EUROPEAN UNION RISK MANAGEMENT PLAN

Otezla® (apremilast)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	15.2
Date:	26 August 2024
Supersedes:	Version 14.1, dated 04 November 2021

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	15.2
Data lock point of this RMP:	27 March 2023 (pediatric clinical study data cut-off) 20 March 2023 (postmarketing exposure data lock point)
Date of final sign-off:	26 August 2024
Rationale for submitting an updated RMP:	To add an indication for the treatment of pediatric and adolescent patients from the age of 6 years with moderate to severe plaque psoriasis.

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part I: Product(s) Overview	• Added an indication for the treatment of pediatric patients 6 years of age and older with moderate to severe plaque psoriasis	Version 15.0; 14 November 2023
	• Updated the pediatric psoriasis indication	Version 15.1; 06 August 2024
Part II: Safety Specification		
SI: Epidemiology of the Indication(s) and Target Population(s)	• Added pediatric psoriasis epidemiology data • Updated the main treatment options for psoriatic arthritis with recent data	Version 15.0; 14 November 2023
SIII: Clinical Trial Exposure	Added pediatric clinical study exposure data and updated adult clinical trial exposure data	Version 15.0; 14 November 2023
SIV: Populations Not Studied in Clinical Trials		
SIV.3: Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs	Updated exposure of special populations included or not in clinical trial development programs	Version 15.0; 14 November 2023
SV: Postauthorization Experience	Updated postauthorization exposure data with DLP of 20 March 2023	Version 15.0; 14 November 2023
SVII.3.1: Presentation of Important Identified Risks and Important Potential Risks	Updated the important identified and important potential risks with pediatric data	Version 15.0; 14 November 2023
Part III.1: Routine Pharmacovigilance Activities	Added hypersensitivity follow-up form information to Table 45 (Specific Adverse Reaction Follow-up Questionnaires)	Version 15.1; 06 August 2024
Part III.2: Additional Pharmacovigilance Activities	• Updated the milestone dates for PASS: Apremilast PsA Registry in the UK – BSRBR-PsA (CC 10004-PSA-012)	Version 15.0; 14 November 2023 Version 15.2; 26 August 2024

Summary of significant changes in this RMP (continued)

Part/Module/Annex	Major Change(s)	Version Number and Date
Part III.2: Additional Pharmacovigilance Activities (continued)	• Removed the 6-year report milestone for PASS Apremilast PsA Registry in the UK – BSRBR-PsA (CC 10004-PSA-012) per PRAC request from BSRBR registry 5th Year report PAM Submission (EMEA/H/C/003746/MEA/008.6)	Version 15.2; 26 August 2024
Part III.3: Summary Table of Additional Pharmacovigilance Activities	• Updated the milestone dates for PASS Apremilast PsA Registry in the UK – BSRBR-PsA (CC 10004-PSA-012)	Version 15.0; 14 November 2023 Version 15.2; 26 August 2024
	• Removed the 6-year report milestone for PASS Apremilast PsA Registry in the UK – BSRBR-PsA (CC 10004-PSA-012) per PRAC request from BSRBR registry 5th Year report PAM Submission (EMEA/H/C/003746/MEA/008.6)	Version 15.2; 26 August 2024
Part VI: Summary of the Risk Management Plan	Updates made to align with the changes to the above sections	Version 15.0; 14 November 2023 Version 15.1; 06 August 2024
Part VII: Annexes		
Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	• Updated the milestone dates for PASS Apremilast PsA Registry in the UK – BSRBR-PsA (CC 10004-PSA-012)	Version 15.0; 14 November 2023 Version 15.2; 26 August 2024
	• Removed the 6-year report milestone for PASS Apremilast PsA Registry in the UK – BSRBR-PsA (CC 10004-PSA-012) per PRAC request from BSRBR registry 5th Year report PAM Submission (EMEA/H/C/003746/MEA/008.6)	Version 15.2; 26 August 2024

Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	14.1
Approved with procedure:	EMEA/H/C/003746/II/0038 (for PsoBest) EMEA/H/C/003746/II/0039 (for UK Clinical Practice Research Database [CPRD])
Date of approval (opinion date):	05 May 2022
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization applicant's QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
ADR	adverse drug reaction
AESI(s)	adverse event(s) of special interest
AHA	American Heart Association
ANA	antinuclear antibody
ATC	Anatomical Therapeutic Chemical
AUC	area under curve
BCRP	breast cancer resistance protein
BD	Behçet's disease
bDMARD(s)	biologic DMARD(s)
BID	twice daily
BMI	body mass index
BSI	Beck Suicide Inventory
BSRBR	British Society for Rheumatology Biologics Register
cAMP	cyclic adenosine monophosphate
CASPAR	Classification of Psoriatic Arthritis
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximum concentration
CPRD	Clinical Practice Research Database
CRP	C-reactive protein
csDMARD(s)	conventional synthetic DMARD(s)
CSR	clinical study report
CVA	cerebrovascular accident
CVD	cardiovascular disease
CYP	cytochrome P450
DMARD(s)	disease modifying antirheumatic drug(s)
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EULAR	European League against Rheumatism
GIMAP	GTPase, IMAP Family Member

Term/Abbreviation	Explanation
HCP	healthcare professional
hERG	human Ether à go-go-Related Gene
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
IL	interleukin
INN	International Nonproprietary Name
M12	glucuronide conjugate of *O*-demethylated apremilast
MAA	Marketing Authorization Application
MACE	major adverse cardiac events
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	multidrug resistance protein
MTX	methotrexate
NICE	National Institute for Health and Care Excellence
NMSC	non-melanoma skin cancer
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PDE	phosphodiesterase
P-gp	permeability glycoprotein
Ph. Eur	European Pharmacopeia
PIL	patient information leaflet
PL	package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PsA/PSA	psoriatic arthritis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PUVA	psoralen and ultraviolet-A light
PY	patient-years

Term/Abbreviation	Explanation
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RR	relative risk
SMQ	Standardised MedDRA Query
SMR	Standardized Mortality Ratio
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent adverse event
THIN	The Health Improvement Network
TNF	tumor necrosis factor
tsDMARD(s)	targeted synthetic DMARD(s)
UK	United Kingdom
US	United States

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Apremilast
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Phosphodiesterase (PDE) 4 Inhibitor ATC Code: L04AA32
Marketing authorization holder (MAH)	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Otezla®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Apremilast is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4).
Summary of mode of action	Apremilast works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. Phosphodiesterase 4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. Phosphodiesterase 4 inhibition elevates intracellular cAMP, which in turn down-regulates the inflammatory response by modulating the expression of tumor necrosis factor (TNF)-alpha (α), interleukin (IL)-23, IL-17, and other inflammatory cytokines. Elevation of cAMP also modulates anti-inflammatory cytokines, such as IL-10, produced by endotoxin-stimulated mononuclear cells. These pro- and anti-inflammatory mediators have been implicated in psoriasis and psoriatic arthritis (PsA).
Important information about its composition	Apremilast has an empirical formula of $C_{22}H_{24}N_2O_7S$ and a molecular weight of 460.5 g/mol. It is a white to pale yellow powder with a melting point of approximately 156.1°C.

Table 1. Product(s) Overview

Hyperlink to the Product Information (PI)	The proposed PI is provided in Module 1.3.1.
Indication(s) in the EEA	
Current	Psoriatic arthritis Otezla, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. Psoriasis Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA). Behçet's disease Otezla is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.
Proposed	Psoriatic arthritis Otezla, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. Psoriasis Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis (PSOR) in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA). Pediatric Psoriasis Otezla is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years and weighing at least 20 kg who are candidates for systemic therapy. Behçet's disease Otezla is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

Table 1. Product(s) Overview

Dosage in the EEA

Current

The recommended dose is 30 mg twice daily (BID) taken orally, morning and evening, approximately 12 hours apart, with no food restrictions. An initial titration is required (as shown below). No re-titration is required after initial titration.

Dose Titration Schedule

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & Thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

AM = morning; PM = evening

Apremilast tablets should be swallowed whole.

Proposed

Adult patients with psoriatic arthritis, psoriasis, or Behçet's disease

The recommended dosage of apremilast for adult patients is 30 mg taken orally twice daily. An initial titration schedule is required as shown below.

Dosage Titration Schedule for Adult Patients

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & Thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Pediatric Patients with Moderate to Severe Plaque Psoriasis

The recommended dosage of apremilast for pediatric patients 6 years of age and older with moderate to severe plaque psoriasis is based on body weight. The recommended dosage of apremilast is 20 mg taken orally twice daily for pediatric patients who weigh from 20 kg to less than 50 kg and 30 mg taken orally twice daily for pediatric patients who weigh at least 50 kg, following the initial titration schedule shown below.

Dosage titration schedule for Pediatric Patients

Body Weight	Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & Thereafter	
	AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
20 kg to less than 50 kg	10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
50 kg or more	10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Table 1. Product(s) Overview

Dosage in the EEA (continued)	
Proposed (continued)	<u>All indications (psoriasis in adults and children, psoriatic arthritis, Behçet's disease)</u> No re-titration is required after initial titration. The recommended twice daily apremilast dosage should be taken approximately 12 hours apart (morning and evening), with no food restrictions.
Pharmaceutical form(s) and strength(s)	
Current (if applicable):	Apremilast is available as 10-, 20-, and 30-mg diamond shaped film-coated tablets.
Proposed (if applicable):	Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Psoriatic Arthritis

Incidence	• In retrospective and prospective studies conducted between 1996 and 2003, the incidence of PsA across various EU countries including Finland, Sweden and Greece ranged from 3 to 23.1 per 100 000 inhabitants (Ogdie and Weiss, 2015; Chandran and Raychaudhuri, 2010; Alamanos et al, 2008). • A recent meta-analysis and systematic review of the literature reported pooled global incidence of PsA was 83 per 100 000 patient-years (PY) but high heterogeneity was found between studies (Scotti et al, 2018). • A retrospective study conducted in the United States (US) in 2000 reported the incidence of PsA as 6.6 per 100 000 inhabitants (Alamanos et al, 2008).
Prevalence	• It is estimated that the prevalence of PsA is 0.1% to 1% of the general population (Committee for Medicinal Products for Human Use [CHMP], 2004). • In cross-sectional and retrospective studies conducted between 1969 and 2005, the prevalence of PsA across various European countries including Sweden, Greece, Italy, France and the Netherlands has been reported to range from 20 to 420 per 100 000 population (Alamanos et al, 2008). • A recent meta-analysis and systematic review of the literature reported pooled global prevalence of PsA was 133 per 100 000 patients but high heterogeneity was found between studies (Scotti et al, 2018). • In the US, a retrospective study in 2000 reported the prevalence of PsA as 101 per 100 000 population, while a cross-sectional study in 2005 reported the prevalence of PsA as 250 per 100 000 population (Alamanos et al, 2008). • In a review of prevalence of arthritis and rheumatic diseases around the world, no population-based studies were found reporting the prevalence of PsA in the adult population residing in Canada (Chandran and Raychaudhuri, 2010). • Most PsA patients are classified using criteria from Moll and Wright (Helliwell, 2005). Using data from the classification of Psoriatic Arthritis (CASPAR) study database (588 patients with PsA), Helliwell 2005 reported frequencies of these sub populations in PsA patients as follows: – Distal Interphalangeal Predominant: 4% – Oligoarthritis: 13% – Polyarthritis: 63% – Spinal involvement: 14% – Arthritis mutilans: 3% – Not defined: 3%

Footnotes, including abbreviations, are defined on the last page of the table.

Table 2. Summary of Epidemiology of Psoriatic Arthritis

Demographics of population in the indication and risk factors for the disease	• Weak (statistically non-significant) association with family history of psoriasis, White ethnicity, trauma, hypertension and use of beta-blockers (Thumboo et al, 2002). • In a population-based study in the Czech Republic, the incidence and prevalence of PsA in males and females were similar. Incidence was 4.5 per 100 000 men and 2.8 per 100 000 women (male to female ratio of 1.3:1), and prevalence was 48.6 per 100 000 men and 50.7 per 100 000 women (male to female ratio of 0.85:1) (Hanova et al, 2010). • A study conducted in Canada reported that men have a higher frequency of axial involvement (42.9% men, 31% women) and higher risk of peripheral joint damage (Eder et al, 2013). • PsA is secondary to psoriasis, with risk factors for PsA including psoriasis involving the scalp and intergluteal/perianal region, psoriasis involving more than 3 affected sites, and nail dystrophy (Wilson et al, 2009; Helliwell and Wright, 2000). • Systemic corticosteroid use in the 2 years prior to psoriasis onset may influence the development of PsA (Thumboo et al, 2002). • It was demonstrated in a case-control study that a number of environmental factors are associated with onset of inflammatory arthritis in patients with psoriasis. The strongest associations were with trauma, such as injury requiring medical consultation, changing residence (moving) and bone fracture. Exposure of the immune system to certain infection-related triggers, including rubella vaccination and recurrent oral ulcers, may also be relevant (Pattison et al, 2008). • In a study of patients with dermatologist-diagnosed psoriasis, obesity at 18 years of age increased the risk of developing PsA (Soltani-Arabshahi et al, 2010).
Main existing treatment options	• Nonsteroidal anti-inflammatory drugs (NSAIDs) (Pitzalis and Pioitone, 2000) and intra-articular corticosteroids (Sharma and Dogra, 2010), especially for patients with milder or oligoarticular forms of the disease, respectively. European League against Rheumatism (EULAR) guidelines recommend that NSAIDs are used as first-line treatment of PsA for most patients (Gossec et al, 2020). The guidelines also suggest that glucocorticoids can be used as adjunctive therapy, and systemic glucocorticoids may be used with caution at the lowest effective dose. • Conventional synthetic (csDMARDs): methotrexate (MTX), sulfasalazine, and leflunomide. These are standard treatments for patients with polyarticular disease (Gossec et al, 2020; Queiro-Silva et al, 2003) or with refractory oligoarticular disease (Pitzalis and Pipitone, 2000) before the occurrence of irreversible joint damage (Weaver, 2004). European League against Rheumatism (EULAR) guidelines recommend that csDMARDs should be used in patients with polyarthritis with MTX preferred for skin involvement. These are also recommended to treat patients who have monoarthritis or oligoarthritis particularly with poor prognostic factors (Gossec et al, 2020).

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 2. Summary of Epidemiology of Psoriatic Arthritis

Main existing treatment options (continued)	• Less commonly used DMARDs: cyclosporine, anti-malarial drugs (Pitzalis and Pipitone, 2000) and azathioprine (Menter et al, 2009). • Biologic cytokine inhibitors: etanercept, adalimumab, infliximab, golimumab (all TNF blockers) and ustekinumab (an IL blocker [IL-12/23) (Gossec et al, 2020; National Institute for Health and Care Excellence [NICE] Guidelines 2017; Salvarani et al, 2006). EULAR guidelines recommend that in patients with peripheral arthritis and inadequate response to at least one csDMARD, treatment with a biologic DMARD (bDMARD) should be considered and when there is relevant skin involvement, an IL-17 or IL-12/23 may be preferred. These are also recommended for patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections. • Biologic cytokine inhibitors are also recommended for nail psoriasis (Coates et al, 2016). • Targeted synthetic DMARDs (tsDMARDs), such as a PDE4 inhibitor or Janus kinase (JAK) inhibitor, should be considered in patients with peripheral arthritis where conventional DMARDs are inadequate and bDMARDs are inappropriate (Gossec et al, 2020). • Stelara (ustekinumab) has been approved for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, MTX and PUVA. Stelara, alone or in combination with MTX, has been approved for the treatment of active PsA in adult patients when the response to previous non-biological DMARD therapy has been inadequate (Stelara Information Page, European Medicines Agency [EMA] website 2013).
Natural history of the indicated condition in the population including mortality and morbidity	• Morbidity – PsA occurs in 6% to 41% of patients with psoriasis (Ogdie and Weiss, 2015; National Psoriasis Foundation, 2009; Shbeeb et al, 2000; Leonard et al, 1978). Psoriasis usually precedes PsA by several years (Ogdie and Weiss, 2015; Leonard et al, 1978). – PsA is a chronic disease that requires long-term treatment and can lead to irreversible joint damage (Leonard et al, 1978). – Clinically, PsA is a heterogeneous disease with a combination of presentation including peripheral arthritis (mono-, oligo-, or poly-articular with or without distal interphalangeal involvement), enthesitis, dactylitis, spondylitis and/or sacroiliitis, as well as psoriatic nail disease (Ogdie and Weiss, 2015).

