on closed Facebook group). The main Psoriasis Association website averages 48,000 visits per month. Other social media channels used by the Psoriasis Association that lend themselves more to “raising awareness” include Twitter (~14,000 followers) and Instagram (~12,450 followers), along with a YouTube channel offering further information. The Psoriasis Association has been passionate about research throughout its 50+ year history. Regularly funding PhD studentships, alongside supporting the PPI of bigger research collaborations, always seeking to improve the lives of those affected by psoriatic disease and in 2021 awarded £1 million to the Biomarkers and Stratification to Optimise outcomes in Psoriasis (BSTOP) research project based at Kings College, London.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No funding has been received from Bristol Myers-Squibb Funding has been received from the following comparator treatment companies in the last 12 months:- Abbvie - £1,500 corporate membership, £8,500 core support Almirral - £1,500 corporate membership Amgen - £1,500 corporate membership, £690 honorarium Eli Lilly - £1,500 corporate membership Janssen - £1,500 corporate membership, £8,500 core support LEO Pharma - £1,500 corporate membership Novartis - £1,500 corporate membership, £1,486 honorarium UCB - £1,500 corporate membership, £5,100 honorarium, £300 sponsored project
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	This submission has been informed by informal, anecdotal information that we hear from patients and carers themselves, through the following channels provided by the Psoriasis Association:- the Psoriasis Association website (570,297 visitors in 2021) helpline (973 enquiries in 2021) online forums (17, 520 registered users in 2021) social media channels (including Facebook Group, Twitter and Instagram, 33,499 people in 2021) The Psoriasis Association analyses the data gathered from all communication channels (mentioned above) and monitors for trends in addition to interesting new requests. We have completed a Priority Setting Partnership on Psoriasis which gave valuable insight into issues affecting people living with psoriasis.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Psoriasis is a lifelong condition with varying degrees of severity. It is a condition that causes great distress to patients and great frustration in what feels like a constant battle to access appropriate services and medications. The patients for whom this treatment (Deucravacitinib) is intended, those with moderate to severe disease, will have a degree of psoriasis that will not only be visible to others, but also be itchy, painful and produce excess scales. It often impacts on sleep, work ability and social interactions. The scales are unsightly, and can cause problems with employment and work colleagues in many industries. Owing to the treatment ladder and trial and error approach of treating psoriasis, patients for whom this treatment is intended will have lived with this highly visible, painful and itchy condition for a number of years. They will have experienced the highs and lows of many treatment expectations and realities and invariably they will have experienced negative effects of living with psoriasis, impacting on their life and life potential. Owing to the highly visible nature of psoriasis, and its unsightliness, patients can often adopt negative coping mechanisms such as avoiding social situations (in the hope of avoiding negative reactions from members of the general public). This can mean that the condition itself is isolating and lonely. This can in turn lead to adopting unhealthy lifestyle choices, such as alcohol and drug use, lack of exercise and smoking. Social isolation limits ability to form close relationships (as the opportunity to meet people decreases) and so dependence on family members can ensue. When psoriasis is first diagnosed, patients will usually be prescribed topical treatments (creams and ointments). Our latest membership survey found that people were spending on average two hours every day treating their (mild) psoriasis with topical therapies. The majority of respondents in our

	membership survey reported psoriasis impacting on their choice of clothing, from regularly "covering up" in the summer months in long sleeves and long trousers, to the colour of clothing on the top half of the body (people reported having light suits for work to help conceal the shedding of scales, or chose certain fabrics so as not to have clothing ruined by treatments). It is often unsustainable to treat psoriasis with topical treatments alone, and patients will need more help to cope with a flare, or to maintain the condition at a manageable level. The traditional next stage has been Ultraviolet Light Therapy, but for some patients this form of treatment is not considered owing to the time commitment required (attending the Dermatology Department three times per week for 10 weeks) or lack of availability in their local area. Traditional systemic treatments for psoriasis would then be considered if the psoriasis was deemed to be moderate to severe in nature. It is vitally important however to measure, record and treat not only the physical symptoms of psoriasis, but the psychological impact the condition can have. Being a lifelong condition, the psychological impact may not initially be realised, which is why it is important for this assessment to be made over the course of the disease. Psoriasis in high impact areas such as the hands, feet, face or genitals is not only a problem for people owing to the visibility of the condition. Deep cracks to the fingertips (not to mention nail psoriasis) can be disabling for those whose trade requires use of the hands and fingers (e.g. musicians, artists, mechanics, carers, healthcare workers, office-based administration roles). Psoriasis on the feet can make walking difficult, even wearing shoes. Psoriasis on the face can be especially distressing, and we know people avoid intimate relationships so as not to have to expose genital psoriasis. For those in steady relationships, sexual relationships can be difficult owing to the pain experienced by genital psoriasis. People report deliberately not having children in case they too develop psoriasis. For those

	with moderate – severe psoriasis who do want children, their choice of treatment is limited owing to the teratogenicity of traditional systemic medications. Psoriasis therefore can affect every stage of life to varying degrees – from bullying in school, through to difficulty writing in exams, choice of career, having children, holidays and long-term relationships. Owing to the largely unpredictable nature of psoriasis, along with its' response to treatments, patients often experience highs and lows along their treatment journey. There is always great hope when a different treatment is able to be prescribed, their skin is deemed to be "bad enough" to now warrant a traditional systemic or biologic treatment. Often there is a period of elation when improvements to the skin are noticed. The impact of a quick response should not be under-estimated – it can often give people the confidence to get married or attend an interview for example, even visit a hairdresser / barber. Sadly, and all too often there then comes a low when the treatment stops working, or the side effects experienced means it must be discontinued. This cycle is then repeated over and over. Patients therefore need access to treatments that are appropriate, suitable and reliable over a long-term.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There has long been a very real postcode lottery in terms of care available on the NHS for people with psoriasis. This situation has been exacerbated by the COVID-19 pandemic. It is often difficult (and a long wait) for patients who need to access secondary care services for the first time, and also those who need to re-access secondary care services when their psoriasis flares (often post-discharge from successful UV therapy). It is disconcerting, and unfair that patients are aware of further treatments that they are entitled to access only for there to be a delay, often in excess of a year before an appointment with the relevant healthcare professional can be made. There has long been a frustration amongst those with clinically moderate psoriasis that their psoriasis is not "bad enough" to warrant systemic, or newer biological therapies, yet it is too severe to manage with topical treatments alone. This patient population are stuck in limbo. For many people with psoriasis there is little access to secondary care (where drugs for moderate to severe psoriasis are prescribed) as lists are closed or extremely lengthy or GPs are unwilling / unable to refer. It is incredibly frustrating when NICE Guidelines and Technology Appraisals are over-ruled at a local level. There are many treatments that are theoretically available, but in practice are denied to patients e.g. due to local formularies, and restrictions as to how many opportunities a patient is entitled to try newer treatments. It is worth remembering that treatments are still trial and error in psoriasis, and so a large armamentarium is necessary in order to manage this lifelong disease. The COVID-19 pandemic has made people question interfering with the body's immune system, and re-evaluating the risk: benefit ratio of some treatments for psoriasis. The more traditional, less targeted systemic therapies whilst they have a long-term safety profile pose more concern to patients than the newer, more targeted biologic therapies. However, an ability to stop the medication with almost immediate effect is seen as an advantage to many (for example, the biologic injections only required every 8-12 weeks were often highly regarded pre-pandemic, but many people now prefer a greater control over their treatment).

8. Is there an unmet need for patients with this condition?	Yes – until we can better target therapies, or until we have a therapy that doesn't ultimately lose efficacy, there will remain an unmet need for patients with psoriasis. Pre-COVID, the waiting times from point of referral to appointment in secondary care were around 8-10 months. Sadly this situation has become much worse. Therefore it is imperative that people with moderate-severe psoriasis are offered the most appropriate treatment at the first opportunity, and not left on suboptimal therapies. The reluctance to change therapies when unable to have face to face appointments is also resulting in patients remaining on suboptimal therapies for even longer – they must have better access to these drugs that have been licensed to treat their condition. Some Dermatology Departments have moved location, sometimes as a result of COVID-19 response and have lost their access to specialist pharmacy services, where traditional biologic injections can be stored. This can impact on prescribing habits. As an oral therapy with few storage restrictions, this treatment is able to be prescribed more widely and doesn't require the patient education / nurse support that an injection would.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	**For reasons explained above, the oral nature of this medication is a big advantage for many patients over injections. These reasons include:-** • **Ease of administration (e.g. tablet as opposed to injection, some patients are needle-phobic)** • **Ease of storage (which in turn means that patients can travel more easily with the medication)** • **Short-term nature of treatment (as a twice daily tablet patients can stop taking the medication and not be concerned that there is "still 10 weeks supply in their system".** • **Time from prescription to drug being dispensed to commencing active therapy (e.g. no need to wait for home delivery / nurse training)**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	No long-term safety data yet. Some patients may prefer the longer term relief of symptoms with less frequent administration of the biologic injections. The less frequent administration of injections means that patients don't have the daily reminder of having to medicate to control their psoriasis.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who are needle-phobic and those who travel or live in multiple locations e.g. students may benefit more from this therapy. Those for whom other treatments have failed – many people with moderate to severe psoriasis will eventually lose efficacy from biologic treatments and, as psoriasis is a lifelong condition, it is essential to have new options for this cohort to move on to. Those for whom regular monitoring is an issue.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The PASI is not a suitable assessment for psoriasis on high impact sites (such as the hands, feet, face and genitals). It is also not as robust a measure in black skin. The increased use of telephone or video consultations can also cause issues with assessing the severity of psoriasis (in all skin types). The psychological impact is being overlooked with many consultations regressing to speaking about the physical manifestations only. The true severity of psoriasis may therefore be being under-estimated and so patients under-treated / denied access to targeted therapies. Early access to effective treatments is necessary in order to limit the negative life course impairment associated with this debilitating disease.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Psoriasis is a lifelong condition in which individuals respond differently to different treatments. For this reason a range of treatment options for all degrees of severity is required. • There is currently unmet need in the treatment of people with moderate psoriasis (for whom topical treatments nor biologics are suitable), and those where high impact sites (such as the face, hands, feet and genitals should not be overlooked when defining treatment criteria*) *these sites will not produce a high PASI score • Itch should be considered as a treatment outcome. • A range of effective treatments with different modes of administration are required in order to provide shared-care decision making • Access to effective treatments early in the course of the disease could greatly improve outcomes for patients who are not currently able to achieve their full life potential.

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Deucravacitinib for treating moderate-to-severe plaque psoriasis [ID3859]

Produced by Aberdeen HTA Group

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Moira Cruickshank and Clare Robertson summarised and critiqued the clinical effectiveness evidence submitted by the company; David Cooper and Lorna Aucott checked and critiqued the statistical analyses presented in the company submission; Alan Crozier and Graham Scotland reviewed and critiqued the cost-effectiveness evidence submitted by the company and conducted additional scenario analyses; Paul Manson checked and critiqued the company's search strategies; Anthony Ormerod provided clinical guidance and comments on the draft report. Miriam Brazzelli coordinated all aspects of this appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

AE	Adverse event
AEI	Adverse event of interest
BAD	British Association of Dermatologists
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CRD	Centre for reviews and dissemination
CS	Company submission
CSR	Clinical study report
DLQI	Dermatology life quality index
DMF	Dimethyl fumarate
EAIR	Exposure adjusted incident rate
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions
EQ-5D-3L	EuroQol 5-Dimensions 3-level
EQ-5D-5L	EuroQol 5-Dimensions 5-level
ERG	Evidence review group
FAS	Full analysis set
GP	General practice
HRQoL	Health-related quality of life
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
IL	Interleukin
iNHB	Incremental net health benefit
IV	Intravenous
MACE	Major adverse cardiovascular events
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
NRI	Non-responder imputation
ONS	Office for national statistics
PAS	Patient access scheme
PASI	Psoriasis area severity index
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
p-y	Person-years
QALY	Quality adjusted life year
SAE	Serious adverse event
SCS	Summary of clinical safety
SLR	Systematic literature review
SmPC	Summary of product characteristics
sPGA	Static physician global assessment
TA	Technology appraisal
TNF	Tumour necrosis factor
TYK2	Tyrosine kinase 2

1. Executive Summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the evidence submitted by the company and ERG's key issues

The focus of the submission received from Bristol Myers Squibb is deucravacitinib for treating moderate-to-severe plaque psoriasis. Plaque psoriasis is an incurable chronic, immune-mediated, inflammatory skin disease mainly affecting adults and is the most common form of psoriasis.

The clinical evidence submitted by the company consists of two multi-centre, randomised, double-blind, placebo- and active-comparator (apremilast) controlled, international phase 3, 52-week trials: POETYK-PSO-1 and POETYK-PSO-2. Pooled analyses of the two trials showed that [redacted]% of the deucravacitinib group achieved sPGA 0/1 response at week 16, as compared to [redacted]% of the placebo group ([redacted]]. The co-primary endpoint of PASI 75 at week 16 was achieved by [redacted]% of the deucravacitinib group and [redacted]% of the placebo group ([redacted]).

[redacted] Interim results for the long-term, open-label extension studies of these two trials, POETYK-PSO-LTE, [redacted]

[redacted] Overall, the ERG agrees that the company's analysis shows deucravacitinib as [redacted] to apremilast and placebo. Because of the lack of direct evidence assessing deucravacitinib versus other relevant comparators other than apremilast, the company conducted an NMA.

The NMA results show that deucravacitinib is [redacted]

Table 1 Summary of the key issues

• ID3859	• Summary of issue	• Report sections
1	Best supportive care utility reverts to baseline, rather than receiving utility based on the PASI response for placebo observed in the NMA	4.2.6 and 4.2.7
2.	Application of averaged treatment acquisition costs per cycle, rather than full dose costs applied to those on treatment during the cycles that doses are due.	4.2.8
3.	Best supportive care and non-responded costs. Not clear they can all be attributed to stopping treatment or non-response, respectively.	4.2.8

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are the application of costing adjustments to reflect the periodic dosing/prescribing of treatments in the model, rather than cycle averaged acquisition costs, and the application of age adjustment to health state utility.

1.2 Overview of key model outcomes

The company utilise a Markov sequence model to compare deucravacitinib, as first line treatment, with 14 comparators in people with moderate to severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not and option. The model utilised a 2-week Markov cycle over the lifetime horizon. The modelled comparators have all been assessed and approved by NICE for, with the exception of infliximab, "people with severe or very severe psoriasis [defined by a total PASI of 10 or more, and a DLQI of more than 10] for whom systemic non-biological treatment (including methotrexate, ciclosporin and acitretin) and phototherapy are inadequately

effective, not tolerated or contraindicated". Infliximab has been approved for use in people with very severe psoriasis only.

The company model allows for two further lines of active therapy following first line treatment, with these held constant across the comparators. Following third line treatment patients move to best supportive care (BSC). Each active treatment line is modelled using an induction and a maintenance state. All surviving patients remain in the induction state up to the recommended time for assessing response, which varies across treatments (from 10-28 weeks). At the end of the induction phase for each line of therapy, the proportion of the patients that achieve a PASI75 response (derived from the NMA) transition to the corresponding maintenance state. Those who do not achieve a PASI75 response transition to the induction state for the next line of therapy, or to BSC following third line treatment. Patients in the maintenance state are assumed to retain their response until discontinuation. Within the induction and maintenance, health state utility is a linked to the level of PASI response achieved based on the estimates for each treatment obtained from the NMA. Discontinuation, for any reason, is modelled as a constant 2-weekly probability that is set equal between all treatments in the company base case.

Overall, the technology is modelled to affect QALYs by:

- Having a different PASI75 response rate compared to comparator treatments, which determines the proportion moving into maintenance and the rate at which people transition through to subsequent lines of therapy and ultimately BSC. Deucravacitinib has a superior PASI75 response rate compared to some treatments, resulting in QALY gains, and an inferior response profile compared to others, resulting in QALY losses.
- Having different PASI response distribution (<50, 50-74, 75-89, 90-99, 100) compared to comparator treatments, which determines the weighted average utility within the induction and maintenance health states of the model.
- The rate of adverse events applied which has a very minor impact on QALYs.

Overall, the technology is modelled to affect costs by:

- Having different acquisition costs compared to comparator therapies

- Affecting the rate of transition through to subsequent lines of therapy and BSC.
- Having different rates of adverse events which attract health care costs

The modelling assumptions that have the greatest effect on the ICER are:

- The comparative PASI75 response rates for the different treatments, based on different specifications of the NMA
- The source of utility values applied to PASI response categories.
- The assumption that health state utility on BSC returns to baseline, rather than receiving utility based on the PASI response distribution of the placebo arm of the NMA

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed by the company deviated from the NICE final scope in several ways; firstly, the population addressed in the submission was adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option. This definition of the severity of the disease suggests a PASI score of ≥10 but the inclusion criteria for the trials presented in the clinical effectiveness evidence specify participants who are candidates for phototherapy or systemic therapy and with a PASI score ≥12. The company's rationale was that the difference between PASI scores of 10 and 12 is small and that people with a PASI score of ≥12 would require a larger absolute decrease to yield the same percentage reduction as those with a baseline score ≥10. The ERG's clinical expert agrees with the company's explanation but notes that it could equally be easier for people with a higher baseline PASI score to achieve a clinical improvement than those with a lower starting score and milder symptoms. Overall, the population addressed in the submission is considered appropriate. Secondly, the comparators addressed in the company's decision problem differed from the NICE final scope, i.e., intended for adults with severe to very severe disease, defined by PASI ≥10 and DLQI ≥10, for whom systemic non-biological treatment and phototherapy are not adequately effective, not tolerated or contraindicated. The company's justification was that the population addressed in the decision problem was eligible for all treatment options available after third-line treatment, i.e., biologics, apremilast, dimethyl fumarate and deucravacitinib. The ERG's clinical expert is of the opinion that deucravacitinib is

likely to be used as a fourth-line treatment and, therefore, the comparators addressed in the company's decision problem are appropriate.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The main evidence submitted by the company consists of two RCTs, POETYK-PSO-1 and POETYK-PSO-2. The ERG is of the opinion that the clinical evidence submitted by the company is relevant to the decision problem specified by NICE and the results are generalisable to patients seen in UK clinical practice. The ERG agrees that these two trials should form the basis of the submission and has no major concerns about their conduct or the company's reporting of them. The ERG is satisfied that the methods used to conduct the NMA were appropriate and that the evidence from the NMA is consistent with the evidence from the two trials.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The modelling approach used by the company is generally consistent with that used in previous NICE appraisals of psoriasis drugs. With fourteen comparators already approved for this indication, the modelling approach has been critiqued and refined over the years, and the company have generally aligned their structure and assumptions with those that were accepted in the most recent relevant appraisal to use a full cost-effectiveness model (TA575, Tildrakizumab for treating moderate to severe plaque psoriasis). Given this, the ERG is broadly satisfied that the model is appropriate for decision making but identify three areas of uncertainty that the committee may wish to consider when assessing the cost-effectiveness results. These are summarised in the following boxes.

Issue 1 Best supportive care utility reverts to baseline

• **Report section**	4.2.6. (Treatment effectiveness and extrapolation); 4.2.7 (Health-related quality of life)
• **Description of issue and why the ERG has identified it as important**	Upon transition to best supportive care, patients are assumed to revert to their baseline utility level, and not a weighted average utility based on the placebo arm PASI response categories of trials in the NMA. This removal any benefit associated with observed placebo arm PASI reductions from the BSC state, with no similar adjustment to active treatment, risks overestimating quality of life benefits of each active treatment versus BSC; i.e. the mechanism underpinning PASI improvements in the placebo arms of the trials may also contribute to the observed response for active treatments. The company justified the approach taken by reference to TA575 where a similar issue was raised by the ERG and the committee concluded, at that time, that the use of baseline utility was more appropriate than the approach originally taken by the company in that instance of applying the utility of the lowest PASI response category (<50). The committee took account of the level of uncertainty associated with the response of patients not taking biologic therapy, as would be the case in BSC, and the opinion of the company's clinical expert that patients on BSC would revert to baseline utility shortly after switching off active treatment. Notwithstanding the above the ERG believes that this issue merits further consideration. Satisfactory resolution to this issue lies in obtaining best evidence as to whether the placebo response is a trial effect unique to the placebo arm (and not active treatment) or whether it may reflect natural improvement and retained in the model to reflect expected outcomes for BSC.
• **What alternative approach has the ERG suggested?**	The ERG's recommended alternative approach would be to allow utility of BSC to map to the PASI response rates observed for the placebo arm of the NMA, as it does for the active treatments.
• **What is the expected effect on the cost-effectiveness estimates?**	Application of a higher utility value for BSC serves to reduce the QALY gains for treatments with higher versus lower PASI response rates, hence increasing ICERs for more versus less effective treatments.
• **What additional evidence or analyses might help to resolve this key issue?**	Further clinical expert opinion on what is responsible for the PASI response rates observed in the placebo arm of psoriasis trials: • A trial effect due to increased monitoring/compliance with topical therapies • Natural improvement from baseline, when patients were meeting the PASI threshold for recruitment (regression to the mean) And whether the placebo response is unique to the placebo arm or could also explain some of the response observed for active treatments.

Issue 2 Application of averaged treatment acquisition costs per cycle

• **Report section**	4.2.8 (Resources and Costs)
• **Description of issue and why the ERG has identified it as important**	The application of average two-week treatment acquisition costs for the induction period and the maintenance period fails to recognise the overlap between the dosing schedule during the induction and maintenance phases of the model for some treatments. For those treatments where the first maintenance dose is not due for several weeks into the maintenance period, the application of average cycle costs tends to overestimate cumulative acquisitions costs as compared to applying full dose costs to those still on treatment during the cycle that each dose is due. Conversely, for treatments with a dose or pack prescription required during the first cycle of maintenance, there is a tendency for the application of averaged two-week acquisition costs to underestimate cumulative acquisition costs.
• **What alternative approach has the ERG suggested?**	The ERG believe it would be preferable for the full dose (or pack) costs to be applied the proportion of the cohort still on treatment when a dose (or pack) is due. However, the ERG acknowledges that this is not possible for second- and third-line treatments without greatly complicating the structure for the model to allow for counting of time in maintenance. However, the ERG suggest scenarios that explore the potential impact through adjusting the averaged costs to approximate this approach.
• **What is the expected effect on the cost-effectiveness estimates?**	Changes are expected to decrease the incremental costs of risankizumab and secukinumab compared to other comparators, which will improve the ICERs for these treatments versus others. Conversely, the incremental cost of tildrakizumab is expected to increase relative to other treatments and will increase the ICER for this treatment. Deucravacitinib will have lower cost savings per QALY lost (SW quadrant) against risankizumab and secukinumab, but higher cost-savings per QALY lost (SW quadrant) against tildrakizumab.
• **What additional evidence or analyses might help to resolve this key issue?**	Potentially, refinement of the model to allow more formal implementation of the approach suggested above, to apply full dose (or pack) costs to those who are still on maintenance when the dose is due.

Issue 3 Best supportive care and non-responder costs

• **Report section**	4.2.8 Health care resource use and costs
• **Description of issue and why the ERG has identified it as important**	The company include costs of best supportive care in their model, which are estimated as the total secondary care costs incurred by a sample of patients in the 12 months following discontinuation from biologic therapy. These are converted to expected 2-weekly cycle costs for application to all those in BSC over the duration of the model time horizon. There is no similar cost category (all secondary care costs) included for those remaining stable on maintenance treatment, and it is not clear that these costs can all be attributed to the discontinuation from biologic therapy to BSC. A similar issue also applies for non-responder costs.
• **What alternative approach has the ERG suggested?**	The ERG, based on expert clinical advice, accept that severe psoriasis patients who discontinue to BSC can be expected to have substantially elevated secondary care costs compared to those remaining stable on active treatment, but the magnitude of this increase has not been well informed. The ERG therefore suggest scenarios that reduce the annual BSC costs by fixed percentages to illustrate the uncertainty in the ICERs. The ERG acknowledge that the company costs on BSC and non-response are generally in line with those that have been accepted in prior NICE appraisal of psoriasis drugs.
• **What is the expected effect on the cost-effectiveness estimates?**	Reducing the cost of BSC will reduce the downstream BSC cost savings that accrue with more versus less effective first-line treatments, thus increasing their ICERs. Deucravacitinib's cost-effectiveness can be expected to reduce against apremilast, dimethyl fumarate, and etanercept, but improve (in the SW quadrant) against more effective biologics.
• **What additional evidence or analyses might help to resolve this key issue?**	Any further evidence that the can be offered to inform the comparative increase in secondary care costs that can be attributed to discontinuing psoriasis treatment to BSC versus remaining stable on active treatment.

1.6 Other key issues: summary of the ERG's view

The company report that, under the new methods guidance, the total QALY shortfall for the population under consideration does not meet the criteria for a severity weight. The ERG agrees with this statement.

The company identified an issue related to the high baseline utility observed in their POETYK trial participants, compared to that observed in previous psoriasis trials informing previous NICE appraisals in moderate to severe psoriasis. They argue that this acts as a ceiling effect, limiting the range in utility between low and high PASI response categories compared to that accepted in previous appraisals. Having

explored potential reasons for the difference and not identifying one, the company have pooled their own utility data with that used in two previous NICE moderate to severe psoriasis appraisals. Accepting that the POETYK trial population is sufficiently comparable to that of the previous trials for informing the comparative efficacy in the NMA, the ERG have accepted the company's approach for consistency. However, the committee may want to explore the uncertainty around the utility source, and the company have provided scenarios covering this.

1.7 Summary of ERG's preferred assumptions and resulting ICER

The ERG is broadly satisfied that the company's economic model is aligned with the NICE reference case, and consistent with the structure and assumptions that have been accepted in previous relevant NICE appraisals. Being cognisant of the modelling assumptions that have been accepted in this disease area, with many previously appraised comparator therapies, the ERG has made only two revisions to the company's base case. The first applies adjustments to the company's cumulative acquisition costs for first, second and third line therapy, to better reflect the actual dosing schedules of the alternative drug treatments. The second applies age adjustment to the health state utilities used in the model. The combined impact of these changes is relatively modest. Given the challenges of presenting stepwise changes in the ICERs for 15 alternative treatment sequences, for comparison we present the fully incremental analysis company's ERG corrected base case and the ERGs alternative base case incorporating the changes described above in Table 2. These analyses also correct for two treatment cost calculation errors that were identified in the company's model (see section 5.3)

Table 2 Summary of the ERG's preferred assumptions and ICER

Sequence	Total Costs (£)	QALYs	Incremental Cost (£)	Incremental QALY's	ICER (£)
ERG corrected company base case					
DMF-SEC-RIS	[redacted]	[redacted]			
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	£14,206

APR-SEC-RIS	£182,471	[redacted]	[redacted]	[redacted]	Dominated
ETA-SEC-RIS	£185,111	[redacted]	[redacted]	[redacted]	Dominated
ADA-SEC-RIS	£185,882	[redacted]	[redacted]	[redacted]	£93,397
CER-SEC-RIS	£187,333	[redacted]	[redacted]	[redacted]	£148,889
UST-SEC-RIS	£193,022	[redacted]	[redacted]	[redacted]	Ext Dominated
TIL-SEC-RIS	£197,263	[redacted]	[redacted]	[redacted]	Ext Dominated
SEC-UST-RIS	£198,251	[redacted]	[redacted]	[redacted]	Dominated
RIS-SEC-UST	£200,372	[redacted]	[redacted]	[redacted]	Dominated
INF-SEC-RIS	£204,866	[redacted]	[redacted]	[redacted]	Ext Dominated
GUS-SEC-RIS	£218,046	[redacted]	[redacted]	[redacted]	Ext Dominated
IXE-SEC-RIS	£222,521	[redacted]	[redacted]	[redacted]	£189,271
BRO-SEC-RIS	£226,855	[redacted]	[redacted]	[redacted]	Dominated
BIM-SEC-RIS	£231,685	[redacted]	[redacted]	[redacted]	£239,797
ERG alternative base case, incorporating combined changes from Scenario 3b (acquisition cost adjustments) and 7 (age adjustment of utility)					
DMF-SEC-RIS	[redacted]	[redacted]			
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	£14,873
APR-SEC-RIS	£180,702	[redacted]	[redacted]	[redacted]	Dominated
ETA-SEC-RIS	£183,191	[redacted]	[redacted]	[redacted]	Dominated
ADA-SEC-RIS	£184,163	[redacted]	[redacted]	[redacted]	£97,505
CER-SEC-RIS	£185,632	[redacted]	[redacted]	[redacted]	£160,662
UST-SEC-RIS	£190,321	[redacted]	[redacted]	[redacted]	Ext Dominated
SEC-UST-RIS	£195,589	[redacted]	[redacted]	[redacted]	Ext Dominated
TIL-SEC-RIS	£196,243	[redacted]	[redacted]	[redacted]	Ext Dominated
RIS-SEC-UST	£197,471	[redacted]	[redacted]	[redacted]	Dominated
INF-SEC-RIS	£202,907	[redacted]	[redacted]	[redacted]	Ext Dominated
GUS-SEC-RIS	£216,053	[redacted]	[redacted]	[redacted]	Ext Dominated
IXE-SEC-RIS	£220,019	[redacted]	[redacted]	[redacted]	£192,131

BRO-SEC-RIS	£224,820	[redacted]	[redacted]	[redacted]	Dominated
BIM-SEC-RIS	£228,555	[redacted]	[redacted]	[redacted]	£231,622

For further details of the exploratory and sensitivity analyses done by the ERG, see sections 6.1 and 6.2.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Bristol Myers Squibb is moderate-to-severe plaque psoriasis in adults. The company's description of this health condition in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is deucravacitinib (brand name not yet available).