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Table 2. Summary of Epidemiology of Psoriatic Arthritis

Natural history of the indicated condition in the population including mortality and morbidity (continued)	• Morbidity (continued) – Patients with PsA have also been reported to be at a higher risk of developing infections, gastrointestinal disorders, liver disease, depression/anxiety, and neurological conditions compared to psoriasis populations without arthritis (Husted et al, 2011). • Mortality – The Standardized Mortality Ratio (SMR) of PsA was reported as 1.5 (95% CI: 1.32 1.71) in 2007 according to data from the United Kingdom (UK) Clinical Practice Research Database (CPRD), and in Sweden SMR was determined to be 1.5 (95% CI: 1.44 - 1.60) based upon cardiovascular mortality only (Gladman, 2008). – However, in a recent analysis of The Health Improvement Network (THIN) database in the UK, cardiovascular (hazard ratio [HR] 1.09, 95% CI: 0.91 - 1.32), malignancy (HR 1.03, 95% CI: 0.86 - 1.25) and infection (HR 1.05, 95% CI: 0.79 - 1.39) deaths were not significantly different from non-PsA controls (Ogdie et al, 2017).
Important comorbidities	• Metabolic syndrome (Raychaudhuri et al, 2010). • Ischemic cardiovascular disease (CVD) (Kaine et al, 2018; Ogdie et al, 2015; Ogdie and Weiss, 2015; Gladman et al, 2009; Han et al, 2006). • Obesity (Reddy et al, 2010; Kimhi et al, 2007). • Hypertension (Kaine et al, 2018; Gladman et al, 2009; Han et al, 2006). • Insulin resistance/diabetes mellitus (Kaine et al, 2018; Han et al, 2006). • Hyperlipidemia/dyslipidemia (Kaine et al, 2018; Han et al, 2006). • Cancer (Rohekar et al, 2008). • Depression/anxiety (Kaine et al, 2018; Wu et al, 2017; Pompili et al, 2016; Husted et al, 2011). • Non-alcoholic fatty liver disease (Coates et al, 2016). • Sleep disorder (Callis Duffin et al, 2009). • Inflammatory bowel disease (ulcerative colitis and Crohn's disease) (Husted et al, 2011; Cohen et al, 2008; Palm et al, 2001). • Inflammatory arthritis (PsA) (Gulliver, 2008; Zachariae et al, 2002). • Infections (Haddad et al, 2016; Husted et al, 2011). • Osteoporosis and fracture (Kaine et al, 2018; Husted et al, 2011). • Uveitis (inflammatory eye disease) (Kaine et al, 2018; Linder et al, 2004; Lambert and Wright, 1976).

CASPAR = Classification of Psoriatic Arthritis; CHMP = Committee for Medicinal Products for Human Use; CPRD = Clinical Practice Research Database; CVD = cardiovascular disease; DMARD = disease modifying antirheumatic drug; EMA = European Medicines Agency; EU = European Union; EULAR = European League against Rheumatism; HR = hazard ratio; IL = interleukin; MTX = methotrexate; NICE = National Institute for Health and Care Excellence; NSAID = nonsteroidal anti-inflammatory drug; PDE = phosphodiesterase; PsA = psoriatic arthritis; PUVA = psoralen and ultraviolet-A light; PY = patient-years; SMR = standardized mortality ratio; THIN = The Health Improvement Network; TNF = tumor necrosis factor; UK = United Kingdom; US = United States

Table 3. Summary of Epidemiology of Psoriasis

Incidence	• Studies that report information on the incidence of psoriasis are limited (Parisi et al, 2020). A systematic analysis showed that the incidence of psoriasis in adults around the world varied from 30.3 per 100 000 PY in Taiwan to 321.0 per 100 000 PY in Italy. The analysis showed the incidence of psoriasis for all ages varied from 31.4 per 100 000 PY in eastern Europe (Russia) to 521.1 per 100 000 PY in western Europe (Germany). The incidence of psoriasis in children increased with age from 13.5 per 100 000 PY (0 to 3 years old) to 53.1 per 100 000 PY (14 to 18 year olds). Despite higher estimates of psoriasis incidence from the UK than the US, all of the studies showed a similar trend of increasing psoriasis incidence up to 39 years of age (Parisi et al, 2020).
Prevalence	• Psoriasis affects 1.5% to 3% of the general population in Europe and approximately 2% of the US population, with approximately 80% of patients experiencing mild to moderate disease (Menter et al, 2011; EMA CHMP, 2005). European populations have a higher prevalence than African and Asian populations (Michalek et al, 2017). The worldwide prevalence of psoriasis in children ranges from 0% to 1.37% (Michalek et al, 2017). In the US, the prevalence of psoriasis in children from birth to age 18 years is 1%, with an incidence of 40.8 per 100 000 (Tollefson et al, 2010). In Europe, the prevalence of pediatric psoriasis ranges between 0.17% and 1.5% (Peris et al, 2022). Plaque psoriasis, the most common form of psoriasis in both adults and children, represents approximately 80% to 90% of all psoriasis cases (Menter et al, 2008).
Demographics of population in the indication and risk factors for the disease	• Demographics of psoriasis from literature reports show that males have higher incidence than females after age 30 in the UK (Huerta et al, 2007). • Forty percent of psoriasis is diagnosed prior to 40 years of age in the UK (Huerta et al, 2007). • Up to 30% of all psoriatic patients show their first symptoms during childhood and adolescence. In a quarter of these children, psoriatic lesions appear within the first 2 years (Zappel et al, 2004). An analysis by Paller et al, 2018 of nearly 700 patients, showed that most children (72%) with moderate to severe psoriasis were aged between 12 to 17 years old. • In a study conducted in Denmark in 1981 (Schäfer, 2006), prevalence in men was 3.2% and 2.5% in women. Development of psoriasis is associated with family history, smoking, alcohol, stress, bacterial and viral infections (Neimann et al, 2006; Plunkett and Marks, 1998). • An analysis of the CPRD database (Huerta et al, 2007) reported statistically significant risk factors for psoriasis that included: body mass index (BMI) 30+ (relative risk [RR] = 1.33; 95% CI: 1.16-1.52), smoking (RR = 1.45; 95% CI: 1.31-1.59) and alcohol consumption of 20+ grams/week (RR = 1.06; 95% CI: 0.90-1.25).

Footnotes, including abbreviations, are defined on the last page of the table

Table 3. Summary of Epidemiology of Psoriasis

Main existing treatment options	• For patients with mild to moderate plaque psoriasis, topical agents, including topical corticosteroids, vitamin D analogues, calcineurin inhibitors, and keratolytics, remain the first line of treatment (Armstrong and Read, 2020). Systemic, conventional therapies, such as MTX, retinoids, and cyclosporine (approved for moderate to severe psoriasis) are often used off-label in mild to moderate cases when response to topical treatment is inadequate; however, these treatments have varied levels of effectiveness and are often associated with adverse reactions and dose-limiting toxicities (Nast et al, 2012; Menter et al, 2009). • Advances in the understanding of the biochemical mechanisms associated with psoriasis have led to the development of more specific biological therapies, across a variety of mechanisms of action (TNF, IL-17, IL-12/23, and IL-23). However, injection site reactions, infections, reactivation of tuberculosis, congestive heart failure, and new onset or exacerbation of demyelinating diseases may be safety concerns of these agents. Baseline and regular monitoring are advised for these biological therapies. In addition, these therapies are only approved for patients with moderate to severe disease (Singri et al, 2022; Krueger et al, 2007; Desai and Furst, 2006; Lebwohl et al, 2003; Chaudhari et al, 2001; Ellis et al, 2001; Gottlieb, 2001; Keane et al, 2001). Most pediatric patients present with mild, localized psoriasis that can be treated with topical therapy. Phototherapy is usually reserved for older children and adolescents with extensive areas of involvement or refractory plaque disease. Systemic medications, including conventional therapies such as methotrexate, retinoids, and cyclosporine or biologics, are utilized in children with moderate to severe plaque psoriasis. However, fewer therapies, including antibody therapies across mechanisms of action, are approved for pediatric patients with moderate to severe psoriasis compared with adults. Many children are treated off-label with the same agents approved for adults despite limited safety and efficacy information to support the use of these agents in a pediatric population (Kragballe et al, 2013; Marqueling and Cordoro, 2013; Shah, 2013; Ståhle et al, 2010; Chan et al, 2009).

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Footnotes, including abbreviations, are defined on the last page of the table

Table 3. Summary of Epidemiology of Psoriasis

Natural history of the indicated condition in the population including mortality and morbidity	• Psoriatic symptoms include scaling, flaking, itching, soreness, and pain of the skin. Other symptoms may include dry or cracked skin that may bleed, and thickened, pitted, or ridged nails. Symptoms can have considerable detrimental effects on a patient's quality of life, ability to function in daily activities, and overall social and societal engagement (Armstrong et al, 2012). Because plaque psoriasis is a chronic and lifelong disease, earlier diagnosis during childhood can have a profound long-term impact on children as well as their family's quality of life. When psoriasis affects body areas that are difficult to treat or are associated with a distinctly higher additional burden, such as the face, scalp, nails, genitals, palms, and soles, the impairment of the patient's quality of life can be profound. These difficult to treat body areas can be affected in patients regardless of the extent of body surface involvement or disease severity. As such, in patients with limited skin involvement, disease manifestations in difficult to treat areas can have a disproportionately negative impact on patient's quality of life and may not be adequately controlled by topical therapies alone (Egeberg et al, 2020). • Mortality estimates from large population-based studies range from 2.1% to 2.6% for all-cause mortality (Abuabara et al, 2010; Gelfand et al, 2007). • In an analysis of the CPRD database, patients with psoriasis were found to have a higher mortality rate compared to non-psoriasis patients (HR = 1.2; 95% CI: 1.13-1.3) (Springate et al, 2017).

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Footnotes, including abbreviations, are defined on the last page of the table

Table 3. Summary of Epidemiology of Psoriasis

Important comorbidities	• Psoriatic arthritis (Menter et al, 2020; Elmets et al, 2019). • Infection (Haddad et al, 2016). • Suicide (Wu et al, 2017; Egeberg et al, 2016). • Metabolic syndrome (Menter et al, 2020; Elmets et al, 2019; Augustin et al, 2010; Gisondi et al, 2007; Sommer et al, 2006). • Cardiovascular disease (Menter et al, 2020; Elmets et al, 2019; Augustin et al, 2010; Wakkee, 2010; Brauchli et al, 2008; Kaye et al, 2008; Gelfand et al, 2006). • Ischemic cerebrovascular disease (stroke and transient ischemic shock) (Takeshita et al, 2017; Ogdie and Weiss, 2015; Ogdie et al, 2015; Brauchli et al, 2009; Prodanovich et al, 2009; Brauchli et al, 2008; Kaye et al, 2008). • Obesity (Menter et al, 2020; Elmets et al, 2019; Takeshita et al, 2017; Augustin et al, 2010; Kaye et al, 2008; Neimann et al, 2006). • Hypertension (Takeshita et al, 2017; Augustin et al, 2010; Kaye et al, 2008; Neimann et al, 2006). • Insulin resistance/diabetes mellitus (Takeshita et al, 2017; Augustin et al, 2010; Kaye et al, 2008; Neimann et al, 2006). • Hyperlipidemia/dyslipidemia (Menter et al, 2020; Elmets et al, 2019; Takeshita et al, 2017; Augustin et al, 2010; Kaye et al, 2008; Neimann et al, 2006). • Cancer (Takeshita et al, 2017; Yong et al, 2012; Ji et al, 2009; Brauchli et al, 2008; Gelfand et al, 2003; Boffetta et al, 2001; Frentz and Olsen, 1999; Bhate et al, 1993). • Depression and anxiety (Takeshita et al, 2017; Pompili et al, 2016; Kurd et al, 2010; Schmitt and Ford, 2007; Esposito et al, 2006). • Sleep disorders (Takeshita et al, 2017; Gowda et al, 2010). • Inflammatory bowel disease (ulcerative colitis and Crohn's disease) (Takeshita et al, 2017; Augustin et al, 2010; Gulliver, 2008).

BMI = body mass index; CHMP = Committee for Medicinal Products for Human Use; CPRD = Clinical Practice Research Database; EMA = European Medicines Agency; HR = hazard ratio; IL = interleukin; MTX = methotrexate; PY = patient-years; RR = relative risk; TNF = tumor necrosis factor; UK = United Kingdom; US = United States

Table 4. Summary of Epidemiology of Behçet's Disease

Incidence	• There are few estimates of incidence of BD in Europe. Published rates range from 0.2 to 7.1 per 100 000 PY from available studies in the literature (Mohammad et al, 2013; Mahr et al, 2008; Salvarani et al, 2007; Zouboulis, 1999; Zouboulis et al, 1997). Incidence rates vary by population studied and country of study.
Prevalence	• Prevalence varies greatly by geography and population studied. Rates are higher in Turkey and Japan and lower in Northern Europe and US (Mendes et al, 2009). • In Europe, the prevalence ranges from 0.64 per 100 000 inhabitants in the UK to 7.5 per 100 000 inhabitants in Spain (Davatchi et al, 2017). • Prevalence in Turkey and Asian nations ranges from 2.1 per 100 000 inhabitants (in Kuwait) to 420 per 100 000 in Turkey (Mahr et al, 2008; Zouboulis, 1999). • Prevalence ranges from 0.27 to 7.5 per 100 000 inhabitants in Europe and North America (Mohammad et al, 2013; Calamia et al, 2009; Mahr et al, 2008; Salvarani et al, 2007; Papoutsis et al, 2006; Zouboulis, 1999; Zouboulis et al, 1997).
Demographics of population in the indication and risk factors for the disease	• Distribution of BD by gender varies greatly depending on the population studied. • Overall, prevalence in males is higher and estimated to be 8.1 per 100 000 inhabitants while prevalence in females is estimated to be 6.1 per 100 000 inhabitants in a French study (Davatchi et al, 2017; Mahr et al, 2008). • In Asia, studies show male to female ratios ranging from 0.63:1 (South Korea) to 3.4:1 (Saudi Arabia) (Zouboulis, 1999). • In Europe, studies show male to female ratios ranging from 0.36:1 (Scotland) to 2.44:1 (Italy) (Zouboulis, 1999). • In the Americas, studies show male to female ratios ranging from 0.42:1 (US) to 4:1 (Chile) (Zouboulis, 1999). • A study of 6500 BD patients in Iran reported highest distribution of cases in the 21 to 30 age group (41.3%) (Davatchi et al, 2010). • Several risk factors have been proposed for BD (Alpsoy, 2016; Hatemi et al, 2014; Mendes et al, 2009). • Genetic: – Human leukocyte antigen (HLA)-B51 and HLA-A26: Shown in several studies to be associated with BD in German and Turkish populations. – GTPase, IMAP Family Member (GIMAP): Studies of Korean and Japanese BD patients showed association with GIMAP locus. – Interleukin-10: A study in China showed association between IL10 polymorphisms and BD initiation. – Complement C4 copy number variations: A study of a Chinese BD population showed increased frequency of more than 2 copies of C4A as compared to non-BD patients.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 4. Summary of Epidemiology of Behçet's Disease

Demographics of population in the indication and risk factors for the disease (continued)	• Environmental: – Bacterial: Several studies suggest an association between *Streptococcus sanguinis* and *Helicobacter pylori* infections with BD. – Viral: Herpes simplex I has been proposed but not definitively proven to play a role in the pathogenesis of BD.
Main existing treatment options	• There are currently no approved drugs for the treatment of BD or any BD-related manifestation, throughout the EU via the centralized procedure. A few drugs are approved nationally for the treatment of the various manifestations of BD, which are generally consistent with the EULAR guideline (Hatemi et al, 2018). • The treatment of mucocutaneous involvement depends on the severity of the disease: – Topical treatment with steroid preparations is often used first-line for the treatment of mucocutaneous manifestations. In addition to topical corticosteroids, supportive care, including lidocaine gel and/or chlorhexidine, are also used for oral ulcers (Hatemi et al, 2008). – For patients with more severe disease or who have recurrent mucocutaneous lesions (especially when the dominant lesion is erythema nodosum or genital ulcer), colchicine is recommended to be tried first for prevention (Hatemi et al, 2018). – Drugs such as azathioprine, thalidomide, interferon-α, or TNF-α inhibitors are recommended to be considered in selected and resistant cases (Hatemi et al, 2018).
Natural history of the indicated condition in the population including mortality and morbidity	• A study of 817 French patients with BD reported 5% mortality after a median follow up of 7.7 years. Mortality rates at years 1, 3, 5, and 10 were 1.2%, 2.1%, 3.3%, and 4.3%, respectively, with a mean age of death at 34.8 years (Saadoun et al, 2010). • The age of onset (ie, morbidity) for the majority of reported cases of BD occurs in the third decade of life (Davatchi et al, 2017). • In most cases, patients start with 1 manifestation and a secondary manifestation occurs several months later. The most frequent first manifestation is oral aphthosis (82.1% in 1 study) followed by genital aphthosis (10%), uveitis (8.6%), retinal vasculitis (0.3%), joint manifestations (4.3%), and all other manifestations in 7.5% of patients (Davatchi et al, 2017).

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 4. Summary of Epidemiology of Behçet's Disease

Important comorbidities	• Depression/suicide (de Oliveira Ribeiro et al, 2014; Dursun et al, 2007; Taner et al, 2007; Gur et al, 2006). • Anxiety (Dursun et al, 2007; Karlidag et al, 2003). • Major adverse cardiovascular event (MACE)/cardiovascular disease (Ulusan et al, 2014; Owlia and Mehrpoor, 2012). • Vasculitis (Cebeci et al, 2014; Ulusan et al, 2014; Owlia and Mehrpoor, 2012). • Serious infections (Talarico et al, 2013). • Malignancy (Ahn et al, 2010; Cengiz et al, 2001). • Eye disorders (Hatemi et al, 2014; Davatchi et al, 2010; Dinc et al, 2005; Zierhut et al, 1995). • Gastrointestinal (Vaiopoulos et al, 2014; Davatchi et al, 2010). • Headaches (Davatchi et al, 2010; Kidd, 2006).

BD = Behçet's disease; EU = European Union; EULAR = European League against Rheumatism; GIMAP = GTPase, IMAP Family Member; HLA = human leucocyte antigen; IL = interleukin; MACE = major adverse cardiovascular event; PY = patient-years; TNF = tumor necrosis factor; UK = United Kingdom; US = United States

Part II: Module SII - Nonclinical Part of the Safety Specification

Nonclinical data of apremilast revealed no special hazard for humans based on conventional studies of safety pharmacology, single- and repeat-dose toxicity. Apremilast is not genotoxic, carcinogenic, nor teratogenic. There is also no evidence for immunotoxic, dermal irritation, or phototoxic potential.

A summary of the nonclinical findings and their relevance to human usage is outlined in Table 5.

Table 5. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity		
• Repeat-dose Toxicity	Following repeated administration of apremilast, clinical manifestations of toxicity in mice, rats, and monkeys were dose-related and included mortality (mouse and rat only), increases in body weight and food consumption (mouse), and emesis (monkey). Reversible dose-related inflammatory responses included neutrophilia, lymphopenia, and changes in serum proteins (decreased albumin, increased globulin, and increased haptoglobin, C-reactive protein [CRP], and/or fibrinogen) which were predominantly observed in mice and rats. These inflammatory responses were associated with arteritis and perivascular inflammation in various organs (mesentery, heart, lungs, thymus, liver, skeletal muscle, mammary gland, skin, and pancreas) in mice and rats, but not in monkeys even at higher systemic exposures than those achieved in mice and rats. Other target organs of apremilast toxicity include non-adverse centrilobular hepatocellular hypertrophy in the liver (mouse) and variable lymphoid depletion in lymphoid tissues (mouse and rat). The inflammatory response and findings of lymphoid depletion were largely resolved even in the presence of continued treatment of apremilast. In a mouse recovery study, histological lesions that were observed in the thymus, mesenteric lymph nodes and liver after 3 or 14 days of dosing were fully recovered/resolved after either a 31- or 76-day recovery period, or with continued dosing for 90 days.	In a phase 2 study (PSOR-003), a pro-inflammatory panel that included antinuclear antibody (ANA) and serum antineutrophilic cytoplasmic antibody was routinely measured at baseline, weeks 4, 8, and 12. In this study, there were no differences between treatment groups in the number of subjects with improvement or worsening of ANA titers at the end of the treatment phase. None of the mean changes in the pro-inflammatory syndrome biomarker panel was considered to be clinically relevant, and no subject exhibited any clinical signs or symptoms of a pro-inflammatory syndrome. In addition, there were no notable findings in the immunology parameters. Furthermore, there were no notable changes in clinical laboratory tests or peripheral blood markers of inflammation (white blood cell or neutrophil counts, erythrocyte sedimentation rate, albumin, fibrinogen, or CRP) monitored in the phase 2 clinical studies. Lymphocyte and neutrophil counts were assessed in the clinical studies on a regular basis. At the end of the placebo-controlled period, the proportions of subjects with shifts from normal to abnormal lymphocytes (normal to low) and neutrophils (normal to high) were similar between treatment groups and the mean SD changes in these laboratory parameters were also similar between treatment groups. Long-term exposure to apremilast did not indicate that apremilast has any effect on lymphocyte or neutrophil counts, based on laboratory shift tables.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 5. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity (continued)		
• Repeat-dose Toxicity (continued)	The no observed adverse effect levels (NOAELs) for the 6-month mouse and 12-month monkey studies, the longest duration repeat-dose toxicity studies completed in rodent and non-rodent species, were 10 and 600 mg/kg/day, respectively. Plasma exposures at these NOAEL dosages were 5728 and 34 772 ng•h/mL, respectively (0.8- and 4.8-fold clinical exposure). Because of the low exposure multiple at the NOAEL in mice and the findings that apremilast appears to cause inflammation in rodents, a series of investigative studies was performed. An in vitro study (Report 5265-117) demonstrated that PDE4 inhibitors, including apremilast, roflumilast, and cilomilast, are pro-inflammatory in rodents, but not in monkeys or humans. These in vitro findings indicate that rodents are more sensitive to PDE4 inhibitor-induced inflammatory response than humans and monkeys, and provided potential mechanistic support for the absence of overt inflammatory effects in monkeys treated with apremilast and the established safety profile for apremilast in human clinical trials.	Small vessel cutaneous vasculitis was reported in 3 subjects: 2 in the phase 2 Study RA-002 (1 in the apremilast 30 mg BID treatment group and 1 in the placebo treatment group) and 1 case of mild cutaneous vasculitis was reported in a subject receiving apremilast 30 mg BID in Study PSA-005. Overall, there is no evidence of an increased risk of vasculitis with apremilast treatment. Markedly abnormal laboratory test results (including liver function tests) among apremilast treated subjects over the longer term were infrequent and transient. There were no cases of liver enzyme elevations meeting Hy's Law criteria. Centrilobular hepatocellular hypertrophy has not been reported in the apremilast clinical development program.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 5. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity (continued)		
• Reproductive/ developmental toxicity	Reproductive and developmental effects of apremilast included prolongation of estrous cycles in mice, prenatal embryo-fetal loss in mice and monkeys, and delayed fetal development (reduced ossification and fetal weight) in mice. The NOAEL for male fertility in mice was > 50 mg/kg/day (2.9-fold clinical area under curve [AUC]), and the no observed effect level (NOEL) for female fertility in mice was 10 mg/kg/day (1.0-fold clinical AUC). In the embryo-fetal development studies, the maternal and developmental NOEL in mice and NOAEL in monkeys were 10 and 20 mg/kg/day (1.3- and 1.4-fold clinical AUC), respectively. In a pre- and post-natal study in mice, a low incidence of maternal clinical signs (in 1 animal/group) associated with delivering pups, and increased peri- and postnatal pup mortality and reduced pup body weights through day 7 of lactation were observed at 80 and 300 mg/kg/day; the NOEL for maternal toxicity and F_1 generation was 10 mg/kg/day (1.3-fold clinical AUC). Apremilast was not teratogenic in mice or monkeys. Apremilast was detected in the milk of lactating mice.	Effects of apremilast on pregnancy included embryo-fetal loss in mice and monkeys, and reduced fetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. There are no adequate and well-controlled studies of apremilast in pregnant women. It is not known whether apremilast, or its metabolites, are excreted in human milk. Apremilast is contraindicated in pregnancy. Information concerning the use of apremilast in pregnancy and breastfeeding is provided in the product label. Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast is included as an important potential risk (see Table 42).
• Genotoxicity/ carcinogenicity	Apremilast is not genotoxic or carcinogenic. Carcinogenicity studies showed no increase in tumor incidence related to treatment with apremilast in mice or rats.	No relevance to human usage.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 5. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Safety pharmacology		
• Safety pharmacology/ cardiovascular effects	The nonclinical safety pharmacology studies established that there were no major safety concerns resulting from apremilast in the central nervous system and behavioral function, or on gastrointestinal motility in mice. Also, there were no major safety concerns with cardiovascular and respiratory functions in dogs. In the repeat-dose toxicity studies in monkeys with durations of up to 12 months, there were no treatment related abnormalities in electrocardiogram (ECG) parameters or heart rate in any studies. The highest dosage in the longest duration 12-month study was 600 mg/kg/day (mean AUC_{24h} = 34 772 ng•h/mL, which was 4.8-fold clinical exposure; mean maximum concentration (C_{max}) = 3450 ng/mL, which was 5.1-fold clinical C_{max} value). In addition, the half maximal inhibitory concentration (IC_{50}) for the inhibitory effect of apremilast on the human Ether à go-go-Related Gene (hERG) current was estimated to be 184.2 µM (84.8 µg/mL; Hill coefficient = 1.1); this represents a margin of 127-fold over the clinical C_{max}.	Apremilast was evaluated in a human thorough QT/QTc study up to 50 mg BID and demonstrated no treatment related effects on QT/QTc interval or heart rate, vital signs or clinical laboratory parameters. For the PsA and psoriasis phase 3 studies, few male or female subjects showed QTc elevations of ≥ 450 or ≥ 470 msec, respectively, and few subjects had a change from baseline of ≥ 60 msec. Dose dependent changes were not observed. The majority of these subjects had abnormal ECGs at screening or at baseline. In conclusion, there is no relevance of these nonclinical findings to human use.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 5. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Other toxicity-related information or data		
• Nonclinical pharmacokinetics	The nonclinical absorption, distribution, metabolism and excretion of apremilast have been well characterized in the animal models used for toxicity testing and are similar to the profile observed in humans. Overall, the metabolites formed in humans are formed in 1 or more animal species used for safety evaluation and there are no unique human metabolites. In vitro apremilast undergoes non enzymatic hydrolysis as well as *O*-demethylation, which is primarily catalyzed by cytochrome P450 (CYP) 3A4. The major circulating inactive metabolite is the glucuronide conjugate of *O*-demethylated apremilast (M12). Apremilast is not anticipated to cause clinically relevant inhibition or induction of CYP enzymes at therapeutic doses. Apremilast is a substrate for permeability glycoprotein (P-gp), but still has good oral bioavailability in humans (> 70%). Apremilast is not a substrate for other drug transporters (breast cancer resistance protein [BCRP], organic anion transporter [OAT]1, OAT3, organic cation transporter [OCT]2, organic anion transporting polypeptide [OATP]1B1 or OATP1B3). Additionally, apremilast is not expected to cause clinically relevant inhibition of drug transporters (P-gp, BCRP, multidrug resistance protein [MRP]1, MRP2, MRP3, MRP4, OAT1, OAT3, OCT2, OATP1B1, or OATP1B3) at therapeutic doses.	Apremilast exposure is decreased when administered concomitantly with strong inducers of CYP3A4 (eg, US Adopted Name rifampicin, INN rifampin) and may result in a reduced clinical response. Ketoconazole co-administration increased mean apremilast $AUC_{0-\infty}$ and C_{max} by approximately 36% and by 5%, respectively, which is not clinically meaningful. Apremilast can be co-administered with a potent CYP3A4 inhibitor like ketoconazole.

ANA = antinuclear antibody; AUC = area under curve; BCRP = breast cancer resistance protein; BID = twice daily; C_{max} = maximum concentration CRP = C-reactive protein; CYP = cytochrome P450; ECG = electrocardiogram; hERG = human Ether à go-go-Related Gene; IC_{50} = half maximal inhibitory concentration; INN = International Nonproprietary Name; M12 = glucuronide conjugate of *O*-demethylated apremilast; MRP = multidrug resistance protein; NOAEL = no observed adverse effect level; NOEL = no observed effect level; OCT = organic cation transporter; OAT = organic anion transporter; OATP = organic anion transporting polypeptide; PDE = phosphodiesterase; P-gp = permeability glycoprotein; PsA = psoriatic arthritis; US = United States

Part II: Module SIII - Clinical Trial Exposure

The data presented in this section for PsA are for 4 completed adult phase 3 studies CC-10004-PSA-002, CC-10004-PSA-003, CC-10004-PSA-004, and CC-10004-PSA-005 (hereafter referred to as PSA-002, PSA-003, PSA-004, and PSA-005).

For psoriasis, data are provided for 3 pediatric studies (completed Study CC-10004-PPSO-001 [phase 2], completed Study CC-10004-PPSO-003 [phase 3], and ongoing long-term extension Study CC-10004-PPSO-004 [phase 3b; data cut-off 27 March 2023]; hereafter referred to as PPSO-001, PPSO-003, and PPSO-004) and 2 completed adult phase 3 studies CC-10004-PSOR-008 and CC-10004-PSOR-009 (hereafter referred to as PSOR-008 and PSOR-009). Pooled data are also provided for the PsA and psoriasis adult studies combined.

The data presented in this section for BD are for 1 completed adult phase 3 study CC-10004-BCT-002 (hereafter referred to as BCT-002)

A total of 1945 adult subjects who have received apremilast in the 4 PsA clinical studies, 1184 adult subjects and 277 pediatric subjects who have received apremilast in the 2 adult and 3 pediatric psoriasis clinical studies, respectively, and 207 subjects who have received apremilast in the BD clinical study, are included in the RMP.

Additional exposure data for the pediatric and adult studies are presented below.

Pediatric Clinical Studies

Table 6. Duration of Exposure in Subjects Exposed to Apremilast in Study PPSO-001 (Safety Population)

	Group 1 (Adolescents[a])			Group 2 (Children[b])	Group 1 and 2		
	APR 20 BID n (%) (N = 13)	APR 30 BID n (%) (N = 8)	Total n (%) (N = 21)	APR 20 BID n (%) (N = 21)	APR 20 BID n (%) (N = 34)	APR 30 BID n (%) (N = 8)	Total n (%) (N = 42)
Treatment Duration, Weeks[c]							
Mean (SD)	39.01 (17.620)	48.14 (7.055)	42.49 (14.978)	41.31 (17.970)	40.43 (17.603)	48.14 (7.055)	41.90 (16.350)
Median (Min, Max)	50.00 (0.3, 53.0)	50.57 (30.7, 51.3)	50.14 (0.3, 53.0)	50.00 (0.7, 55.9)	50.00 (0.3, 55.9)	50.57 (30.7, 51.3)	50.07 (0.3, 55.9)
Distribution of Treatment Duration (Weeks), n (%)							
< 1	1 (7.7)	0	1 (4.8)	1 (4.8)	2 (5.9)	0	2 (4.8)
1 to < 4	0	0	0	1 (4.8)	1 (2.9)	0	1 (2.4)
4 to < 8	0	0	0	1 (4.8)	1 (2.9)	0	1 (2.4)
8 to < 16	1 (7.7)	0	1 (4.8)	0	1 (2.9)	0	1 (2.4)
16 to < 24	1 (7.7)	0	1 (4.8)	0	1 (2.9)	0	1 (2.4)
24 to < 32	1 (7.7)	1 (12.5)	2 (9.5)	2 (9.5)	3 (8.8)	1 (12.5)	4 (9.5)
32 to < 40	0	0	0	0	0	0	0
40 to < 48	1 (7.7)	0	1 (4.8)	0	1 (2.9)	0	1 (2.4)
≥ 48	8 (61.5)	7 (87.5)	15 (71.4)	16 (76.2)	24 (70.6)	7 (87.5)	31 (73.8)

APR 20 BID = apremilast 20 mg twice daily; APR 30 BID = apremilast 30 mg twice daily; Max = maximum; Min = minimum

[a] Adolescents are 12 to 17 years of age.

[b] Children are 6 to 11 years of age.

[c] Treatment duration was the time interval in weeks between the date of the first dose of apremilast and the last dose of apremilast in the Treatment Period, inclusive.

The N value was the number of subjects in the Safety Population.

Source: PPSO-001 CSR Table 14.1.10

Table 7. Duration of Exposure in Study PPSO-003

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated		
Parameter	PBO (N = 80)	20 mg BID (N = 116)	30 mg BID (N = 119)	Apremilast Total (N = 235)
Treatment duration (weeks)[a,b]				
Mean	15.24	42.79	41.09	41.93
SD	2.649	13.425	13.898	13.664
Median	16.00	51.70	51.30	51.70
Q1, Q3	15.90, 16.10	36.10, 52.10	35.70, 52.00	36.00, 52.00
Min, Max	3.7, 17.0	2.3, 58.9	1.7, 57.0	1.7, 58.9
Treatment duration categories - n (%)				
< 4 weeks	2 (2.5)	2 (1.7)	3 (2.5)	5 (2.1)
≥ 4 to < 8 weeks	1 (1.3)	3 (2.6)	3 (2.5)	6 (2.6)
≥ 8 to < 12 weeks	4 (5.0)	3 (2.6)	2 (1.7)	5 (2.1)
≥ 12 to < 16 weeks	20 (25.0)	0 (0.0)	1 (0.8)	1 (0.4)
≥ 16 to < 20 weeks	53 (66.3)	3 (2.6)	2 (1.7)	5 (2.1)
≥ 20 to < 24 weeks	NA	0 (0.0)	4 (3.4)	4 (1.7)
≥ 24 to < 28 weeks	NA	2 (1.7)	1 (0.8)	3 (1.3)
≥ 28 to < 32 weeks	NA	1 (0.9)	2 (1.7)	3 (1.3)
≥ 32 to < 36 weeks	NA	8 (6.9)	17 (14.3)	25 (10.6)
≥ 36 to < 40 weeks	NA	26 (22.4)	19 (16.0)	45 (19.1)
≥ 40 to < 44 weeks	NA	1 (0.9)	5 (4.2)	6 (2.6)
≥ 44 to < 48 weeks	NA	1 (0.9)	0 (0.0)	1 (0.4)
≥ 48 to < 52 weeks	NA	16 (13.8)	12 (10.1)	28 (11.9)
≥ 52 weeks	NA	50 (43.1)	48 (40.3)	98 (41.7)

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Footnotes are defined on the last page of the table.

Table 7. Duration of Exposure in Study PPSO-003

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated		
Parameter	PBO (N = 80)	20 mg BID (N = 116)	30 mg BID (N = 119)	Apremilast Total (N = 235)
Exposure category - n (%)				
≥ 1 day	80 (100)	116 (100)	119 (100)	235 (100)
≥ 4 weeks	78 (97.5)	114 (98.3)	116 (97.5)	230 (97.9)
≥ 8 weeks	77 (96.3)	111 (95.7)	113 (95.0)	224 (95.3)
≥ 12 weeks	73 (91.3)	108 (93.1)	111 (93.3)	219 (93.2)
≥ 16 weeks	53 (66.3)	105 (90.5)	104 (87.4)	209 (88.9)
≥ 24 weeks		105 (90.5)	104 (87.4)	209 (88.9)
≥ 32 weeks		102 (87.9)	101 (84.9)	203 (86.4)
≥ 36 weeks		94 (81.0)	84 (70.6)	178 (75.7)
≥ 40 weeks		68 (58.6)	65 (54.6)	133 (56.6)
≥ 48 weeks		66 (56.9)	60 (50.4)	126 (53.6)
≥ 52 weeks		50 (43.1)	48 (40.3)	98 (41.7)

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BID = twice daily; NA = not applicable; PBO = placebo
The 20 mg BID, 30 mg BID, and apremilast total groups include data during the apremilast treatment for subjects who received apremilast 20 mg BID, 30 mg BID, and either 20 or 30 mg BID regardless of whether the apremilast started at week 0 or week 16.
[a] Treatment duration (in weeks) is calculated from the date of the first dose of investigational product at week 0/Visit 2 to either the date 1 day before the first dose date in the apremilast extension phase for the investigational product dispense at week 16/Visit 7, or the date of the last dose of investigational product in the study for subjects who discontinue in the phase.
[b] Treatment duration for apremilast-exposure period is calculated from the date of the first dose of apremilast, which is the date of the first dose of apremilast after randomization at week 0/Visit 2 or switched to apremilast at week 16/Visit 7, to the last apremilast dose date for subjects who discontinue in the first 52 weeks or who complete the study at week 52/Visit 16.
Source: PPSO-003 CSR Table 14-5.1.1 and Table 14-5.1.2

Table 8. Treatment Duration in Study PPSO-004 (Long-term Extension Treatment Population)

Parameter	APR Total (N=160)
Treatment Duration (weeks)[a]	
Mean	48.52
SD	36.264
Median	37.90
Q1, Q3	13.60, 78.70
Min, Max	2.1, 157.0
Treatment Duration Categories (weeks) - n (%)	
< 1	0 (0.0)
≥ 1 to < 4	2 (1.3)
≥ 4 to < 13	9 (5.6)
≥ 13 to < 26	46 (28.8)
≥ 26 to < 39	24 (15.0)
≥ 39 to < 52	12 (7.5)
≥ 52 to < 78	21 (13.1)
≥ 78 to < 104	18 (11.3)
≥ 104 to < 130	26 (16.3)
≥ 130 to < 156	1 (0.6)
≥ 156 to < 182	1 (0.6)
≥ 182 to < 208	0 (0.0)
≥ 208	0 (0.0)

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Footnotes are defined on the last page of the table.