2.2 Background

The company submission (CS) describes plaque psoriasis as an incurable chronic, immune-mediated, inflammatory skin disease that mainly affects adults, and is typified by a relapsing-remitting presentation of symptoms.[1-4] The CS focuses on moderate-to-severe plaque psoriasis.

Plaque psoriasis is the most common form of psoriasis.[5] Plaque psoriasis occurs when the inflammatory response of the body's immune system speeds up skin cell growth causing an increase in keratinocyte proliferation, causing the body to rapidly produce new skin cells every few days, which then build up on the skin's surface and turn into the characteristic areas of thickened skin that appear red and scaly.[6] Skin plaques usually present on the knees, elbows, and scalp, but can affect any area of the body, and can affect isolated areas or have more widespread involvement across several bodily sites, causing itching, skin pain, bleeding, skin cracking, and dry skin.[7-9] Nail psoriasis can include pitting, onycholysis, subungual hyperkeratosis, and nail discoloration.[10] The severity and extent of psoriasis is assessed using the Psoriasis Area Severity Index (PASI) scoring system. The impact of psoriasis on physical, psychological, and social wellbeing is assessed using the Dermatology Life Quality Index (DLQI). Scores of PASI ≥10 and DLQI >10 indicate severe disease.[2] Body surface area (BSA) and failure of previous systemic treatment are also taken into consideration when assessing the severity of disease.[11]

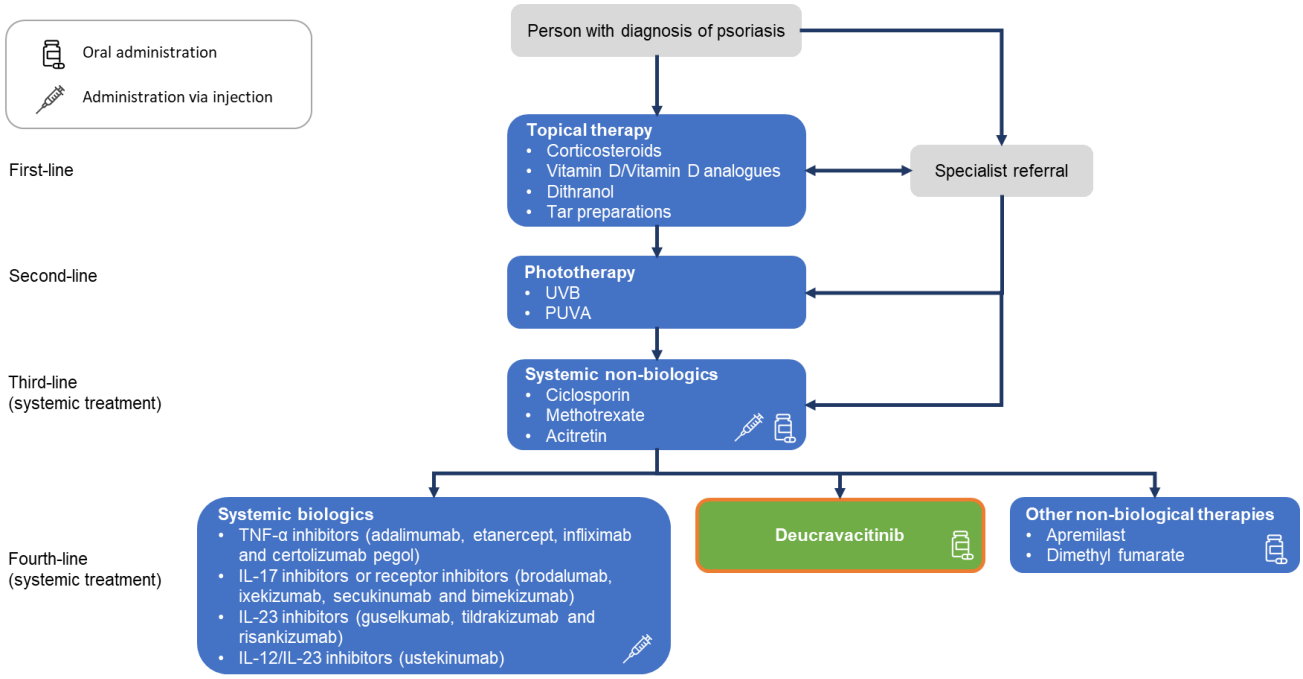
Psoriasis is associated with poorer health-related quality of life (HRQoL) and increased risk of developing depression, anxiety, and suicidality compared to the general population.[12, 13] Chronic itch is one of the most distressing symptoms of psoriasis and the visibility of plaques

can cause patients to withdraw from social environments and activities, resulting in feelings of loneliness, isolation, being unattractive and frustration.[1] Patients with moderate-to-severe plaque psoriasis can also suffer comorbidity, including mental health disorders, hypertension, cardiovascular disease, and diabetes.[14] The prevalence of psoriasis is between 1.3% to 2.2% in the UK, and approximately 90% of people with psoriasis will have plaque psoriasis.[2, 15] Of those individuals with plaque psoriasis, approximately 41% will have moderate-to-severe disease (34% moderate and 7% severe).[2, 15] In England, approximately 289,453 adults will have moderate-to-severe plaque psoriasis in 2023.[16] Psoriasis is financially costly to the NHS in terms of inpatient admissions, and secondary and primary care visits,[14, 17] and at a societal level in terms of lost work hours.[18]

Current treatments for psoriasis aim to reduce disease burden, alleviate symptoms, and improve HRQoL; however, therapies do not always result in a durable response and patients can experience multiple therapy changes over the course of their disease.[19] Patients with severe psoriasis for whom systemic non-biologic treatment or phototherapy is not an option due to lack of response, contraindication or being poorly tolerated, are eligible to receive fourth line biologic treatments. Biologic treatments reduce inflammation by targeting overactive cells in the immune system.[20] Biologic treatments involve several pre-treatment screening examinations and are usually administered by subcutaneous injection, either in the hospital setting or by the patient at home following injection training. Patients who receive biologic treatment require ongoing monitoring.[2] Biologic therapy is administratively burdensome and financially costly to the NHS.[17] Self-administration of treatment by subcutaneous injection can also be unappealing to some patients due to fear, anxiety, or inconvenience involved.[21] There are currently no orally administered biologics available for moderate-to-severe plaque psoriasis. Fourth line non-biologic, oral small molecule therapy options are limited to apremilast and dimethyl fumarate.

The company presents the proposed positioning of deucravacitinib in the clinical care pathway in Figure B.1.4 of the CS, and this is reproduced by the ERG as Figure 1. The company position deucravacitinib in the care pathway as an orally administered fourth line systemic treatment for adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option. The ERG clinical expert agrees with the company's positioning of deucravacitinib in the care pathway.

Figure 1 NICE clinical pathway of care for adults with plaque psoriasis showing the proposed positioning of deucravacitinib [reproduced from Document B, Figure B.1.4 of the CS]



Abreviations: IL = interleukin; PUVA = psoralen plus ultraviolet A; TNF: tumour necrosis factor; UVB = ultraviolet B.
Note: Methotrexate administration may be parenteral. All biologics are administered by subcutaneous injection, except infliximab which is administered as an intravenous infusion.
Source. Adapted from the NICE pathway for psoriasis.[22]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with moderate-to-severe plaque psoriasis	Adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option	Aligns with the expected use of deucravacitinib in NHS clinical practice	The population addressed by the company in the CS is adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option, which suggests a population with a PASI score of ≥10. The inclusion criteria for the main clinical effectiveness evidence presented in the CS for the POETYK-PSO-1 and POETYK-PSO-2 trials include participants who are deemed by the investigator to be candidates for phototherapy or systemic therapy, and with a PASI score of ≥12. While the company have presented subgroup analyses for prior use of psoriasis therapies in the CS, the ERG notes that the population addressed in the decision problem differs from the population addressed by the clinical effectiveness evidence. In the company's response to the ERG's clarification letter, the company states that the criteria used to define severity for the population for enrolment in POETYK clinical trials included BSA (≥ 10%), and sPGA/IGA (≥ 3) scores, besides PASI scores and that, while the clinical difference between patients with PASI 10 and 12 is small, patients with a PASI score ≥12 would need slightly larger absolute PASI score reduction to yield the same percentage reduction if starting from a higher baseline PASI ≥10 (e.g. a patient with a PASI of 10 would require a 7.5-point reduction to achieve PASI 75, while a patient with a PASI of 12 would require a 9-point reduction to achieve the same PASI outcome.) The ERG clinical expert accepts the company's argument on the difference in baseline PASI scores and the point reduction required to achieve a PASI score of 75 but notes

				that it could equally be easier for patients with a higher starting PASI score to demonstrate a clinical improvement than patients who have a lower starting PASI score and milder symptoms. However, the ERG clinical expert agrees that there is likely to be very little clinical difference between a PASI score of 10 and 12. The ERG also agrees with the company that it is likely that there would be minimal impact on the effect sizes of deucravacitinib versus placebo and versus apremilast whether PASI ≥12 or PASI ≥10 criteria were used for enrolment in the POETYK trials. The ERG therefore agrees that the population addressed in the CS is appropriate for this appraisal.
Intervention	Deucravacitinib	As per scope	N/A	The intervention described in the CS matches that described in the NICE final scope. Deucravacitinib is anticipated to be indicated for [redacted] CHMP positive opinion is anticipated in [redacted], EMA marketing authorisation is anticipated in [redacted], and MHRA (GB) marketing authorisation is anticipated in [redacted]
Comparator(s)	If systemic non-biological treatment or phototherapy is suitable: • Systemic non-biological	If systemic non-biological treatment or phototherapy are inadequately effective, not tolerated or	The target population is adults for whom systemic non-biologic treatment or phototherapy is not an option.	The population considered by the NICE final scope and the company's decision problem is adults with moderate to severe plaque psoriasis. The ERG notes that the comparators addressed by the company's decision problem are intended for adults "*with severe to very severe plaque psoriasis (defined by a total PASI of 10 or more, and a DLQI of more than 10) for whom systemic non-biological treatment (including methotrexate, ciclosporin and acitretin) and phototherapy are inadequately effective, not tolerated, or contraindicated*". In the company's response to the ERG's clarification letter, the company states that the population in the decision problem renders all treatment options which are available after third-line treatment, i.e. biologics, apremilast, dimethyl fumarate as well as

	therapies (including methotrexate, ciclosporin, and acitretin) • Phototherapy with or without psoralen For people with severe or very severe psoriasis [defined by a total PASI of 10 or more, and a DLQI of more than 10] for whom systemic non-biological treatment	contraindicated: • TNF-α inhibitors (adalimumab, etanercept, and certolizumab pegol) • IL-17 family inhibitors or receptor inhibitors (brodalumab, ixekizumab, secukinumab and bimekizumab) • IL-23 inhibitors (guselku	Infliximab is not considered a direct comparator since it is indicated for patients with very severe psoriasis only. Nevertheless, infliximab is included in the network meta-analysis to strengthen the network; it is also included in the economic model for	deucravacitinib, eligible for the patient population addressed in the CS. The company positioning of deucravacitinib in the care pathway is, therefore, in the same treatment line as biologics and apremilast/dimethyl fumarate. The ERG clinical expert agrees that it is likely that deucravacitinib will be used as a fourth line treatment in clinical practice for people who have either failed to respond or have lost treatment response with prior non-biologic or phototherapy treatments or for people who are unsuitable or unable to tolerate these therapies, and that the appropriate comparators have been addressed in the decision problem.

	(including methotrexate, ciclosporin and acitretin) and phototherapy are inadequately effective, not tolerated or contraindicated: • TNF-α inhibitors (adalimumab, etanercept, infliximab [for very severe plaque psoriasis, as defined by a total	mab, tildrakizumab, and risankizumab) • IL-12/IL-23 inhibitors (ustekinumab) • Apremilast • Dimethyl fumarate	completeness. Best supportive care (BSC) is not included as a direct comparator since many active treatment options are now available. As such, patients receive BSC as last resort in clinical practice after having switched from one treatment to another when their treatment	

	PASI of 20 or more, and a DLQI of more than 18] and certolizumab pegol) • IL-17 family inhibitors or receptor inhibitors (brodalumab, ixekizumab, secukinumab and bimekizumab) • IL-23 inhibitors (guselkumab,		loses efficacy, or the treatment becomes contraindicated or not tolerated.	

	tildrakizumab and risankizumab) • IL-12/IL-23 inhibitors (ustekinumab) • Apremilast • Dimethyl fumarate • Best supportive care			
Outcomes	• Severity of psoriasis • Psoriasis symptoms, such as itch, and	• Severity of psoriasis • Psoriasis symptoms, such as itch, and sympto	Relapse rate was not included as an outcome in the clinical trials. However, time to	The ERG clinical expert considers the outcomes to be appropriate for addressing the topic of this appraisal, including time to relapse. The ERG notes that, the company provides evidence in the CS that indicates that mortality risk is increased in people with psoriasis compared with the general population,[24-28] however, the ERG clinical expert agrees that this risk is unlikely to influence the results of trials comparing psoriasis patients and is unlikely to influence trial results given the short time frame of the psoriasis trials.

	symptoms on the following areas: face, scalp, nails and joints, and other difficult-to-treat areas including the hands, feet and genitals • Mortality • Response rate • Duration of response • Relapse rate • Adverse effects	ms on the following areas: face, scalp, nails and joints, and other difficult-to-treat areas including the hands, feet and genitals • Response rate • Duration of response • Time to relapse • Adverse effects of treatment	relapse was assessed in the clinical trials and the results are reported in B2. Mortality was not included as people with psoriasis are not expected to die earlier than the general population. It was also not collected in the pivotal studies due to the short-term nature of	

	of treatment • Health-related quality of life	• Health-related quality of life	psoriasis trials. Impact on mortality is explored in a scenario analysis.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time	Cost-effectiveness is expressed in terms of incremental QALYs	The economic model compares deucravacitinib with 14 comparator therapies, all of which have been appraised by NICE for moderate to severe psoriasis. The comparators, with the	The economic model is broadly aligned with the NICE reference case.

	horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the		exception of inflixibab, are approved for people with severe or very severe psoriasis [defined by a total PASI of 10 or more, and a DLQI of more than 10] for whom systemic non-biological treatment (including methotrexate, ciclosporin and acitretin) and photothera	

	intervention, comparator and subsequent treatment technologies will be taken into account.		py are inadequately effective, not tolerated or contraindicated. Infliximab is restricted for use in those with very severe psoriasis.	
Subgroups	• Previous use of phototherapy and systemic non-biological therapy • Previous use of biologic	In the clinical trials, the efficacy was analysed by the following pre-specified subgroups: • Previous use of phototherapy	N/A	The subgroups reported in the CS match the NICE final scope.

	al therapy • Severity of psoriasis (moderate, severe)	and systemic non-biological therapy • Previous use of biological therapy • Severity of psoriasis by baseline PASI and sPGA scores		
Special considerations including issues related to equity or equality				The company notes that there are two relevant equality considerations that are reported in NICE guidance for moderate-to-severe plaque psoriasis. • Disease severity may be underestimated in darker skin colours. It is therefore necessary to consider the patient's skin type when assessing disease severity using the PASI scoring system, and adjustment should be made as required • The age of the patient as well as any physical, visual, or cognitive impairments, and any language or communication issues should be considered during assessment with the DLQI questionnaire, and adjustment should be made as required
Abbreviations: BSA = body surface area; BSC = best supportive care; DLQI = Dermatology Life Quality Index; IL = interleukin; NHS = National Health Service; N/A = not applicable; PASI = Psoriasis Area Severity Index; sPGA = static physician global assessment; TNF = tumour necrosis factor.				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG'S appraisal of the company's systematic review methods is summarised in Table 4.

Table 4 ERG's appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	YES	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	YES	Sources included Embase, Medline, CENTRAL, and PsycInfo for primary research. Relevant conference proceedings and trial registers were also searched. Bibliographies of recent SLRs were examined to identify relevant studies not captured by the literature searches Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	YES	Searches were not restricted by any eligibility criteria, so all results were discovered and only those relevant to the scope were selected.
Was study selection conducted by two or more reviewers independently?	YES	Appendix D, Section D.1.1.3.2: "*Two independent reviewers reviewed abstracts and full-text papers to determine eligibility based on the pre-specified inclusion/exclusion criteria*"
Was data extraction conducted by two or more reviewers independently?	NO	Appendix D, Section D.1.14: "*Data from the included RCTs was extracted by one investigator and a second investigator validated all extracted data*". The ERG considers the company's approach to be acceptable

Were appropriate criteria used to assess the risk of bias of identified studies?	YES	The seven-item NICE quality assessment checklist was used to assess POETYK-PSO-1 and POETYK-PSO-2 which the ERG considers appropriate. The same tool was used to assess and POETYK-PSO-LTE, a single-arm, extension study for which the majority of the assessment criteria are not relevant. The studies included in the NMA were assessed using the second version Cochrane risk of bias tool for assessing randomised trials, albeit the assessment of individual studies was not reported in the CS. The ERG is satisfied with this approach
Was the risk of bias assessment conducted by two or more reviewers independently?	PARTLY	At clarification, the company confirmed that the risk of bias assessment of the studies included in the network meta-analysis was conducted by two independent reviewers. The quality assessment of POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE was conducted by one reviewer and validated for accuracy by a second reviewer. The ERG considers this strategy to be appropriate
Was identified evidence synthesised using appropriate methods?	YES	The ERG is satisfied that the baseline adjusted random effects multinomial NMA is a suitable method to use with the outcomes and the range of trial data available.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Reviews and Dissemination (CRD) criteria. The results are presented in Table 5.

The ERG noted a discrepancy between the decision problem addressed in the CS ("*Adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option"*) and the populations of the POETYK-PSO-1 and POETYK-PSO-2 trials ("*Deemed by the investigator to be a candidate for phototherapy or systemic therapy"*). The company's rationale for this difference is that the decision problem is in accordance with the expected use of deucravacitinib in clinical practice in the NHS. The ERG's clinical expert agrees with the company's rationale and is of the opinion that deucravacitinib will be used as a fourth line treatment for those who have either failed to

respond or have lost treatment response with prior non-biologic therapy or phototherapy or for people who are unsuitable for these treatments or unable to tolerate them. The ERG notes also that the anticipated indication for deucravacitinib is for [redacted] The CS also presents subgroup analyses to demonstrate the impact on outcomes of prior treatment; these include prior use (yes/no) of systemic treatment, topical treatment, phototherapy, systemic biologic treatment, and systemic non-biologic treatment, and number of prior systemic biologics used. The ERG further notes that the eligibility criteria for the population in the company's SLR specified "*Adult (≥18 years) patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapies*". Overall, the ERG is satisfied that the population of the clinical effectiveness evidence presented in the CS is appropriate.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	No
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are presented in Document B, Section B.2 of the CS. The company presents clinical effectiveness evidence from two multi-centre, randomised, double-blind, placebo- and active-comparator controlled, international phase 3, 52-week trials: POETYK-PSO-1 and POETYK-PSO-2. The CS also presents evidence from the long-term extension studies of these two trials, POETYK-PSO-LTE, an ongoing,

open-label, phase 3b study. An overview of the three studies is reported in Document B, Table B.2.1 of the CS and reproduced as Table 6.

Table 6 Clinical effectiveness evidence [reproduced from Table B.2.1, Document B of the CS]

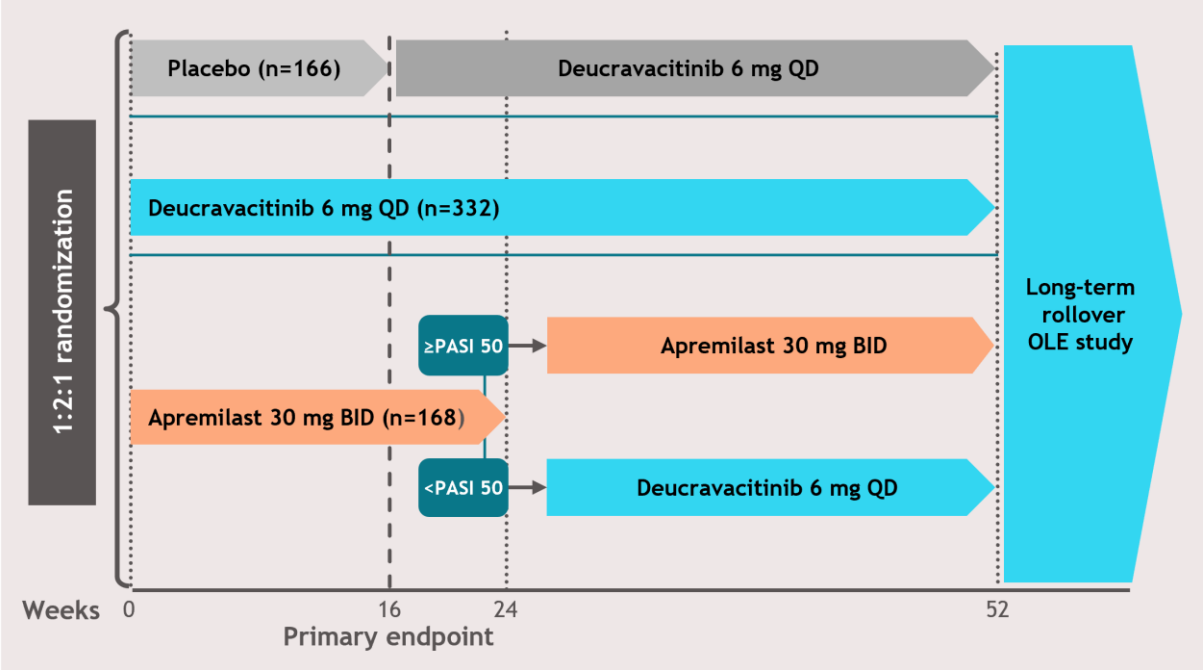
Study	IM011046 (POETYK-PSO-1; NCT03624127)	IM011047 (POETYK-PSO-2; NCT03611751)	IM011075 (POETYK-PSO-LTE; NCT04036435)
Study design	Phase 3, 52-week, international, multicentre, randomised, double-blind, placebo- and active comparator-controlled	Phase 3, 52-week, international, multicentre, randomised, double-blind, placebo- and active comparator-controlled, with a randomised withdrawal and retreatment phase (Week 24–52)	Ongoing, phase 3b, open-label, single-arm, international, multicentre (only interim data available)
Population	Adult patients with moderate-to-severe plaque psoriasis (PASI ≥12, sPGA ≥3 and BSA ≥10%)	Adult patients with moderate-to-severe plaque psoriasis (PASI ≥12, sPGA ≥3 and BSA ≥10%)	Adult patients with moderate-to-severe plaque psoriasis (PASI ≥12, sPGA ≥3 and BSA ≥10%) who completed POETYK-PSO-1 and POETYK-PSO-2
Intervention(s)	Deucravacitinib 6 mg QD (N=332)	Deucravacitinib 6 mg QD (N=511)	Deucravacitinib 6 mg QD (N=1,221)
Comparator(s)	Placebo (N=166) and apremilast 30 mg BID (N=168)	Placebo (N=255) and apremilast 30 mg BID (N=254)	N/A
Indicate if study supports application for marketing	Yes	Yes	Yes
Indicate if study used in the economic model	Yes (pooled with POETYK-PSO-2)	Yes (pooled with POETYK-PSO-1)	No
Rationale if study not used in model	N/A	N/A	POETYK-PSO-LTE data was not included in the economic model because no relative efficacy could be drawn as all patients

Study	IM011046 (POETYK-PSO-1; NCT03624127)	IM011047 (POETYK-PSO-2; NCT03611751)	IM011075 (POETYK-PSO-LTE; NCT04036435)
			received deucravacitinib (see Document B, Section B.3.3.2)
Reported outcomes specified in the decision problem (outcomes marked in bold are used in the model)	• severity of psoriasis: PASI, sPGA • psoriasis symptoms: variations of the PASI adapted for nail (PGA-F), scalp scores (ss)-PGA • **response rate:** PASI 50, **PASI 75**, PASI 90 and PASI 100 • duration of response: response rates at different timepoints e.g. 16, 24 and 52 weeks • time to relapse • adverse effects of treatment: treatment-emergent adverse events (AEs), deaths, serious adverse events, discontinuations due to AEs, and **AEs of interest** • health-related quality of life: **EQ-5D-3L**, DLQI 0/1		

All other reported outcomes	• Change from baseline and percent change from baseline in:
	  ○ PASI
	  ○ BSA
	  ○ BSA x sPGA
	  ○ PSSI
	  ○ mNAPSI
	• mNAPSI response
	• Health-related quality of life: PSSD, SF-36, HADS, PGI-C, PGI-S		

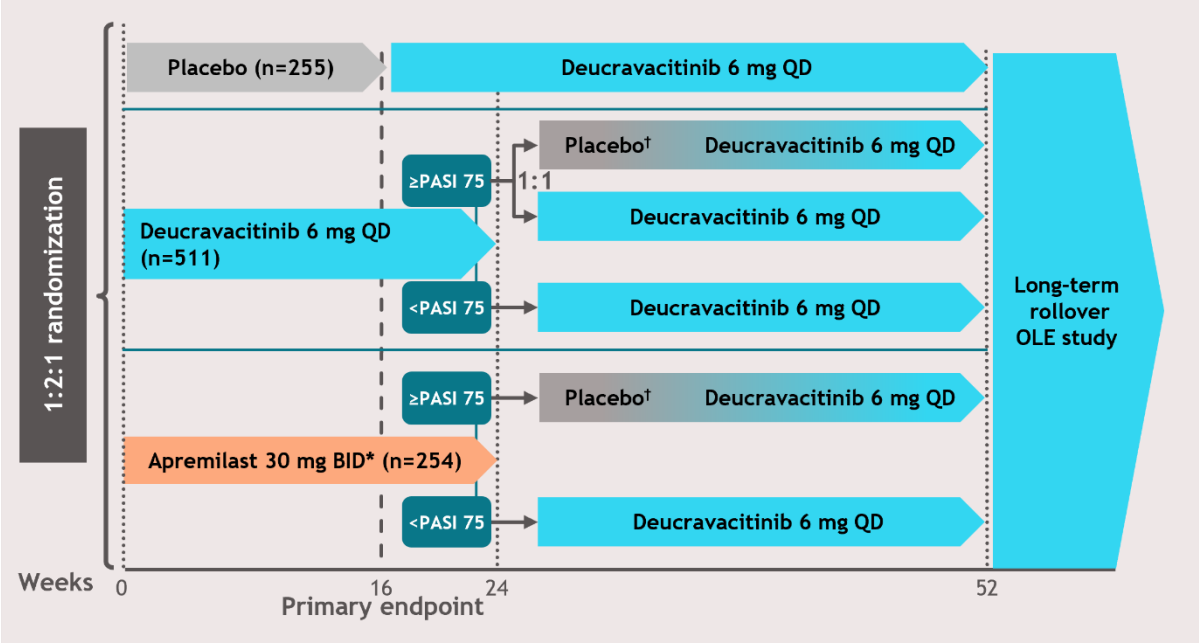
Abbreviations: BID = twice daily; BSA = body surface area; DLQI = dermatology life quality index; HADS = hospital anxiety and depression scale; HRQoL = health-related quality of life; mNAPSI = modified Nail Psoriasis Severity Index; PGA-F = Physician's Global Assessment of Fingernail Psoriasis; PGI-C = Patient's Global Impression of Change; PGI-S = Patient's Global Impression of Severity; PSSD = Psoriasis Symptoms and Signs Diary; PSSI = Psoriasis Scalp Severity Index; QD = once daily; LTE = long-term extension; SF-36 = 36-item short-form; sPGA = Static Physicians Global Assessment; ss-PGA = scalp-specific Physicians Global Assessment.
Source: POETYK-PSO-1 CSR, BMS Data on File;[29] POETYK-PSO-2 CSR, BMS Data on File;[30] POETYK-PSO-LTE CSR, BMS Data on File;[31] Warren et al, 2022[32]

The methods of the three studies are reported in Document B, Section 2.3 of the CS and participant flows are presented in Appendix D, Sections D.1.4.2 and D.1.4.3. The objective of both POETYK-PSO-1 and POETYK-PSO-2 was to assess the efficacy and safety of deucravacitinib as compared to placebo and apremilast in people with moderate-to-severe plaque psoriasis. Key eligibility criteria for all three studies are reported in Document B, Table 2.3 of the CS. As described in Section 3.1 above, there is an apparent mismatch between the population specified in the decision problem and that included in the relevant studies. The ERG is satisfied that the population involved in the trials is appropriate to address the decision problem. The study designs of POETYK-PSO-1 and POETYK-PSO-2 are reported in Document B, Figure B.2.1 and Figure B.2.2, respectively, and reproduced as Figure 2 and Figure 3 below.