Table 8. Treatment Duration in Study PPSO-004 (Long-term Extension Treatment Population)

Parameter	APR Total (N=160)
Exposure Category - n (%)	
≥ 1 day	160 (100)
≥ 1 week	160 (100)
≥ 4 weeks	158 (98.8)
≥ 13 weeks	149 (93.1)
≥ 26 weeks	103 (64.4)
≥ 39 weeks	79 (49.4)
≥ 52 weeks	67 (41.9)
≥ 78 weeks	46 (28.8)
≥ 104 weeks	28 (17.5)
≥ 130 weeks	2 (1.3)
≥ 156 weeks	1 (0.6)
≥ 182 weeks	0 (0.0)
≥ 208 weeks	0 (0.0)

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APR = apremilast
[a] Treatment duration (in weeks) is calculated from the first dose date in PPSO-004 to the last dose date in PPSO-004 for completed subjects or to the latest study date for ongoing subjects.
Source: PPSO-004 Interim CSR Table 14-5.1

Table 9. Treatment Duration in the Apremilast-exposure Period (From Study PPSO-003 to Study PPSO-004) (Long-term Extension Treatment Population)

Parameter	APR Total (N=160)
Treatment Duration (weeks)[a]	
n	160
Mean	95.38
SD	36.891
Median	85.15
Q1, Q3	65.10, 130.30
Min, Max	38.1, 193.3
Treatment Duration Categories (weeks) - n (%)	
< 1	0 (0.0)
≥ 1 to < 16	0 (0.0)
≥ 16 to < 32	0 (0.0)
≥ 32 to < 48	1 (0.6)
≥ 48 to < 52	13 (8.1)
≥ 52 to < 65	21 (13.1)
≥ 65 to < 78	29 (18.1)
≥ 78 to < 91	27 (16.9)
≥ 91 to < 104	9 (5.6)
≥ 104 to < 130	19 (11.9)
≥ 130 to < 156	21 (13.1)
≥ 156 to < 182	18 (11.3)
≥ 182 to < 208	2 (1.3)
≥ 208 to < 234	0 (0.0)
≥ 234 to < 260	0 (0.0)
≥ 260	0 (0.0)

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Footnotes are defined on the last page of the table.

Table 9. Treatment Duration in the Apremilast-exposure Period (From Study PPSO-003 to Study PPSO-004) (Long-term Extension Treatment Population)

Exposure Category - n (%)	APR Total (N=160)
≥ 1 day	160 (100)
≥ 16 weeks	160 (100)
≥ 32 weeks	160 (100)
≥ 48 weeks	159 (99.4)
≥ 52 weeks	146 (91.3)
≥ 65 weeks	125 (78.1)
≥ 78 weeks	96 (60.0)
≥ 91 weeks	69 (43.1)
≥ 104 weeks	60 (37.5)
≥ 130 weeks	41 (25.6)
≥ 156 weeks	20 (12.5)
≥ 182 weeks	2 (1.3)
≥ 208 weeks	0 (0.0)
≥ 234 weeks	0 (0.0)
≥ 260 weeks	0 (0.0)

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APR = apremilast
[a] Treatment duration is calculated from the first APR dose date in PPSO-003 to the last APR dose date in PPSO-004 for completed subjects or to the latest study date for ongoing subjects.
Source: PPSO-004 Interim CSR Table 14-5.2

Table 10. Exposure by Age Group and Gender in Subjects Exposed to Apremilast in Study PPSO-001 (Safety Population)

	Group 1 (Adolescents[a])			Group 2 (Children[b])	Group 1 and 2		
	APR 20 BID n (%) (N = 13)	APR 30 BID n (%) (N = 8)	Total n (%) (N = 21)	APR 20 BID n (%) (N = 21)	APR 20 BID n (%) (N = 34)	APR 30 BID n (%) (N = 8)	Total n (%) (N = 42)
Age (years)							
n	13	8	21	21	34	8	42
Mean	13.8	14.8	14.2	9.3	11.1	14.8	11.8
SD	1.77	2.05	1.89	1.35	2.68	2.05	2.95
Median	13.0	16.0	14.0	10.0	10.5	16.0	11.5
Min, Max	12, 17	12, 17	12, 17	7, 11	7, 17	12, 17	7, 17
Age Category (years), n (%)							
6 to 11	0	0	0	21 (100)	21 (61.8)	0	21 (50.0)
12 to 17	13 (100)	8 (100)	21 (100)	0	13 (38.2)	8 (100)	21 (50.0)
Sex, n (%)							
Male	4 (30.8)	7 (87.5)	11 (52.4)	8 (38.1)	12 (35.3)	7 (87.5)	19 (45.2)
Female	9 (69.2)	1 (12.5)	10 (47.6)	13 (61.9)	22 (64.7)	1 (12.5)	23 (54.8)

APR 20 BID = apremilast 20 mg twice daily; APR 30 BID = apremilast 30 mg twice daily; Max = maximum; Min = minimum

[a] Adolescents are 12 to 17 years of age.

[b] Children are 6 to 11 years of age.

Source: PPSO-001 CSR Table 14.1.5.1

Table 11. Exposure by Age Group and Gender in Study PPSO-003 (Safety Population)

Parameter	Placebo (N = 80)	Apremilast (N = 163)	Total (N = 243)
Age (years)			
Mean	12.3	12.3	12.3
SD	3.23	3.32	3.29
Median	13.0	13.0	13.0
Q1, Q3	9.0, 15.0	10.0, 15.0	9.0, 15.0
Min, Max	6, 17	6, 17	6, 17
Age category - n (%)			
6 to 11 years	32 (40.0)	67 (41.1)	99 (40.7)
12 to 17 years	48 (60.0)	96 (58.9)	144 (59.3)
Sex - n (%)			
Male	43 (53.8)	74 (45.4)	117 (48.1)
Female	37 (46.3)	89 (54.6)	126 (51.9)

Q1 = First quartile; Q3 = Third quartile; Min = minimum; Max = maximum
Note: Percentages are based on the number of subjects in each treatment group.
Source: PPSO-003 Table 14-2.1.1

Table 12. Exposure by Age Group and Gender in Subjects Exposed to Apremilast in Study PPSO-004 (Long-term Extension Treatment Population)

Parameter	Placebo/APR (N = 54)	APR/APR (N = 106)	Total (N = 160)
Age (years)			
Mean	12.8	12.9	12.9
SD	3.01	3.20	3.13
Median	13.0	13.0	13.0
Q1, Q3	10.0, 16.0	11.0, 16.0	10.0, 16.0
Min, Max	8, 17	7, 17	7, 17
Age Categories (years) - n (%)			
6 - 11	20 (37.0)	42 (39.6)	62 (38.8)
12 - 17	34 (63.0)	64 (60.4)	98 (61.3)
Sex - n (%)			
Male	27 (50.0)	48 (45.3)	75 (46.9)
Female	27 (50.0)	58 (54.7)	85 (53.1)

APR = apremilast
This table summarized value at first visit in the Long-term Extension Study.
Placebo/apremilast refers to subjects who received placebo at the start and switched to apremilast at week 16 of the core study; apremilast/apremilast refers to subjects who received apremilast at the start of the core study.
Percentages are based on the number of subjects in each treatment group.
Source: PPSO-004 Interim CSR Table 14-2.1

Table 13. Exposure by Race and Ethnic Origin in Subjects Exposed to Apremilast in Study PPSO-001 (Safety Population)

	Group 1 (Adolescents[a])			Group 2 (Children[b])	Group 1 and 2		
	APR 20 BID n (%) (N = 13)	APR 30 BID n (%) (N = 8)	Total n (%) (N = 21)	APR 20 BID n (%) (N = 21)	APR 20 BID n (%) (N = 34)	APR 30 BID n (%) (N = 8)	Total n (%) (N = 42)
Race, n (%)							
American Indian or Alaska Native	0	0	0	0	0	0	0
Asian	2 (15.4)	0	2 (9.5)	2 (9.5)	4 (11.8)	0	4 (9.5)
Black or African American	0	0	0	2 (9.5)	2 (5.9)	0	2 (4.8)
Native Hawaiian or other Pacific Islander	0	1 (12.5)	1 (4.8)	0	0	1 (12.5)	1 (2.4)
White or Caucasian	10 (76.9)	6 (75.0)	16 (76.2)	16 (76.2)	26 (76.5)	6 (75.0)	32 (76.2)
Other	1 (7.7)	1 (12.5)	2 (9.5)	1 (4.8)	2 (5.9)	1 (12.5)	3 (7.1)

APR 20 BID = apremilast 20 mg twice daily; APR 30 BID = apremilast 30 mg twice daily; Max = maximum; Min = minimum

[a] Adolescents are 12 to 17 years of age.

[b] Children are 6 to 11 years of age.

Source: PPSO-001 CSR Table 14.1.5.1

Table 14. Exposure by Race and Ethnic Origin in Study PPSO-003 (Safety Population)

Parameter	Placebo (N = 80)	Apremilast (N = 163)	Total (N = 243)
Race - n (%)			
White	71 (88.8)	140 (85.9)	211 (86.8)
Black or African American	3 (3.8)	5 (3.1)	8 (3.3)
Asian	3 (3.8)	6 (3.7)	9 (3.7)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaskan Native	0 (0.0)	2 (1.2)	2 (0.8)
Not collected or unknown	3 (3.8)	10 (6.1)	13 (5.3)
Ethnicity - n (%)			
Hispanic or Latino	8 (10.0)	24 (14.7)	32 (13.2)
Not Hispanic or Latino	69 (86.3)	129 (79.1)	198 (81.5)
Not reported	3 (3.8)	5 (3.1)	8 (3.3)
Unknown	0 (0.0)	5 (3.1)	5 (2.1)

Q1 = First quartile; Q3 = Third quartile; Min = minimum; Max = maximum
Note: Percentages are based on the number of subjects in each treatment group.
Source: PPSO-003 Table 14-2.1.1

Table 15. Exposure by Race and Ethnic Origin in Subjects Exposed to Apremilast in PPSO-004 (Long-term Extension Treatment Population)

Parameter	Placebo/APR (N = 54)	APR/APR (N = 106)	Total (N = 160)
Race - n (%)			
White	49 (90.7)	100 (94.3)	149 (93.1)
Black	1 (1.9)	2 (1.9)	3 (1.9)
Asian	3 (5.6)	1 (0.9)	4 (2.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)
Not Collected or Unknown	1 (1.9)	3 (2.8)	4 (2.5)
Ethnicity - n (%)			
Hispanic or Latino	5 (9.3)	14 (13.2)	19 (11.9)
Not Hispanic or Latino	47 (87.0)	89 (84.0)	136 (85.0)
Not Reported	2 (3.7)	1 (0.9)	3 (1.9)
Unknown	0 (0.0)	2 (1.9)	2 (1.3)

APR = apremilast
This table summarized value at first visit in the Long-term Extension Study.
Placebo/apremilast refers to subjects who received placebo at the start and switched to apremilast at week 16 of the core study; apremilast/apremilast refers to subjects who received apremilast at the start of the core study.
Percentages are based on the number of subjects in each treatment group.
Source: PPSO-004 Interim CSR Table 14-2.1

Adult Clinical Studies

Table 16. Duration of Exposure in Subjects Exposed to Apremilast in Phase 3 Clinical Studies of Psoriatic Arthritis (Studies PSA-002, PSA-003, PSA-004, and PSA-005)

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated		
	PBO (N = 671)	20 mg BID (N = 972)	30 mg BID (N = 973)	Total (N = 1945)
Patient-Years				
Mean (SD)	0.34 (0.099)	2.88 (1.956)	3.06 (1.942)	2.97 (1.951)
Median	0.31	3.16	4.12	3.51
Range	≤ 0.01, 0.52	≤ 0.01, 5.12	≤ 0.01, 5.13	≤ 0.01, 5.13
Duration (n [%])				
≥ 1 day	671 (100.0)	972 (100.0)	973 (100.0)	1945 (100.0)
≥ 4 weeks	658 (98.1)	950 (97.7)	935 (96.1)	1885 (96.9)
≥ 8 weeks	633 (94.3)	919 (94.5)	910 (93.5)	1829 (94.0)
≥ 12 weeks	618 (92.1)	900 (92.6)	896 (92.1)	1796 (92.3)
≥ 24 weeks	153 (22.8)	822 (84.6)	843 (86.6)	1665 (85.6)
≥ 32 weeks	NA	763 (78.5)	792 (81.4)	1555 (79.9)
≥ 52 weeks	NA	688 (70.8)	727 (74.7)	1415 (72.8)
≥ 78 weeks	NA	619 (63.7)	662 (68.0)	1281 (65.9)
≥ 91 weeks	NA	597 (61.4)	632 (65.0)	1229 (63.2)
≥ 104 weeks	NA	572 (58.8)	607 (62.4)	1179 (60.6)
≥ 156 weeks	NA	498 (51.2)	540 (55.5)	1038 (53.4)
≥ 208 weeks	NA	439 (45.2)	495 (50.9)	934 (48.0)
≥ 260 weeks	NA	170 (17.5)	178 (18.3)	348 (17.9)

BID = twice daily; NA = not applicable; PBO = placebo

Table 17. Duration of Exposure in Subjects Exposed to Apremilast in Phase 3 Clinical Studies of Psoriasis (Studies PSOR-008 and PSOR-009)

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated
	PBO (N = 418)	30 mg BID (N = 1184)
Patient-Years		
Mean (SD)	0.28 (0.075)	1.84 (1.636)
Median	0.31	1.21
Range	≤ 0.01, 0.34	≤ 0.01, 5.07
Duration (n [%])		
≥ 1 day	418 (100.0)	1184 (100.0)
≥ 4 weeks	397 (95.0)	1137 (96.0)
≥ 8 weeks	377 (90.2)	1101 (93.0)
≥ 12 weeks	363 (86.8)	1072 (90.5)
≥ 24 weeks	NA	968 (81.8)
≥ 32 weeks	NA	855 (72.2)
≥ 52 weeks	NA	657 (55.5)
≥ 78 weeks	NA	507 (42.8)
≥ 91 weeks	NA	458 (38.7)
≥ 104 weeks	NA	404 (34.1)
≥ 156 weeks	NA	291 (24.6)
≥ 208 weeks	NA	213 (18.0)
≥ 260 weeks	NA	65 (5.5)

BID = twice daily; NA = not applicable; PBO = placebo

Table 18. Duration of Exposure in Subjects Exposed to Apremilast in Pooled Phase 3 Clinical Studies (Studies PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008, and PSOR-009)

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated	
	PBO (N = 1089)	20 mg BID (N = 972)	30 mg BID (N = 2157)
Patient-Years			
Mean (SD)	0.32 (0.095)	2.88 (1.956)	2.39 (1.881)
Median	0.31	3.16	1.75
Range	≤ 0.01, 0.52	≤ 0.01, 5.12	≤ 0.01, 5.13
Duration (n [%])			
≥ 1 day	1089 (100.0)	972 (100.0)	2157 (100.0)
≥ 4 weeks	1055 (96.9)	950 (97.7)	2072 (96.1)
≥ 8 weeks	1010 (92.7)	919 (94.5)	2011 (93.2)
≥ 12 weeks	981 (90.1)	900 (92.6)	1968 (91.2)
≥ 24 weeks	153 (14.0)	822 (84.6)	1811 (84.0)
≥ 32 weeks	NA	763 (78.5)	1647 (76.4)
≥ 52 weeks	NA	688 (70.8)	1384 (64.2)
≥ 78 weeks	NA	619 (63.7)	1169 (54.2)
≥ 91 weeks	NA	597 (61.4)	1090 (50.5)
≥ 104 weeks	NA	572 (58.8)	1011 (46.9)
≥ 156 weeks	NA	498 (51.2)	831 (38.5)
≥ 208 weeks	NA	439 (45.2)	708 (32.8)
≥ 260 weeks	NA	170 (17.5)	243 (11.3)

BID = twice daily; NA = not applicable; PBO = placebo

Table 19. Duration of Exposure in Behçet's Disease Phase 3 Clinical Study BCT-002

	PBO/APR 30 mg BID (N = 83)	APR 30 mg BID as Initiated (N = 104)	APR 30 mg BID Total (N = 187)
Patient-Years			
Mean (SD)	0.87 (0.286)	1.03 (0.377)	0.96 (0.347)
Median	1.00	1.22	1.00
Range	0.003, 1.070	0.008, 1.328	0.003, 1.328
Duration (n [%])[a]			
≥ 1 day	83 (100.0)	104 (100.0)	187 (100.0)
< 2 weeks	2 (2.4)	3 (2.9)	5 (2.7)
≥ 2 to < 6 weeks	3 (3.6)	3 (2.9)	6 (3.2)
≥ 6 to < 10 weeks	1 (1.2)	1 (1.0)	2 (1.1)
≥ 10 to < 12 weeks	1 (1.2)	1 (1.0)	2 (1.1)
≥ 12 to < 16 weeks	2 (2.4)	2 (1.9)	4 (2.1)
≥ 16 to < 24 weeks	1 (1.2)	3 (2.9)	4 (2.1)
≥ 24 to < 28 weeks	2 (2.4)	2 (1.9)	4 (2.1)
≥ 28 to < 40 weeks	3 (3.6)	8 (7.7)	11 (5.9)
≥ 40 to < 48 weeks	0 (0.0)	3 (2.9)	3 (1.6)
≥ 48 to < 52 weeks	22 (26.5)	0 (0.0)	22 (11.8)
≥ 52 to < 64 weeks	46 (55.4)	27 (26.0)	73 (39.0)
≥ 64 weeks	0 (0.0)	51 (49.0)	51 (27.3)

APR = apremilast; BID = twice daily; PBO = placebo

[a] Treatment duration is the time interval (in weeks) between the date of the first dose of apremilast and the date of the last dose of apremilast in the period, inclusive.

Table 20. Exposure by Age Group and Gender in Subjects Exposed to Apremilast in Phase 3 Clinical Studies of Psoriatic Arthritis (Studies PSA-002, PSA-003, PSA-004, and PSA-005)

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated		
	PBO (N = 671)	20 mg BID (N = 972)	30 mg BID (N = 973)	Total (N = 1945)
Age (n [%])				
18 to < 65 years	604 (90.0)	886 (91.2)	875 (89.9)	1761 (90.5)
≥ 65 years	67 (10.0)	86 (8.8)	98 (10.1)	184 (9.5)
Gender (n [%])				
Male	330 (49.2)	466 (47.9)	447 (45.9)	913 (46.9)
Female	341 (50.8)	506 (52.1)	526 (54.1)	1032 (53.1)
Patient-Years, Males				
Mean (SD)	0.34 (0.088)	2.89 (1.907)	3.04 (1.935)	2.96 (1.921)
Median	0.31	3.06	4.00	3.32
Range	≤ 0.01, 0.52	≤ 0.01, 5.08	≤ 0.01, 5.10	≤ 0.01, 5.10
Patient-Years, Females				
Mean (SD)	0.34 (0.109)	2.87 (2.001)	3.09 (1.935)	2.98 (1.977)
Median	0.31	3.43	4.00	3.75
Range	≤ 0.01, 0.49	≤ 0.01, 5.12	≤ 0.01, 5.10	≤ 0.01, 5.13

BID = twice daily; PBO = placebo

Table 21. Exposure by Age Group and Gender in Subjects Exposed to Apremilast in Phase 3 Clinical Studies of Psoriasis (Studies PSOR-008 and PSOR-009)

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated
	PBO (N = 418)	30 mg BID (N = 1184)
Age (n [%])		
18 to < 65 years	380 (90.9)	1083 (91.5)
≥ 65 years	38 (9.1)	101 (8.5)
Gender (n [%])		
Male	294 (70.3)	805 (68.0)
Female	124 (29.7)	379 (32.0)
Patient-Years, Males		
Mean (SD)	0.28 (0.071)	1.81 (1.643)
Median	0.31	1.16
Range	≤ 0.01, 0.34	≤ 0.01, 5.06
Patient-Years, Females		
Mean (SD)	0.27 (0.085)	1.92 (1.619)
Median	0.31	1.32
Range	≤ 0.01, 0.34	≤ 0.01, 5.07

BID = twice daily; PBO = placebo

Table 22. Exposure by Age Group and Gender in Subjects Exposed to Apremilast in the Pooled Phase 3 Clinical Studies (Studies PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008, and PSOR-009)

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated		
	PBO (N = 1089)	20 mg BID (N = 972)	30 mg BID (N = 2157)	Total (N = 3129)
Age (n [%])				
18 to < 65 years	984 (90.4)	886 (91.2)	1958 (90.8)	2844 (90.9)
≥ 65 years	105 (9.6)	86 (8.8)	199 (9.2)	285 (9.1)
Gender (n [%])				
Male	624 (57.3)	466 (47.9)	1252 (58.0)	1718 (54.9)
Female	465 (42.7)	506 (52.1)	905 (42.0)	1411 (45.1)

BID = twice daily; N/n = number of subjects; PBO = placebo

Table 23. Exposure by Age Group and Gender in Subjects in Behçet's Disease Phase 3 Clinical Study BCT-002

	Subjects as Initially Treated at week 0		
	PBO (N = 103)	APR 30 mg BID (N = 104)	Total (N = 207)
Age (n [%])			
18 to < 65 years	99 (96.1)	101 (97.1)	200 (96.6)
≥ 65 years	4 (3.9)	3 (2.9)	7 (3.4)
Gender (n [%])			
Male	40 (38.8)	40 (38.5)	80 (38.6)
Female	63 (61.2)	64 (61.5)	127 (61.4)

APR = apremilast; BID = twice daily; PBO = placebo

Table 24. Exposure by Race and Ethnic Origin in Subjects Exposed to Apremilast in Phase 3 Clinical Studies of Psoriatic Arthritis (Studies PSA-002, PSA-003, PSA-004, and PSA-005)

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated		
	PBO (N = 671)	20 mg BID (N = 972)	30 mg BID (N = 973)	Total (N = 1945)
Race (n [%])				
American Indian or Alaska Native	1 (0.1)	2 (0.2)	2 (0.2)	4 (0.2)
Asian	18 (2.7)	34 (3.5)	20 (2.1)	54 (2.8)
Black or African American	4 (0.6)	4 (0.4)	1 (0.1)	5 (0.3)
Native Hawaiian or Other Pacific Islander	2 (0.3)	2 (0.2)	2 (0.2)	4 (0.2)
White	636 (94.8)	920 (94.7)	928 (95.4)	1848 (95.0)
Other	9 (1.3)	10 (1.0)	19 (2.0)	29 (1.5)
Missing	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)
Ethnicity (n [%])				
Hispanic or Latino	20 (3.0)	26 (2.7)	28 (2.9)	54 (2.8)
Non-Hispanic or Latino	650 (96.9)	946 (97.3)	944 (97.0)	1890 (97.2)
Missing	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)
Patient-Years by Race				
White	216.1	2649.0	2846.6	5495.6
Black	0.9	8.6	0.4	9.0
Asian	6.7	99.5	73.4	172.9
Patient-Years by Ethnicity				
Hispanic	6.1	60.6	55.3	116.0
Non-Hispanic	221.3	2739.8	2921.9	5661.7

BID = twice daily; PBO = placebo

Table 25. Exposure by Race and Ethnic Origin in Subjects Exposed to Apremilast in Phase 3 Clinical Studies of Psoriasis (Studies PSOR-008 and PSOR-009)

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated
	PBO (N = 418)	30 mg BID (N = 1184)
Race (n [%])		
American Indian or Alaska Native	6 (1.4)	9 (0.8)
Asian	22 (5.3)	54 (4.6)
Black or African American	12 (2.9)	40 (3.4)
Native Hawaiian or Other Pacific Islander	1 (0.2)	7 (0.6)
White	377 (90.2)	1071 (90.5)
Ethnicity (n [%])		
Hispanic or Latino	33 (7.9)	94 (7.9)
Non-Hispanic or Latino	385 (92.1)	1090 (92.1)
Patient-Years by Race		
White	105.2	2002.8
Black	3.2	61.7
Asian	5.9	89.6
Patient-Years by Ethnicity		
Hispanic	8.6	136.1
Non-Hispanic	107.9	2045.3

BID = twice daily; PBO = placebo

Table 26. Exposure by Race and Ethnic Origin in Subjects Exposed to Apremilast in the Pooled Phase 3 Clinical Studies (Studies PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008, and PSOR-009)

	Subjects as Initially Treated at week 0	Apremilast Subjects as Treated		
	PBO (N = 1089)	20 mg BID (N = 972)	30 mg BID (N = 2157)	Total (N = 3129)
Race (n [%])				
American Indian or Alaska Native	7 (0.6)	2 (0.2)	11 (0.5)	13 (0.4)
Asian	40 (3.7)	34 (3.5)	74 (3.4)	108 (3.5)
Black or African American	16 (1.5)	4 (0.4)	41 (1.9)	45 (1.4)
Native Hawaiian or Other Pacific Islander	3 (0.3)	2 (0.2)	9 (0.4)	11 (0.4)
White	1013 (93.0)	920 (94.7)	1999 (92.7)	2919 (93.3)
Other	9 (0.8)	10 (1.0)	22 (1.0)	32 (1.0)
Missing	1 (0.1)	0 (0.0)	1 (0.0)	1 (0.0)
Ethnicity (n [%])				
Hispanic or Latino	53 (4.9)	26 (2.7)	122 (5.7)	148 (4.7)
Non-Hispanic or Latino	1035 (95.0)	946 (97.3)	2034 (94.3)	2980 (95.2)
Missing	1 (0.1)	0 (0.0)	1 (0.0)	1 (0.0)

BID = twice daily; PBO = placebo

Table 27. Exposure by Race and Ethnic Origin in Subjects in Behçet's Disease Phase 3 Clinical Study BCT-002

	Subjects as Initially Treated at week 0		
	PBO (N = 103)	APR 30 mg BID (N = 104)	Total (N = 207)
Race (n [%])			
American Indian or Alaska Native	1 (1.0)	0 (0.0)	1 (0.5)
Asian	30 (29.1)	32 (30.8)	62 (30.0)
Black or African American	0 (0.0)	1 (1.0)	1 (0.5)
Native Hawaiian or Other Pacific Islander	1 (1.0)	0 (0.0)	1 (0.5)
White	68 (66.0)	69 (66.3)	137 (66.2)
Not collected or reported	3 (2.9)	2 (1.9)	5 (2.4)
Ethnicity (n [%])			
Hispanic or Latino	3 (2.9)	2 (1.9)	5 (2.4)
Non-Hispanic or Latino	100 (97.1)	102 (98.1)	202 (97.6)

APR = apremilast; BID = twice daily; PBO = placebo

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 28. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
Clinically Significant Diseases or Uncontrolled Major Disease.	This population was excluded as such concomitant diseases could influence the interpretation of the study data.	No	Findings from long-term studies did not suggest a disparate safety profile in this population compared to what was studied in clinical trials. These patients may benefit from treatment with apremilast.
Pregnancy	Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in animal studies).	No	Based on the pre-clinical studies this is an important potential risk in this RMP (Table 42). Treatment with apremilast is contraindicated during pregnancy (Summary of Product Characteristics [SmPC], Section 4.3).
History of Positive Human Immunodeficiency Virus (HIV), or Congenital or Acquired Immunodeficiency (eg, Common Variable Immunodeficiency Disease) or Bacterial Infections Requiring Treatment with Oral or Injectable Antibiotics, or Significant Viral or Fungal Infections, Within 4 Weeks of Screening. Any Treatment for Such Infections must have been Completed at Least 4 Weeks Prior to Screening.	This population was excluded as such concomitant diseases could influence the interpretation of the study data.	No	There is no evidence that apremilast increases the risk of any infections or causes immunosuppression. These patients may benefit from treatment with apremilast based on the mechanism of action.

Table 28. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
Active Tuberculosis or a History of Incompletely Treated Tuberculosis.	This population was excluded as such concomitant diseases could influence the interpretation of the study data.	No	There is no evidence that apremilast increases the risk of any infections or causes immunosuppression. These patients may benefit from treatment with apremilast based on the mechanism of action.
Malignancy or History of Malignancy (Except for Treated [ie, Cured] Basal-cell or Squamous Cell In Situ Skin Carcinomas and Treated [ie, Cured] Cervical Intraepithelial Neoplasia or Carcinoma In Situ of the Cervix).	This population was excluded as such concomitant diseases could influence the interpretation of the study data.	No	There is no evidence that apremilast increases the risk of malignancies. These patients may benefit from treatment with apremilast based on the mechanism of action.
Hypersensitivity to the Active Substance or to any of the Excipients.	To ensure patient safety.	No	Treatment with apremilast is contraindicated in those with hypersensitivity to the active substance or any of the excipients (SmPC, Section 4.3). 'Serious events of hypersensitivity' is an important identified risk in the RMP (Table 34).
Hepatitis B Surface Antigen Positive at Screening or Hepatitis C Antibody Positive at Screening	This population was excluded as such concomitant diseases could influence the interpretation of the study data.	No	There is no evidence that apremilast increases the risk in these patients. These patients may benefit from treatment with apremilast based on the mechanism of action.

Table 28. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale (if not included as missing information)
Serum Creatinine ≥ 1.5 mg/dL (≥ 132.6 µmol/L)	To ensure patient safety.	No	Pharmacokinetic data are available for subjects with mild, moderate, or severe renal impairment. In subjects with mild and moderate renal impairment, there were no clinically meaningful differences in the pharmacokinetics of apremilast relative to the matched healthy group (Study CC-10004-CP-029). However, the information is limited due to the low number of subjects. In the PsA and psoriasis clinical studies, the safety profile observed in subjects with mild renal impairment was comparable to that of subjects with normal renal function. No dosage adjustment is needed in patients with mild or moderate renal impairment. Apremilast should be dose reduced to 30 mg once daily in patients with severe renal impairment (Study CC-10004-CP-019). A limited number of subjects with moderate renal impairment have been treated with apremilast in clinical trials. In 8 subjects with severe renal impairment treated with 30 mg apremilast the AUC and C_{max} of apremilast increased by approximately 89% and 42%, respectively. The phase 1 study in subjects with mild and moderate renal impairment was complete after all subjects were enrolled in the phase 3 studies.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions. In addition, clinical trials may not be able to detect a slightly increased risk of adverse events commonly observed in the treated population.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 29. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant or Lactating Women	Pregnant and lactating women were excluded from the study population and throughout the development program. As of 20 March 2023, there have been a total of 491 cases of potential fetal exposure from all sources (prospective postmarketing cases, retrospective postmarketing cases, and prospective cases from interventional clinical trials).
History of Clinically Significant (as Determined by the Investigator) Cardiac, Endocrinologic, Pulmonary, Neurologic, Psychiatric, Hepatic, Renal, Haematologic, Immunologic Disease, or other Major Uncontrolled Disease	Not included in the clinical development program.
Any Condition, Including the Presence of Laboratory Abnormalities that Placed the Subject at Unacceptable Risk if he/she were to Participate in the Study or if it could have Confounded the Ability to Interpret Data from the Study.	Not included in the clinical development program.
Patients with Renal Impairment	There were 24 subjects (0.07 subject-years) with renal impairment in the clinical development program
Patients with Hepatic Impairment	There were 16 subjects (0.04 subject-years) with hepatic impairment in the clinical development program.
Population with Relevant Different Ethnic Origin	Apremilast exposure data by race and ethnic origin are presented in Module SIII.
Sub-populations Carrying Relevant Genetic Polymorphisms	No studies of apremilast in sub-populations with genetic polymorphisms have been conducted.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 29. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Other	
Pediatric Population	A total of 277 pediatric subjects received apremilast in the pediatric clinical studies (PPSO-001 [42 subjects] and PPSO-003 [235 subjects]; PPSO-004 includes 160 subjects from Study PPSO-003]).
Elderly Population	**Elderly Population:** A total of 285/3129 subjects were ≥ 65 years of age in the pooled PsA and psoriasis studies, including 25 subjects who were ≥ 75 years of age (Studies PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008, and PSOR-009). Of the 1945 apremilast-treated subjects in Studies PSA-002, PSA-003, PSA-004, and PSA-005, a total of 184 subjects with PsA were ≥ 65 years, including 18 subjects ≥ 75 years. Of the 1184 apremilast-treated subjects in Studies PSOR-008 and PSOR-009, a total of 101 subjects with psoriasis were ≥ 65 years, including 7 subjects who were ≥ 75 years. Of the 207 apremilast treated subjects in Study BCT-002, 7 subjects with BD were ≥ 65 years.

BD = Behçet's disease; PsA = psoriatic arthritis

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and on drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to a monthly estimate of person-count (when feasible) or patient-time using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

SV.1.2 Exposure

The estimated cumulative commercial exposure to apremilast by number of patients is provided in Table 30 and cumulative exposure by PY to a data lock point of 20 March 2023 is provided in Table 31.

Table 30. Estimated Number of Patients Exposed to Apremilast by Region and Demographic Characteristics in the Postmarketing Setting

Demographic Characteristic	Cumulative Number of Patients Exposed					
	AU	CA	EUR	US	Other	Total
Overall	4789	24 844	212 115	489 802	114 509	846 059
Sex						
Female	2580	13 384	114 266	263 856	61 686	455 772
Male	2209	11 461	97 849	225 946	52 823	390 287
Age						
0 - 34 years	672	3488	29 781	68 768	16 077	118 787
35 - 49 years	1638	8497	72 543	167 512	39 162	289 352
50 - 64 years	2099	10 889	92 970	214 680	50 189	370 828
65 - 74 years	288	1493	12 748	29 437	6882	50 848
≥ 75 years	92	477	4073	9404	2199	16 244
Sex by Age						
Female						
0 - 34 years	358	1858	15 866	36 637	8565	63 285
35 - 49 years	906	4698	40 111	92 622	21 654	159 990
50 - 64 years	1100	5707	48 723	112 508	26 303	194 340
65 - 74 years	163	847	7233	16 702	3905	28 851
≥ 75 years	53	273	2333	5388	1260	9307
Male						
0 - 34 years	315	1632	13 936	32 180	7523	55 586
35 - 49 years	732	3799	32 432	74 891	17 508	129 362
50 - 64 years	999	5180	44 226	102 124	23 875	176 403
65 - 74 years	125	646	5515	12 735	2977	21 998
≥ 75 years	39	204	1739	4016	939	6938

AU = Australia and New Zealand; CA = Canada; EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); Other = countries, not otherwise specified, where Amgen is the Marketing Authorization Holder; US = United States
Note: Data lock point 20 March 2023
Numbers may not add to the total due to rounding.
Age and sex breakdowns are based on patient characteristics in MarketScan, a US health insurance claims database. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.