Abbreviations: BID = twice daily; OLE = open-label extension; PASI = Psoriasis Area Severity Index; QD = once daily.
* Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
Source: Armstrong et al. 2021;[33] POETYK-PSO-1 CSR, BMS Data on File[29]

Figure 2 Study design, POETYK-PSO-1 [reproduced from Figure B.2.1, Document B of the CS]



Abbreviations: BID = twice daily; OLE = open-label extension; PASI = Psoriasis Area Severity Index; QD = once daily.
* Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
† Upon relapse (≥50% loss of Week 24 PASI percent improvement from baseline), patients were switched to deucravacitinib 6 mg QD.
Source: Armstrong et al. 2021;[33] POETYK-PSO-2 CSR, BMS Data on File[30]

Figure 3 Study design, POETYK-PSO-2 [reproduced from Figure B.2.2, Document B of the CS]

POETYK-PSO-1 was conducted in 154 sites in 11 countries (Canada, China, Germany, Japan, Poland, Russia, South Korea, Spain, Taiwan, UK [redacted] and USA) and POETYK-PSO-2 was conducted in 191 sites in 15 countries (Australia, Canada, Czech Republic, Finland, France, Germany, Hungary, Israel, New Zealand, Poland, Puerto Rico, Spain, Sweden, UK [redacted] and USA). A total of [redacted] participants from the UK were included in POETYK-PSO-1 and POETYK-PSO-2. Participants eligible for POETKY-PSO-LTE were these who had completed POETYK-PSO-1 or POETYK-PSO-2 and was conducted in 264 sites in 19 countries, including [redacted] sites in the UK. The company assessed risk of bias of POETYK-PSO-1 and POETYK-PSO-2 using the seven-item NICE checklist. The ERG agrees with the company's assessment that the trials were well designed with appropriate randomisation and allocation concealment, that the groups were balanced at baseline in terms of prognostic factors, that there were no unexpected imbalances in dropouts and that all planned outcomes were reported. The company also assessed risk of bias of POETYK-PSO-LTE using the NICE checklist. As POETYK-PSO-LTE is an open-

label, single-arm extension study, the ERG considers the NICE criteria inappropriate for quality assessment and notes that the study will be subject to the bias inherent in studies of this design. A further consideration is that all three studies were funded by Bristol Myers Squibb and its role in the conduct of the study is unknown. Details of the baseline characteristics, disease characteristics and prior psoriasis-related treatment for POETYK-PSO-1 and POETYK-PSO-2 are presented in Appendix M, Table B.5.73 and reproduced as Table 7 below.

Table 7 Baseline demographics and disease characteristics (POETYK-PSO-1 and POETYK-PSO-2 studies) – As randomised population [reproduced from Table B.5.73, Appendix M of the CS]

Parameter	POETYK-PSO-1			POETYK-PSO-2		
	Deucravacitinib (N=332)	Placebo (N=166)	Apremilast (N=168)	Deucravacitinib (N=511)	Placebo (N=255)	Apremilast (N=254)
Age, years, mean (min, max)	45.9 (18, 80)	47.9 (19, 81)	44.7 (20, 77)	46.9 (18, 84)	47.3 (18, 83)	46.4 (18, 79)
Weight, kg, mean (min, max)	87.90 (36.0, 173.0)	89.13 (46.3, 181.6)	87.52 (45.4, 187.3)	92.26 (40.0, 180.0)	91.53 (48.3, 160.0)	93.47 (49.7, 173.3)
Female, n (%)	102 (30.7)	53 (31.9)	58 (34.5)	175 (34.2)	74 (29.0)	97 (38.2)
Race, n (%)						
White	267 (80.4)	128 (77.1)	139 (82.7)	474 (92.8)	232 (91.0)	229 (90.2)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	59 (17.8)	34 (20.5)	28 (16.7)	24 (4.7)	8 (3.1)	12 (4.7)
Other	4 (1.2)	1 (0.6)	0	5 (1.0)	6 (2.4)	4 (1.6)
Disease duration, years, mean	17.2[c]	17.3	17.7	19.6	19.9	18.9
sPGA score, n (%)						

Parameter	POETYK-PSO-1			POETYK-PSO-2		
	Deucravacitinib (N=332)	**Placebo (N=166)**	**Apremilast (N=168)**	**Deucravacitinib (N=511)**	**Placebo (N=255)**	**Apremilast (N=254)**
3 = moderate	257 (77.4)	128 (77.1)	139 (82.7)	408 (79.8)	217 (85.1)	196 (77.2)
4 = severe	75 (22.6)	37 (22.3)	29 (17.3)	103 (20.2)	38 (14.9)	58 (22.8)
PASI, mean	21.8	20.7	21.4	20.7	21.1	21.6
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic treatment use						
Naïve to prior systemic treatment[a], n (%)	132 (39.8)	57 (34.3)	59 (35.1)	237 (46.4)	116 (45.5)	114 (44.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic biologic use[b], n (%)	130 (39.2)	63 (38.0)	66 (39.3)	165 (32.3)	83 (32.5)	79 (31.1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AA = African American; BSA = body surface area; max = maximum; min = minimum; n = number of patients in the category; N = number of patients evaluable; PASI = Psoriasis Area and Severity Index; ; sPGA = static Physician's Global Assessment.

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

[b] Prior biologic treatment use includes patients who had ever received a biologic. Patients could have also received a non-biologic. [c]The ERG notes that disease duration for the Deucravacitinib group is reported as 17.1 in the CSR
Source: Armstrong et al 2021;[33] Summary of Clinical Efficacy, BMS Data on File.[34]

In general, baseline characteristics were balanced within and across POETYK-PSO-1 and POETYK-PSO-2. Mean age was 46.1 in POETYK-PSO-1 and 46.9 in POETYK-PSO-02. Participants in POETYK-PSO-2 were slightly heavier at baseline than those in POETYK-PSO-2. Around one-third of participants were female, and most participants were white in both trials. Mean disease duration was longer for participants in POETYK-PSO-2 (19.5 years) than those in POETYK-PSO-1 (17.3 years). Most participants were in the moderate category for sPGA score, with the apremilast group in POETYK-PSO-1 (82.7%) and the placebo group in POETYK-PSO-2 (85.1%) having higher numbers in the moderate category (and corresponding lower in the severe group) than the remaining groups. Mean PASI score was 21 in both studies; the respective CSRs report that the minimum PASI score was [redacted] in all groups of both trials, with the exception of the placebo group of POETYK-PSO-1, in which the minimum score was [redacted]. Mean BSA involvement was [redacted] and [redacted] respectively. Higher proportions of participants were naïve to prior systemic treatment in POETYK-PSO-2 (45.8%) than in POETYK-PSO-1 (37.2%). A greater number of participants in POETYK-PSO-1 [redacted] had prior systemic treatment use than those in POETYK-PSO-2 ([redacted] A similar number of participants across the studies had prior systemic biologic use (62.0% and 59.1%, respectively) and a greater number in POETYK-PSO-2 ([redacted] had prior phototherapy use than those in POETYK-PSO-1 ([redacted]

Pooled baseline characteristics of participants in POETYK-PSO-1 AND POETYK-PSO-2 are presented in Document B, Table B.2.5 and reproduced as Table 8 below.

Table 8 Baseline characteristics (pooled analysis POETYK-PSO-1 and POETYK-PSO-2) [reproduced from Table B.2.5, Document B of the CS]

Parameter	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)	Total (N=1,686)
Age, years, mean (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg, mean (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)				
White	[redacted]	[redacted]	[redacted]	[redacted]
Black or AA	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration, years, mean	[redacted]	[redacted]	[redacted]	[redacted]
sPGA score, n (%)				
3 = moderate	[redacted]	[redacted]	[redacted]	[redacted]
4 = severe	[redacted]	[redacted]	[redacted]	[redacted]
PASI, mean	[redacted]	[redacted]	[redacted]	[redacted]
BSA, mean	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic treatment use, n (%)				
Naïve to prior systemic treatment[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic treatment use[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior systemic biologic use[b], n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior phototherapy use, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AA = African American; BSA = body surface area; max = maximum; min = minimum; n = number of patients in the category; N = number of patients evaluable; PASI = Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment.

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

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

Source: Summary of Clinical Efficacy, BMS Data on File.[34]

The ERG agrees with the company that the pooled baseline characteristics are generally well balanced and consistent with the individual studies. Baseline

characteristics of POETYK-PSO-LTE (stratified by last treatment received) are reported in Document B, Table B.2.6, in which the ERG notes an error with the numbers of participants in the placebo to deucravacitinib group (correct value as reported in the CSR: n=197) and those in the apremilast to deucravacitinib (correct value as reported in the CSR: n=80) being apparently transposed. The table is reproduced as Table 9, with the correct values inserted.

Table 9 Baseline demographics and disease characteristics (POETYK-PSO-LTE) [reproduced from Table B.2.6, Document B of the CS]

Characteristic	Stratification by last treatment received			Total (n = 1,221)
	Deucravacitinib to deucravacitinib (n=944)	Placebo to deucravacitinib (n=197)[a]	Apremilast to deucravacitinib (n=80)[a]	
Age, years, mean (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
Weight, kg, mean (min, max)				
Baseline in parent studies	[redacted]	[redacted]	[redacted]	[redacted]
Last visit in parent studies	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)				
White	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration, years, mean (min, max)	[redacted]	[redacted]	[redacted]	[redacted]
sPGA, n (%)				
Baseline in parent studies				
3 = moderate	[redacted]	[redacted]	[redacted]	[redacted]
4 = severe	[redacted]	[redacted]	[redacted]	[redacted]
Last visit in parent studies				
3 = moderate	[redacted]	[redacted]	[redacted]	[redacted]
4 = severe	[redacted]	[redacted]	[redacted]	[redacted]
PASI, mean (min, max)				

Baseline in parent studies	[redacted]	[redacted]	[redacted]	[redacted]
Last visit in parent studies	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: min = minimum; max = maximum; n = number of patients in the category; N = number of patients evaluable; PASI = Psoriasis Area and Severity Index; sPGA = static Physician's Global Assessment. [a]These value are incorrectly reversed in the CS
Source: Summary of Clinical Efficacy, BMS Data on File.[34]

Overall, the ERG's clinical expert is satisfied that the baseline characteristics of participants in POETYK-PSO-1, POETYK-PSO-2 and POETYK-PSO-LTE are representative of patients with moderate-to-severe plaque psoriasis seen in clinical practice in the UK.

3.2.2 Primary and secondary efficacy endpoints

The outcome measures listed in the NICE final scope for this appraisal were: severity of psoriasis; psoriasis symptoms, such as itch and symptoms on the following areas: face, scalp, nails and joints, and other difficult-to-treat areas including the hands, feet and genitals; mortality; response rate; duration of response; relapse rate; adverse effects of treatment; and health-related quality of life. The company did not include relapse rate or mortality as outcomes in the trials. The ERG considers the company's strategy to be acceptable. The full analysis sets (FAS; i.e. all patients who were randomised following the intention-to-treat principle) of POETYK-PSO-1 and POETYK-PSO-2 were analysed for the individual and pooled efficacy analyses.

Primary endpoint: POETYK-PSO-1 and POETYK-PSO-2

The co-primary endpoints of POETYK-PSO-1 and POETYK-PSO-2 were:

- **sPGA 0/1 response** (defined as sPGA score of 0 or 1 at week 16 in patients with ≥2-point improvement from baseline): In POETYK-PSO-1, 53.6% of the deucravacitinib group and 7.2% of the placebo group achieved sPGA 0/1 response ([redacted]). In POETYK-PSO-2, 49.5% of the deucravacitinib group achieved sPGA 0/1 response as compared to 8.6% of the placebo group ([redacted]). In the pooled analysis of POETYK-PSO-1 and POETYK-PSO-2, [redacted]% of the deucravacitinib group achieved sPGA 0/1 response, as compared to [redacted]% of the placebo group

([redacted]]. Deucravacitinib was superior to apremilast at week 16 in both POETYK-PSO-1 (53.6% vs 32.1%, [redacted]) and POETYK-PSO-2 (49.5% vs 33.9%, [redacted]). The CS presents an overview of the pooled analyses of sPGA 0/1 response (weeks 1-24) in Figure B.2.4, reproduced below as Figure 4.

- [redacted]

Abbreviations: FAS = Full analysis Set; NRI = non-responder imputation; sPGA = static Physician's Global Assessment.
Source: Summary of Clinical Efficacy, BMS Data on File.[34]

Figure 4 sPGA 0/1 response by treatment group Week 1–24 (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS) [reproduced from Figure B.2.4, Document B of the CS]

- **PASI 75** (defined as ≥75% improvement at week 16 from baseline in PASI score): In POETYK-PSO-01, 58.4% of participants in the deucravacitinib group achieved PASI 75 response, as compared to 12.7% of the placebo group ([redacted]). In POETYK-PSO-2, 53.0% of the deucravacitinib group and 9.4% of the placebo group achieved PASI 75 ([redacted]). In the pooled analysis of POETYK-PSO-1 and POETYK-PSO-2, [redacted]% of the deucravacitinib group and [redacted]% of the placebo group achieved PASI 75

([redacted]). Deucravacitinib was superior to apremilast at week 16 in both POETYK-PSO-1 (58.4% vs 35.1%, [redacted]) and POETYK-PSO-2 (53.0% vs 39.8%, [redacted]. The CS presents an overview of the pooled analyses of PASI 75 response (weeks 1-24) in Document B, Figure B.2.3, reproduced below as Figure 5.

Abbreviations: FAS = Full analysis Set; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index
Source: Summary of Clinical Efficacy, BMS Data on File.[34]

Figure 5 PASI 75 response by treatment group Week 1–24 (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS) [reproduced from Figure B.2.3, Document B of the CS]

A summary of sPGA 0/1 and PASI 75 responses at week 16 is reported in Table 10 below.

Table 10 Summary of sPGA 0/1 and PASI 75 responses at week 16

Outcome	Deucravacitinib	Placebo	Apremilast
POETYK-PSO-1	**N=332**	**N=166**	**N=168**
sPGA 0/1 at Week 16, n (%)	[redacted] (53.6)	[redacted] (7.2)	[redacted] (32.1)
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI), p-value		[redacted]	
PASI 75 at Week 16, n (%)	[redacted] (58.4)	[redacted] (12.7)	[redacted] (35.1)
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI), p-value		[redacted]	[redacted]
POETYK-PSO-2	**N=511**	**N=255**	**N=254**
sPGA 0/1 at Week 16, n (%)	[redacted] (49.5)	[redacted] (8.6)	[redacted] (33.9)
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI), p-value		[redacted]	[redacted]
Pasi 75 at Week 16, n (%)	[redacted] (53.0)	[redacted] (9.4)	[redacted] (39.8)
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI), p-value		[redacted]	[redacted]
POOLED ANALYSIS: POETYK-PSO-1 and POETYK-PSO-2	**N=843**	**N=421**	**N=422**
sPGA 0/1 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI), p-value		[redacted]	[redacted]
PASI 75 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI), p-value		[redacted]	[redacted]

Note. Nominally significant p-values are in *italics*

Secondary endpoints: POETYK-PSO-1 and POETYK-PSO-2

- **PASI-related outcomes:** The CS presents a summary of PASI-related outcomes of the pooled POETYK-PSO-1 and POETYK-PSO-2 analyses in Table B.2.10, reproduced as Table 11 below.

Table 11 Results of PASI-related outcomes (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS) [reproduced from Document B, Table B.2.10 of the CS]

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
PASI 75 at Week 16, n (%)[a]	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
PASI 75 at Week 24, n (%)	[redacted]	-	[redacted]
Difference (95% CI)		-	[redacted]
Odds ratio (95% CI)		-	[redacted]
p-value[b]		-	[redacted]
PASI 90 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
PASI 90 at Week 24, n (%)	[redacted]	-	[redacted]
Difference (95% CI)		-	[redacted]
Odds ratio (95% CI)		-	[redacted]
p-value[b]		-	[redacted]
PASI 100 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
PASI 100 at Week 24, n (%)	[redacted]	-	[redacted]
Difference (95% CI)		-	[redacted]
Odds ratio (95% CI)		-	[redacted]
p-value[b]		-	[redacted]

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; n = number of patients in the category; N = number of patients evaluable; NRI = non-responder imputation; PASI = Psoriasis Area and Severity Index.
[a] Co-primary efficacy outcome in the individual studies.
[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.
Source: Summary of Clinical Efficacy, BMS Data on File.[34]

Equivalent data are presented for the individual studies in Appendix N, Table B.5.73 of the CS, with comparable results showing superiority of deucravacitinib over placebo and apremilast in all analyses.

- **sPGA-related outcomes:** The CS presents a summary of sPGA-related outcomes of the pooled POETYK-PSO-1 and POETYK-PSO-2 analyses in Table B.2.11, reproduced as Table 12 below.

Table 12 Results of sPGA-related outcomes (pooled POETYK-PSO-1 and POETYK-PSO-2) – NRI (FAS) [reproduced from Table B.2.11, Document B of the CS]

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
sPGA 0/1 at Week 16, n (%)[a]	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
sPGA 0/1 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
sPGA 0 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
sPGA 0 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; n = number of patients in the category; N = number of patients evaluable; NRI = non-responder imputation; sPGA = static Physician's Global Assessment.

[a] Co-primary efficacy outcomes in the individual studies.

[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.

Source: Summary of Clinical Efficacy, BMS Data on File.[34]

Equivalent data for the individual studies are presented in Table B.5.74, Appendix N of the CS. The results are comparable to the pooled results, showing superiority of deucravacitinib over placebo and apremilast in all analyses.

- **Difficult-to-treat regions:** outcomes relating to difficult-to-treat areas reported in the CS were scalp psoriasis and fingernail psoriasis. Table 13 presents a summary of the pooled analyses of scalp psoriasis (assessed using the scalp-specific PGA [ss-PGA]) and fingernail psoriasis (assessed using the Physician's Global

Assessment – Fingernails [PGA-F]. Patients with moderate-to-severe fingernail psoriasis at baseline (PGA≥3 were included).

Table 13 Summary of pooled POETYK-PSO-1 and POETYK-PSO-2 analyses of scalp psoriasis and fingernail psoriasis at week 16 and week 24 [adapted from Tables B.2.14 and B.2.15, Document B of the CS and Table 3.2.6.3-1, BMS 2021 SCE]

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
SCALP PSORIASIS			
Baseline, n[a]	[redacted]	[redacted]	[redacted]
ss-PGA 0/1 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
ss-PGA 0/1 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
FINGERNAIL PSORIASIS			
Baseline, n[C]	[redacted]	[redacted]	[redacted]
PGA-F 0/1 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
PGA-F 0/1 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
PALMOPLANTAR PSORIASIS			
Baseline, n[d]	[redacted]	[redacted]	[redacted]
pp-PGA 0/1 at Week 16, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
pp-PGA 0/1 at Week 24, n (%)	[redacted]	[redacted]	[redacted]
Difference (95% CI)		[redacted]	[redacted]
Odds ratio (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; n = number of patients in the category; N = number of patients evaluable; NRI = non-responder imputation; ss-PGA = scalp severity Physician's Global Assessment.

[a] Number of patients with a baseline ss-PGA score ≥3.

[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.

[C] Number of patients with a baseline PGA-F score ≥3. [d]Number of patients with baseline pp-PGA score ≥3. Source: Summary of Clinical Efficacy, BMS Data on File.[34]

The pooled analyses showed that [redacted] Results for ss-PGA and PGA-F for the respective studies are reported in Appendix N, sections N.1.3.1 and N.1.3.2 and are in accordance with the pooled analyses.

The respective CSRs also report palmoplantar psoriasis, which was assessed using the palmoplantar PGA (pp-PGA) in participants with pp-PGA≥3 (i.e. moderate-to-severe palmoplantar psoriasis). In the pooled analyses, [redacted].

- **HRQoL:** Pooled analysis of adjusted change from baseline in EQ-5D-3L VAS scores at week 16 and week 24 is reported in Document B, Table B.2.18 of the CS and reproduced as Table 14 below. Details of the equivalent POETYK-PSO-1 and POETYK-PSO-2 results are reported in Appendix N, Table B.5.82 of the CS and are generally in keeping with the pooled results.

Table 14 Results EQ-5D-3L VAS at Week 16 and Week 24 (pooled POETYK-PSO-1 and POETYK-PSO-2) – ANCOVA/(mBOCF) [reproduced from Table B.2.18, Document B of the CS]

Outcome	Deucravacitinib (N=843)	Placebo (N=421)	Apremilast (N=422)
Baseline, n[a]	[redacted]	[redacted]	[redacted]
Baseline mean (SD)	[redacted]	[redacted]	[redacted]
Adjusted mean change from baseline at Week 16 (SE)	[redacted]	[redacted]	[redacted]
Adjusted mean difference (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]
Adjusted mean change from baseline at Week 24 (SE)	[redacted]	[redacted]	[redacted]
Adjusted mean difference (95% CI)		[redacted]	[redacted]
p-value[b]		[redacted]	[redacted]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; EQ-5D-3L VAS = EuroQol 5-Dimensions 3-Level Visual Analogue Scale; mBOCF = modified baseline observation carried forward; n = number of patients in the category; N = number of patients evaluable; SD = standard deviation; SE = standard error.
[a] Number of patients with an EQ-5D-3L VAS score at baseline and with ≥1 score post baseline.
[b] p-values were obtained using a stratified Cochran-Mantel-Haenszel test, p-values are deucravacitinib versus placebo and deucravacitinib versus apremilast. Nominally significant p-values are designated using *italicised* type.
Source: Summary of Clinical Efficacy, BMS Data on File.[34]

Subgroup analyses

The CS reports results of subgroup analyses using the pooled POETYK-PSO-1 and POETYK-PSO-2 data for PASI 75 and sPGA 0/1 response at week 16. The CS reports in Appendix E results for the following subgroups: baseline demographic factors (age, sex, ethnicity, body weight, BMI and geographic region); baseline disease characteristics (PASI score, sPGA score, BSA involvement and disease duration); prior psoriasis therapies (systemic, topical, phototherapy, systemic non-biologic, systemic biologic, and the number of prior biologics used). Overall, the pooled subgroup analyses [redacted] the results of the individual trials [redacted]

Interim results of POETYK-PSO-LTE

The company reports interim results of POETYK-PSO-LTE in Document B, Section B.2.6.6 of the CS, which states that key efficacy outcomes from week 0 (of POETYK-PSO-1 or POETYK-PSO-2) to [redacted] were available. The company explains that POETYK-PSO-LTE is ongoing and some participants have not reached assessments [redacted]. Outcomes were reported in the CS in terms of

groups to which the participants were originally randomised in the parent study: deucravacitinib → deucravacitinib (n=[redacted]), placebo → deucravacitinib (n=[redacted]) and apremilast → deucravacitinib (n=[redacted]). The company states that the results of POETYK-PSO-LTE to date

[redacted]

[redacted] PASI 75 and sPGA 0/1 response over time are summarised below.

- **PASI 75 response:** PASI response over time is presented in Document B, Figure B.2.7 and Table B.2.19 of the CS and reproduced as Figure 6 and Table 15 below.

[redacted]

Abbreviations: DEUC-DEUC = deucravacitinib: deucravacitinib; PBO-DEUC = placebo: deucravacitinib; APR-DEUC = apremilast: deucravacitinib; PASI = Psoriasis Area and Severity Index.
[a] ≥75% improvement from baseline in the PASI score
[redacted]
Source: Summary of Clinical Efficacy, BMS Data on File.[34]

Figure 6 PASI 75 response[a,b] over time (POETYK-PSO-LTE) [reproduced from Figure B.2.8, Document B of the CS]

Table 15 PASI 75 response[a] over time (POETYK-PSO-LTE) [reproduced from Table B.2.19, Document B of the CS]

Group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deucravacitinib → deucravacitinib, (n/N)					
Placebo → deucravacitinib, (n/N)					
Apremilast → deucravacitinib, (n/N)					
Total, (n/N)					

Abbreviations: n = number of patients in the category; N = number of patients evaluable; PASI = Psoriasis Area and Severity Index.
[a] ≥75% improvement from baseline in the PASI score.
Source: Summary of Clinical Efficacy, BMS Data on File.[34]

The POETYK-PSO-LTE CSR further reports that a total of [redacted].

- **sPGA 0/1 response:** sPGA 0/1 response over time is presented in Document B, Figure B.2.9 and Table B.2.20 of the CS and reproduced as Figure 7 and Table 16 below.

Abbreviations: DEUC-DEUC = deucravacitinib: deucravacitinib; PBO-DEUC = placebo: deucravacitinib; APR-DEUC = apremilast: deucravacitinib; sPGA = static Physician's Global Assessment. [a] Score of 0/1 in patients with ≥2-point improvement from baseline.

Source: Summary of Clinical Efficacy, BMS Data on File.[34]

Figure 7 sPGA 0/1 response[a,b] over time (POETYK-PSO-LTE) [reproduced from Figure B.2.9, Document B of the CS]

Table 16 sPGA 0/1 response[a] over time (POETYK-PSO-LTE) [reproduced from Table B.2.20, Document B of the CS]

Group					
Deucravacitinib → deucravacitinib, (n/N)					
Placebo → deucravacitinib, (n/N)					
Apremilast → deucravacitinib, (n/N)					
Total, (n/N)					

Abbreviations: n = number of patients in the category; N = number of patients evaluable; sPGA = static Physician's Global Assessment.

[a] Score of 0/1 in patients with ≥2-point improvement from baseline.

Source: Summary of Clinical Efficacy, BMS Data on File.[34]

The POETYK-PSO-LTE CSR further reports that a total of

3.2.3 Adverse events

The company presents an overview of safety data in section B.2.10 and Appendix F of the CS. Integrated clinical safety data are presented by the company in two separate data pools: the Controlled Safety Pool and the Phase 3 Safety Pool. The Controlled Safety Pool includes the POETYK-PSO-1 and POETYK-PSO-2 trials and is presented by the company as the main safety data for the licensed indication of deucravacitinib. The Phase 3 Safety Pool includes data for the POETYK-PSO-1 and POETYK-PSO-2 deucravacitinib patients and interim data from POETYK-PSO-LTE (database lock safety: 1 October 2021[32]). Only patients who completed POETYK-PSO-1 and POETYK-PSO-2 and entered POETYK-PSO-LTE were included in the Phase 3 Safety Pool. The company reports the safety results using the exposure adjusted incident rate (EAIR) per 100 person-years (p-y). A summary of adverse events for the placebo-controlled periods of the individual POETYK-PSO-1 and POETYK-PSO-2 studies is presented in Appendix F.1.3.2 of the CS.

Controlled safety pool

The Controlled Safety Pool included a total of 1,364 patients who were treated with ≥1 dose of deucravacitinib, 666 patients received ≥1 dose of placebo, and 422 patients received ≥1 dose of apremilast, with [redacted] person-years of exposure. The company presents an overall safety summary for the deucravacitinib exposure period (Week 0–52) in the Controlled Safety Pool (as-treated population) in Table B.2.24 of the CS and these data are presented by the ERG in Table 17. The proportion of adverse events (AEs) [redacted] in the deucravacitinib group were comparable with the apremilast group. AEs leading to treatment discontinuation were lower for the deucravacitinib group than the apremilast group (deucravacitinib: n=43 [3.2%]; apremilast n=26 [6.2%]. The company reports that [redacted]

The most common AEs for the deucravacitinib group were nasopharyngitis (229/1364 [16.8%]), upper respiratory tract infection (URTI) (124/1364 [9.1%]), headache (80/1364 [5.9%]) and diarrhoea (69/1364 [5.1%]). Headache, diarrhoea, nausea, and vomiting were

experienced by more people in the apremilast group than the deucravacitinib group (12.6% versus 5.9%, 12.8% versus 5.1%, 11.1% versus 1.5%, and [redacted] versus [redacted] respectively). The ERG clinical expert notes that this higher incidence of gastrointestinal AEs in the apremilast group is in keeping with the known safety profile of apremilast.

Data for the Controlled Safety Pool during the placebo-controlled period (week 0-16) are presented by the company in Appendix F. The ERG notes that the safety profiles of the two treatment phases are similar for all treatment arms.

Phase 3 Safety Pool

Safety results from the Phase 3 Safety Pool are presented by the company in Appendix F of the CS. At two years of treatment exposure, there was a total of 2,484.0 person-years of exposure with 1,519 patients treated with deucravacitinib in the Phase 3 safety pool.[32, 35] The company presents an overall safety summary of the Phase 3 Safety Pool data at two years in Appendix F, Table B.5.25 of the CS, and these data are presented in Table 17 by the ERG.

[redacted] AEs leading to treatment discontinuation in ≥2 of patients for the Phase 3 Safety Pool are reported in Appendix F, **Error! Reference source not found.** of the CS.