Table 31. Estimated Number of Patient-years of Exposure to Apremilast by Region and Demographic Characteristics in the Postmarketing Setting

Demographic Characteristic	Cumulative Patient-years of Exposure					
	AU	CA	EUR	US	Other	Total
Overall	4597	19753	163246	466888	92502	746987
Sex						
Female	2476	10641	87941	251513	49831	402402
Male	2121	9112	75305	215375	42671	344585
Age						
0 - 34 years	645	2773	22920	65551	12987	104877
35 - 49 years	1572	6755	55830	159676	31636	255470
50 - 64 years	2015	8658	71551	204637	40544	327404
65 - 74 years	276	1187	9811	28060	5559	44894
≥ 75 years	88	379	3134	8964	1776	14342
Sex by Age						
Female						
0 - 34 years	344	1478	12211	34923	6919	55875
35 - 49 years	869	3735	30870	88289	17492	141255
50 - 64 years	1056	4537	37498	107244	21248	171583
65 - 74 years	157	674	5567	15921	3154	25472
≥ 75 years	51	217	1796	5136	1018	8217
Male						
0 - 34 years	302	1298	10725	30675	6077	49077
35 - 49 years	703	3020	24960	71387	14144	114214
50 - 64 years	958	4118	34037	97346	19287	155747
65 - 74 years	120	514	4244	12139	2405	19422
≥ 75 years	38	162	1339	3828	759	6125

AU = Australia and New Zealand; CA = Canada; EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); Other = countries, not otherwise specified, where Amgen is the Marketing Authorization Holder; US = United States
Note: Data lock point 20 March 2023
Numbers may not add to the total due to rounding.

Age and sex breakdowns are based on patient characteristics in MarketScan, a US health insurance claims database. Applying these distributions to regions outside the US requires strong assumptions that are not easily testable.

Postauthorization Use From Business Partners

Cumulatively through 20 March 2023, an estimated 2052 patients (2223 PY) were treated in the territories of Amgen's business partner, Fosun.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

There are no specific risks of abuse or misuse of apremilast for illegal purposes based on the known pharmacological properties.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The summary of the safety concerns in the first approved RMP for apremilast (Version 6.0W) is presented in Table 32. A description of the changes to the list of safety concerns in the approved RMPs is presented in Annex 8.

Table 32. Summary of Safety Concerns in the First Approved RMP (Version 6.0W)

Important identified risks	• Hypersensitivity • Pharmacokinetic interaction with strong CYP3A4 inducers • Weight decrease in patients with BMI < 20 kg/m^2 • Depression
Important potential risks	• Vasculitis • Risk of triggering suicide • Malignancies • Nervousness and anxiety • Serious infections • Major adverse cardiac events (MACE) and tachyarrhythmia • Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast
Missing information	• Pediatric use • Patients with moderate and severe renal impairment • Long-term safety • Limited data in long-term efficacy • Patients with moderate and severe hepatic impairment • Use in patients of different racial origin • Live vaccination • Potential pharmacokinetic interactions of apremilast metabolite M12

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Adverse reactions related to weight decrease in patients with a body mass index (BMI) < 20 kg/m^2 are known and are not considered to impact the benefit-risk profile of apremilast in the target population. The most current product information advises for underweight patients to have their weight monitored regularly (SmPC Section 4.4). In addition, weight decrease is included in Section 4.8 of the SmPC. No additional risk minimization measures are in place for reactions related to weight decrease in patients with a BMI < 20 kg/m^2. Adverse reactions related to weight decrease in patients with a

BMI < 20 kg/m^2 are not considered to be important for the target population and these adverse drug reactions (ADRs) are included in Section 4.8 of the SmPC.

Pharmacokinetic interaction of apremilast with strong CYP3A4 inducers is already well known to healthcare professionals (HCPs). The HCPs have appropriate measures in place as part of routine clinical practice. Such interactions are discussed in Sections 4.5 and 5.2 of the SmPC.

Mesenteric vasculitis/ischemic colitis is included as an Important Potential Risk in the roflumilast (Daxas™; another PDE4 inhibitor) EU RMP (Daxas Public Assessment Report, 2010) and, in nonclinical studies with apremilast, inflammatory responses associated with arteritis and perivascular inflammation in various organs were reported in mice and rats (see Table 5). However, based on the clinical data, there is no evidence of an increased risk of vasculitis with apremilast treatment.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 33. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Identified Risks	
Serious events of Hypersensitivity	Hypersensitivity to apremilast was infrequently observed in the pivotal clinical trials. Please see Table 34 for further details.
Suicidality	Instances of suicidal ideation and behavior, including suicide, have been observed in patients with or without history of depression. In clinical studies and postmarketing experience, uncommon cases of suicidal ideation and behavior were reported, while completed suicide was reported in the postmarketing setting. Please see Table 35 for further details.
Serious Events of Depression	In clinical studies, uncommon cases of serious events of depression were reported with apremilast. Please see Table 36 for further details.
Important Potential Risks	
Vasculitis	In the apremilast clinical studies, small vessel cutaneous vasculitis was reported in three patients. Two of these patients participated in a rheumatoid arthritis study and the third patient participated in a PsA study. Please see Table 37 for further details.
Malignancies	Malignant tumours are not listed as adverse reactions for roflumilast (Daxas SmPC, 2018); however, Section 4.4 of the roflumilast SmPC states that due to lack of relevant experience, treatment with roflumilast should not be initiated or existing treatment with roflumilast should be stopped in patients with cancers (except basal cell carcinoma). Rodent-specific toxicity in the nasal mucosa was observed in repeat-dose toxicity and carcinogenicity studies of roflumilast. This effect seems to be due to an 4-amino-3,5-dichloro-pyridine N-oxide intermediate specifically formed in rodent olfactory mucosa, with special binding affinity in these species (ie, mouse, rat and hamster; Daxas SmPC, 2018). No similar findings were reported in apremilast animal studies. Please see Table 38 for further details.
Serious Events of Anxiety and Nervousness	Anxiety and nervousness are listed as uncommon and rare adverse reactions, respectively, for roflumilast (Section 4.8 of Daxas SmPC, 2018). During the phase 3 PsA and psoriasis studies, serious events of anxiety and nervousness were reported in 2 patients in the phase 3 PsA studies. Please see Table 39 for further details.

Table 33. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concern	Risk-benefit Impact
Important Potential Risks (continued)	
Serious Infections Including Opportunistic Infections and Transmission of Infections through Live Vaccines	Respiratory tract infections (excluding pneumonia) are listed as rare adverse reactions for roflumilast (Section 4.8 of Daxas SmPC, 2018). In the apremilast clinical studies, the incidences of serious infections were comparable between the treatment groups. Please see Table 40 for further details.
MACE and Tachyarrhythmia	For roflumilast, cardiac disorders (palpitations) are listed as uncommon adverse reactions (Section 4.8 of Daxas SmPC, 2018). In the apremilast clinical studies, the incidences of MACE or tachyarrhythmia were comparable between the treatment groups. Please see Table 41 for further details.
Prenatal Embryo-fetal Loss and Delayed Fetal Development (Reduced Ossification and Fetal Weight) in Pregnant Women Exposed to Apremilast	Effects of apremilast on pregnancy included embryo-fetal loss in mice and monkeys, and reduced fetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. There are no adequate and well-controlled studies of apremilast in pregnant women. Please see Table 42 for further details.
Missing Information	
Long-term Safety	Long-term registry studies are ongoing to collect data on long-term safety in the real-world post-marketing setting. Please see Table 43 for further details.

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SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable, as there are no new safety concerns or reclassification of safety concerns.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 34. Important Identified Risk: Serious Events of Hypersensitivity

Potential mechanisms	The exact mechanism by which hypersensitivity reactions occur is often unclear and may vary among drugs (Lenz, 2007). Important drug-related risk factors for drug hypersensitivity are its chemical properties, molecular weight, and route of administration. Higher molecular weight drugs and those with topical, intramuscular and intravenous administration are more likely to cause hypersensitivity reactions (Riedl and Casillas, 2003).
Evidence source(s) and strength of evidence	This risk was identified during the clinical study setting. Events pertinent to the risk of serious events of hypersensitivity were observed during the clinical development programs for PsA and psoriasis. Hypersensitivity is listed as an uncommon side effect of roflumilast treatment (another PDE4 inhibitor), occurring in fewer than 1 in 100 people but more than 1 in 1000.
Characterization of the risk	
Frequency	Phase 3 PsA Adult Studies No serious adverse events pertaining to hypersensitivity were reported in subjects treated with apremilast. However, during weeks 0 to 16, serious hypersensitivity was noted in 1/671 (0.1%) placebo treated subject. This subsequently resolved. Phase 3 Adult Psoriasis Studies During weeks 0 to 16, 1/1184 (0.1%) apremilast treated subjects (30 mg BID) experienced an serious adverse event of hypersensitivity (Preferred Term [PT]: urticaria). An outcome of recovered/resolved was reported for this serious adverse event. No placebo treated subjects experienced serious adverse events of hypersensitivity. In the apremilast exposure period, a serious event of hypersensitivity was experienced by 1/1184 (0.1%) subject (PT: urticaria). The outcome of the serious adverse event was recovered/resolved. Pediatric Psoriasis Studies No serious events of hypersensitivity were reported in completed Studies PPSO-001 and PPSO-003, or ongoing Study PPSO-004 (data cut-off 27 March 2023). Phase 3 Adult BD study During weeks 0 to 12, 1/103 (1.0%) placebo treated subject experienced an serious adverse event of hypersensitivity (PT: erythema multiforme). An outcome of resolved was reported for this serious adverse event approximately 3 weeks after onset. No apremilast treated subjects experienced serious adverse events of hypersensitivity. In the apremilast exposure period, no serious adverse events of hypersensitivity were reported. Other Adult Studies An event of anaphylactic reaction, reported in a subject treated with apremilast in a phase 2 psoriasis study, was not considered serious.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 34. Important Identified Risk: Serious Events of Hypersensitivity

Characterization of the risk (continued)	
Severity	The majority of the events of hypersensitivity across all studies were mild or moderate; severe events of hypersensitivity have been reported in subjects treated with apremilast.
Reversibility	Hypersensitivity reactions may be self-limiting or may require medical management to resolve.
Long-term outcomes	No long-term outcome is expected after resolution of hypersensitivity reactions.
Impact on quality of life	Hypersensitivity reactions may cause a range of symptoms from minor inconvenience to anaphylactic shock.
Risk groups or risk factors	General factors that increase the likelihood of experiencing a Type 1 hypersensitivity reaction include repeated exposure to the drug and a history of drug hypersensitivity, particularly if hypersensitivity occurred with a drug of the same chemical class (Lenz, 2007). Patient risk factors for hypersensitivity drug reactions include female gender, adulthood, human immunodeficiency virus (HIV) infection, concomitant viral infection, previous hypersensitivity to chemically related drug, asthma, use of beta blockers, specific genetic polymorphisms and the Caucasian race (Gomes and Demoly, 2005; Riedl and Casillas, 2003).
Preventability	It is generally difficult to predict and prevent allergic reactions. It is important; however, that both the physician and patient are aware that such reactions can occur. Routine clinical practice includes eliciting patient history of allergies, including drug allergies, in order for the prescriber to assess the benefit risk of prescribing drugs such as apremilast. Apremilast is contraindicated in patients who have hypersensitivity to the active substance(s) or any of the excipients (see product label).

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 34. Important Identified Risk: Serious Events of Hypersensitivity

Impact on the risk-benefit balance of the product	Treatment for allergic reactions may be required. Severe anaphylactic reaction requires hospitalization and can be potentially fatal; however, the incidence of hypersensitivity in the apremilast clinical studies is low and none of the observed reactions were serious. The risk of serious events of hypersensitivity has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive. Hypersensitivity is included in the product label and the impact of this risk can be minimized through product labelling.
Public health impact	In light of the low frequency and mild severity of hypersensitivity reactions associated with apremilast, the public health impact can be considered to be low. With appropriate management, hypersensitivity, including anaphylactoid reactions, are fully reversible in most cases.

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BD = Behçet's disease; BID = twice daily; HIV = human immunodeficiency virus; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term

Table 35. Important Identified Risk: Suicidality

Potential mechanisms	There are distinct differences in the pharmacodynamics and pharmacokinetics of apremilast and roflumilast. Therefore, the potential mechanism for roflumilast may not be applicable for apremilast. No mechanism by which apremilast may trigger suicide has been identified.
Evidence source(s) and strength of evidence	Events pertinent to the risk of triggering suicide were observed during the clinical development programs for PsA and psoriasis. Suicidal thoughts (ideation) and behaviour are rare side effects of roflumilast treatment (another PDE4 inhibitor), occurring in fewer than 1 in 1000 people but more than 1 in 10 000.
Characterization of the risk	
Frequency	Phase 3 Adult PsA Studies During weeks 0 to 16, suicide/self-injury events were experienced by 2/1945 (0.1%) apremilast treated subjects in the 20 mg BID group (PTs: suicidal ideation [1 subject] and suicide attempt [1 subject]) and no placebo treated subjects. In the apremilast exposure period, there was an additional event of suicide attempt in the 30 mg BID group. Phase 3 Adult Psoriasis Studies During weeks 0 to 16, suicide/self-injury events were experienced by 1/1184 (0.1%) apremilast treated subjects (PT: suicide attempt). One subject (0.2%) randomized to placebo completed suicide. In the apremilast exposure period, no additional events of suicide/self-injury were reported. Pediatric Psoriasis Studies In completed Study PPSO-001, 1 subject answered yes on the Columbia-Suicide Severity Rating Scale; the event led to discontinuation from the study. Subsequent psychiatric evaluations were negative, and there was no risk of suicide. In completed Study PPSO-003, an event of suicidal ideation was reported for 1 subject (1.3%) in the placebo group; the adverse event led to discontinuation of investigational product. No events of suicidality were reported in ongoing Study PPSO-004 (data cut-off 27 March 2023).Phase 3 Adult BD Study No subjects in BD Study BCT-002 experienced events of suicidality. Other Adult Studies In Study PSOR-005 (phase 2 study), a male subject randomized to the placebo group, was found dead with a pink complexion in his closed garage with a motorcycle running on study day 84. Autopsy did not establish the cause of death in this potential suicide.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 35. Important Identified Risk: Suicidality

Characterization of the risk (continued)	
Severity	There were no fatal events of suicidality reported in subjects treated with apremilast during the clinical development program, though fatal events were observed in subjects treated with placebo. In the postmarketing setting fatal events of suicide have been reported in patients treated with apremilast.
Reversibility	Suicidal behavior may lead to death or long-term sequelae. However, recovery can be achieved with appropriate and timely intervention.
Long-term outcomes	Suicidal behavior may lead to death or long-term sequelae.
Impact on quality of life	The impact on quality of life can be variable. Events of suicidality may be fatal or lead to disability. However, recovery can be achieved with appropriate and timely intervention.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 35. Important Identified Risk: Suicidality

Risk groups or risk factors	Suicide rates are twice as high in families of suicide victims (Fancher and Kravitz, 2007). Suicidal behavior has a large number of complex underlying causes, including poverty, unemployment, loss of loved ones, arguments, breakdown of relationships, and legal or work-related problems. A family history of suicide, as well as alcohol and drug abuse, childhood abuse, social isolation and some mental disorders including depression and schizophrenia, also play a central role in a large number of suicides. Physical illness and disabling pain can also increase suicide risks. One study showed the risk of depression was higher in severe psoriasis compared with mild psoriasis, and higher in younger compared to older patients with psoriasis (Kurd et al, 2010).
Preventability	It is generally difficult to predict which patients are at risk of triggering suicide. As in general practice, the physician should evaluate the patient when any change in the patient's behavior occurs.
Impact on the risk-benefit balance of the product	Self-destructive behavior including suicidality may lead to death. Suicide is among the top 20 leading causes of death globally for all ages. Every year, nearly 1 million people die from suicide. The risk of suicidality has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labelling.
Public health impact	The potential public health impact is not known. While psychiatric events appear to be common among patients with psoriasis, there are fewer published studies in the PsA population (none on suicide in the PsA population). Patients with psoriasis have been observed to have a higher rate of depression and suicide than the general population (Gupta and Gupta, 1998; Gupta et al, 1993). A recent study found psoriasis patients to have higher adjusted HRs for receiving a diagnosis of depression and anxiety of 1.39 (95% CI: 1.37 1.41) and 1.31 (95% CI: 1.29 1.34), respectively (Kurd et al, 2010). Studies have also shown an increase in suicide risk in patients with psoriasis. Two population-based studies reported HRs for suicide in patients with psoriasis ranging from 1.44 to 3.35 when compared to patients without psoriasis (Abuabara et al, 2010; Kurd et al, 2010). A study based on the UK population with psoriasis also reported incidence rates of suicidality (defined as suicidal ideation, suicide attempt and suicide) similar to the suicidal behavioral rates in apremilast exposed patients (exposure-adjusted incidence rate [EAIR] 0.1 per 100 PY). Incidence rates of suicidality were 0.093 per 100 PY in patients with mild psoriasis and 0.092 per 100 PY in patients with severe psoriasis (defined as those with psoriasis diagnosis and current use of systemic treatment). In comparison, the control non-psoriasis population was reported to have an incidence of suicidality of 0.066 per 100 PY (Kurd et al, 2010). In a small familial observational study conducted in 1979, 1.15 (6.7%) of patients with BD committed suicide (de Oliveira Ribeiro et al, 2014).