Table 17 Overall safety summary for the Controlled Safety Pool (Week 0-52) and the Phase 3 Safety Pool (2 years) – As-treated populations

	Controlled Safety Poo						Phase 3 Safety Pool	
AE category	Deucravacitinib (N=1,364)		Placebo (N=666)		Apremilast (N=422)		Deucravacitinib (N=1,519)	
	n (%)	100 IR/P-Y	n (%)	100 IR/P-Y	n (%)	100 IR/P-Y	n (%)	IR/100 P-Y
AEs	995 (72.9)	229.2	347 (52.1)	217.4	299 (70.9)	281.1	1,214 (79.9)	154.4
Drug-related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Severe AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
SAEs	55 (4.0)	5.7	14 (2.1)	5.7	9 (2.1)	4.0	145 (9.5)	6.1
SAEs in ≥2 patients								
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cholecystitis acute	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COVID-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pericarditis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Angina unstable	-	-	-	-	-	-	[redacted]	[redacted]
Cholelithiasis	-	-	-	-	-	-	[redacted]	[redacted]
Diverticulitis	-	-	-	-	-	-	[redacted]	[redacted]
Acute myocardial infarction	-	-	-	-	-	-	[redacted]	[redacted]
Acute respiratory failure	-	-	-	-	-	-	[redacted]	[redacted]
Myocardial infarction	-	-	-	-	-	-	[redacted]	[redacted]
Respiratory failure	-	-	-	-	-	-	[redacted]	[redacted]
Ureterolithiasis	-	-	-	-	-	-	[redacted]	[redacted]
Thrombosis	-	-	-	-	-	-	[redacted]	[redacted]
Cerebrovascular accident	-	-	-	-	-	-	[redacted]	[redacted]
Dehydration	-	-	-	-	-	-	[redacted]	[redacted]
COVID-19 pneumonia	-	-	-	-	-	-	[redacted]	[redacted]
Discontinued due to AEs	43 (3.2)	4.4	23 (3.5)	9.3	26 (6.2)	11.6	69 (4.5)	2.8
Deaths	2 (0.1)	0.2	1 (0.2)	0.4	1 (0.2)	0.4	10 (0.7)	0.4

Abbreviations: AEs = adverse events; IR/100 P-Y = incidence rate per 100 person-years of exposure; NA = not available; n = number of patients in the category; N = number of patients evaluable; SAEs = serious adverse events. SAEs = serious adverse events.
Source Armstrong et al. 2021;[33] Summary of Clinical Safety, BMS Data on File.[35] Warren et al. 2022,[32]

Adverse events of interest

AEs of interest (AEIs) are reported in Sections B.2.10.2 and B.3.3 of the CS for the Controlled Safety Pool, and in Appendix F, Section F.1.2.6 of the CS for the Phase 3 Safety Pool. The company considers the cost of treatment of severe infections, non-melanoma skin cancer (NMSC) and malignancies other than NMSC in the economic model base case, and presents rates for these adverse events from the POETYK PSO-1 and POETYK PSO-2 pooled data in Table B.3.7 of the CS. With the exception of skin events, the incidence of these events with deucravacitinib was infrequent and generally comparable to placebo and apremilast. None of the skin AEIs were reported as being severe or serious.[33, 35] AEIs in the Phase 3 Safety Pool versus Controlled Safety Pool (Week 0-52) for the as-treated population are reported in Appendix F, Table Table B.5.29 of the CS. The ERG agrees with the company that there is no evidence of increased risk for any of these events with longer-term deucravacitinib use from the Phase 3 safety pool.[33, 35] The ERG presents a summary of the main AEIs for the Controlled Safety Pool from the data reported in the Summary of Clinical Safety (SCS) document in Table 18 below. The ERG notes that the data reported for MACE events in Table 2.7.4.3-1 of the SCS do not appear to correspond to data reported for MACE events in Appendix Table S.6.12.3 of the SCS. The ERG has checked the MACE events reported in Table S.6.11.3 of the POETYK PSO-1 CSR and Table S.6.11.3 of the POETYK PSO-2 CSR and these data correspond with the data reported in Table S.6.12.3 of the SCS. The ERG, therefore, reports the data presented in Table S.6.12.3 of the SCS in Table 18.

Table 18 Summary of adverse events of special interest Controlled Safety Pool – as treated population (week 0 to 52)

	Deucravactinib (n=1364)			Placebo (n=666)			Apremilast (n=422)		
AE category	N (%)	P-Y	IR/100 P-Y	N (%)	P-Y	IR/100 P-Y	N (%)	P-Y	IR/100 P-Y
Skin events	163 (12.0)	905.1	18.0	19 (2.9)	245.1	7.8	19 (4.5)	220.2	8.6
Severe infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMSC	7 (0.5)	983.4	0.7	0	-	-	1 (0.2)	226.1	0.4
Malignancies other than NMSC	3 (0.2)	986.5	0.3	0	-	-	1 (0.2)	226.4	0.4
Adjudicated MACE [a.b]	3 (0.2)	986.5	0.3	2 (0.3)	249.7	0.8	3 (0.7)	225.7	1.3
Adjudicated extended MACE [a.b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Venous thromboembolic events	2 (0.1)	986.6	0.2	0	-	-	0	-	-
Suicidal ideation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Adjudication Committees were used to adjudicate specified AEs during the studies. 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 subject treatment assignment. [b] MACE = cardiovascular death, nonfatal myocardial infarction, nonfatal stroke; Extended MACE = MACE plus unstable angina requiring hospitalization
Abbreviations MACE = major adverse cardiovascular events, NMSC = non-melanoma skin cancer
Source: BMS Summary of Clinical Safety SCS[35]

Mortality

[redacted] participant in the POETYK PSO-1

[redacted]

[redacted] deaths were reported during the POETYK PSO-2 study:

[redacted][30] Six deaths are reported in the POETYK PSO-LTE clinical study report: Five were reported as caused by COVID-19, and one death was reported as caused by a ruptured aortic aneurysm.[31] All deaths, except one case of COVID-19 pneumonia, were considered unrelated to study treatment.[29-31]

3.3 Critique of trials identified and included in the comparison and/or multiple treatment comparison

The ERG is of the opinion that POETYK PSO-1 and POETYK PSO-2 are suitable trials for comparing deucravacitinib, apremilast and placebo. The trial set-up, methodology and populations are all similar, and, therefore, pooling the data is considered appropriate. The ERG reviewed the analysis of the range of outcomes included in the NICE final scope and company decision problem. The analyses of PASI 75, 90 and 100 show [redacted]. The ERG agrees that the analysis shows a [redacted] in comparison to those receiving apremilast or placebo.

Participants who remain on deucravacitinib are [redacted] their PASI75 and sPGA response, while switching at 24 weeks to deucravacitinib [redacted] the PASI75 response rate. The percentage relapsing is also [redacted] among those who received deucravacitinib. At both 16 and 24 weeks, a significantly [redacted] percentage of deucravacitinib participants obtain the scalp psoriasis outcome. For fingernail psoriasis, deucravacitinib has a significantly [redacted] response rate than placebo and [redacted] response rate to apremilast.

The Psoriasis Symptoms and Signs Diary shows a [redacted] percentage of deucravacitinib participants achieving a [redacted]. The ERG also agrees that the change from baseline scores [redacted] deucravacitinib [redacted] apremilast and placebo. The ERG is also in agreement that in comparison to apremilast and placebo a [redacted] percentage of participants receiving deucravacitinib achieve the dermatology life quality index. The ERG notes that the adjusted mean difference is significantly [redacted] for those receiving deucravacitinib compared to apremilast and placebo. These differences are, [redacted]. The ERG agrees that the company's analysis shows deucravacitinib as [redacted] to apremilast and placebo.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Because of the lack of head-to-head trials comparing deucravacitinib with other relevant comparators, other than apremilast, the company decided to conduct a network meta-analysis

(NMA) according to the methods recommended by the NICE DSU. The company conducted a systematic literature review which identified 84 trials to be used in the NMA. These are shown in table 19 below.

Table 19 Interventions considered in the NMA [reproduced from Table B.2.21, Document B of the CS]

Class	Interventions
TYK2	• Deucravacitinib
TNFα inhibitors	• Certolizumab • Adalimumab • Etanercept • Infliximab
IL-17 family or receptor inhibitors	• Brodalumab • Ixekizumab • Secukinumab • Bimekizumab • Mirikizumab[a]
IL-23 inhibitors	• Risankizumab • Tildrakizumab • Guselkumab
IL-12/IL-23 inhibitors	• Ustekinumab
ADORA3 antagonists	• Piclidonoson[a]
Systemic non-biologics	• Apremilast • Methotrexate[a] • Ciclosporin[a] • Dimethyl fumarate • Acitretin[a]

[a]While these treatments were considered in the NMA, they are not considered for the NMA results as they reflect a broader scope than relevant in standard UK clinical practice.
ADORA3 = Adenosine A3 receptor; IL = interleukin; TNFα = tumour necrosis factor-alpha; TYK2 = tyrosine kinase 2 inhibitor

The ERG reviewed the summary of the studies used in the NMA from Appendix D 1.3.2. The ERG highlights that there are differences in psoriatic arthritis between the trials included in the network indicated by PSA values ranging between 3% and 36%. The ERG also notices that some of the studies are in a population which is 100% Asian and there are other variances in ethnicity too. In most included studies, the prior biologic use is lower, but this is likely to negatively affect the comparison with deucravacitinib. The severity definitions and disease duration are similar between the trials being used in the network. Inclusion in the NMA was restricted to participants who remained on their initial treatment assigned at randomisation. In clinical practice, it is more likely that patients will be on and off treatment and may also receive different treatments.

The NMA used by the company is a multinomial model with four different categories of PASI response at 50%, 75%, 90% and 100%. The relationship between PASI thresholds allows the model to fill in any gaps caused by missing data. It is the opinion of the ERG that

this multinomial NMA, as suggested by the NICE DSU, is an appropriate model to use. The ERG also supports the adjustment for baseline risk to allow for the relative effect of drugs depending on the baseline risk and the exploration of inclusion and exclusion of this term via sensitivity analyses. The ERG agrees with the company's decision to include a random effect allowing treatments to have different rankings for the various PASI levels and is satisfied with the details provided by the company on the choice of priors, length of burn-in and assessment of convergence. The ERG has also looked at TA511, TA521, TA574, TA575 and TA723 which were all appraisals in a similar area. The ERG notes that the NMA model is consistent either with the model used in these five appraisals or it is the model which the ERG for the respective appraisal suggested should have been used.

The ERG has reviewed the forest plots provided by the company related to the adjusted random-effects model, sensitivity analyses and subgroup analyses and the summary comments and conclusions made by the company. The ERG agrees with the company that deucravacitinib appears [redacted] apremilast and dimethyl fumarate at all time points where it was possible to make comparisons. The ERG also agrees that deucravacitinib is [redacted] to etanercept and at most time points and PASI levels, the effect size is [redacted]. In general, the ERG agrees with the company observations that deucravacitinib is [redacted] apremilast, dimethyl fumarate and etanercept. In the sensitivity analyses, when deucravacitinib was assessed at [redacted] rather than at 16 weeks, the effect sizes become [redacted] deucravacitinib apart from when compared to tildrakizumab when it was assessed at 28 weeks. In sensitivity analyses 1 and 2 (where the multinomial adjusted random effects model is used) all of the effect sizes for deucravacitinib compared to apremilast, dimethyl fumarate and etanercept (25mg twice weekly) are [redacted] in the main analysis for all of the PASI levels. In sensitivity analysis 3 where deucravacitinib was assessed later and a binomial replaced the multinomial model the effect sizes are [redacted] for deucravacitinib. In terms of the comparison with adalimumab and secukinumab, the effect sizes either [redacted] adalimumab or secukinumab or show deucravacitinib [redacted]. The comparison with tildrakizumab shows tildrakizumab [redacted] for all four PASI levels.

As sensitivity analysis 1 is used in the cost-effectiveness model, the ERG has also reviewed it closely. The ERG supports the sensitivity analysis of assessing deucravacitinib and tildrakizumab at the later time points where the respective effectiveness is highest.

The ERG agrees with the company's statement that longer deucravacitinib treatment improves the comparability against adalimumab and infliximab and compared to ustekinumab, tildrakizumab and secukinumab. The ERG would, however, highlight that in these comparisons the effect sizes still [redacted] of deucravacitinib.

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG attempted to reproduce the different NMA using the code and data provided by the company but without success. There were various error messages provided such as undefined variables being used in the code and an error message possibly indicating an array being transformed to a scalar.

3.6 Conclusions of the clinical effectiveness section

Overall, the clinical evidence submitted by the company is relevant to addressing the NICE decision problem and the results are generalisable to the patients seen in the UK clinical practice. The direct trials evidence submitted by the company shows that deucravacitinib is more effective than apremilast and placebo. PASI responses at all levels are significantly better among patients treated with deucravacitinib. There are also significant differences in favour of deucravacitinib for the various physician global assessment outcomes and the dermatology life quality index and PSSD. The response is also maintained in the long-term for deucravacitinib patients. The evidence from the NMA is also consistent with the direct trial evidence of deucravacitinib as more effective in terms of PASI response rate than apremilast and in addition deucravacitinib also appears [redacted] dimethyl fumarate. The NMA also shows that deucravacitinib has [redacted] effectiveness than etanercept. The ERG considers the methods used by the company to conduct the NMA appropriate for the data available. The ERG has inspected the pooled safety data for the POETYK PSO-1, POETYK PSO-2 and POETYK-PSO-LTE studies and has no concerns about the rates of reported AEs or SAEs. Adverse event rates in the deucravacitinib group were comparable to the apremilast group. It is the case that some of the commonly reported adverse events (headache, diarrhoea and nausea) were observed less frequently in patients treated with deucravacitinib. Deucravacitinib showed a higher SAE rate

than apremilast but only 4% of deucravacitinib participants experienced an SAE. No unexpected new safety signals were observed during deucravacitinib treatment.

4 COST-EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted literature searches in four categories:

a) **Cost-effectiveness of deucravacitinib**

The company undertook a Systematic Literature Review (SLR) for relevant literature on the cost-effectiveness of psoriasis treatments. The primary search was performed on 31 May 2021 and a subsequent update on 21 December 2021. The SLR identified 84 relevant publications, of which 66 were full publications and 18 were conference abstracts. There were 67 Health Technology Appraisals, (HTAs), of which 14 were NICE Technical Appraisals (TAs).

The SLR did not identify any studies examining the cost-effectiveness of deucravacitinib and so a *de novo* economic analysis was conducted.

b) Health-related-quality-of-life (HRQoL) studies

The company conducted an SLR, on 31 May 2021 and 21 December 2021, to identify relevant HRQoL studies. A total of 290 publications were identified and 37 of the studies reported health utilities using the EQ-5D.

c) Cost and healthcare resource use data

An SLR was conducted on cost and healthcare resource use data with searches conducted on 31 May 2021 and 21 December 2021.Some of the identified studies informed the unit costs and the BSC and non-responder costs applied in the model.

d) Previous NICE appraisals

All of the comparators in the company model have been subject to Technical Appraisal by NICE and many of the issues and uncertainties faced in the current appraisal have been considered previously by NICE. Where appropriate the company commented on these previous NICE findings.

TA 103 (Efalizumab and Etanercept) introduced a Markov model (referred to as the York Model) for the economic evaluation of psoriasis treatments.[36] This approach was utilised and enhanced in TA 575 (Tildrakizumab), to compare 8 treatment sequences each comprising three active treatment lines followed by BSC.[37] Each of the active treatments in the sequences was represented by an induction state and a maintenance state, and within each state patients were distributed across four PASI response categories. The ERG for TA 575 conducted an extensive critique of the model, and the committee's preferences for various modelling assumptions are recorded in the appraisal determination. This provides a useful reference for the current appraisal.

As the most recent psoriasis appraisal that utilised a full cost-effectiveness model, the company have relied heavily on TA575 to guide their modelling approach for deucravacitinib. They use a very similar Markov structure, allowing three active lines of treatment followed by BSC, but with 5 PASI response categories within the treatment states. They have incorporated many of the ERG's recommendations from TA575, and have provided justification where they have deviated. Departures from previous NICE appraisals as detailed by the company (Source, Company Submission, Document B, Table B.3.2. included:

- The use of more recent data from the BAD Biologic Interventions Register to inform treatment discontinuation rates.
- The use of crude pooling to address the ceiling effect resulting from the high baseline utility in the POETYK trials from which the company drew its clinical effectiveness data.
- The use of an alternative source to Fonia et al (2010)[17] study to inform BSC and non-responder costs. The Fonia study was employed in TA 575 but was criticised by NICE who requested further research in this area.[37] The company conducted the DISCOVER study to inform BSC and non-responder costs. Scenarios were run using the Fonia equivalent data.

The ERG is satisfied that the Systematic Literature Reviews conducted by the company are comprehensive and appropriate for the objectives the company sought to address.

An appropriate selection of databases was included in the search strategies and the eligibility criteria are comprehensive.

The ERG agrees that the SLR has not identified any studies assessing the cost-effectiveness of deucravacitinib and that the approach taken by the company of conducting a de novo analysis was appropriate.

The approach taken by the company to the decision problem closely aligns with the relevant previous NICE TAs and the company presented a helpful tabulation of the features of the economic analysis, a comparison of parameters utilised in previous relevant NICE appraisals and a justification for any departures therefrom.

The ERG believes that the company has appropriately reflected on the modelling approaches and assumptions taken in previous relevant NICE appraisals, and has, generally, justified any major departures. In conducting its critique of the company's de novo model, the ERG has also been cognisant of the committee's preferences on key assumptions and inputs as expressed in the committee paper for the previous relevant appraisals. However, a number of limitations are flagged throughout following critique.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 20 NICE reference case checklist[38]

Element of health technology assessment	Reference case	ERG comment on the company's submission
Defining the decision problem	The scope developed by NICE	Aligns with the reference case.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Aligns with the reference case.
Perspective on costs	NHS and personal social services (PSS)	Aligns with the reference case.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis Cost-comparison analysis	Aligns with the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with the reference case.
Synthesis of evidence on health effects	Based on a systematic review	Aligns with the reference case. A systematic review was conducted along with a Network Meta-Analysis aligning the evidence with the company's clinical trials.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Aligns with the reference case. Health effects were expressed in QALYs established using the EQ-5D
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligns with the reference case.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligns with the reference case.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health	Aligns with the reference case.

	benefit, except in specific circumstances	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Aligns with the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with the reference case.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, a standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company's schematic of the model framework, showing the transition pathways in summary form, is reproduced as Figure 8 below.

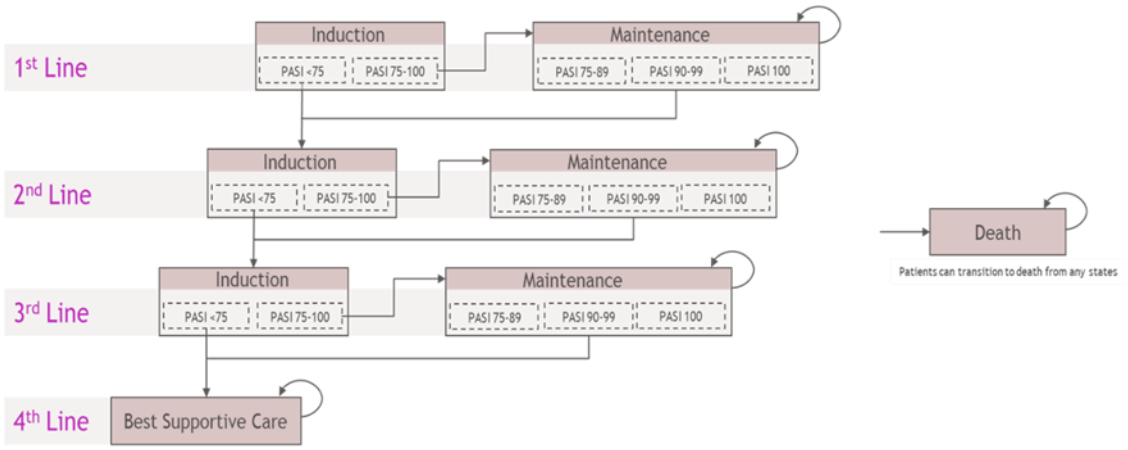


Figure 8 Schematic of the company's model structure (Source, Company Submission, Document B, Figure B.3.1.)

The company developed a Markov model to compare deucravacitinib with fourteen comparator treatments in a three-line treatment sequence, with BSC as the fourth line. Each treatment line in the model is represented by an induction and a maintenance phase health state, and there is a subsequent BSC state to which patients transition after third line treatment. Patients can also transition to death from all other states in the model based on the age matched general population mortality rate. The model utilises a two-week Markov cycle over a life-time horizon (up to age 100 years for the modelled cohort).

The induction states in the model are defined as tunnel states to allow time from treatment initiation to be counted in each line of therapy. The number of cycles spent in induction is aligned with the recommended time for assessing response which varies across the different treatments (from 10-28 weeks). At the end of the induction phase for each line of therapy, the proportion of the patients that achieve a PASI75 response (derived from the NMA) transition to the corresponding maintenance state. Those who do not achieve a PASI75 response transition to the induction state for the next line of therapy, or to BSC following third line treatment. Patients in the maintenance states are assumed to retain their response until discontinuation. Discontinuation, due to any reason, is modelled as a constant 2-weekly probability that is set equal between all treatments in the company base case.

Health effects, measured in QALY's, are accrued based on health state and the level of PASI response achieved (<50, 50-74, 75-89, 90-99, 100) within health states. Utility gains are based on the PASI response achieved and not on treatment so equivalent responses across treatments receive the same utility. Further utility decrements are applied to modelled adverse events which differ by treatment arm. The model assumes that the health state utility of patients in the BSC state defaults back to baseline.

Drug acquisition costs, administration costs, monitoring costs, non-responder costs, BSC costs and adverse event costs are allocated to the health states and over the cycle periods in which they are incurred. The ERG comments below regarding the manner in which drug acquisition costs are applied to the two-week cycle period.

The ERG believes that structurally, the company's model is generally appropriate for addressing the decision problem. The use of a Markov approach is justified based on the need to appropriately model treatment sequences over an appropriate time horizon.

The health states selected for the model are appropriate and are sufficiently detailed to capture the clinical treatment pathway and health benefits to patients. Based on the ERG's clinical expert advice, contemporary clinical treatment pathways for the population in question often consist of more than three treatment lines. However, given the practical constraints of an excel based model and the nature of the decision problem the three-line

treatment sequencing approach is considered to be appropriate and is consistent with TA575 and the recommendations arising therefrom.

The cycle length is appropriate to the decision problem and checks were performed on a to ensure that costs and benefits were correctly allocated within the cycle length.

4.2.3 Population

The company state the population for their economic analysis to be "Adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option" (Company Submission, Document B, Table B.1.1.1.). This is a sub-population within the wider marketing authorisation.

The ERG noted that this wording is not fully aligned with the wording of the population restriction placed on the comparator therapies that the company include in their model: "*People with severe or very severe psoriasis [defined by a total PASI of 10 or more, and a DLQI of more than 10] for whom systemic non-biological treatment (including methotrexate, ciclosporin and acitretin) and phototherapy are inadequately effective, not tolerated, or contraindicated*". [39]The ERG, therefore, asked the company to clarify if they wanted deucravacitinib to be considered an option for people who would not otherwise be eligible for the comparator therapies included in their model (see clarification letter, question A6).

With reference to the NICE pathway,[22] the company responded that they believe their defined population is aligned with the severity definition set out in previous NICE appraisals, and that all the comparator therapies in their model would be available for the population they propose.

From the response, it is the ERG's understanding that the company want deucravacitinib to be considered an option only for patients who would otherwise be eligible for the comparators included in their model. However, there does, in the ERG's opinion, remain some inconsistency in the company's stated definition of the population in the decision problem and the more specific population for which an economic case has been made.

The modelled cohort had an average starting age of [redacted] years, a gender split of [redacted] male and [redacted] female and an average weight of [redacted]. Weight is relevant as the protocols for tildrakizumab and ustekinumab use patient weight to determine dosage intensity.

The ERG note that the trial population comprises patients with and without prior exposure to systemic non-biologic and biologic therapy while the modelled population assumes that patients have had inadequate response to or are contraindicated for non-biologic systemic therapy. Whilst ideally the modelling for each treatment would be based on data from patients matching the proposed positioning, the ERG recognises the challenges of making relevant comparisons between all treatments for the restricted group in question.

4.2.4 Interventions and comparators

The intervention, deucravacitinib, is an orally dispensed selective TYK2 inhibitor which is described by the company as having a "unique mechanism of action, representing a new class of small molecules". The oral modality of the medication is seen as conferring a significant advantage on deucravacitinib over the other subcutaneously injected or intravenous systemic alternatives. Deucravacitinib is positioned by the company as having the clinical effectiveness of some biologics with the administration benefits of an oral medication.

A total of fourteen comparators were examined in the evaluation, all of which have been subject to the NICE Technical Appraisal process. Dosage protocols were taken from the Summary of Product Characteristics for each comparator. As noted in the discussion of the population above, all the comparators in the model are generally restricted to "*People with severe or very severe psoriasis [defined by a total PASI of 10 or more, and a DLQI of more than 10] for whom systemic non-biological treatment (including methotrexate, ciclosporin and acitretin) and phototherapy are inadequately effective, not tolerated, or contraindicated*".[39]

The model allows for three lines of active therapy followed by BSC. The intervention and each of the comparators are compared as first line treatments in the sequences, with the second and third line treatment remaining consistent to ensure comparability across sequences. The second (secukinumab) and third (risankizumab) line treatments were determined by a combination of market share for the second line and expert opinion for the

third line. Where secukinumab or risankizumab were the first line treatment they were replaced by ustekinumab (Source, Company Submission, Document B, Table B.3.4).

The ERG is satisfied with the choice of comparators in the model, noting the slight discrepancy in the definition of the company's stated population and the wording of the eligible population for the comparator therapies. It is the ERGs understanding that if deucravacitinib is considered a cost-effective use of resources against these chosen comparators, it would have to have the same eligibility criteria placed on it. No case has been made against relevant comparators for patients who would not otherwise be eligible for the comparators included in the model.

Accepting the simplification of assuming only three active lines of treatment, the ERGs clinical expert advised that the choice of second- and third-line treatments are clinically plausible. He further noted that guselkumab may also be appropriate for consideration at the second line, given its recent approval based on a cost-comparison with ixekizumab and secukinumab.

The ERG also notes that BSC was not examined as a direct comparator by the company in the model on the basis that there are so many active treatments available for the population in question, meaning that BSC is a treatment of last resort. The company also postulates that in practice many patients would be subjected to many more lines of treatment than the three lines considered in the model. The ERG believes that the exclusion of BSC as a comparator is justified. However, it would be reassuring to know if the treatments included at second and third line in the modelled sequences represent cost-effective options compared to BSC in their own right. The ERG report for TA575 explores the validity of the sequencing approach and how it may, in certain circumstances, distort the calculated ICERs.[37]
However, the FAD for TA575 reports that the committee:

> *"was also aware that additional factors should be considered when comparing treatment sequences, such as the best ordering of sequences and the effect of including treatments that may not be cost effective. The committee agreed that, in principle, it was appropriate to compare treatment sequences in this appraisal."*[37]

4.2.5 Perspective, time horizon and discounting

The perspective on outcomes is all health benefits accruing directly to patients. The perspective on costs is that of the NHS and personal social services (PSS).

The model assesses costs and benefits over a lifetime horizon. The model shows that an insignificant proportion of patients are projected to survive beyond the age of 100 and the evaluation of QALY's and costs ceases at that point.

An annual discount rate of 3.5%, as per the NICE reference case, was applied to both costs and health benefits.

The ERG is satisfied that the perspective, time horizon, and approach to discounting are in line with the reference case. The extent to which all NHS and PSS costs related to psoriasis are captured in the model, particularly primary/community care, is questionable. Discounting calculations were checked by the ERG to ensure correct and consistent application across both costs and health benefits.

4.2.6 Treatment effectiveness and extrapolation

The matrices of two-week transition probabilities that govern the flow of the cohort through the model are determined from a combination of treatment response rates, the treatment discontinuation rate, and background mortality rate. Treatments are further differentiated by the rates of selected adverse events included in the model.

<u>Treatment response</u>

Patients transition from induction to maintenance based on their PASI response to treatment at the end of the induction phase; those who meet the defined response criteria make the transition to maintenance whilst 'non-responders' move to the next treatment line. In line with previous NICE psoriasis appraisals, the treatment response threshold is a 75% reduction from baseline PASI (PASI75). The comparative response rates for each treatment are derived from the company's multinomial NMA model, which allows for comparative PASI response rates to be estimated at multiple cut-off thresholds (50%, 75%, 90% and 100%) for each treatment. The cost-effectiveness model uses the random effects specification with adjustment for baseline placebo response and further random effects which allow treatment efficacy rankings at different PASI thresholds to vary. For example, the first ranked treatment

on PASI75 response may not be first ranked on PASI90. Rather than using the primary NMA presented in 2.9 of their submission, which compares the 10-16 week outcome data for each treatment, the cost-effectiveness model uses the results of a sensitivity analysis which compares [redacted] outcome data for deucravacitinib and 28 week outcome data for tildrakizumab with 10-16 week outcome data for the other comparators. The company justify this as being more in line with clinical practice, as these represent the recommended optimal timepoints for assessing response to treatment.

As well as informing the percentage of patients meeting the PASI75 response for each treatment, for transition to maintenance, the NMA model provides the comparative distribution of PASI response rates (50, 75%, 90%, and 100%) for each treatment. These comparative response rates are used to categorise patients in the induction and maintenance states across different categories of PASI response (PASI 0-49, PASI 50-74, PASI 75-89, PASI 90-99, and PASI 100). This categorisation allows the weighted average health state utility assigned to the induction and maintenance state for each treatment to differ according to the within state PASI response distribution.

The ERG is broadly satisfied with the company's approach to incorporating the NMA response rates into the economic model. As discussed in section 3.4 above, the NMA output is consistent with previous published NMAs undertake for this indication, and the methodological approach has been justified (see section 3.4). The reliance on the NMA sensitivity analysis that utilised [redacted] and 28-week outcome data for deucravacitinib and tildrakizumab respectively, is justified on grounds that these are likely to be the chosen time points for assessing response to these treatments in routine clinical practice as set out on the relevant SmPCs.[23, 40] The company have addressed the uncertainty related to this assumption by conducting a scenario analysis that utilises response rate estimates from the primary NMA, which uses the 16-week outcome data for deucravacitinib and the 12-week outcome data for tildrakizumab.

Within the model, sequences of three lines of treatment are allowed, with the assumption that the response rates from the NMA are applicable across all modelled lines, irrespective of modelled response to the previous treatment line. This is a simplifying assumption that is consistent with previous NICE appraisals. The company do provide a scenario that allows for waning efficacy of second/third line treatment. This is to reflect a registry-based research

finding that patients with prior biologic exposure may have shorter duration of response to subsequent biologic therapy compared to those without prior biologic exposure. It is applied in the model by inflating the discontinuation rate.[41] No scenarios consider the possibility of lower initial response rates in subsequent treatment lines, but applying higher discontinuation rates has a similar effect.

The model incorporates the assumption of 100% adherence to treatment protocols across all treatments. The ERG noted that the studies included in the NMA were conducted in a trial setting, where adherence levels would be expected to be high, and that the trial results have then been extrapolated with the assumption that they would be replicated in routine practice. The ERG also noted that deucravacitinib is an oral medication with a daily dosage regimen. Given this background the ERG questioned (B1) whether the company had conducted comparisons of relative adherence to oral and injectable therapies in routine practice and whether any expected differences in relative adherence might affect the generalisability of the comparative response rates from the NMA.

The company conducted further research on relevant studies and obtained expert opinion on the specific aspect of adherence (see company response to the clarification letter, B1) and suggest that adherence to a daily oral may be higher than with an injection cycle. They also suggested that since deucravacitinib has a constant dosage protocol (doesn't require titration), adherence in routine practice may be less impacted relative to other oral treatments.

In considering the impact on treatment effectiveness of a less than 100% adherence to deucravacitinib, the company referred to the durability of response observed in the POETYK-PSO-2 trial for deucravacitinib 24-week responders who were re-randomised to receive placebo. The relatively slow loss of response, they suggest, means that efficacy would be expected to be maintained at below 100% levels of adherence, although no efficacy threshold for adherence was ascertained. They further note that missed doses of periodically administered biologics may have a greater impact on efficacy.

Given the paucity of data around relative adherence to daily oral and injectable psoriasis therapy, and any impacts on efficacy, the ERG accepts the company's conclusion that the assumption of 100% adherence across all treatments is reasonable and that the comparative response rates from the NMA can be generalised to routine practice.

There is no cure/remission health state in the model as psoriasis is a chronic condition, and so all patients who discontinue from the third line of treatment are assumed to spend the remainder of their life on BSC. The model distributes those in BSC across the PASI response categories derived from the placebo arm of the NMA. In this respect the model allows for a proportion of patients on BSC to have an improved PASI relative to their baseline score (see Table B.3.5 of the company submission). However, there is a retrospective adjustment of the PASI response based QALYs that accrue in the BSC state of the model (see 4.2.7 below), which assumes baseline utility for all those on BSC. This is essentially the same as assuming zero PASI response for those on BSC.

The ERG is concerned that this adjustment could overestimate the PASI response-based quality of life benefits of all the active treatments relative to BSC, as it removes the placebo response (observed in the placebo arms of trials in the NMA) driven QALYs from the BSC state but retains the full response rates for the active treatments. The ERG believes that the placebo response in the trials, whether due to natural variation or a trial effect, may also apply, at least in part, to the observed active treatment response rates. Implications of the utility adjustment, which negates the BSC PASI response, are discussed further under 4.2.7.

Treatment discontinuation and subsequent treatment extrapolation

In the company base a case, a constant probability of all-cause treatment discontinuation is applied to all those on maintenance treatment. The same probability is applied irrespective of treatment type or treatment line. The company note that since the POETYK trials were treat-through (i.e. patients continued to receive deucravacitinib irrespective of response) the discontinuation data are not applicable to routine practice. They, therefore, applied a common annual discontinuation rate to all treatments informed by observational registry data.[42] They further note that this approach is in line with the approach accepted in several previous NICE psoriasis appraisals. However, the company estimate a new common discontinuation probability of 14.3% per year (transformed to a constant 2-week probability) based on more recent data.[42] The company performed further scenario analyses around this parameter, including the application of the discontinuation probability used in previous appraisals (TA511 and TA575) based on older data,[43] and a scenario that uses best estimates of treatment specific discontinuation rates (see Table B.3.6 of the CS).

The ERG raised a clarification question (B2) in relation to the annual discontinuation rate of 9% applied to deucravacitinib in the treatment specific scenario. This was based on a rate reported for guselkumab, which the company justified on grounds of it acting partly on the same IL-23 pathway. The ERG noted the higher rate of discontinuation rates estimated for the other oral treatments and queried whether other factors such as mode of administration should be considered when assuming a rate for deucravacitinib.

In response, the company revisited its work in this area and advised that an error had arisen in the derivation of the rate for guselkumab which should be stated as 4.5% and not 9% per year. This correction also adjusted the rates for risankizumab and tildtrakizumab which were also based on guselkumab. A similar error had arisen in the derivation of the annual discontinuation rate for ixekizumab which should have been modelled as 12% and not 24%.

The company's prior approach of basing the rate for deucravacitinib on guselkumab was then revisited, and they instead based this on the observed discontinuation of [redacted] for those who achieved a PASI75 response at 16 weeks in the POETYK trials and were intended for maintenance treatment through to week 52. This equates to a 12-month probability of [redacted], which the company apply in their revised scenario.

The company also reviewed evidence to inform the comparative discontinuation rates for the other oral therapies in the model (apremilast and dimethyl fumarate), including efficacy and adverse event rates from the POETYK trials, and published studies reporting on treatment persistence with apremilast and dimethyl fumarate. Based on this the company concluded that the appropriate discontinuation rate for dimethyl fumarate should be assumed to be 12.4% as per deucravacitinib (previously 31%) and that apremilast's rate should remain unchanged at 31%.

The ERG is satisfied that the revised table of discontinuation rates are conservative and credible.

Mortality

Notwithstanding that psoriasis is associated in some studies with elevated mortality, the company has applied age and gender-dependent all-cause mortality rates drawn from the Office of National Statistics (ONS) National Life Tables for England and Wales.[29] Mortality is applied by age in the model, using a weighted average of male and female mortality rates

based on the observed baseline gender distribution in the POETYK trials. Based on evidence to suggest that more severe psoriasis (BSA >10%) is associated with an elevated risk of mortality compared to the age matched general population,[27] the company also explored a scenario that adjusted general population mortality upwards. Under this scenario the total costs and QALYs were reduced for all treatments, but there was little impact on the incremental costs and QALYs and the overall pattern of results.

The approach taken by the company in applying the general population mortality rate across all the treatments is in line with previous TAs. Given the short time frames in the POETYK and the other trials included in the NMA, neutrality of treatment in respect of mortality is a reasonable assumption to make.

Adverse events rates

The company included selected adverse events of interest in their model. In line with TA350 and TA 442, these were severe infections, non-melanoma skin cancer, and malignancies other than non-melanoma skin cancer. Following a clarification question, the company confirmed that the adverse event rates included in the model represented numbers of events per patient year. However, a decision had been made to include these on a one-off basis during the first cycle of treatment, rather than converting them to equivalent two-weekly rates and applying them throughout time on treatment. The company justified this simplifying assumption as being in line with previous NICE appraisals and having been accepted by the ERG for TA633 as a "reasonable simplifying assumption".[44]

The ERG accepts this simplifying approach is sometimes used in economic modelling but did have some concern that it could underplay the potential impact of adverse events as it is assuming there is no ongoing risk of adverse events for those remaining on treatment beyond one year. In response to the clarification letter, the company did also provide the results of a scenario analysis whereby the AE rates for each treatment, applied in the first cycle of treatment, were doubled. This had negligible impact on the ICERs. However, this may be partly due to the limited impact on costs and QALYs they are assumed to have. This is discussed further in section 4.2.7 and 4.2.8 below.

Whilst the ERG believes there are limitations in the way adverse event rates are applied in the model, they are unlikely to be an important driver of cost-effectiveness.

4.2.7 Health related quality of life

PASI response-based improvements in health-related quality of life

The key driver of improvements in health-related quality of life in the model are the achievement and maintenance of PASI response. The key structural assumptions related to this are:

- Health effects for each treatment sequence are determined by the change in PASI relative to the baseline.
- Patients accrue utility based on their health state as determined by their PASI response. Treatment efficacy is therefore the driver of utility gains.
- Utility associated with a PASI response is the same regardless of treatment.
- The utility of patients on BSC defaults back to the baseline value.
- PASI response is accrued linearly during induction, so utility gains (relative to baseline also accrue linearly during induction).

The EQ-5D-3L data collected in the POETYK trials were used to inform health state utilities applied in the model. EQ-5D data was collected from patients in both POETYK trials at baseline and weeks 4, 8 12 and 16 (the induction period for deucravacitinib is 24 weeks) and was valued, in terms of utility, using the Dolan algorithm which is applicable to the UK general population.[45]

The data were analysed using linear regression to estimate the average health state utility for subgroups defined by the level of PASI response (<50, 50-74, 75-89, 90-99, 100). Utility at week 16, as the chosen dependent variable, was regressed on week 16 PASI response categories, and baseline EQ-5D. Other models that included treatment arm as an explanatory variable, with and without other covariates (prior biologic exposure (yes/no), prior systemic therapy (yes/no), and baseline body weight (≥90 kg and <90 kg)) were explored, but the more parsimonious model provided the best statistical fit (based on Akaike information criterion and Bayesian information criterion) to the observed data in each trial and in the pooled dataset. For the purpose of informing the cost-effectiveness model, the preferred regression model was applied to the pooled subgroup of POETYK trial participants with baseline DLQI>10, as this represents the patient population seen in routine practice in England (in line

with the access criteria for the comparator therapies in the model). The estimated utility increments associated with achieving the different PASI response categories at 16 weeks are provided in Table B.3.8 of the company submission document.

The company commented in its submission on the magnitude of variation in mean baseline utility between the DLQL>10 subgroup in the POETK trials and the corresponding subgroups in other trials informing previous TAs. They noted that this may result in a ceiling effect, limiting the magnitude of utility gains that can be attributed to PASI improvements based on the POETYK data. They, therefore, conducted a review of utility values used in previous TAs, and applied specific criteria (Company submission, Document B, Table B.3.9) to identify sources of utility data that could be pooled with their PASI response-based utility estimates from the POETYK trials. Based on this they identified only TA511 (Brodalumab) and TA350 (Secukinumab) as providing the required data (Company submission, Table B.3.10).[46, 47] The pooled POETYK trial data was therefore pooled, weighted by sample size, with trial-based utility estimates used in TA511 and TA350. The resultant weighted average utility values were applied in the cost-effectiveness base case (Company Submission, Document B, Table B.3.11)

The ERG had some concern about the magnitude of the discrepancy in baseline utility between the POETYK trials and the trials used to inform utility values in the previous appraisals (TA511 and TA350). Such variation could point to significant differences in the population of patients included in the relevant trials, which also inform the comparative efficacy of treatments through the NMA. The company advised, in its submission, that it had explored this issue and possible causes, including differences in populations between the studies, but found no satisfactory explanation.

Acknowledging the work already done by the company the ERG requested the company to re-examine the discrepancy.

In its response the company advised that it had undertaken a more detailed comparison of baseline characteristics across the trials, but no satisfactory explanation of the discrepancy had emerged.

They also conducted an additional analysis, whereby alternative EQ-5D values were mapped, using a published algorithm, from the DLQI response data from the pooled

POETYK trial subgroup with DLQI>10.[48] This approach generated lower baseline utility compared to the directly measured EQ-5D data, and utility differences between the PASI response categories that were more aligned with values used in previous appraisal (see Table 9 of the company response to clarification).

Applying these values in the model, the ICERs for deucravacitinib remained favourable against all comparator treatments.

The ERG has also been unable to identify an obvious reason why such a discrepancy exists in baseline EQ-5D between the DLQI>10 subgroup of the pooled POETYK trials and the corresponding subgroups of previous trials. Accepting that the trial populations are sufficiently comparable to inform comparative efficacy estimates through the NMA, the ERG accept the company's approach of pooling utility estimates across the available trials. This ensures better consistency with health state utility values that have been used and accepted in previous NICE psoriasis technology appraisals.

BSC health state utility

The model assumes that patients on BSC revert to baseline health state utility, rather than receiving utility gains in line with the PASI response rates estimated for placebo from the NMA.

The ERG queried why the PASI response state of patients who transition to BSC is based on the PASI response distribution derived for placebo in the NMA, but utility is set to baseline (inferring zero PASI response).

The company stated that the approach taken was consistent with TA575 where a concern was raised by the ERG with respect to the assumption that patients on BSC would accrue utility based on a PASI < 50 response level. This approach was criticised by the ERG and a clinical expert, and the committee concluded that utility for BSC should revert to baseline.[37]

The company followed the approach accepted by the committee in TA575.

Given the committee's previous conclusion on this issue the ERG accepts the approach taken by the company in its base case. However, the ERG would suggest that this is similar to removing the NMA placebo PASI response estimate from BSC, whilst retaining the full response estimates from the NMA for active treatments. The ERG has some concern that the

placebo response observed in trials feeding into the NMA, may reflect some natural improvement among patients who were recruited into the trials during a period of exacerbation. There is, therefore, potential for this assumption to overestimate the health benefits of all the active treatments relative to BSC. Thus, the ERG suggests alternative scenario analyses that a) apply PASI response-based utilities to BSC according to the response distribution of the placebo arm of the NMA; and b) apply PASI response-based utilities to the proportions of the placebo arm that achieve PASI50 or better but assume baseline utility for the proportion that achieve < PASI50.

Related to the above, question B5 in the ERG's clarification letter queried the derivation of an adjustment factor (0.825) used in the company's original model to align the BSC QALYs with assumed baseline utility.

The company explained its methodology. As the ERG anticipated, the value represents the weighted average of PASI response-based utility for BSC, but an error had been made in its calculation or coding in the model. The company clarified that the correct value should be 0.759 and revised the model correspondingly.

QALY losses due to adverse events

The company notes the sparsity of evidence on the impact of adverse events on HRQoL for psoriasis patients with only TA511 incorporating disutility for AE's in the base case.[46]

As per TA511, the company drew on a study relating to rheumatoid arthritis (Diamantopoulos et al., 2014)[49] which in turn drew on a study by Sisk et al. (1997),[50] to derive a utility multiplier for severe infections. The company converted this value to a utility decrement per event to be applied in their model. No separate disutility was factored into the model for non-melanoma skin cancer or other malignancies on the basis that:

- These are long term conditions any disutility associated therewith would be captured in the overall health utility measurement process through the EQ-5D.
- These conditions would endure beyond the duration of treatment rendering their inclusion in the model overly complex.

The magnitude of the utility decrement estimated for severe infections appeared very small in the original submission, with negligible impact on QALYs. Therefore, the ERG asked for more clarity on how it has been calculated. The adjustment for number of weeks per year also appeared to have been applied twice in the calculation of associated QALY losses, and so the ERG asked the company to check the calculations in the model.

The company confirmed that the utility decrement used in their model was based on a utility multiplier of 0.986 derived by Diamantopoulos et al, using health state utility data reported by Sisk et al,1997.[49, 50] However, the ERG has subsequently reviewed these studies and find that the assumptions informing the multiplier are not transparent. Since Diamantopoulos et al describe it as being adjusted for the duration of the event, the ERG suspect it is supposed to be QALY multiplier for application over a defined time period, rather than a health state utility multiplier as the company have treated it. The original study by Sisk et al. reports a utility value for pneumococcal bacteraemia of 0.21, compared to reported utility values without infection ranging from 0.51 (age 85) to 0.76 (age 65-69).[50] Thus, a utility multiplier for pneumococcal bacteraemia would be in the region of 0.412 (=0.21/0.51) and 0.276 (=0.21/0.76). Taking the average of these two values (0.344) and applying it to the average model-based utility of patients on deucravacitinib at 16 weeks ([redacted]), would suggest an average utility decrement of 0.554 (=0.844-(0.844x0.344)) for the duration of severe infection events (assumed 7 days in the model). This is much larger than the company estimate of 0.014.

The company further confirmed that their estimate of QALY losses attributable to severe infections had been adjusted for the number of weeks per year twice and corrected this in their revised model. However, with the very small utility decrement and rates applied it had negligible impact on the reported results.

Whilst there are several limitations related to the way in which adverse event rates have been incorporated in the model, and associated QALY losses estimated, the ERG is of the opinion that this has not introduced any major bias in favour of deucravacitinib. The ERG explored a scenario that applies the larger utility decrement of 0.554 as calculated above, assuming the event lasts for seven days. This makes very little difference to the ICERs given the low rates being applied only in the first cycle on each treatment.

4.2.8 Resources and costs

The company conducted an SLR to identify cost and healthcare resource use data relevant to the decision problem. The study identified 66 publications of which 58 were full text articles and 8 were conference abstracts. Details are reported in appendix H of the company's submission.

Costs incorporated into the model are; drug acquisition costs, drug administration, treatment monitoring, BSC, non-response and adverse events

Drug acquisition costs

For all comparators, drug acquisition costs were derived from the British National Formulary[51] and dosing schedules were drawn from the relevant SmPCs.

The base case utilises the list price for all comparators as the company is not party to confidential patient access scheme discounts available for comparators. The ERG will produce a confidential appendix with results that reflect discounted comparator prices. Note that biosimilars are currently available for adalimumab, etanercept and infliximab, and the prices of these biosimilars have been applied in company's results.

A PAS value of [redacted] has been advised for deucravacitinib compared to the list price of [redacted] and has been applied in the company's revised model.

The structure of the model reflects separate induction and maintenance periods, with many comparators subject to loading doses during the induction, prior to stable dosing throughout maintenance. From the recommended dosing schedules (Table B.3.12, Document B of the CS), the company constructed average drug costs for each treatment per 2-week cycle in induction and maintenance and apply these costs on per cycle basis in the model. It should be noted, however, that dosing schedules do not always align with the length of the induction periods as defined in the model (i.e. up to the timepoint response assessment is assumed). Therefore, for some treatments, a patient may not be due their first maintenance phase dose until several weeks into the maintenance phase. Drug acquisition costs per 2-week treatment cycle for induction and maintenance are shown in Table B.3.13 of the company submission.

The ERG notes that the application of averaged two-weekly costs for induction and maintenance, may create a degree of bias/inaccuracy in the calculation of cumulative acquisition costs. This is particularly pertinent for some of the biologics where there are several weeks between scheduled doses. In cases where a first scheduled maintenance dose is due at the start of the maintenance period, the application of average two-week costs per cycle may underestimate the cumulative acquisition costs, as everyone alive and on treatment at this timepoint should incur the full cost of the dose. Conversely, if the first scheduled dose is due several cycles into the maintenance phase (and the prior dose has been fully attributed to the induction phase), then applying 2-week average acquisition costs may overestimate the cumulative cost stream, since this applies averaged dose costs to fractions of the cohort who discontinue or die prior to the dose actually being due. The ERG explored the impact of averaged versus fixed schedule dosing for first line treatments in the model, and found that there is a tendency to overstate the acquisition costs in such cases. Taking the example of risankizumab, where the first maintenance dose is due 12 weeks after non-responders stop treatment at week 16, Table 21 below outlines the implications of the company average cycle costs approach. For the company's base case model, the ERG calculates that the application of average 2 week cycle costs generates a discounted acquisition cost stream that is £1,700 more compared to full dose costs being applied to all those remaining on maintenance at the time each 12 week dose is due.

Table 21 Implications of applying averaged 2-weekly maintenance costs for risankizumab

Issue	Company's approach	ERG preferred approach
1. The last dose of the induction period is indicated, according to the dosing schedule, at week 16 (counting from week 0). However, the response assessment to risankizumab is assumed to take place after exactly 16 weeks (end of week 15	The company has accrued the cost of the final week 16 dose of induction as part of the induction period average 2-week costs. The final dosage cost is therefore applied to all patients in the induction cohort.	The ERG agrees that the final dose of induction should be received by all patients prior to response assessment. However, this then suggests that the first maintenance dose is not due until 12 weeks (6 cycles) into the

counting from time 0) in the model. A similar issue applies to secukinumab and ustekinumab.		maintenance phase for risankizumab.
2. The application of cycle average dose costs from the first cycle of maintenance, when the first dose would not be due until 12 weeks in.	The cost per dose of risankizumab is £3326.09 every 12 weeks which is a cost per two-week cycle of £554.35. This cost is applied to the proportion of patients in each cycle. The implicit assumption is that patients accrue costs on a cycle period basis even when those costs are accrued periodically.	The acquisition cost calculations should ideally recognise that the intermittent costs of 12-week doses are only accrued by those patients remaining in maintenance at the time each dose is due. In the case of ranibizumab, the application of average 2-week costs from the start of maintenance leads to overestimation of costs for the fraction of the cohort that die or discontinue from maintenance prior to the first maintenance dose being due (at 12 weeks in). This effect then repeats throughout time in maintenance state, leading to a fairly substantial overestimation.

Treatment administration costs

Oral medicines were assumed to have zero administration costs, whereas subcutaneous injections were modelled to incur some upfront training costs to enable self-administration.

This was set at three hours of GP nurse time as a one-off cost at the beginning of induction with the assumption that the patient would self-administer thereafter. Costs for IV administered therapies were modelled to be recurring based on dosage schedules.

Monitoring Costs

A matrix of costs (Table B.3.15. of the company submission) for each monitoring intervention; physician visits, full blood counts, urea and electrolyte tests and liver function tests was compiled with the requirement for each treatment obtained from a review of BAD guidelines and prior NICE TAs and unit costs from the NHS reference costs for 2019-2020.[52]

The model accounts for the expected frequency of usage of these resources during induction and maintenance to arrive at an average monitoring cost per treatment per cycle in each of the induction in maintenance states.

The company submits that the application of a monitoring cost to deucravacitinib is conservative as in practice little monitoring would be required based on its draft SmPC.

The ERG is satisfied that monitoring and administration costs have been adequately dealt with the in the model.

Best Supported Care and non-responder costs

The NICE committee review of TA575 criticised the use of the Fonia study[17] to inform BSC and non-responder costs on the basis of the age of the study which was published in 2010 (using 2008 costs) and requested further research in this area.

The company conducted the DISCOVER study to provide an alternative cost basis, which assesses total health service costs in a sample of patients before and after stopping biologic therapy.[14] The company believe this measure is aligned with the BSC health state.

The company has stated and clarified that costs covered in the DISCOVER study are all inpatient admissions, outpatient visits, critical care admissions, accident and emergency visits, day case admissions and phototherapy.

The company compared the results of the Fonia study (inflated by an appropriate index) and the DISCOVER study and tabulated the resulting costs per year and per 2-week cycle for comparison in Table B.3.5.2. of their submission.

The DISCOVER estimate, which is somewhat lower, was used in the company base case and the Fonia costs were used in a scenario analysis with little impact on cost-effectiveness. BSC costs are applied in each cycle to the proportion of the cohort in the BSC state over the entire time horizon of the model.

The ERG raised clarification questions on the derivation of costs for BSC (B9) and Non responders (B10). These questions were adequately addressed, and the appropriate detailed sources and references were provided.

The ERG has some concerns regarding the calculation/application of BSC costs. The company note that these are representative of total secondary care resource use in patients in the year following discontinuation of biologic therapy. Given the follow-up period, we do not know if they are appropriate for extrapolation over the entire remining time horizon of the model. Further, there is an implicit assumption, which has not been well justified, that all these secondary care costs are attributable to moving off psoriasis treatment to BSC. Given they represent all secondary care use, this is unlikely to be the case. Note, this broad category of costs is not included in the model for those patients remaining on biologic therapy – although some secondary care use will be captured through monitoring and adverse events. Unfortunately, we do not have comparative data on the total secondary care costs for those who remain stable on biologic therapy to determine the marginal effect of discontinuing to BSC.

Non-responder costs

Non-responder costs were similarly estimated from the company's DISCOVER study, using the costs incurred in the 12 months prior to discontinuation of biologics, as representative of costs incurred by those not responding to treatment.

Similarly, to BSC costs, we do not know the extent to which these costs incurred by patients in the 12 months prior to biologic discontinuation, can be attributed to non-response.

For the above reasons, the ERG suggests further exploratory analyses to assess the impact of reducing the BSC and non-responder costs.

Adverse event unit costs and resource use

Rates for the adverse events for each of the treatments incorporated in the model were derived from the POETYK trials in the case of deucravacitinib, apremilast and BSC and from published literature for the remining treatments. The rates are tabulated at Table B.3.7. of Company Submission, Document B. Rates were expressed as the number of events per patient year.

Costs for included adverse events were reflective of average 2019-2020 NHS reference costs[52] as follows:

- Severe infection – a weighted average the reference cost for six different types of infection
- Non-melanoma skin cancer (NMSC) – reference cost JC41Z (Major Skin Procedures)
- Malignancies, other than NMSC – a weighted average reference the costs related to lymphoma and melanoma; SA31 (Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's) and JC41Z (Major Skin Procedures).

The company note that this costing approach is in line with TA 442 (Ixekizumab for treating moderate to severe plaque psoriasis).

As with QALY losses, costs attributable to adverse events are applied only in the first cycle of induction for each line of therapy.

Given the potentially long-term nature of the cancer events included, the model will not be capturing all the costs, or health impact, attributable to these. However, given the low rates applied and the lack of data to accurately inform comparative differences in event rates between treatments, the ERG accepts the simplifying approach, and do not consider adverse events to be an important driver of cost-effectiveness.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company presented their base case deterministic results in section of B.3.10.1 of their submission document (v1.1). However, in response to the clarification letter, the company implemented a correction to the BSC utility adjustment and provided a revised results document, titled "ID3859_Deucravacitinib_ERG amended base case analysis 14062022 SS [CIC]". The results provided account for the confidential discount being offered by the company for deucravacitinib, and a non-confidential complex PAS available for certolizumab pegol (first 12 weeks of treatment free of charge). As noted above, the prices of biosimilars for adalimumab, etanercept and infliximab are also used, but the results do not take account of PAS discounts that are available for other comparator treatments. The ERG will provide a set of results that reflect the comparator discounts in a confidential appendix to this report.

Based on the results presented by the company, deucravacitinib generates QALY gains and cost savings against apremilast, dimethyl fumarate, and etanercept (i.e. dominates these comparator sequences). Compared to the other biologic comparators deucravacitinib generates less QALYs at lower cost (i.e. lies in the SW quadrant of the incremental cost-effectiveness plane). In all these comparisons, the cost saving per QALY forgone exceeds £30,000. Consequently, at a cost-effectiveness threshold value of £20,000 or £30,000 per QALY gained deucravacitinib delivers positive incremental net health benefit (iNHB) against all comparators in the model (see Table B.3.22 of the company's revised results document).

With treatment discontinuation set equal across all treatment options in the company base case, the key driver of incremental QALYs is the comparative response rates for the different first line treatments (derived from the NMA). These determine the proportion of the cohort that move to maintenance following induction therapy with each first line treatment option. First line treatments with higher response rates result in the cohort moving to subsequent treatment lines, and ultimately BSC, less quickly than those with lower response rates. As a result, more time is spent in treatment maintenance and more QALYs are accrued.

The main drivers of the incremental cost are differences in first line treatment acquisition costs, followed by subsequent line treatment acquisition costs and then BSC costs.

Subsequent line treatment and BSC care costs accrue more for sequences with less efficacious first line treatments, i.e. more efficacious first line treatments generate savings in subsequent treatment and BSC care costs compared to less efficacious treatments. This is due to the competing risk of death (with more efficacious first line treatment, fewer patients reach subsequent treatment lines or BSC and/or spend less time on them) and discounting (with more efficacious first line treatments, subsequent treatment and BSC care costs are incurred further into the future).