BD = Behçet's disease; BID = twice daily; EAIR = exposure-adjusted incidence rate; HR = hazard ratio; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term; PY = patient-years; UK = United Kingdom

Table 36. Important Identified Risk: Serious Events of Depression

Potential mechanisms	There are distinct differences in the pharmacodynamics and pharmacokinetics of apremilast and roflumilast. Therefore, the potential mechanism for roflumilast may not be applicable for apremilast. No mechanism by which apremilast may result in serious events of depression has been identified.
Evidence source(s) and strength of evidence	Events pertinent to the risk of serious events of depression were observed during the clinical development programs for PsA and psoriasis. Depression is listed as a rare side effect of roflumilast treatment (another PDE4 inhibitor), occurring in fewer than 1 in 1000 people but more than 1 in 10 000.
Characterization of the risk	
Frequency	<u>Phase 3 Adult PsA Studies</u> During weeks 0 to 16, serious depression was experienced by 2/1945 (0.1%) apremilast treated subjects (1 subject each from the apremilast 20 mg BID and 30 mg BID groups) and no placebo-treated subjects. All events resolved without sequelae. In the apremilast exposure period, serious events of depression were reported in 2/1945 (0.1%) subjects in the 20 mg BID group and 1 (0.1%) subject in the apremilast 30 mg BID group. All events resolved without sequelae. <u>Phase 3 Adult Psoriasis Studies</u> During weeks 0 to 16, no serious events of depression were experienced by apremilast-treated subjects. Overall, in the apremilast exposure period, a serious event of depression was reported in 1/1184 (0.1%) subject. The outcome of the serious adverse event was recovered/resolved. <u>Pediatric Psoriasis Studies</u> No serious events of depression were reported in completed Studies PPSO-001 and PPSO-003, or ongoing Study PPSO-004 (data cut-off 27 March 2023). <u>Phase 3 Adult BD Study</u> No subjects in BD Study BCT-002 experienced serious events of depression.
Severity	The majority of events of depression were mild or moderate, severe events of depression have been reported in subjects treated with apremilast.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 36. Important Identified Risk: Serious Events of Depression

Characterization of the risk (continued)	
Reversibility	Recovery without sequelae is likely with appropriate timely treatment.
Long-term outcomes	Recovery without sequelae is likely with appropriate timely treatment.
Impact on quality of life	Depression can have very little impact to very severe impact, interfering with daily functioning, depending on the severity of the symptoms.
Risk groups or risk factors	One study showed that patients with psoriasis are at increased risk of depression compared to the general population (Kurd et al, 2010). The risk of depression was higher in patients with severe compared with mild psoriasis, and higher in younger compared to older patients with psoriasis. No risk groups or risk factors have been identified for patients with PsA beyond those described for psoriasis. Depression is typically measured using scores from psychometric instruments. Studies on depression among patients with BD show consistently higher depression scores regardless of instruments used when compared to patients without BD (de Oliveira Ribeiro et al, 2014; Taner et al, 2007; Gur et al, 2006). One study of Turkish patients with BD reported 45.5% of the study population experienced depression (Taner et al, 2007). Another study of Turkish patients with BD reported a prevalence of major depression in 17.8% of the study population and a prevalence of dysthymic disorder of 6.8 (Dursun et al, 2007). A small study of Turkish patients with BD showed that 32.3% of the study population experienced sadness related to their disease (Karlidag et al, 2003). A small study comparing patients with BD and controls using the Beck Suicide Inventory (BSI) showed a much higher BSI among the BD group (61.3) as compared to controls (30.4) (de Oliveira Ribeiro et al, 2014).
Preventability	Depression has been reported in this population. As in general practice, patients who have signs or symptoms of depression may require additional evaluation and treatment.
Impact on the risk-benefit balance of the product	The risk of serious events of depression has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive. The impact of this risk can be minimized through product labelling.
Public health impact	The potential public health impact varies depending on the event reported.

BD = Behçet's disease; BID = twice daily; BSI = Beck Suicide Inventory; PDE4 = phosphodiesterase 4;; PsA = psoriatic arthritis

Table 37. Important Potential Risk: Vasculitis

Potential mechanisms	The PDE4 inhibitors, including apremilast, have been shown to produce inflammatory perivascular histopathological changes in rodent studies. With apremilast, vasculitis has only been observed in rodents. However, vasculitis has been reported with other PDE4 inhibitors in non-rodents (Hanton et al, 2008; Losco et al, 2004). No mechanism by which apremilast may cause vasculitis has been identified.
Evidence source(s) and strength of evidence	Animal studies have shown that PDE4 inhibitors, including apremilast, roflumilast, and cilomilast, are pro-inflammatory in rodents, but not in monkeys or humans. Therefore, vasculitis has been included as an important potential risk for apremilast. In the apremilast clinical studies, small vessel cutaneous vasculitis was reported in 3 subjects. Two of these subjects participated in a rheumatoid arthritis study and the third subject participated in a PsA study.
Characterization of the risk	
Frequency	Phase 3 Adult PsA Studies One case of mild cutaneous vasculitis was reported in 1/1945 (0.1%) subject receiving apremilast 30 mg BID for approximately 1 year in Study PSA-005. Phase 3 Adult Psoriasis Studies Vasculitis was not reported in the adult psoriasis clinical studies. Pediatric Psoriasis Studies No events of vasculitis were reported in completed Studies PPSO-001 and PPSO-003, or ongoing Study PPSO-004 (data cut-off 27 March 2023). Phase 3 Adult BD Study Two cases of SMQ Vasculitis were reported in subjects receiving apremilast 30 mg BID in Study BCT-002 (both PTs: Behçet's syndrome). Other Adult Studies There were 2 subjects in phase 2 Study RA-002 who experienced small vessel cutaneous vasculitis: 1 in the apremilast 30 mg BID treatment group (rheumatoid vasculitis involving small vessels with cutaneous manifestations only leading to study drug discontinuation, ongoing at the time of reporting), and 1 in the placebo treatment group (cutaneous vasculitis that has resolved).
Severity	Severe events of vasculitis have been reported in subjects treated with apremilast.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 37. Important Potential Risk: Vasculitis

Reversibility	The reversibility of vasculitis will depend upon the severity and clinical presentation.
Long-term outcomes	Long-term outcomes of vasculitis will depend upon the severity and clinical presentation.
Impact on quality of life	Vasculitis can lead to mural destruction with hemorrhage, aneurysm formation, infarction, intimal-medial hyperplasia, and subsequent stenosis causing tissue ischemia (Carlson et al, 2005). The skin is often involved in vasculitis syndromes that range from localized and self-limited conditions to generalized and life-threatening symptoms involving multi-organ disease (Carlson et al, 2005).
Risk groups or risk factors	Risk factors in the general population include immune disorders, connective tissue diseases, infections, atherosclerotic CVDs, exposure to chemicals, medications, and malignancies. Behçet's disease is a chronic multisystem variable vessel vasculitis characterized by oral and genital ulcers, skin lesions, uveitis, arthritis, vascular, central nervous system, and gastrointestinal involvement (Cho et al, 2012; Keino and Okada, 2007) that requires long-term treatment.
Preventability	Predictability and preventability of the development of an autoimmune event such as vasculitis are unknown.
Impact on the risk-benefit balance of the product	The risk of vasculitis has been incorporated in the benefit risk assessment, with the overall benefit risk balance remaining positive.
Public health impact	The public health impact of developing vasculitis during the treatment of PsA or psoriasis is unknown. Vasculitis is considered an important potential risk due to nonclinical findings in rodents with apremilast. However, the frequency of reports in the clinical studies is very low and there is no evidence of an increased risk of vasculitis with apremilast treatment.

BD = Behçet's disease; BID = twice daily; CVD = cardiovascular disease; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term; SMQ = Standardised MedDRA Query

Table 38. Important Potential Risk: Malignancies

Potential mechanisms	No mechanism by which apremilast may cause malignancy has been identified.
Evidence source(s) and strength of evidence	Although there was no clear imbalance in the frequency of malignancies between apremilast and placebo treatment during the clinical development programs for PsA, psoriasis and BD, the duration of treatment was relatively short. Therefore, malignancies have been included as an important potential risk for apremilast. Many of the subjects who had events of malignancy in the clinical studies had risk factors such as a family history, history of prior skin cancer, or exposure to agents known to be associated with increased risk of cancer. In addition, most of the malignancies were diagnosed in the first 6 months of starting treatment with apremilast, meaning it is unlikely that the occurrence of the malignancies is connected with apremilast.
Characterization of the risk	
Frequency	<u>Phase 3 Adult PsA Studies</u> During weeks 0 to 16, events of malignancies were experienced by 3/972 (0.3%) and 1/973 (0.1%) apremilast-treated subjects in the 20 mg BID and 30 mg BID treatment groups, respectively, and in 4/671 (0.6%) placebo-treated subjects. In the apremilast exposure period, events of malignancies were experienced by 17/1945 (0.9%) subjects treated with apremilast (8/972 [0.8%] and 9/973 [0.9%] subjects in the 20 mg and 30 mg BID groups, respectively). <u>Phase 3 Adult Psoriasis Studies</u> During weeks 0 to 16, events of malignancies were experienced by 10/1184 (0.8%) apremilast-treated subjects (30 mg BID) and by 2/418 (0.5%) placebo-treated subjects. In the apremilast exposure period, 17/1184 (1.4%) subjects reported events of malignancies. <u>Pediatric Psoriasis Studies</u> No events of malignancy were reported in completed Studies PPSO-001 and PPSO-003, or ongoing Study PPSO-004 (data cut-off 27 March 2023). <u>Phase 3 Adult BD Study</u> During weeks 0 to 12, no events of malignancy were experienced in Study BCT-002. In the apremilast exposure period, 2/187 (1.1%) subjects reported events of malignancies (PTs: breast cancer and endometrial cancer).
Severity	Some events of malignancy were mild or moderate; severe events of malignancies have also been reported in subjects treated with apremilast.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 38. Important Potential Risk: Malignancies

Characterization of the risk (continued)	
Reversibility	The reversibility of malignancy will depend upon the type and stage of disease at diagnosis.
Long-term outcomes	Long-term outcomes of malignancy will depend upon the type and stage of disease at diagnosis.
Impact on quality of life	The impact of the malignancy on a patient is dependent on the type and stage of the malignancy at diagnosis. There may be no to very little impact to significant morbidity and mortality.
Risk groups or risk factors	A systematic review of epidemiological studies in patients with psoriasis showed a small increased risk of some solid cancers in psoriasis, based on unadjusted estimates (Pouplard et al, 2013). However, confounding factors such as alcohol drinking and smoking may have contributed to the increase in risk seen in this population. A higher risk of non-melanoma skin cancer (NMSC), especially squamous cell carcinoma, was also shown. This was considered to be mainly due to previous exposure to PUVA, cyclosporine, and possibly MTX. The incidence of malignancy in the patients with PsA is not thought to differ from that in the general population (Rohekar et al, 2008).
Preventability	Routine physical examinations as per clinical practices. Based on the patient's medical history (eg, smoking), careful evaluation should be made when patients report potential signs and symptoms associated with different types of malignancies.
Impact on the risk-benefit balance of the product	The risk of malignancy has been incorporated in the benefit risk assessment, with the overall benefit risk balance remaining positive.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 38. Important Potential Risk: Malignancies

Public health impact	Although nonclinical carcinogenicity findings were observed with roflumilast, this is not the case for apremilast. Many of the subjects who had events of malignancy in the PsA and psoriasis phase 3 studies had risk factors such as a family history, history of prior skin cancer, or exposure to agents known to be associated with increased risk of cancer. In addition, most of these events were diagnosed in the first 6 months of starting treatment with study medication, making a causal connection with apremilast unlikely. PsA The incidence rate of hematologic malignancies in the general PsA population estimated from the CPRD is 0.07 per 100 person-years. The range of estimates in the literature for general population estimates of NMSC is < 0.001 to 1.54 per 100 person-years (Lomas et al, 2012; Yong et al, 2012; Madan et al, 2010). Incidence rates of skin and solid malignancies estimated from the CPRD database are 0.54 per 100 PY and 0.25 per 100 PY. Psoriasis The rate of lymphohematopoietic malignancies in the literature is 0.262 per 100 PY (Brauchli et al, 2009). The range of estimates in the literature for the general population of NMSC is < 0.001 to 1.54 per 100 person-years (Papp et al, 2013; Lomas et al, 2012; Boffetta et al, 2001). The solid malignancy rate reported in an observational study of a psoriasis population followed for up to 11 years was an EAIR per 100 PY of 0.51 (Brauchli et al, 2009). BD A retrospective analysis of 400 subjects with BD at 1 university hospital reported a 10-year prevalence of cancer of 2.32% (Cengiz et al, 2001). A retrospective analysis of 1769 subjects with BD in 1 university hospital center in South Korea reported a prevalence of 1.8% for all cancers, 1.2% for solid cancers and 0.6% for hematological cancers (Ahn et al, 2010).

BD = Behçet's disease; BID = twice daily; CPRD = Clinical Practice Research Database; EAIR = exposure-adjusted incidence rate; MTX = methotrexate; NMSC = non-melanoma skin cancer; PsA = psoriatic arthritis; PT = Preferred Term; PUVA = psoralen and ultraviolet-A light; PY = patient-years;

Table 39. Important Potential Risk: Serious Events of Anxiety and Nervousness

Potential mechanisms	There are distinct differences in the pharmacodynamics and pharmacokinetics of apremilast and roflumilast. Therefore, the potential mechanism for roflumilast may not be applicable for apremilast. No mechanism by which apremilast may trigger anxiety and nervousness has been identified.
Evidence source(s) and strength of evidence	Anxiety is listed as an uncommon side effect of roflumilast treatment (another PDE4 inhibitor), occurring in fewer than 1 in 100 people but more than 1 in 1000, and nervousness is listed as a rare side effect of roflumilast treatment, occurring in fewer than 1 in1000 people but more than 1 in 10 000. During the phase 3 PsA and psoriasis studies, serious events of anxiety and nervousness were reported in 2 subjects in the phase 3 PsA studies. Although these events can be associated with depression, anxiety and nervousness has been included in the RMP for apremilast as an Important Potential Risk specifically for serious events.
Characterization of the risk	
Frequency	Phase 3 Adult PsA Studies During weeks 0 to 16, serious events of anxiety and nervousness were experienced by 1/972 (0.1%) apremilast treated subject in the 20 mg BID group (PT of anxiety). No subjects treated with 30 mg BID apremilast or placebo experienced a serious event of anxiety and nervousness. The event of anxiety was reported in a subject with a history of anxiety and depression, occurring after the subject's first dose of apremilast, was mild in severity, and did not require treatment. The investigator assessed this event as "medically important" making this a serious event. The event resolved. In the apremilast exposure period, serious events of anxiety and nervousness were experienced by 1/1945 (0.1%) apremilast-treated subject (20 mg BID group; PT of anxiety). The event resolved. Phase 3 Adult Psoriasis Studies During weeks 0 to 16, no serious events of anxiety and nervousness were experienced by apremilast- or placebo-treated subjects. Overall, in the apremilast exposure period, there were no serious events of anxiety and nervousness. Pediatric Psoriasis Studies No serious events of anxiety or nervousness were reported in completed Studies PPSO-001 and PPSO-003, or ongoing Study PPSO-004 (data cut-off 27 March 2023). Phase 3 Adult BD Study No subjects in BD study BCT-002 experienced events of serious anxiety and nervousness.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 39. Important Potential Risk: Serious Events of Anxiety and Nervousness

Severity	Most events of anxiety and nervousness were mild or moderate, severe events of anxiety and nervousness have been reported in subjects treated with apremilast.
Reversibility	Recovery without sequelae is likely with appropriate timely treatment.
Long-term outcomes	Recovery without sequelae is likely with appropriate timely treatment.
Impact on quality of life	Anxiety and nervousness can have very little impact to very severe impact, interfering with daily functioning, depending on the severity of the symptoms.
Risk groups or risk factors	One study showed that patients with psoriasis are at increased risk of anxiety compared to the general population (Kurd et al, 2010). The risk of anxiety was similar in those with severe and mild psoriasis, but was higher in younger compared to older patients with psoriasis (Kurd et al, 2010). No risk groups or risk factors have been identified for patients with PsA beyond those described for psoriasis. In a small study of Turkish patients with BD, 29.4% of the study population reported fear related to their disease (Karlidag et al, 2003). Another small study of Turkish patients with BD reported a prevalence of any anxiety disorder of 35.6% (Dursun et al, 2007).
Preventability	Anxiety and nervousness have been reported in the PsA and psoriasis populations and anxiety in the BD population. As in general practice, patients who have signs or symptoms of anxiety and nervousness may require additional evaluation and treatment.
Impact on the risk-benefit balance of the product	The risk of serious events of anxiety and nervousness has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive.
Public health impact	The potential public health impact varies depending on the event reported.