5.2 Company's sensitivity analyses

Probabilistic sensitivity analysis

The company's base case probabilistic results are presented in Section 3.11.1 of the revised results document. The company note that the model allowed for a maximum of 13 sequences to be compared at one time, and so performed the analysis in two batches; one excluding the bimekizumab and infliximab sequences, the other including only the deucravacitinib, bimekizumab and infliximab sequences. Mean ICER estimates are broadly consistent with the deterministic results, with deucravacitinib dominating apremilast, dimethyl fumarate and etanercept, and in the SW quadrant compared to all other comparators, with cost savings per QALY lost all exceeding £30,000 (See Tables B.3.22 and B.3.23 of the company revised results document for comparison of deterministic and probabilistic ICERs). Scatter plots and CEACs are presented in Figures B.3.2 to B.3.5 of the company's revised results document.

The ERG acknowledges the computational burden of running the PSA with 15 comparators and accepts the requirement to split the analysis, but also notes the relatively low number of random draws (n=1000) used to run the PSA. No justification was given for this, and no reassurance provided that results are stable at 1000 iterations. This may become more important once discounts are placed on comparator treatments.

Deterministic sensitivity analysis

The company note that due to the number of comparators, deterministic one-way sensitivity analysis was presented for deucravacitinib versus only three of the comparators: apremilast, adalimumab, and brodalumab. The results are presented in tornado diagrams in section B.3.11.2 of the revised results document. Across these three analyses, the starting age of the cohort, discontinuation rate, PASI threshold response rates for deucravacitinib and/or

comparator, and the utility values applied to various PASI response states tended to appear in the top ten most influential parameters on the ICER for deucravacitinib.

The ERG are satisfied with the number and range of comparators chosen for one-way sensitivity analysis, including apremilast as an oral therapy, adalimumab as one of the less efficacious biologic treatments, and brodalumab as one of the more efficacious biologics based on output from the NMA. The ICERs, without discounts applied to comparators, appears more sensitive to variation in efficacy (including response parameters and discontinuation rate) and utility related inputs within assigned ranges, than it is to variation in cost inputs.

In addition to one-way sensitivity analysis, the company reported a set of 15 scenario analyses as described in section.3.11.3 of their submission document. The results are provided in their revised results document (submitted in response to clarification). The scenarios explored the impact of different structural assumptions and data sources, including efficacy inputs based on different NMA analyses, different treatment sequencing assumptions, a single treatment line comparison, different treatment discontinuations rates (including a treatment specific discontinuation rates scenario), a waning efficacy scenario, different individual sources of health state utility inputs, increased mortality associated with psoriasis, a shorter time horizon, and a different source for BSC and non-responder costs.

The iNHBs for deucravacitinib remain positive against all comparators at the threshold of £30,000 per QALY gained, but without discounts on comparators the ICERs and iNHBs are not relevant for decision making. However, some notable scenarios that result in greater shifts in the ICERs and iNHBs for deucravacitinib include:

- applying comparative efficacy results based on the NMA that used the 16-week outcome data for deucravacitinib and 12 week outcome for tildrakizumab (Company revised results document, Table B.5.59). iNHBs for deucravacitinib versus each comparator (except tildrakizumab) were reduced compared to the base case in this scenario.
- applying comparative efficacy results based on the NMA that used long term outcome data for all treatments (40-60 weeks). Under this scenario, the iNHB improved for deucravacitinib versus some of the biologics,

[redacted] (Company revised results document, Table B.5.60). The company suggest this [redacted].

- the single treatment line comparison. Under this scenario, the QALY loss versus risankizumab and secukinumab is increased, but so too is the incremental cost saving, resulting in an increased iNHB for deucravacitinib against these comparators.
- applying utility inputs from the pooled POETYK trial data alone. This reduced QALY gains for deucravacitinib versus less efficacious treatments (reducing the iNHB versus these comparators), and reduced QALY losses versus more efficacious treatments (increasing the iNHB).
- applying utility inputs based on TA511. This generally increased QALY gains versus less efficacious treatment (increasing iNHB) and increased QALY losses versus more efficacious treatments (reducing iNHB).

In general, the ERG is of the opinion that the company's scenarios have explored most of the relevant uncertainties in the model. However, the ERG did have some concerns related to the adverse events being applied only in the first cycle of the model, not allowing for an ongoing incidence during the extrapolated time on treatment. In response to a clarification question on this issue, the company provided a further scenario that doubled the incidence of adverse events, which had negligible impact on the ICER. The ERG is satisfied that the way in which adverse events are dealt with in the model does not result in any major bias.

The ERG have further identified some additional uncertainties in the company's model related to the application of baseline utility for those transitioning to best supportive care, the application of 2-weekly averaged treatment acquisition costs, and the cost of BSC and non-response. A number of further scenario analyses related to these issues are explored by the ERG in chapter 6.

5.3 Model validation and face validity check

The company describe how the model's internal validity was reviewed by two modelling experts not involved in the study, and how a number of internal consistency tests were performed. The company further note that two health economists and two UK clinical experts were consulted to validate the model structure, assumptions and key inputs for applicability to clinical practice in England and Wales.

The ERG has performed its own interval consistency checks on the model to confirm that it performs in the expected manner. Discounted and undiscounted costs were equal when the discount rate as set to 0%, QALYs equalled life years when utility was set to 1 in all states (other than Death) and outcomes were common across all treatments when equal costs and response rates were applied to all of the treatments. No major issues were identified.

Further to the internal consistency checks, the ERG checked through the cohort trace, QALY and cost calculations in the model and identified four errors. Two of these were identified prior to the clarification stage and have subsequently been corrected it the company revised results:

- the adjustment of BSC QALYs to reflect baseline utility
- the calculation of QALY losses associated with severe infection adverse events

Following submission of the clarification letter, the ERG identified what it believes are four further errors related to the calculation of treatment acquisition costs:

- The incorrect price per mg being applied to dimethyl fumarate acquisition after the first three weeks of dose escalation, this being based on the cost of 30mg tables rather than 120mg tablets. Since the price per 30mg and per 120mg tablet is equal based on the list prices provided in the BNF, this results in the cumulative acquisition costs being fourfold too high.
- Underestimation of the dosing units being calculated for tildrakizumab. This is related to the misplacement of a parenthesis in the formula used to calculate the weighted average tildrakizumab dose requirements for the induction phase of the model, in cell H71 of the "Drug costs" worksheet (economic model). This has resulted in underestimation of tildrakizumab costs.

- The addition of QALY losses associated with adverse events to QALY streams, instead of their subtraction (Economic Model, “Outcomes”, cells D105:P105)
- Cell referencing errors in the calculation of PASI response based QALYs for sequence 13, whereby the sequence 1 PASI response distribution was being used (Economic Model, “Calcs_Trace_seq13”, cells DU12:EI1510).

The ERG amends these errors in the further exploratory analyses conducted in Chapter 6.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG identified what it believes are calculation errors in two of the drug acquisitions cost calculations feeding in the company's model (4.2.8 above). These relate to 1) the inappropriate pack/tablet strength (30mg as opposed to 120mg) being used for dimethyl fumarate following initial dose escalation to 90mg; and 2) a calculation error in the weighted average number of doses of tildrakizumab required during induction. Therefore, the ERG corrects these two apparent errors in the company's base case prior to running any further analyses. Two further corrections are implemented to 1) subtract rather than add QALY losses associated with adverse events from sequence QALY streams, and 2) correct the cell referencing of the PASI response distribution for treatment sequence 13 (see section 5.3 above). The results of the corrected company base case are provided in Table 22. Net health benefits, and incremental health benefits for deucravacitinib versus each other comparator sequence are expressed for a cost-effectiveness threshold of £30,000 per QALY.

A fully incremental analysis is provided in Table 23 for this corrected base case. It can be observed that dimethyl fumarate, deucravacitinib, adalimumab(bs), certolizumab pegol, ixekizumab and bimekizumab lie on the cost-effectiveness frontier, with deucravacitinib having the highest NHB at a £30,000 per QALY threshold.

Table 22 Company base case with correction of costs of tildrakizumab and dimethyl fumarate and other errors

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICER(deucravacitinib versus comparator)	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£182,471	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£12,777)	0.35
DMF-SEC-RIS	£176,400	[redacted]	[redacted]	[redacted]	[redacted]	£14,206 per QALY gained	0.11
ADA-SEC-RIS	£185,882	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£93,397 per QALY foregone)	0.15
BIM-SEC-RIS	£231,685	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£172,204 per QALY foregone)	1.44
BRO-SEC-RIS	£226,855	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£191,920 per QALY foregone)	1.34
CER-SEC-RIS	£187,333	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£100,167 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICER(deucravacitinib versus comparator)	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£185,111	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£27,664)	0.40
GUS-SEC-RIS	£218,046	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£171,307 per QALY foregone)	1.06
INF-SEC-RIS	£204,866	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£158,870 per QALY foregone)	0.69
IXE-SEC-RIS	£222,521	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£162,486 per QALY foregone)	1.17
RIS-SEC-UST	£200,372	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£212,425 per QALY foregone)	0.60
SEC-UST-RIS	£198,251	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£203,643 per QALY foregone)	0.54
TIL-SEC-RIS	£197,263	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£145,622 per QALY foregone)	0.47
UST-SEC-RIS	£193,022	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£157,027 per QALY foregone)	0.37

Table 23 Company base case with correction of costs of tildrakizumab and dimethyl fumarate and other errors (full incremental analysis)

Sequence	Total Costs (£)	QALYs	Incremental Cost (£)	Incremental QALY's	ICER (£)
DMF-SEC-RIS	[redacted]	[redacted]			
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	£14,206
APR-SEC-RIS	£182,471	[redacted]	[redacted]	[redacted]	Dominated
ETA-SEC-RIS	£185,111	[redacted]	[redacted]	[redacted]	Dominated
ADA-SEC-RIS	£185,882	[redacted]	[redacted]	[redacted]	£93,397
CER-SEC-RIS	£187,333	[redacted]	[redacted]	[redacted]	£148,889
UST-SEC-RIS	£193,022	[redacted]	[redacted]	[redacted]	Ext Dominated
TIL-SEC-RIS	£197,263	[redacted]	[redacted]	[redacted]	Ext Dominated
SEC-UST-RIS	£198,251	[redacted]	[redacted]	[redacted]	Dominated
RIS-SEC-UST	£200,372	[redacted]	[redacted]	[redacted]	Dominated
INF-SEC-RIS	£204,866	[redacted]	[redacted]	[redacted]	Ext Dominated
GUS-SEC-RIS	£218,046	[redacted]	[redacted]	[redacted]	Ext Dominated
IXE-SEC-RIS	£222,521	[redacted]	[redacted]	[redacted]	£189,271
BRO-SEC-RIS	£226,855	[redacted]	[redacted]	[redacted]	Dominated
BIM-SEC-RIS	£231,685	[redacted]	[redacted]	[redacted]	£239,797

Following the corrections in Table 22 above, and given the uncertainties raised in the preceding sections, the ERG has undertaken a number of further scenario analyses using the company's model. These are outlined and justified as follows:

1) Allowing health state utility for those on BSC to align with the PASI response distribution estimated for placebo in the NMA, rather than reverting to baseline. This is discussed in section 4.2.6 above. The ERG believe that the placebo response observed in the trials included in the NMA may in fact reflect some natural improvement that can be expected in cohorts recruited to trials with a PASI severity threshold. Ignoring this in the model may overestimate benefits of active treatments relative to BSC. The ERG acknowledge that this approach appears to have been accepted in previous appraisals, but believe a scenario is justified.
2) Similar to 1) a further scenario is explored, whereby those in BSC with a PASI50 or better are assumed to attract the appropriate PASI response-based health state utility, but those with PASI<50 attract baseline utility. This is to reflects the fact that PASI<50 is a broad category, and the utility data informing it is based on patients treated with active treatments as well as BSC. It may, therefore, overestimate the utility of PASI<50 for those on BSC.
3) a-c) The best supportive care cost is factored down by 10%, 25% and 50%, to explore the impact on the ICER and NHB of this uncertain parameter. The ERG believes this is justified because it is an unadjusted mean cost of all secondary care contact for those on BSC, and no comparative cost category is included in the model for those on active treatments. We cannot determine the proportion of this mean cost that can be attributed to discontinuing active treatment for psoriasis and moving to BSC.
4) a-c) Related to 3, a similar issue applies to the non-responder costs included in the model. It is unclear to what extent the estimated non-responder costs, based on 12 month average secondary care costs prior to discontinuation of biologic treatment, can be attributed to non-response. Therefore, the ERG assesses the impact of reducing these by 10%, 25% and 50%.
5) Adjustments are made to the treatment acquisition costs, to address the issues related to application of averaged 2-week costs for induction and maintenance, in the context of overlap in the dosing schedules between these two phases

(see section 4.2.8) and ongoing chances of discontinuation and death. Two scenarios are explored:

   a. Under this scenario, alternative acquisition cost streams are calculated for each first line treatment, with the full dose/pack cost being applied to everyone still on treatment during the cycle in which the dose is due. The difference between cumulative acquisition costs with this approach and the company's averaging approach is used to adjust the total first line treatment costs in the model output.
   b. Similar to 5 above, a further scenario makes adjustments to the second and third line therapy costs. This is done by applying the estimated overestimate of cumulative secukinumab/ustekinumab and third line risankizumab/ustekinumab costs to the fraction of the cohort commencing second and third line therapy in each cycle of the model, and using the sum of this to adjust the expected total costs in the model output.

6) In the context of limited treatment sequences being explored by the company, a further scenario is assessed whereby guselkumab is used in place of secukinumab in the treatment sequence. This is justified on grounds that guselkumab was approved in a cost-comparison with secukinumab (TA521)
7) Application of age adjustment to utility in the model. The company base case makes no adjustment for aging, and this is recommended in the NICE methods guidance (https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).
8) Related to uncertainty surrounding the optimal sequence of treatments, the ERG conducts a further analysis whereby the ICER for each treatment, followed by BSC, is compared directly with BSC. This is to assess the cost-effectiveness of each individual treatment versus BSC in the company's model, to understand if the second and third line treatments are cost-effective against BSC.

The caveat on all these scenarios, is that they do not include confidential discounts available for many of the comparator treatments included in the model. A full set of results, incorporating all the confidential discounts, will be provided by the ERG in a confidential appendix.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Given the space requirements with each scenario with 15 treatment sequences, a full results Table for each scenario is provided in appendix A. We summarise the overall findings from these additional analyses as follows:

The scenarios generally have only a modest impact on the ICERs for deucravacitinib at the list prices applied to comparators. Deucravacitinib retains the highest NHB across all the scenarios explored. The application of placebo PASI response based utilities to those on BSC has the greatest impact on the cost-effectiveness results (scenario 1). Under this scenario the QALYs are increase for all sequences, and differences are reduced. This increases the ICER for deucravacitinib versus less effective/less costly treatments, with the ICER versus dimethyl fumarate increasing from £14,206 to £26,212. Conversely, the cost savings per QALY forgone (SW quadrant) with deucravacitinib versus more effective and more costly treatments are substantially increased – favouring deucravacitinib. Scenario 2, which applies baseline utility to BSC patients with PASI<50, but otherwise applies utility to BSC patients based on the placebo PASI response, has a similar but less marked impact on the QALY difference between the treatments.

The scenarios that reduce the cost of BSC (Scenario 3a-c) tend to result in increases in the incremental cost of sequences with more versus less efficacious first line treatments, pushing the ICERs upwards. For example, versus dimethyl fumarate, the ICER for deucravacitinib increases to £21,767 with a 50% reduction in BSC costs. A similar directional effect is seen with the scenarios that reduce non-responder costs (scenario4a-c), but upward impact on incremental costs is only very slight.

Those scenarios (5a-b) that adjust acquisition costs to account for potential bias resulting from the application of averaged two-weekly costs per cycle, have variable impacts on cost increments between strategies. The comparison with risankizumab is most affected, as the acquisition costs for this treatment are most affected by overestimation from the application of averaged 2-weekly costs.

Switching in guselkumab for secukinumab in the treatment sequence (scenario 6) had only a modest impact on the cost differences between the sequences, resulting in small increases in the ICERs for sequences with more versus less efficacious first line treatments.

Application of age adjustments for utility (scenario 7) resulted in modest reductions in QALYs across all sequences, but only small impacts on QALY differences between sequences. This tends to slightly increase in the ICERs of more versus less effective/less costly sequences.

Finally, the scenario comparing each single treatment individually with BSC shows that deucravacitinib, apremilast, and dimethyl fumarate have ICERs below £20,000, and adalimumab, bimekizumab, certolizumab pegol and etanercept have ICERs below £30,000 per QALY gained with the company's base case settings. Note, these findings do not account for confidential discounts that are available for many of the comparators.

6.3 ERG's preferred assumptions

As discussed throughout this report, the ERG is broadly satisfied that the company's economic case is in line with the approach and assumptions which have been discussed and accepted in previous related technology appraisals. However, the ERG believes that the company approach to applying 2-weekly average treatment acquisition costs should be ideally corrected for, as this does tend to overstate the costs for some of the biologic treatments with wider dosing intervals. Further, applying pack costs when a new prescription of daily oral therapy is required, also allows for a degree of wastage to be accounted for in the calculation of cumulative costs. In addition, the ERG believe it is preferable for health state utility to be age adjusted for given the guidance and the long time horizon of the model. The impact of these combined changes is illustrated in Table 24. A full incremental analysis of this ERG base case is then provided in Table 25. It can be noted that whilst total costs and QALYs are somewhat reduced in this combined scenario the impact on the differences is quite small. As general rule, QALY gains of more effective versus less effective treatments are slightly reduced. The impact on cost differences is less consistent with some increasing and some decreasing, but changes are generally

modest. The most affected comparison with deucravacitinib is risankizumab, where the cost difference is reduced by about [redacted]. However, the cost saving per QALY forgone remains favourable to deucravacitinib with list prices applied to Risankizumab. Deucravacitinib retains the highest NHB at the £30,000 threshold across all the treatment sequences.

Table 24 ERG alternative base case, incorporating combined changes from Scenario 5b (acquisition cost adjustments) and 7 (age adjustment of utility)

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICER(deucravacitinib versus comparator)	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]			[redacted]		
APR-SEC-RIS	£180,702	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£13,444)	0.34
DMF-SEC-RIS	£174,629	[redacted]	[redacted]	[redacted]	[redacted]	£14,873 per QALY gained	0.10
ADA-SEC-RIS	£184,163	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£97,505 per QALY foregone)	0.15
BIM-SEC-RIS	£228,555	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£174,201 per QALY foregone)	1.41
BRO-SEC-RIS	£224,820	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£198,033 per QALY foregone)	1.34
CER-SEC-RIS	£185,632	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£105,010 per QALY foregone)	0.19
ETA-SEC-RIS	£183,191	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£28,332)	0.39

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICER(deucravacitinib versus comparator)	iNHB (deucravacitinib versus comparator)
GUS-SEC-RIS	£216,053	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£177,135 per QALY foregone)	1.07
INF-SEC-RIS	£202,907	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£163,798 per QALY foregone)	0.69
IXE-SEC-RIS	£220,019	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£165,933 per QALY foregone)	1.16
RIS-SEC-UST	£197,471	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£206,299 per QALY foregone)	0.57
SEC-UST-RIS	£195,589	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£200,211 per QALY foregone)	0.51
TIL-SEC-RIS	£196,243	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£158,375 per QALY foregone)	0.51
UST-SEC-RIS	£190,321	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£151,902 per QALY foregone)	0.34

Table 25 ERG alternative base case, incorporating combined changes from Scenario 5b (acquisition cost adjustments) and 7 (age adjustment of utility) (full incremental analysis)

Sequence	Total Costs (£)	QALYs	Incremental Cost (£)	Incremental QALY's	ICER (£)
DMF-SEC-RIS	[redacted]	[redacted]			
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	£14,873
APR-SEC-RIS	£180,702	[redacted]	[redacted]	[redacted]	Dominated
ETA-SEC-RIS	£183,191	[redacted]	[redacted]	[redacted]	Dominated
ADA-SEC-RIS	£184,163	[redacted]	[redacted]	[redacted]	£97,505
CER-SEC-RIS	£185,632	[redacted]	[redacted]	[redacted]	£160,662
UST-SEC-RIS	£190,321	[redacted]	[redacted]	[redacted]	Ext Dominated
SEC-UST-RIS	£195,589	[redacted]	[redacted]	[redacted]	Ext Dominated
TIL-SEC-RIS	£196,243	[redacted]	[redacted]	[redacted]	Ext Dominated
RIS-SEC-UST	£197,471	[redacted]	[redacted]	[redacted]	Dominated
INF-SEC-RIS	£202,907	[redacted]	[redacted]	[redacted]	Ext Dominated
GUS-SEC-RIS	£216,053	[redacted]	[redacted]	[redacted]	Ext Dominated
IXE-SEC-RIS	£220,019	[redacted]	[redacted]	[redacted]	£192,131
BRO-SEC-RIS	£224,820	[redacted]	[redacted]	[redacted]	Dominated
BIM-SEC-RIS	£228,555	[redacted]	[redacted]	[redacted]	£231,622

6.4 Conclusions of the cost effectiveness section

In general, the ERG finds the company's economic model to be aligned with the NICE reference case, and consistent with the structure, assumptions and inputs that have been accepted in previous relevant NICE appraisals.

The case for deucravacitinib is that it provides QALY gains at acceptable incremental cost compared to existing oral therapies and etanercept, and that it delivers cost savings in the SW quadrant that outweigh QALY losses against more efficacious biologics.

The company's results show deucravacitinib to sit on the cost-effectiveness frontier, and to have the highest net benefit at thresholds of £20,000 - £30,000 per QALY. These results are stable to further scenario analyses conducted by the company and the ERG. The caveat being that these results do not reflect the confidential discounts available on many of the comparator drugs.

The further uncertainties in the company's case, which could impact on cost-effectiveness findings, include the assumption that patients revert to baseline utility when they discontinue third line treatment and move to BSC. Further uncertainty around the cost of secondary care for those on BSC, relative to those remaining on active treatments, adds further uncertainty.

Finally, the ERG has some concerns that the approach of applying 2-weekly averaged treatment acquisition costs leads to inaccuracies and potential biases in the calculation of cumulative treatment costs for different sequences. Full correction for this is challenging in the context of the Markov sequence model, but the ERG has applied approximating adjustments in its alternative base case, which suggest limited impacts on cost-effectiveness findings at the prices applied. Nevertheless, cost-effectiveness of the different treatment sequences at given thresholds may be more sensitive to these changes, and others, when confidential discounts are applied to the comparator drugs. The ERG will provide a confidential appendix that reflect available discounted prices when it receives them.

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Appendix A – Results of further scenario analysis undertaken by the ERG

A table of model output is provided for each of the scenarios considered (see section 6.1 above) in the following pages.

Table 26 Scenario 1 - BSC utility based on placebo PASI response

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£182,471	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£23,113)	0.24
DMF-SEC-RIS	£176,400	[redacted]	[redacted]	[redacted]	[redacted]	£26,212 per QALY gained	0.01
ADA-SEC-RIS	£185,882	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£129,582 per QALY foregone)	0.17
BIM-SEC-RIS	£231,685	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£256,000 per QALY foregone)	1.54
BRO-SEC-RIS	£226,855	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£281,449 per QALY foregone)	1.42
CER-SEC-RIS	£187,333	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£147,910 per QALY foregone)	0.21

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£185,111	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£51,546)	0.30
GUS-SEC-RIS	£218,046	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£260,652 per QALY foregone)	1.14
INF-SEC-RIS	£204,866	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£236,514 per QALY foregone)	0.74
IXE-SEC-RIS	£222,521	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£243,044 per QALY foregone)	1.26
RIS-SEC-UST	£200,372	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£292,708 per QALY foregone)	0.63
SEC-UST-RIS	£198,251	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£287,803 per QALY foregone)	0.56
TIL-SEC-RIS	£197,263	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£234,477 per QALY foregone)	0.52
UST-SEC-RIS	£193,022	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£228,102 per QALY foregone)	0.40

Table 27 Scenario 2 - BSC utility at baseline for those with PASI response <50, otherwise utility based on PASI response

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£182,471	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£18,264)	0.28
DMF-SEC-RIS	£176,400	[redacted]	[redacted]	[redacted]	[redacted]	£20,520 per QALY gained	0.05
ADA-SEC-RIS	£185,882	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£114,962 per QALY foregone)	0.16
BIM-SEC-RIS	£231,685	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£220,742 per QALY foregone)	1.51
BRO-SEC-RIS	£226,855	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£244,076 per QALY foregone)	1.39
CER-SEC-RIS	£187,333	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£127,900 per QALY foregone)	0.20

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£185,111	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£40,165)	0.34
GUS-SEC-RIS	£218,046	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£222,553 per QALY foregone)	1.12
INF-SEC-RIS	£204,866	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£203,818 per QALY foregone)	0.73
IXE-SEC-RIS	£222,521	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£209,028 per QALY foregone)	1.23
RIS-SEC-UST	£200,372	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£260,404 per QALY foregone)	0.62
SEC-UST-RIS	£198,251	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£253,426 per QALY foregone)	0.56
TIL-SEC-RIS	£197,263	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£195,351 per QALY foregone)	0.51
UST-SEC-RIS	£193,022	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£198,597 per QALY foregone)	0.39

Table 28 Scenario 3.a - 10% reduction in BSC costs

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£179,077	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£11,301)	0.34
DMF-SEC-RIS	£173,057	[redacted]	[redacted]	[redacted]	[redacted]	£15,719 per QALY gained	0.10
ADA-SEC-RIS	£182,915	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£94,319 per QALY foregone)	0.15
BIM-SEC-RIS	£228,983	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£173,284 per QALY foregone)	1.45
BRO-SEC-RIS	£224,084	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£192,970 per QALY foregone)	1.35
CER-SEC-RIS	£184,387	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£101,233 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£181,761	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£26,134)	0.39
GUS-SEC-RIS	£215,271	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£172,439 per QALY foregone)	1.07
INF-SEC-RIS	£202,009	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£159,954 per QALY foregone)	0.70
IXE-SEC-RIS	£219,781	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£163,580 per QALY foregone)	1.18
RIS-SEC-UST	£197,431	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£213,330 per QALY foregone)	0.61
SEC-UST-RIS	£195,309	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£204,609 per QALY foregone)	0.54
TIL-SEC-RIS	£194,386	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£146,873 per QALY foregone)	0.48
UST-SEC-RIS	£190,080	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£158,056 per QALY foregone)	0.37

Table 29 Scenario 3.b - 25% reduction in BSC costs

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£173,986	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£9,087)	0.32
DMF-SEC-RIS	£168,043	[redacted]	[redacted]	[redacted]	[redacted]	£17,987 per QALY gained	0.08
ADA-SEC-RIS	£178,466	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£95,702 per QALY foregone)	0.15
BIM-SEC-RIS	£224,929	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£174,905 per QALY foregone)	1.47
BRO-SEC-RIS	£219,927	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£194,545 per QALY foregone)	1.36
CER-SEC-RIS	£179,968	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£102,831 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£176,734	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£23,840)	0.38
GUS-SEC-RIS	£211,108	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£174,136 per QALY foregone)	1.09
INF-SEC-RIS	£197,724	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£161,579 per QALY foregone)	0.71
IXE-SEC-RIS	£215,670	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£165,222 per QALY foregone)	1.20
RIS-SEC-UST	£193,019	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£214,688 per QALY foregone)	0.61
SEC-UST-RIS	£190,897	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£206,057 per QALY foregone)	0.55
TIL-SEC-RIS	£190,070	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£148,750 per QALY foregone)	0.49
UST-SEC-RIS	£185,668	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£159,599 per QALY foregone)	0.38

Table 30 Scenario 3.c - 50% reduction in BSC costs

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£165,501	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£5,396)	0.29
DMF-SEC-RIS	£159,686	[redacted]	[redacted]	[redacted]	[redacted]	£21,767 per QALY gained	0.06
ADA-SEC-RIS	£171,050	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£98,007 per QALY foregone)	0.16
BIM-SEC-RIS	£218,173	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£177,607 per QALY foregone)	1.50
BRO-SEC-RIS	£213,000	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£197,170 per QALY foregone)	1.38
CER-SEC-RIS	£172,604	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£105,495 per QALY foregone)	0.20

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£168,358	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£20,016)	0.35
GUS-SEC-RIS	£204,170	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£176,965 per QALY foregone)	1.11
INF-SEC-RIS	£190,582	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£164,289 per QALY foregone)	0.72
IXE-SEC-RIS	£208,820	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£167,957 per QALY foregone)	1.22
RIS-SEC-UST	£185,666	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£216,952 per QALY foregone)	0.62
SEC-UST-RIS	£183,544	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£208,470 per QALY foregone)	0.55
TIL-SEC-RIS	£182,878	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£151,877 per QALY foregone)	0.50
UST-SEC-RIS	£178,315	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£162,171 per QALY foregone)	0.38

Table 31 Scenario 4.a - 10% reduction in non-responder costs

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£182,304	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£12,730)	0.35
DMF-SEC-RIS	£176,235	[redacted]	[redacted]	[redacted]	[redacted]	£14,255 per QALY gained	0.11
ADA-SEC-RIS	£185,729	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£93,427 per QALY foregone)	0.15
BIM-SEC-RIS	£231,541	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£172,239 per QALY foregone)	1.44
BRO-SEC-RIS	£226,708	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£191,953 per QALY foregone)	1.34
CER-SEC-RIS	£187,181	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£100,202 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£184,946	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£27,615)	0.40
GUS-SEC-RIS	£217,900	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£171,344 per QALY foregone)	1.06
INF-SEC-RIS	£204,717	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£158,905 per QALY foregone)	0.69
IXE-SEC-RIS	£222,375	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£162,521 per QALY foregone)	1.17
RIS-SEC-UST	£200,227	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£212,520 per QALY foregone)	0.60
SEC-UST-RIS	£198,077	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£203,446 per QALY foregone)	0.54
TIL-SEC-RIS	£197,113	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£145,662 per QALY foregone)	0.47
UST-SEC-RIS	£192,870	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£157,061 per QALY foregone)	0.37

Table 32 Scenario 4.b - 25% reduction in non-responder costs

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£182,054	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£12,659)	0.35
DMF-SEC-RIS	£175,988	[redacted]	[redacted]	[redacted]	[redacted]	£14,328 per QALY gained	0.11
ADA-SEC-RIS	£185,500	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£93,473 per QALY foregone)	0.15
BIM-SEC-RIS	£231,324	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£172,291 per QALY foregone)	1.44
BRO-SEC-RIS	£226,489	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£192,004 per QALY foregone)	1.34
CER-SEC-RIS	£186,953	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£100,254 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£184,699	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£27,542)	0.40
GUS-SEC-RIS	£217,680	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£171,399 per QALY foregone)	1.07
INF-SEC-RIS	£204,493	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£158,958 per QALY foregone)	0.69
IXE-SEC-RIS	£222,157	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£162,574 per QALY foregone)	1.17
RIS-SEC-UST	£200,009	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£212,662 per QALY foregone)	0.60
SEC-UST-RIS	£197,818	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£203,149 per QALY foregone)	0.54
TIL-SEC-RIS	£196,888	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£145,722 per QALY foregone)	0.48
UST-SEC-RIS	£192,642	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£157,111 per QALY foregone)	0.37

Table 33 Scenario 4.c - 50% reduction in NR costs

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£181,638	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£12,541)	0.35
DMF-SEC-RIS	£175,575	[redacted]	[redacted]	[redacted]	[redacted]	£14,449 per QALY gained	0.11
ADA-SEC-RIS	£185,118	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£93,548 per QALY foregone)	0.15
BIM-SEC-RIS	£230,964	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£172,378 per QALY foregone)	1.44
BRO-SEC-RIS	£226,123	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£192,089 per QALY foregone)	1.34
CER-SEC-RIS	£186,573	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£100,340 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£184,286	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£27,419)	0.40
GUS-SEC-RIS	£217,313	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£171,490 per QALY foregone)	1.07
INF-SEC-RIS	£204,120	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£159,046 per QALY foregone)	0.69
IXE-SEC-RIS	£221,794	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£162,662 per QALY foregone)	1.18
RIS-SEC-UST	£199,645	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£212,900 per QALY foregone)	0.60
SEC-UST-RIS	£197,384	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£202,654 per QALY foregone)	0.53
TIL-SEC-RIS	£196,513	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£145,823 per QALY foregone)	0.48
UST-SEC-RIS	£192,262	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£157,194 per QALY foregone)	0.37

Table 34 Scenario 5a Adjustment to treatment acquisition costs at 1st line

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit (£)	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£182,700	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£13,389)	0.36
DMF-SEC-RIS	£176,607	[redacted]	[redacted]	[redacted]	[redacted]	£13,584 per QALY gained	0.11
ADA-SEC-RIS	£185,996	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£93,892 per QALY foregone)	0.15
BIM-SEC-RIS	£230,285	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£167,339 per QALY foregone)	1.39
BRO-SEC-RIS	£226,577	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£190,476 per QALY foregone)	1.32
CER-SEC-RIS	£187,457	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£100,725 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit (£)	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£185,172	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£27,574)	0.40
GUS-SEC-RIS	£217,811	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£169,917 per QALY foregone)	1.05
INF-SEC-RIS	£204,697	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£157,323 per QALY foregone)	0.68
IXE-SEC-RIS	£221,764	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£159,339 per QALY foregone)	1.15
RIS-SEC-UST	£198,673	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£194,466 per QALY foregone)	0.54
SEC-UST-RIS	£197,484	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£194,541 per QALY foregone)	0.51
TIL-SEC-RIS	£198,042	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£151,305 per QALY foregone)	0.50
UST-SEC-RIS	£192,144	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£146,047 per QALY foregone)	0.34

Table 35 Scenario 5b Adjustments to treatment acquisition costs at 1st, 2nd and 3rd lines

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit (£)	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£180,702	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£12,818)	0.35
DMF-SEC-RIS	£174,629	[redacted]	[redacted]	[redacted]	[redacted]	£14,168 per QALY gained	0.11
ADA-SEC-RIS	£184,163	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£94,255 per QALY foregone)	0.15
BIM-SEC-RIS	£228,555	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£167,759 per QALY foregone)	1.40
BRO-SEC-RIS	£224,820	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£190,885 per QALY foregone)	1.33
CER-SEC-RIS	£185,632	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£101,143 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit (£)	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£183,191	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£26,985)	0.40
GUS-SEC-RIS	£216,053	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£170,358 per QALY foregone)	1.06
INF-SEC-RIS	£202,907	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£157,746 per QALY foregone)	0.68
IXE-SEC-RIS	£220,019	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£159,765 per QALY foregone)	1.15
RIS-SEC-UST	£197,471	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£201,090 per QALY foregone)	0.56
SEC-UST-RIS	£195,589	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£194,136 per QALY foregone)	0.51
TIL-SEC-RIS	£196,243	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£151,790 per QALY foregone)	0.50
UST-SEC-RIS	£190,321	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£146,451 per QALY foregone)	0.34

Table 36 Scenario 6 - Replace Secukinumab with Guselkumab

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-GUS-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-GUS-RIS	£175,922	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£10,964)	0.33
DMF-GUS-RIS	£169,916	[redacted]	[redacted]	[redacted]	[redacted]	£16,182 per QALY gained	0.09
ADA-GUS-RIS	£179,873	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£94,841 per QALY foregone)	0.15
BIM-GUS-RIS	£226,010	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£174,125 per QALY foregone)	1.46
BRO-GUS-RIS	£221,094	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£193,851 per QALY foregone)	1.35
CER-GUS-RIS	£181,351	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£101,852 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-GUS-RIS	£178,618	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£25,857)	0.39
GUS-UST-RIS	£190,785	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£190,856 per QALY foregone)	0.49
INF-GUS-RIS	£198,997	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£160,765 per QALY foregone)	0.70
IXE-GUS-RIS	£216,799	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£164,402 per QALY foregone)	1.19
RIS-GUS-UST	£194,769	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£217,249 per QALY foregone)	0.62
SEC-GUS-RIS	£219,860	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£216,778 per QALY foregone)	1.34
TIL-GUS-RIS	£191,366	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£147,743 per QALY foregone)	0.48
UST-GUS-RIS	£187,045	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£158,826 per QALY foregone)	0.37

Table 37 Scenario 7 - Age adjusted utilities

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
DEU-SEC-RIS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
APR-SEC-RIS	£182,471	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£13,401)	0.34
DMF-SEC-RIS	£176,400	[redacted]	[redacted]	[redacted]	[redacted]	£14,913 per QALY gained	0.10
ADA-SEC-RIS	£185,882	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£96,618 per QALY foregone)	0.15
BIM-SEC-RIS	£231,685	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£178,816 per QALY foregone)	1.45
BRO-SEC-RIS	£226,855	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£199,107 per QALY foregone)	1.35
CER-SEC-RIS	£187,333	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£103,997 per QALY foregone)	0.19

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (deucravacitinib versus comparator)
ETA-SEC-RIS	£185,111	[redacted]	[redacted]	[redacted]	[redacted]	Dominant (-£29,044)	0.39
GUS-SEC-RIS	£218,046	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£178,123 per QALY foregone)	1.07
INF-SEC-RIS	£204,866	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£164,964 per QALY foregone)	0.70
IXE-SEC-RIS	£222,521	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£168,759 per QALY foregone)	1.18
RIS-SEC-UST	£200,372	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£217,928 per QALY foregone)	0.60
SEC-UST-RIS	£198,251	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£210,015 per QALY foregone)	0.54
TIL-SEC-RIS	£197,263	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£151,940 per QALY foregone)	0.48
UST-SEC-RIS	£193,022	[redacted]	[redacted]	[redacted]	[redacted]	SW quadrant (£162,872 per QALY foregone)	0.37

Table 38 Scenario 8 - ICER's for single treatments relative to BSC

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (comparator v BSC)
BSC-BSC-BSC	£68,121	[redacted]			[redacted]		
DEU-BSC-BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,039 per QALY gained	0.37
APR-BSC-BSC	£76,082	[redacted]	[redacted]	[redacted]	[redacted]	£19,677 per QALY gained	0.14
DMF-BSC-BSC	£71,122	[redacted]	[redacted]	[redacted]	[redacted]	£6,467 per QALY gained	0.36
ADA-BSC-BSC	£88,886	[redacted]	[redacted]	[redacted]	[redacted]	£23,438 per QALY gained	0.19
BIM-BSC-BSC	£140,414	[redacted]	[redacted]	[redacted]	[redacted]	£59,164 per QALY gained	-1.19
BRO-BSC-BSC	£134,102	[redacted]	[redacted]	[redacted]	[redacted]	£57,924 per QALY gained	-1.06
CER-BSC-BSC	£90,782	[redacted]	[redacted]	[redacted]	[redacted]	£25,077 per QALY gained	0.15

Sequence	Total Costs (£)	QALYS	Incremental Costs (£)	Incremental QALY's	Net Health Benefit	Deterministic ICUR	iNHB (comparator v BSC)
ETA-BSC-BSC	£79,798	[redacted]	[redacted]	[redacted]	[redacted]	£25,467 per QALY gained	0.07
GUS-BSC-BSC	£125,196	[redacted]	[redacted]	[redacted]	[redacted]	£51,155 per QALY gained	-0.79
INF-BSC-BSC	£110,151	[redacted]	[redacted]	[redacted]	[redacted]	£41,243 per QALY gained	-0.38
IXE-BSC-BSC	£130,436	[redacted]	[redacted]	[redacted]	[redacted]	£53,298 per QALY gained	-0.91
RIS-BSC-BSC	£129,294	[redacted]	[redacted]	[redacted]	[redacted]	£52,616 per QALY gained	-0.88
SEC-BSC-BSC	£132,310	[redacted]	[redacted]	[redacted]	[redacted]	£58,533 per QALY gained	-1.04
TIL-BSC-BSC	£102,183	[redacted]	[redacted]	[redacted]	[redacted]	£35,003 per QALY gained	-0.16
UST-BSC-BSC	£96,569	[redacted]	[redacted]	[redacted]	[redacted]	£31,169 per QALY gained	-0.04

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check and confidential information check

Deucravacitinib for treating moderate to severe plaque psoriasis [ID3859]

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 20 July 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Deucravacitinib PAS value

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect PAS value for deucravacitinib is given on p. 67.	PAS value should read [redacted] instead of [redacted].	The PAS value should be correct to enable correct interpretation of analysis outcomes.	Change accepted. This was just a typo [redacted] is the price that has been applied in all company and ERG analyses.

Issue 2 Incorrect data reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG incorrectly reports on p. 26 that response rate was not included in the POETYK trials.	The text should read "The company did not include relapse rate and mortality as an outcome in the trials."	The trial outcomes should be presented correctly to ensure that there are no misconceptions.	Text amended as described
The ERG incorrectly reports on p. 53 that in table B.1.1.1 of the CS, the population is defined as "adult patients with moderate-to-severe plaque	The definition of the population should be provided as follows on p. 53: "Adults with moderate-to-severe plaque psoriasis for whom systemic non-biologic treatment or phototherapy is not an option"	The definition of the population in the decision problem needs to reflect the definition in the company submission.	Change accepted

psoriasis for whom systemic non-biologic treatment is not an option" In the Company Submission, Document B, Table B.1.1.1), also patients for whom phototherapy is not an option, are included.			
There is an incorrect formula (double minus-sign) in the economic model on worksheet *Scenarios*, cell E28.	The formula: =+output_costs4-IF(ERG_drug_cost_adj="yes",J28,0)--IF(ERG_drug_cost_adj_2nd_3rd="Yes",(K28+L28),0) Should be replaced by: =+output_costs4-IF(ERG_drug_cost_adj="yes",J28,0)-IF(ERG_drug_cost_adj_2nd_3rd="Yes",(K28+L28),0)	This error leads to erroneous outcomes for the brodalumab sequence in scenario 5b	Accepted, we have corrected this and updated the results accordingly.
Related to the issue above, the ERG incorrectly reports scenario 5b results on p.115 (Table 35).	For the brodalumab sequence the following outcomes should be replaced: Total costs: £228,334 should read £224,820 Incremental costs: [redacted] should read [redacted] Net Health Benefit: [redacted] should read [redacted]	The outcomes presented from scenario 5b need to be reflective of the model outcomes to ensure that there are no misconceptions.	Accepted, results of scenario 5b have been updated. Note, this also carries through into the ERG base case

	Deterministic ICUR: SW quadrant (£205,077 per QALY foregone) should read: SW quadrant (£190,887 per QALY foregone) iNHB (deucravacitinib versus comparator: 1.45 should read: 1.33		Tables 24 and 25, and the summary ICER Table 2 in the Exec summary. All have been updated. The results tables have also been updated to reflect two further bugs the ERG identified during the FAC response to the company (see further FAC corrections below)
The ERG incorrectly reports scenario 8 results on p.121 (Table 38).	For the bimekizumab sequence the following should be changed: • Incremental costs: from [redacted] to [redacted] • Incremental QALYs from [redacted] to [redacted] ICUR: from £29,827 per QALY gained to £59,257 per QALY gained. In addition to the above, for the infliximab sequence the following should be changed:	The outcomes presented from scenario 8 need to be reflective of the model outcomes to ensure that there are no misconceptions.	The ERG agrees with the first two corrections but not the correction relating to Ustekinumab. The results have been updated accordingly.

	• Incremental costs: from [redacted] to [redacted] • Incremental QALYs: from [redacted] to [redacted] ICUR: from £45,889 per QALY gained to £41,242 per QALY gained. In addition to the above, for the ustekinumab sequence the following should be changed: • QALYs: from [redacted] to [redacted] • Incremental QALYs: from [redacted] to [redacted] • ICUR: from £31,232 per QALY gained to £66,123 per QALY gained.		Note, the results tables have also been updated to reflect the correction two further bugs the ERG identified during the FAC response to the company (see below). ICERs therefore vary slightly from those suggested by the company.

Further FAC corrections implemented by ERG, relating to two further calculation errors identified.

Description of problem	**Description of ERG amendment**	**Justification for amendment**
Page xx stated: These analyses also correct for two treatment cost calculation errors that were identified in the company's model (see section 5.3)	The text should read "These analyses also correct for two treatment cost calculation errors, a sign error on QALY losses associated with adverse events, and a cell referencing error relating to the PASI response distribution for sequence 13, that were identified in the company's model (see section 5.3)"	AS indicated above, when addressing the company's FAC issues, the ERG uncovered these two additional bugs and have corrected them in their results tables.
Page 79 stated: Following submission of the clarification letter,	Following submission of the clarification letter, the ERG identified what it believes are **four** further errors	These errors need to be flagged to reflect the

the ERG identified what it believes are **two** further errors related to the calculation of treatment acquisition costs:	related to the calculation of treatment acquisition costs: Two further bullet points added to the report • The addition of QALY losses associated with adverse events to QALY streams, instead of their subtraction (Economic Model, “Outcomes”, cells D105:P105) • Cell referencing errors in the calculation of PASI response based QALYs for sequence 13, whereby the sequence 1 PASI response distribution was being used (Economic Model, “Calcs_Trace_seq13”, cells DU12:EI1510).	further updates to the results tables.
Page 81 states: “The ERG identified what it believes are calculation errors in two of the drug acquisitions cost calculations feeding in the company’s model (4.2.8 above). These	Sentence added to reflect the further correction of the two further errors in the model calculations, identified by the ERG during the FAC response: “Two further corrections are implemented to 1) subtract rather than add QALY losses associated with adverse events from sequence QALY streams, and 2) correct the cell referencing of the PASI	The text needs to reflect all the changes that have been made in the revised results tables for the report. Note all results Tables in the ERG report have now

relate to 1) the inappropriate pack/tablet strength (30mg as opposed to 120mg) being used for dimethyl fumarate following initial dose escalation to 90mg; and 2) a calculation error in the weighted average number of doses of tildrakizumab required during induction. Therefore, the ERG corrects these two apparent errors in the company's base case prior to running any further analyses."	response distribution for treatment sequence 13 (see section 5.3 above)."	been updated to address the company's identified errors and the two additional errors identified by the ERG. These further errors have only a very minor impact on reported ICERS, and do not change the findings of the report.
Page 87, The ERG report states: This increases the ICER for deucravacitinib versus less effective/less costly treatments, with the ICER versus dimethyl fumarate increasing from £**14,207** to £26,212	Changed sentence to: "This increases the ICER for deucravacitinib versus less effective/less costly treatments, with the ICER versus dimethyl fumarate increasing from £**14,206** to £26,212"	The change reflects the updates to the results tables for correction of the additional errors identified.

Page 87, The ERG report states: “For example, versus dimethyl fumarate, the ICER for deucravacitinib increases to £**21,768** with a 50% reduction in BSC costs”	Changed sentence to: “For example, versus dimethyl fumarate, the ICER for deucravacitinib increases to **£21,767** with a 50% reduction in BSC costs”	The change reflects the updates to the results tables for correction of the additional errors identified
Page 89. The ERG report states: “The most affected comparison with deucravacitinib is risankizumab, where the cost difference is reduced by about [redacted]”	Change sentence to: “The most affected comparison with deucravacitinib is risankizumab, where the cost difference is reduced by about [redacted]”	The ERG noted incorrect reporting of the difference when checking the report.

Issue 3 Typographic errors

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
The incorrect submitting company is named on p. ii: “Copyright is retained by Novartis”. This	Text reads “Novartis” should read “Bristol Myers Squibb”.	This amendment is required to ensure that copyright is assigned to	Text amended as described

should read Bristol Myers Squibb.		the correct entity.	
For the health effects, there is a small error in one of the five PASI response levels described on p. xiv and p. 52.	Text reads “50>74” should read “50-74”.	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text ammended as described
Misspelled word on p. xiv (2nd bullet point on costs).	Text reads “BCS” should read “BSC”.	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text ammended as described
Wording error on p. xvi.	Text reads: “Given this, the ERG is broadly satisfied that the model is appropriate for decision making but identify **a** three areas of uncertainty that the committee may wish to consider when assessing the cost-effectiveness results.” Should read: “Given this, the ERG is broadly satisfied that the model is appropriate for decision making but identify three areas of uncertainty that the committee may wish to consider when assessing the cost-effectiveness results.”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text ammended as described

Spelling error in table header and incomplete sentence in the table on p. xix.	Table title: “Issue 3 Best supportive care and non-responded costs” Should read: “Issue 3 Best supportive care and non-responde**r** costs” Incomplete sentence: “A similar issue also applies“ Should read: “A similar issue also applies for non-responder costs.”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text ammended as described
Incorrect spelling of the trial names on p. 14: PSO spelled with a lower case and missing for the POETYK-PSO-LTE study. Also on p. 41, 42 and 46 where POETYK-PSO is not hyphenated	Text reads: “The quality assessment of POETYK-PSO-1, POETYK-**pSO**-2 and POETYK-LTE” Should read: “The quality assessment of POETYK-PSO-1, POETYK-**PSO**-2 and POETYK-**PSO**-LTE.” Text reads “POETYK PSO” should read “POETYK-PSO”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Misspelled word on p. 26	Text reads: “The outcome measures listed in the NICE **finals cope** for this appraisal were”	Typographic error. This amendment will have no	Text amended as described

	Should read: "The outcome measures listed in the NICE **final scope** for this appraisal were"	impact on the report, or its conclusions.	
On two occasions, a section from the original company submission is referenced as "section Error! Reference source not found." (p. 16 and p. 39).	The error on p.16 should refer to CS "Document B, Section B.3.3.2". The error on p. 39 should refer to CS "Appendix F, Section F.1.2.5".	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
The report incorrectly refers to PASI-related outcomes on p. 30. The sentence should refer to sPGA outcomes instead	"PASI-related" should be replaced by "sPGA-related" on p. 30.	This statement is required to provide correct data on study outcomes.	Text amended as described
For the outcomes relating to difficult-to-treat areas it is incorrectly reported that for ssPGA participants with ss-PGA≥3 at baseline	The statement that participants with ss-PGA≥3 at baseline were included should be removed from p. 32. Instead, the following statement needs to be added for fingernail psoriasis: "patients with moderate-to-severe fingernail psoriasis at baseline (PGA-F ≥3) were included."	This statement is required to provide correct data on the baseline	Text amended as described

were included. This statement needs to be removed on p. 32. Instead, the statement on fingernail psoriasis needs to be corrected as to patients with moderate-to-severe fingernail psoriasis at baseline (PGA-F ≥3) were included.		characteristics of included patients.	
Misspelled word on p.48	Text reads: "This provides a useful **refence** for the current appraisal." Should read: "This provides a useful **reference** for the current appraisal."	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Incomplete sentence on the 10th line of table 20.	Add the word "population"	Typographic error. This amendment will have no impact on the report, or its conclusions.	Corrected to "Source of preference data for valuation of changes in health-related

			quality of life”
Misspelled word on p.52	Text reads: “Health effects, measured in **QALY’s**.” Should read: “Health effects, measured in **QALYs**.”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Misspelled word on p.55	Text reads: “*eligible population for the **compactor** therapies*” Should read: “*eligible population for the **comparator** therapies*.”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Missing word in sentence on p. 58.	Text reads: “They also that since deucravacitinib has a constant dosage protocol (doesn’t require titration), adherence in routine practice may be less impacted relative to other oral treatments.” Should read: “They also **suggested** that since deucravacitinib has a constant dosage protocol (doesn’t require titration), adherence in routine practice may be less impacted relative to other oral treatments.”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described

Missing word in sentence on p. 59.	Text reads: “They, therefore, applied a common annual discontinuation rate to all treatments informed observational registry data.” Should read: “They, therefore, applied a common annual discontinuation rate to all treatments informed **by** observational registry data.”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Wording error on p. 61.	Text reads: “Under this scenario the total costs and QALYs were reduced for all treatments, but there was little impact on the incremental costs and QALYs and the overall patter of results.” Should read: “Under this scenario the total costs and QALYs were reduced for all treatments, but there was little impact on the incremental costs and QALYs and the overall patter**n** of results.”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Wording error on p. 61.	Text reads: “*but found **to** satisfactory explanation*.” Should read: “*but found **no** satisfactory explanation*.”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described

Wording error and missing word in sentence on p. 67.	Text reads: “Therefore, for some treatments, a patient may not be **a** due their first maintenance phase dose until several weeks into the maintenance phase.“ Should read: “Therefore, for some treatments, a patient may not be due **for** their first maintenance phase dose until several weeks into the maintenance phase.“	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Wording error on p. 68.	Text reads “Remining” should read “remaining”.	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Several wording error in Table 21 on p. 68.	Text reads “Patents” should read “patients”. Text reads “Ranibizumab” should read “Risankizumab”.	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Wording error on p. 70.	Text reads “Discover” should read “DISCOVER”.	Typographic error. This	Text amended

		amendment will have no impact on the report, or its conclusions.	as described
Wording errors on p. 71.	Text reads “DISCOVERY” should read “DISCOVER”. Text reads “remining” should read “remaining” (this error occurs twice on this page).	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Wording errors on p. 76.	Text reads: [redacted]” Should read: [redacted]” Text reads: “resulting in increased iNHB for deucravacitinib **for** against these comparators.”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described

	Should read: “resulting in **an** increased iNHB for deucravacitinib against these comparators.” Text reads: “the application 2-weekly averaged treatment acquisition costs” Should read: “the application **of a** 2-weekly averaged treatment acquisition costs”		Text amended as described Text amended as described
Drug name for ustekinumab spelled incorrectly on p. 83.	Text reads: “This is done by applying the estimated overestimate of cumulative secukinumab/u**z**tekinumab and third line risankizumab/u**z**tekinumab costs” Should read:	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described

	"This is done by applying the estimated overestimate of cumulative secukinumab/u**s**tekinumab and third line risankizumab/u**s**tekinumab costs"		
Wording errors on P.84	Text reads: "The scenarios generally have **a** only a modest impact on the ICERs for deucravacitinib at the list prices applied to comparators." Should read: "The scenarios generally have only a modest impact on the ICERs for deucravacitinib at the list prices applied to comparators." Text reads: "Conversely, the cost savings per QALY forgone (S**Q** quadrant) with deucravacitinib versus more effective and more costly treatments are substantially increased – favouring deucravacitinib." Should read: "Conversely, the cost savings per QALY forgone (S**W** quadrant) with deucravacitinib versus more effective and more costly treatments are substantially increased – favouring deucravacitinib."	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described Text amended as described

Wording error on p.87	Text reads: “Table 24 ERG alternative base case, incorporating combined changes from Scenario **3b** (acquisition cost adjustments) and 7 (age adjustment of utility)” Should read: “Table 24 ERG alternative base case, incorporating combined changes from Scenario **5b** (acquisition cost adjustments) and 7 (age adjustment of utility)“	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Wording error on p.89	Text reads: “Table 25 ERG alternative base case, incorporating combined changes from Scenario **3b** (acquisition cost adjustments) and 7 (age adjustment of utility) (full incremental analysis)” Should read: “Table 25 ERG alternative base case, incorporating combined changes from Scenario **5b** (acquisition cost adjustments) and 7 (age adjustment of utility) (full incremental analysis)”	Typographic error. This amendment will have no impact on the report, or its conclusions.	Text amended as described
Wording error on p. 90.	Text reads:	Typographic error. This amendment	Text amended

	“The caveat being that these results **to** not reflect the confidential discounts available on many of the comparator drugs.” Should read: “The caveat being that these results **do** not reflect the confidential discounts available on many of the comparator drugs.”	will have no impact on the report, or its conclusions.	as described

AIC/CIC marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
ERG report, p. xiii	To protect the confidentiality of the NMA results, the following statement should be marked as academic in confidence: "[redacted]"	"The NMA results show that deucravacitinib is [redacted]."	AIC marking amended as described
ERG report, p. 23	To protect the confidentiality of the POETYK-PSO-1 and POETYK-PSO-2 trial data, mean BSA should be marked as academic in confidence.	"Mean BSA involvement was [redacted]% and [redacted]%, respectively."	AIC marking amended as described
ERG report, p. 23	To protect the confidentiality of the POETYK-PSO-1 and POETYK-PSO-2 trial data, prior systemic treatment use should be marked as academic in confidence.	"A greater number of participants in POETYK-PSO-1 ([redacted]%) had prior systemic treatment use than those in POETYK-PSO-2 ([redacted]%)."	AIC marking amended as described
ERG report, p. 23	To protect the confidentiality of the POETYK-PSO-1 and POETYK-PSO-2 trial data, prior phototherapy use should be marked as academic in confidence.	"and a greater number in POETYK-PSO-2 ([redacted]%) had prior phototherapy use than those in POETYK-PSO-1 ([redacted]%)."	AIC marking amended as described

ERG report, p. 27	Incorrect AIC marking. The AIC marking should be applied as follows: - Deucravacitinib was superior to apremilast at week 16 in both POETYK-PSO-1 (53.6% vs 32.1%, [redacted]) and POETYK-PSO-2 (49.5% vs 33.9%, [redacted]). - Deucravacitinib was superior to apremilast at week 16 in both POETYK-PSO-1 (58.4% vs 35.1%, [redacted]) and POETYK-PSO-2 (53.0% vs 39.8%, [redacted]).	The data is in the public domain and do not need to be marked as confidential.	AIC marking amended as described
ERG report, p. 34	The sample sizes of the POETYK-PSO-LTE interim results should be marked as AIC: "deucravacitinib -> deucravacitinib (n=[redacted]), placebo -> deucravacitinib (n=[redacted]) and apremilast -> deucravacitinib (n=[redacted])"	The amendment is required to ensure that data that is not yet in the public domain remains confidential until publication.	AIC marking amended as described
ERG report, p. 39	AIC marking should be applied to the percentage of patients experiencing vomiting in the deucravacitinib and the apremilast groups on p. 39: [redacted] versus [redacted]	The amendment is required to ensure that data that is not yet in the public domain remains confidential until publication.	AIC marking amended as described

ERG report, p. 40	AIC marking should be applied to the incidence rate per 100 person-years of exposure for drug-related AEs for apremilast in table 17 on p. 40: [redacted]	The amendment is required to ensure that data that is not yet in the public domain remains confidential until publication.	AIC marking amended as described
ERG report, p. 42	AIC marking should be applied to each value of the following AE category reported in table 18 (Summary of adverse events of special interest Controlled Safety Pool – as treated population (week 0 to 52)) on p. 42 of the ERG report: skin events, severe infections and infestations, adjudicated extended MACE and suicidal ideation	The amendment is required to ensure that data that is not yet in the public domain remains confidential until publication.	AIC marking amended as described
ERG report, p. 40	AIC marking should be removed for SAE values in table 17 on p. 40.	The data is in the public domain and do not need to be marked as confidential.	AIC marking amended as described
ERG report, p.42	AIC marking should be applied to mortality data on p. 42 as follows: "[redacted] participant in the POETYK PSO-1 [redacted]. [redacted] deaths were reported during the POETYK PSO-2 study:	The amendment is required to ensure that data that is not yet in the public domain remains confidential until publication.	AIC marking amended as described

	[redacted]”		
ERG report, p. 43	AIC marking should be applied to the following sentence: “The ERG also agrees that the change from baseline scores [redacted] deucravacitinib [redacted] apremilast and placebo.”	The amendment is required to ensure that data that is not yet in the public domain remains confidential until publication.	AIC marking amended as described
ERG report, p. 45	AIC and CIC marking should be applied on p. 45 as follows: “The ERG agrees with the company that deucravacitinib appears [redacted] apremilast and dimethyl fumarate at all time points where it was possible to make comparisons.” “The ERG also agrees that deucravacitinib is [redacted] to etanercept and at most time points and PASI levels, the effect size [redacted]. In general, the ERG agrees with the company observations that	The amendment is required to ensure that data that is not yet in the public domain remains confidential until publication.	AIC marking amended as described

	deucravacitinib is [redacted] apremilast, dimethyl fumarate and etanercept. In the sensitivity analyses, when deucravacitinib was assessed at [redacted] rather than at 16 weeks, the effect sizes become [redacted] deucravacitinib apart from when compared to tildrakizumab when it was assessed at 28 weeks. In sensitivity analyses 1 and 2 (where the multinomial adjusted random effects model is used) all of the effect sizes for deucravacitinib compared to apremilast, dimethyl fumurate and etanercept (25mg twice weekly) are [redacted] in the main analysis for all of the PASI levels. In sensitivity analysis 3 where deucravacitinib was assessed later and a binomial replaced the multinomial model the effect sizes are [redacted] for deucravacitinib. In terms of the comparison with adalimumab and secukinumab, the effect sizes either [redacted] adalimumab or secukinumab or show deucravacitinib [redacted]. The comparison with tildrakizumab shows tildrakizumab		

	[redacted] for all four PASI levels.”		
ERG report, p. 46	AIC marking should be applied on p. 46 as follows: “The ERG would, however, highlight that in these comparisons the effect sizes still [redacted] of deucravacitinib.” “The evidence from the NMA is also consistent with the direct trial evidence of deucravacitinib as more effective in terms of PASI response rate than apremilast and in addition deucravacitinib also appears [redacted] dimethyl fumarate. The NMA also shows that deucravacitinib has [redacted] effectiveness than etanercept.”	The amendment is required to ensure that data that is not yet in the public domain remains confidential until publication.	AIC marking amended as described
ERG report, p. 60	AIC marking should be applied to the 12-month discontinuation probability for deucravacitinib on p. 60: [redacted]. This should be applied in two sentences on p. 60.	The amendment is required to ensure that data that is not yet in the public domain remains confidential until publication. The observed discontinuation rate can be back-calculated using the annual number.	AIC marking amended as described

NICE National Institute for Health and Care Excellence

Technical engagement response form

Deucravacitinib for treating moderate-to-severe plaque psoriasis [ID3859]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

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Technical engagement response form

Deucravacitinib for treating moderate-to-severe plaque psoriasis [ID3859]

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Bristol Myers Squibb
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Best supportive care utility reverts to baseline	Yes	BMS maintain that it is appropriate to assume that the utility of patients who transition to BSC will revert to baseline. The EAG expressed concerns about the assumption that patients revert to their baseline utility level upon transition to best supportive care (BSC). They suggested this approach removes any benefit associated with observed placebo arm PASI reductions from the BSC state. In its base case, BMS has aligned their approach with TA575 (tildrakizumab) whereby the EAG and the committee concluded, at that time, that the use of baseline utility was appropriate. This was supported by a clinical expert involved in the appraisal, who advised that "a patient who switched from an active treatment to BSC would revert to their baseline quality of life shortly after switching". The EAG of the current appraisal noted that this issue merits further consideration and that clinical experts' opinions should be sought to better understand why we see a placebo response in psoriasis trials and whether it is attributable to a trial effect unique to the placebo arm (and not active treatment) or whether it may reflect natural improvement and therefore should be retained in the model to reflect expected outcomes for BSC.

		During the technical engagement period, BMS sought the opinions of four clinical experts, see Appendix 1 for details. These are 'thought leader' dermatologists from UK secondary and tertiary care centres with research backgrounds, extensive experience in the clinical management of patients with psoriasis and prescribing advanced treatments. The clinical expert engagement highlighted a consensus amongst the experts regarding what is causing the PASI response rates observed in the placebo arm of psoriasis trials. Specifically, the clinical experts stipulated that the placebo response observed in the placebo arms of psoriasis trials can predominantly be attributed to the trial itself rather than the disease. A number of different elements for this were highlighted, such as alleviation of stress and anxiety, a key exacerbation factor of psoriasis, due to enhanced care from participating to a clinical trial (e.g., regular interaction with care team, more handholding). Additionally, the belief of taking a medicine that works (the placebo effect) and how this might affect the stress of the patient, also known as the expectation bias, can play a role in the placebo response. Also, a patient in a clinical trial has an improved adherence to BSC due to the increased monitoring. It was mentioned that the placebo response could be attributed to the investigator bias by which the investigator expects the patient to improve and therefore scores a patient higher than they actually are (i.e., PASI 10 instead of PASI 9) at entry of a clinical trial. When explaining the context of the questions, one HCP further commented that, after having cycled through multiple failed treatments, patients receiving BSC would see their quality of life impacted due to factors such as comorbidities, for example psoriatic arthritis (see appendix 1 for details of each clinical expert's discussion). As a result, using the baseline utility for patients who transition to BSC is a reasonable assumption to capture the experience of patients in UK clinical practice.
Application of averaged treatment acquisition costs per cycle	No	BMS has not submitted a refined model to account for exact dosing as the expected refinement would have minimal impact on the results and would further complicate the model. Whilst it is correct that applying an average treatment acquisition cost per cycle does not fully reflect the exact dosing scheme of all treatments evaluated, no (systematic) bias is introduced by modelling costs on a per cycle basis. This can be seen in the scenarios that were run by the EAG, where the impact on the ICERs varied (i.e., the ICER for deucravacitinib decreased versus some comparators and increased versus others) depending on the relationship between dosing and time point of response assessment for these comparators.

<table>
<tr><td></td><td></td><td>The impact of averaged treatment acquisition costs per cycle is marginal and does not affect all comparisons. As the model progresses through treatment sequences, the effect on the acquisition costs is expected to reduce further. This approach was taken to ensure that the model retained an appropriate level of complexity whilst still reflecting clinical practice closely and not biasing results. The application of exact dosing would complicate the model further without having material impact on the cost-effectiveness results.</td></tr>
<tr><td>Uncertainty around best supportive care and non-responder costs</td><td>No</td><td>The EAG raised concerns about how the cost associated with BSC (estimated as the total secondary care costs from patients in the 12 months following discontinuation from biologic, in the DISCOVER study) is applied in the model and whether it is appropriate to extrapolate this cost over the entire remaining time horizon. Firstly, it would be complex to estimate the pattern of resource use in BSC over time, as this would necessitate an assessment of which costs would be incurred when (and as an extreme, which costs would only be incurred once and as such would not warrant extrapolation over the remainder of the patient’s lifetime). This would introduce further uncertainty to the estimation of BSC costs and therefore should be avoided.

Furthermore, it should be noted that the current modelling approach for BSC (i.e., applying BSC costs for the remaining time horizon of the model) is in line with all previous submissions in psoriasis. The same reasoning also applies to non-responder costs.

To give further insight into the individual cost components constituting secondary care costs, BMS has provided a breakdown of the total secondary care costs and number of visits for patients with moderate to severe psoriasis in the 12 months post-discontinuation of a biologic from the DISCOVER study. Those include costs for outpatient visits, inpatient admissions and accident and emergency [A&E] visits. Tables I and II, reporting those costs, has been reproduced from the DISCOVER report (shared at EAG clarification stage) from supplementary tables 14 and 16.

Table I: Break down of cost of secondary healthcare costs
<table>
<tr><th>Component of secondary healthcare costs</th><th>12 months post-discontinuation of a biologic</th></tr>
<tr><td>Outpatient visit</td><td></td></tr>
<tr><td>Mean number visit per patient (SE)</td><td>[redacted]</td></tr>
<tr><td>Mean cost, £ (SE)</td><td>[redacted]</td></tr>
</table>
</td></tr>
</table>

		Inpatient admission*
		Mean number of admissions per patient (SE) [redacted]
		Mean cost, £ (SE) [redacted]
		A&E visit
		Mean number of visits per patient (SE) [redacted]
		Mean cost, £ (SE) [redacted]
		Total secondary healthcare
		Mean cost, £ (SE) [redacted]

*A breakdown of some of the cost for inpatient admissions (critical care admissions, day care admission and phototherapy) can be found in Table II below
SE: standard error

Table II: Break down of individual cost contributing to inpatient admissions (critical care admissions, day care admission and phototherapy)

Component of secondary healthcare costs	12 months post-discontinuation of a biologic
Critical care admissions	
Mean number of admissions per patient (SE)	[redacted]
Mean cost, £ (SE)	[redacted]
Day case admission	
Mean number of admissions per patient (SE)	[redacted]
Mean cost, £ (SE)	[redacted]
Phototherapy	
Mean number of phototherapy per patient (SE)	[redacted]
Mean cost, £ (SE)	[redacted]

		SE: standard error BMS would like to highlight that the EAG acknowledged that the cost associated with BSC from the DISCOVER study are in line with, and actually lower, than the costs from the Fonia study (£4,074.39) previously used in psoriasis appraisals, although criticised. In its original submission, BMS has run a scenario using the costs from the Fonia study and the impact was minimal on the cost effectiveness (a decrease of approximately £2,500 per QALY versus less effective treatments, and a similar decrease versus more effective treatments in the south west quadrant, thus favouring the comparison of deucravacitinib vs less effective therapies).

Additional issues

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Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Absence of waning of treatment effect with subsequent lines of biologic treatment.	Section 4.2.6	No	BMS has explored the impact of treatment waning in a scenario by increasing the discontinuation rate for all treatments in later lines based on registry data. In their report, the ERG noted that BMS has not considered a scenario with the possibility of lower initial response rates in subsequent treatment lines, but also stated that applying higher discontinuation rates has a similar effect. Therefore, BMS did not submit additional scenario analysis.

Summary of changes to the company's cost-effectiveness estimate(s)

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Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
NR	NR	NR	NR

Sensitivity analyses around revised base case
NR

Appendix 1. Issue 1: Best supportive care utility reverts to baseline – clinical expert opinion

1. **Health care professional (HCP) engagements:**

Four HCPs were consulted between 15 to 25 of August 2022:

Date	Health care professional
August 15	[redacted] Professor of Dermatology and Therapeutics and Honorary Consultant Dermatologist
August 17	[redacted] Consultant Dermatologist, King's College Hospital
August 19	[redacted] Consultant Dermatologist, St John's Institute of Dermatology, Guy's & St Thomas' Hospital
August 25	[redacted] Consultant Dermatologist, Nuffield Health Glasgow Hospital and Spire Murrayfield Hospital in Edinburgh

2. **Questions asked to HCPs**

What is responsible for the PASI response rates observed in the placebo arm of psoriasis trials?

- Could it be a trial effect due to increased monitoring/compliance with topical therapies?
- Could it be a natural improvement from baseline, when patients were meeting the PASI threshold for recruitment?

Is the placebo response unique to the placebo arm (and not active treatment)?

Or is the placebo response a reflection of natural improvement and could also explain some of the response observed for active treatments?

3. **Engagement summary:**

Engagement 1: August 15 – [redacted]	
	• The PASI response rates observed in the placebo arm of psoriasis trials can probably be attributed to a combination of two factors: 1. Natural fluctuation of the disease 2. Effect of the trial [redacted] thinks this will mostly be driven by the effect of the trial, given that psoriasis, like most skin diseases, causes stress and anxiety. Specifically, a trend towards improvement may be experienced based on the following two trial effects: ○ Patients will get close supervision and time with nurses and Drs talking about the disease ○ Patients think they may be receiving an effective therapy • As for the quality of life of patients receiving BSC, the following factors could negatively impact their quality of life: ○ These patients will have cycled and failed multiple therapies and, depending on their geographic location, these patients may not have access to all available treatment options which would cause frustration, stress, anxiety and worsening of disease.

	○ These patients may have to deal with associated comorbidities, such as PsA.
Engagement 2: August 17 – [redacted]	
	• The PASI response rates observed in the placebo arm of psoriasis trials can probably be attributed to two aspects: 1. Placebo effect ▪ When patients take what they believe is a medicine, it may produce improvement in their disease. As psoriasis is exacerbated by stress and anxiety this may be alleviated by the thought that something positive is being done not only in the form of treatment but in the nurturing environment of a clinical study where they feel valued. ▪ This is a common finding in psoriasis. No perfect understanding. 2. Participation in the trial, due to enhanced care: ▪ Psoriasis is associated with psychological components: the disease is made worse by stress and stigma, such as other people not caring about their disease. Patients in a clinical trial feel that people are interested in them and get more confident about themselves; they are treated like someone very special. [redacted] does not believe that the PASI response rates observed in the placebo arm of psoriasis trials is the result of natural improvement.
Engagement 3: August 19 – [redacted]	
	• The reason PASI response rates are observed in the placebo arm of psoriasis trials is multifactorial: 1. Due to the clinical trial environment ▪ Regular treatment, interactions, more hand-holding and better adherence 2. Expectation bias ▪ Expectation bias is demonstrated through the placebo effect and is strong across trials. Psoriasis is psychological, stress is a major contributor. If a patient gets something that might work, it will affect their stress • It is difficult to fathom how some patients achieve PASI90 on placebo. However, very few placebo patients do indeed achieve this. ○ No more than 5% of placebo patients reach the primary outcome, which is much lower than what has been observed in some other diseases. ○ In general, the fluctuation observed in the PASI score of patients receiving placebo is not huge, despite the many factors that influence the disease, such as infection, stress, alcohol and weight gain. • An observed placebo effect is small and whilst this may be seen in the short term it is unlikely to persist once patients go onto BSC. The placebo effect does not necessarily reflect what will happen in the long term.
Engagement 4: August 25 – [redacted]	
	• The reason PASI response rates are observed in the placebo arm of psoriasis trials is multi-facetted, and the contribution of the individual elements in a particular trial is unknown. • It is observed in all psoriasis trials and various reasons could contribute: 1. Genuine placebo response ▪ People improve because they think they will improve. 2. Investigator bias ▪ The investigator expects the patient to improve and therefore scores a patient lower than they actually are. ▪ Investigators who are motivated to enrol patients in the trial may overscore at baseline to meet eligibility criteria. If the cut off to enrol is PASI of 10, a physician may assign a patient with PASI of 9 a score of PASI of 10 and the

patient may go back to their initial PASI score during the trial, i.e. they revert back to their mean PASI.

3. Issues with trial design
    - An improvement may have been observed because:
        Patients may have received multiple treatments at the same time. For instance, topical treatments, including emollients. In addition, patients may be more assiduous in using topical treatments because they are under closer supervision
        - Patients may have previously received treatments with slow onset of action or long wash out period.
        - Patients may have been about to improve for other reasons. For instance, in relapsing/remitting disease, a spontaneous relapse may cause disease of a severity that qualifies for enrolment, subsequent spontaneous remission then looks like a treatment response (i.e. a reversion to the mean)
        - Inadvertently patients with less stable disease may have been enrolled which could contribute to a higher placebo response.
            - Unlikely to have selected a group with less stable disease. There is always some variability but it is unlikely to have been substantially greater than in other trials.
4. Natural history
    - There is a very rough correlation between stability and severity of disease:
        - More fluctuation in patients with high PASI scores.
        - Moderate disease more likely to be unchanging.

- Hard to know the source of variation.
- Unless a patient is inherently unstable, once they discontinue treatment, they would revert back to baseline quality of life. Caveats to this include rebound on discontinuation of some treatments (e.g. systemic corticosteroids) and loss of coping strategies and raised expectations while on effective treatment

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Technical engagement response form

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NICE National Institute for Health and Care Excellence

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Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Abbvie Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

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Application of averaged treatment acquisition costs per cycle	No	No comment
Uncertainty around best supportive care and non-responder costs	No	No comment

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NICE National Institute for Health and Care Excellence

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	**Luiz Causin – Senior HEMAR Manager**
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Janssen**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Deadline for comments by **5pm** on **24th August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Deucravacitinib for treating moderate-to-severe plaque psoriasis [ID3859]

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	**Munna Ibrahim**
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Novartis Pharmaceuticals UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Breezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD)) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) has acquired Vectura Group Limited (formerly Vectura Group plc)

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Best supportive care utility reverts to baseline	**No**	No comment.
Application of averaged treatment acquisition costs per cycle	**No**	No comment.
Uncertainty around best supportive care and non-responder costs	**No**	No comment.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Absence of waning of treatment effect with subsequent lines of biologic treatment.	Section 4.2.6	**No**	No comment.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Deucravacitinib for treating moderate-to-severe plaque psoriasis [ID3859]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Technical engagement response form

Deucravacitinib for treating moderate-to-severe plaque psoriasis [ID3859]

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **<<insert deadline>>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Technical engagement response form

Deucravacitinib for treating moderate-to-severe plaque psoriasis [ID3859]

About you

Table 1 About you

Your name	Frank J K Ababio
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UCB Pharma Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Best supportive care utility reverts to baseline	Yes/No	UCB agrees with the ERG that best supportive care (BSC) utility should not revert to baseline but should account for the placebo response distribution across the different PASI categories derived from the NMA. Improvement in psoriasis symptoms among placebo patients may be part of the natural history of the disease; therefore, failing to account for placebo effect introduces bias in favour of the active comparators – this makes them look better than they should. It was therefore not surprising that the ICERs increased for all the active treatments after the ERG mapped BSC utility to the PASI response rates for placebo from the NMA. Despite the placebo adjustment, there are still some methodological limitations since placebo treatment arms in clinical trials do not entirely reflect the treatment patients receive after transitioning to BSC in routine practice. Trial patients on placebo are not allowed to use systemic non-biologics, such as methotrexate, ciclosporin or acitretin, which form part of the standard of care therapies for patients on BSC in real life. Thus, the PASI response-based utility of the placebo arm may still not be an accurate representation of the health benefits associated

		with BSC. Therefore, the committee could consider exploring the following scenarios: 1. Anchor BSC utility on one of the systemic non-biologic therapies using data from the company's NMA. Methotrexate could be the ideal candidate since it is recommended by NICE (CG153) as the first-line systemic non-biologic agent of choice and evidence suggests it is the most frequently prescribed conventional DMARD in psoriasis. The NICE committee that reviewed TA574 requested this scenario based on reasons stated above 2. Represent BSC utility with the weighted average utility of a mix of therapies reflective of BSC treatments in clinical practice ie all systemic treatments. Similarly, the company's NMA can be used to inform the PASI response-based utilities for each treatment, whilst the composition/shares of the treatment mix can be informed by RWEs or expert opinion
Application of averaged treatment acquisition costs per cycle	Yes/No	No comments
Uncertainty around best supportive care and non-responder costs	Yes/No	UCB believes that more evidence is required to address the uncertainty surrounding BSC and non-responder costs since Fiona et al and DISCOVER studies both have important limitations. As pointed out by the NICE committee that reviewed TA575, Fiona et al data, which has been the reference source for previous submissions, needs an update because of age. Since the data was synthesised over 14 years ago, it does not provide an accurate estimation of current NHS costs. Though the DISCOVER study is current, it fails to explain the proportion of total secondary care costs attributable to biologic therapy discontinuation. Patients who stop biologic treatments may visit A&E, attend outpatient consultations or even go on admission for reasons other than psoriasis. Therefore, the assumption that the entire secondary care costs relate to biologic discontinuation is inappropriate and can potentially lead to overestimation of BSC and non-responder costs.

		In the absence of robust evidence to tackle the uncertainty associated with BSC and non-responder costs, UCB considers it appropriate to explore conservative scenarios where Fiona et al and DISCOVER data are reduced by reasonable factors to help understand the uncertainty in this area.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG reportIssue from the ERG report	**Relevant section(s) and/or page(s)**	**Does this response contain new evidence, data or analyses?**	**Response**
Absence of waning of treatment effect with subsequent lines of biologic treatment.	Section 4.2.6	Yes/No	No comments

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

References

Deucravacitinib for treating moderate-to-severe plaque psoriasis [ID3859]

ERG critique of the company's response to technical engagement

Produced by Aberdeen HTA Group

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Date completed **21 September 2022**

Contains redacted AIC information

In their response to technical engagement, the company addressed each of the main issues raised in the ERG report. This addendum to the ERG report provides a brief critique of the company's response. It should be read in conjunction with the company's technical engagement response document, dated 26 Aug 2022.

The key issues raised in the ERG report are outlined in Table 1. A detailed summary of each issue can be found in the Executive summary of the main ERG report:

Table 1 Summary of key issues identified by the ERG

Issues	Summary of issue	ERG Report sections
Issue 1	Best supportive care utility reverts to baseline, rather than receiving utility based on the PASI response for placebo observed in the NMA	4.2.6 and 4.2.7
Issue 2	Application of averaged treatment acquisition costs per cycle, rather than full dose costs applied to those on treatment during the cycles that doses are due.	4.2.8
Issue 3	Best supportive care and non-responder costs. Not clear they can all be attributed to stopping treatment or non-response, respectively.	4.2.8

Issue 1 Best supportive care utility reverts to baseline

This relates to the ERG's concern that removing the placebo arm response-based utility from the BSC state, with no adjustment to active treatment states, may overestimate the quality of life benefits of all active treatments versus BSC.

In our report we suggested the following might help resolve the uncertainty:

"*Further clinical expert opinion on what is responsible for the PASI response rates observed in the placebo arm of psoriasis trials:*

- *A trial effect due to increased monitoring/compliance with topical therapies*
- *Natural improvement from baseline, when patients were meeting the PASI threshold for recruitment (regression to the mean)*

And whether the placebo response is unique to the placebo arm or could also explain some of the response observed for active treatments."

In response, the company have engaged with four clinical experts who suggest that the response observed in the placebo arm of psoriasis trials can predominantly be explained by a trial effect rather than natural variation in the disease. They further note that one expert

suggested patients receiving BSC after multiple failed treatments could see their quality of life impacted by comorbidities such as psoriatic arthritis (see company response to TE for details). The company use this to defend their position of applying baseline utility to the BSC state.

The consultation has been useful in that it appears to suggest the placebo arm responses in this cohort are more likely to be driven by a trial effect rather than natural improvements that can be expected due to variation in the disease. This suggests that it may be reasonable to assume baseline utility for those on BSC in routine practice. However, the clinical expert responses do not rule out the possibility of naturally relapsing/remitting disease playing a role. Furthermore, there is no discussion as to why a trial effect should be applicable only to the placebo arm of the trials as assumed in the company's modelling approach, which uses the absolute PASI response rates derived from the NMA for the active treatments but ignores those derived for the placebo arm [redacted] *for PASI50, 75, 90 and 100 respectively). If a trial effect could also partly explain observed responses in the active treatment arms of trials, an alternative approach could have been to use relative treatment effects for the active treatments versus placebo derived from the NMA, applied to a flat PASI baseline for BSC in the model. However, the company model is not set up to use relative treatment effects. The ERG acknowledges that the company's approach is consistent with that accepted by the committee in TA575.*

Issue 2 Application of averaged treatment acquisition costs per cycle

The company respond to the point on the potential inaccuracy of using cycle averaged treatment costs in the context of relatively high-cost drugs with sometimes quite long intervals between doses. They do not make any changes to allow for more formal incorporation of exact dose-based costing (i.e. applying costs only to the proportion of patients on treatment at the beginning of model cycles in which doses are due). They refer to the scenarios provided by the ERG, which approximate dose-based costing, and note that these have marginal and mixed impacts on the ICERs, suggesting no systematic bias.

The ERG is generally satisfied with the company response. Formal incorporation of exact dose-based costing would require substantive structural changes to the model; i.e. to allow time in subsequent treatment states to be tracked using tunnels. The ERGs scenarios can be used to guide potential impacts on the ICERs and NHBs.

Issue 3 Best supportive care and non-responder costs

This point relates to the ERG's concern that total secondary health care resource use (HCRU) costs applied to the BSC state in the company's model (derived from the DISCOVER study), may include costs that cannot be attributed to discontinuing active biologic psoriasis treatment. This is potentially problematic as there is no comparative estimate of total secondary care costs applied to those who remain on biologic therapy included in the model. The total secondary care costs observed in those who discontinued biologic therapy in the DISCOVER study will be driven partly by unrelated conditions and events. A similar issue applies to the estimated costs of non-response, where total secondary care costs in the year preceding discontinuation are assumed to be reflective of non-responder costs.

In response, the company have provided a breakdown of types of secondary care resource use that inform the BSC costs in the model (see Table 1 of company response document). However, this is of limited value as it does nothing to help explain the proportion of overall secondary care costs that may be attributable to the discontinuation of biologic therapy and moving to BSC. It may have been more useful had there been a full breakdown of outpatient and inpatient activity by the primary clinical reason, so that judgments could be made on the potential association with psoriasis and its treatment. Furthermore, the estimates of secondary care resource use reported in the company response relate to contacts judged in the DISCOVER study to be dermatology related, whereas the reported costs correspond to all secondary care contacts.

From further scrutiny of the DISCOVER study report, dermatology related inpatient admissions were a minority of the total inpatient admissions informing total secondary care costs (mean of [redacted] versus [redacted] per patient year respectively). This suggests that total secondary care costs derived from the DISCOVER study may overstate the increase in costs that can be expected with discontinuation from biologic therapy to BSC.

The company note that the ERG "acknowledged that the costs associated with BSC from the DISCOVER study are in line with, and actually lower, than the costs derived from the Fonia study (£4,074.39 [2022 prices]) used in psoriasis appraisals". This is true but uncertainties remain regarding the applicability of the Fonia study to current practice and also how it should be used to inform the BSC health state cost.

Fiona et al. (2010) compared secondary HCRU costs for 76 UK NHS patients in the 12-month period before and after commencing biologic therapy. In line with previous psoriasis appraisals (NICE, TA57%; NICE TA511), the company conducted a scenario analysis

whereby they inflated the annual pre-biologic therapy, total secondary care costs reported by Fonia et al. (£2,956.7 in 2008 prices) to represent BSC care costs. Whilst consistent with what seems to have been accepted in previous appraisals, this approach does not consider the comparative annual secondary care costs during time on active biologic treatment. Note, the difference in annual secondary care costs reported by Fonia et al. between the 12-month periods before and after initiation of biologic therapy was £1,682, which is ~57% of the total annual cost preceding initiation. However, previous appraisals have also included the estimated cost of systemic non-biologic drugs in the 12-month period prior to biologic treatment in the cost estimate for BSC (NICE, TA57%; NICE TA511). In this respect, the company's BSC cost estimates (based on both the DISCOVER study and Fonia et al.) are more conservative than those applied in previous appraisals. However, applying active non-biologic systemic treatment costs for BSC would be inconsistent with the baseline utility assumption applied to the BSC state in their model.

Summary

In summary, the impact of transition from active biologic treatment to BSC on both health-related quality of life and secondary care costs are not well informed or fully justified in the company's model or in previous NICE appraisals of biologic therapies. The company use assumptions that are broadly consistent with those accepted by committees in previous appraisals, but these assumptions remain uncertain and their impact on ICERs and NHBs may be considered using scenario analyses that the ERG provided in their main report.

References

1. NICE TA575. (2019). Tildrakizumab for treating moderate to severe plaque psoriasis; https://www.nice.org.uk/guidance/ta575 [accessed 21/09/2022]
2. Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. Br J Dermatol. 2010;163(4):807-16.
3. NICE TA 511. (2018). Brodalumab for treating moderate to severe plaque psoriasis; https://www.nice.org.uk/guidance/ta511 [accessed 21/09/2022]