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BD = Behçet's disease; BID = twice daily; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term; RMP = Risk Management Plan

Table 40. Important Potential Risk: Serious Infections Including Opportunistic Infections and Transmission of Infections Through Live Vaccines

Potential mechanisms	Apremilast works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. Phosphodiesterase 4 (PDE4) is a cAMP-specific PDE and the dominant PDE in inflammatory cells. Phosphodiesterase 4 (PDE4) inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17, and other inflammatory cytokines. Cyclic adenosine monophosphate (cAMP) also modulates levels of anti-inflammatory cytokines such as IL-10. The effects of apremilast on the immune system may result in an increased risk of infection.
Evidence source(s) and strength of evidence	It has been proposed that because apremilast can decrease the effects in the pro-inflammatory mediators, the response of the body to microorganisms may be compromised. During the clinical development program for PsA, psoriasis and BD, the incidence of infections was comparable between subjects treated with placebo and those treated with apremilast. The incidence of infections did not increase when subjects continued treatment with apremilast for a longer time. Despite this, because infections are an important potential risk for roflumilast (another PDE4 inhibitor) and because of the modulation of pro-inflammatory modulators by apremilast, serious infections including opportunistic infections and transmission of infections through live vaccines is considered an important potential risk for apremilast.
Characterization of the risk	
Frequency	Serious infections, including tuberculosis, were adjudicated by an independent, blinded, subspecialty adjudicator. Events of infection were classified into 4 categories: non-opportunistic non-serious infection, non-opportunistic serious infection, non-systemic opportunistic infection, and systemic opportunistic infection. There were no infections associated with the use of live vaccines. <u>Phase 3 Adult PsA Studies</u> Systemic opportunistic infection was identified in 1/671 (0.1%) subject in the placebo group. One event (urinary tract infection) was adjudicated as non-opportunistic non serious infection in 1/972 (0.1%) subject in the apremilast 20 mg BID group. The adjudicator assessed the urinary tract infection as a non-opportunistic non-serious infection even though it was reported as a serious adverse event by the investigator and therefore sent for adjudication. Events were adjudicated as non-opportunistic serious infections in 0.3% of subjects (2/671; 0.9 per 100 PY) in the placebo group, 0.4% of subjects (4/972; 0.4 per 100 PY) in the apremilast 20 mg BID group, and 0.6% of subjects (6/973; 0.6 per 100 PY) in the apremilast 30 mg BID group.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 40. Important Potential Risk: Serious Infections Including Opportunistic Infections and Transmission of Infections Through Live Vaccines

Characterization of the risk (continued)

Frequency (continued)

Events adjudicated as non-systemic opportunistic infections were reported in 0/671 (0%) subjects in the placebo group, 0.1% of subjects (1/972, 0.1 per 100 PY) in the apremilast 20 mg BID group, and 0.2% of subjects (2/973, 0.2 per 100 PY) in the apremilast 30 mg BID group.

		Apremilast		
	Placebo (N = 671) PY = 227.8	20 mg BID (N = 972) PY = 931.6	30 mg BID (N = 973) PY = 947.1	Total (N = 1945) PY = 1878.7
	EAIR per 100 PY	EAIR per 100 PY	EAIR per 100 PY	EAIR per 100 PY
Non-opportunistic non-serious infection[a]	0	0.1	0	0.1
Non-opportunistic serious infection	0.9	0.4	0.6	0.5
Non-systemic opportunistic infection	0	0.1	0.2	0.2
Systemic opportunistic infection	0.4	0	0	0

BID = twice daily; EAIR = exposure-adjusted incidence rate; PY = patient-years

[a] The adjudicator was provided with all infections reported as serious adverse events in the clinical studies. One event of urinary tract infection was reported as a serious adverse event by the investigator; however, the adjudicator assessed this event as non-opportunistic non-serious infection (data on file).

Note: The placebo group includes all data during the placebo-controlled period of each study. For the apremilast groups, all data while subjects were exposed to apremilast were included, regardless of when the apremilast exposure started.

Each subject was counted once for each applicable event type.

EAIR per 100 patient-years is 100 times the number (n) of subjects reporting the event divided by patient-years (up to the first event start date for subjects reporting the event).

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 40. Important Potential Risk: Serious Infections Including Opportunistic Infections and Transmission of Infections Through Live Vaccines

Characterization of the risk (continued)

Frequency (continued)

Phase 3 Adult Psoriasis Studies

	Placebo (N = 418) PY = 116.5	Apremilast 30 mg BID (N = 1184) PY = 1127.9
	EAIR per 100 PY	EAIR per 100 PY
Non-opportunistic serious infection	1.7	1.0
Non-opportunistic non-serious infection	0.0	0.0
Systemic opportunistic infection	0.0	0.0

BID = twice daily; EAIR = exposure-adjusted incidence rate; PY = patient-years
Note: The placebo group includes data from weeks 0 to 16. For the apremilast group, all data for subjects exposed to apremilast were included, regardless of when the apremilast exposure started.
Each subject was counted once for each applicable event type.
EAIR per 100 patient-years is 100 times the number (n) of subjects reporting the event divided by patient-years (up to the first event start date for subjects reporting the event).

There were no cases of tuberculosis reactivation in the PsA or psoriasis phase 3 data pools or in the data pool of phase 2 and 3 apremilast studies; however, a positive skin test was reported in 3 subjects. These subjects were discontinued from the study.

Pediatric Psoriasis Studies

No serious events of infection were reported in completed Studies PPSO-001 and PPSO-003, or ongoing Study PPSO-004 (data cut-off 27 March 2023).

Phase 3 Adult BD Study

During weeks 0 to 12, no apremilast treated subjects experienced events of serious infection (30 mg BID) and 2/103 (1.9%) placebo treated subjects experienced events of serious infection.

In the apremilast exposure period, 2 subjects were judged to have had events of serious opportunistic infection (PTs: herpes zoster and lymph node tuberculosis).

Severity

Over half of the events of serious infection, including opportunistic infections and transmission of infections through live vaccines reported in subjects treated with apremilast were severe. Fatal events of serious infections, including opportunistic infections and transmission of infections through live vaccines have been reported in subjects treated with apremilast.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 40. Important Potential Risk: Serious Infections Including Opportunistic Infections and Transmission of Infections Through Live Vaccines

Characterization of the risk (continued)	
Reversibility	Generally, patients recover when their infection is treated.
Long-term outcomes	Generally, patients recover when their infection is treated.
Impact on quality of life	For severe infection, patients may be hospitalized for treatment.
Risk groups or risk factors	Loss of skin integrity is associated with an increased risk of infections such as bloodstream infections (Emori and Gaynes, 1993). Since psoriasis causes loss of skin integrity, these patients are already at risk of these infections (Emori and Gaynes, 1993). In general, factors predisposing an individual to infection also include very young (≤ 1 year) or old (≥ 60 years) age, immunosuppressive chemotherapy, chronic lung disease (respiratory tract infections), female gender (urinary tract infection) and malnutrition (Emori and Gaynes, 1993).
Preventability	Serious infections prevention varies from hand washing to avoiding endemic areas of transmissible infectious diseases. In general, the patients should consult their physician when they are exposed to a known potential infection vector or show persistent signs or symptoms of infections. The incidence of infections in the clinical studies was low and most of the microorganisms were treatable with standard treatments.
Impact on the risk-benefit balance of the product	Apremilast works by modulating the pro- and anti-inflammatory mediators. These pro- and anti-inflammatory mediators have been implicated in psoriasis and PsA. It has been proposed that because apremilast can decrease the effects in the pro-inflammatory mediators, the response of the body to microorganisms may be compromised. However, during the clinical studies, the incidence of infections was comparable between subjects treated with placebo and those treated with apremilast. The incidence of infections did not increase when subjects continued treatment with apremilast for a longer time. The risk of serious infection including opportunistic infections and transmission of infections through live vaccines has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 40. Important Potential Risk: Serious Infections Including Opportunistic Infections and Transmission of Infections Through Live Vaccines

Public health impact	Depending on the type of infection, there is the potential risk of transmission, depending on the time of diagnosis and transmission pathway of the microorganisms. Early implementation of barriers to decrease transmissions will impact the outcome. The incidence of infections in the clinical studies was low and most of the microorganisms were treatable with standard treatments. General PsA population estimates from the CPRD database show that the rate of systemic opportunistic infection events is 2.5 per 100 person-years. The results of a meta-analysis and overview by the Cochrane group of trials of biologic therapies for various indications (including rheumatoid arthritis, psoriasis, and PsA) show that the overall risk of serious infections in the pooled population exposed to biologics is 2.7 per 100 person-years (Singh et al, 2011). The clinical trials had similar follow-up periods to the clinical studies of apremilast (median duration randomized controlled, 6 months; open label extension, 13.5 months). There is no natural history study of serious infections in the BD population in the literature; however, 1 small study of patients with BD undergoing biologic treatment reported an incidence rate of 4.3/100 person-months of serious infection in this population (Talarico et al, 2013).

BD = Behçet's disease; BID = twice daily; cAMP = cyclic adenosine monophosphate; CPRD = Clinical Practice Research Database; EAIR = exposure-adjusted incidence rate; IL = interleukin; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term; PY = patient-years; TNF = tumor necrosis factor

Table 41. Important Potential Risk: MACE and Tachyarrhythmia

Potential mechanisms	Selective PDE4 inhibitors augment catecholamine-stimulated cAMP levels and induce arrhythmias in human atrial preparations (Eschenhagen, 2013); however, PDE4 does not control the inotropic and lusitropic effects mediated through β1 and β2 adrenoceptors in human heart (Molenaar et al, 2013). There are distinct differences in the pharmacodynamics and pharmacokinetics of apremilast and roflumilast. Therefore, the potential mechanism for roflumilast may not be applicable for apremilast. No mechanism by which apremilast may cause cardiac events has been identified.
Evidence source(s) and strength of evidence	The rate of major adverse cardiac events is higher in patients with psoriasis and PsA than in the normal population (Li et al, 2015; Mehta et al, 2011). The incidence of MACE during the clinical studies was similar between subjects treated with placebo and those treated with apremilast.
Characterization of the risk	
Frequency	For this risk, the following events are described: MACE, potential MACE, and tachyarrhythmia. <u>Phase 3 Adult PsA Studies</u> Events were adjudicated as MACE in 0% of subjects (0/671) in the placebo group, 0.3% of subjects (3/972; 0.3 per 100 PY) in the apremilast 20 mg BID group, and 0.1% of subjects (1/973; 0.1 per 100 PY) in the apremilast 30 mg BID group. Events were adjudicated as potential MACE in 0.1% of subjects (1/671; 0.4 per 100 PY) in the placebo group, 0.6% of subjects (6/972; 0.6 per 100 PY) in the apremilast 20 mg BID group, and 0.4% of subjects (4/973; 0.4 per 100 PY) in the apremilast 30 mg BID group. Tachyarrhythmia events were reported in 0.1% of subjects in the placebo group, 0.4% of subjects in the apremilast 20 mg BID group, and 0.5% of subjects in the apremilast 30 mg BID group during weeks 0 to 16. Based on EAIR per 100 PY there was no evidence of an increased incidence of tachyarrhythmia events with longer exposure to apremilast in the PsA phase 3 Data Pool (0.9 and 1.6 per 100 PY for the apremilast exposure period and weeks 0 to 16, respectively, in the apremilast group). <u>Phase 3 Adult Psoriasis Studies</u> Events were adjudicated as MACE in 0.2% of subjects (1/418; 0.9 per 100 PY) in the placebo group and 0.5% of subjects (6/1184; 0.5 per 100 PY) in the apremilast 30 mg BID group. Five of the 6 apremilast treated subjects adjudicated with MACE had 2 or more major risk factors associated with MACE (eg, hypertension, smoking, hyperlipidemia, elderly age, or obesity/overweight), along with additional confounding factors.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 41. Important Potential Risk: MACE and Tachyarrhythmia

Characterization of the risk (continued)	
Frequency (continued)	Events were adjudicated as potential MACE in 0.2% of subjects (1/418; 0.9 per 100 PY) in the placebo group and 0.8% of subjects (9/1184; 0.8 per 100 PY) in the apremilast 30 mg BID group. Eight of the 9 subjects adjudicated with potential MACE had 2 or more major confounding factors associated with MACE (eg, history of coronary artery disease, hypertension, dyslipidemia, smoking, obesity/overweight, diabetes mellitus, or family history of coronary artery disease). During weeks 0 to 16, tachyarrhythmia events were reported in 0.2% of subjects in the placebo group and 0.6% of apremilast 30 mg BID subjects as treated. Based on EAIR per 100 PY there was no evidence of an increased incidence of tachyarrhythmia events with longer exposure to apremilast in the psoriasis phase 3 Data Pool (1.3 and 2.1 per 100 PY for the apremilast exposure period and during weeks 0 to 16, respectively, in the apremilast 30 mg BID group). <u>Pediatric Psoriasis Studies</u> No events of MACE were reported in completed Study PPSO-001 or ongoing Study PPSO-004 (data cut-off 27 March 2023). There was 1 event of sinus tachycardia reported in completed Study PPSO-003. No adjudication of this event was reported. <u>Phase 3 Adult BD Study</u> No events were adjudicated as MACE in Study BCT-002. During weeks 0 to 12, tachyarrhythmia events were reported in 1/103 (1.0%) subjects in the placebo group and no apremilast 30 mg BID treated subjects. Based on EAIR per 100 PY there was no evidence of an increased incidence of tachyarrhythmia events with longer exposure to apremilast (1.1 and 0 per 100 PY for the apremilast exposure period and during weeks 0 to 12, respectively, in the apremilast 30 mg BID group).
Severity	Most of the reported events of MACE were considered to be severe. Fatal and life-threatening events of MACE have been reported in subjects treated with apremilast
Reversibility	The reversibility of the cardiac disorders described above will depend upon the severity and overall health of the individual.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 41. Important Potential Risk: MACE and Tachyarrhythmia

Long-term outcomes	The long-term outcomes of the cardiac disorders described above will depend upon the severity and overall health of the individual.
Impact on quality of life	The cardiac disorders described above may impact the quality of life of patients. The impact varies from minimal to physical limitations and death.
Risk groups or risk factors	Epidemiological studies have shown a high prevalence of CVD risk factors, including metabolic syndrome, cigarette smoking, obesity, hypertension, diabetes mellitus, insulin resistance and dyslipidemia, in patients with psoriasis (Horreau et al, 2013). The severity of psoriatic skin disease influences cardiovascular risk, (González-Gay et al, 2012), as does early onset of disease (Horreau et al, 2013). An increased (but low absolute) myocardial infarction risk has been reported in patients with psoriasis aged < 60 years (adjusted odds ratio 1.66; 95% CI: 1.03-2.66) compared with patients without psoriasis (Brauchli et al, 2009).
Preventability	According to the updated 2002 recommendation from the American Heart Association (AHA), activities such as smoking cessation, weight management, physical activity, diabetes management should be suggested for prevention of CVD and stroke (Pearson et al, 2002). Several large population-based studies show significant reduction in risk of CVD and stroke. All of these studies showed that regardless of the risk factor (smoking, diabetes, high BMI, etc) at baseline, moderate physical activity (30 minutes moderate activity, 5 days a week) will result in significant reduction of risk of CVD and stroke (Hamer and Stamatakis, 2009; Joyner and Green, 2009; Mora et al, 2007). A study comparing bus conductors and drivers in London showed that conductors had half the incidence of sudden cardiac death compared to drivers (Joyner and Green, 2009).
Impact on the risk-benefit balance of the product	The rate of major heart problems is higher in patients with psoriasis and PsA than in the normal population. The incidence of these events during the clinical studies was similar between subjects treated with placebo and those treated with apremilast. The risk of MACE and tachyarrhythmia has been incorporated in the benefit-risk assessment, with the overall benefit-risk balance remaining positive.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 41. Important Potential Risk: MACE and Tachyarrhythmia

Public health impact	The impact of the cardiac disorders described above is more on an individual patient basis. MACE estimates from the MarketScan database reported MACE prevalence in PsA patients to be 2.1 per 100 persons in the population, which suggests that MACE is not an uncommon event among PsA patients. A meta-analysis of psoriasis patients receiving biologic agents reported MACE rates in individual studies ranging from 0 to 4.6 per 100 person-years (Ryan et al, 2011). A published study using the CPRD estimated the incidence rate of MACE in the psoriasis population (defined as acute myocardial infarction, ischemic stroke, death due to myocardial infarction, and arrhythmia) to be 1.64 per 100 PY (Mehta et al, 2011). There was no specific literature found for tachyarrhythmia in psoriasis or PsA patients; however, there were a few studies on arrhythmia and abnormal cardiac rhythm issues in these patients. One study found a high prevalence (65%) of subclinical left ventricular dysfunction in a Chinese PsA population (N = 94) living in Hong Kong (Shang et al, 2011). This study also reported high prevalence of diastolic dysfunction (38%) and combination of diastolic and systolic dysfunction (22%) in these patients (Shang et al, 2011). A smaller study on the rhythmic profile of 22 PsA patients in Portugal reported 68.1% had tachycardia, 36% of patients had bradycardia, and 9% of patients had supraventricular tachycardia (Carvalho et al, 1990). A review of the ECG of 169 psoriasis patients who had cardiac catheterization reported 17% with left ventricular hypertrophy, 15% with presence of Q-wave, 6% with left bundle branch block, and 5% with right bundle branch block (Armstrong et al, 2013). Two studies on arrhythmia found significantly higher P-wave dispersion in psoriasis patients as compared to non-psoriasis controls (Bacaksiz et al, 2013; Simsek et al, 2013). There is no information on MACE in BD in the literature; however, a review article of CVD in the BD population reported 1% to 5% of patients with BD had some form of CVD. Two studies reviewed reported silent myocardial infarction in 20% to 25% of the study population (Owlia and Mehrpoor, 2012). A small study of Turkish patients with BD reported 16% of the study population as having aortic valve problems (Ulusan et al, 2014).

Footnotes, including abbreviations, are defined on the last page of the table.

AHA = American Heart Association; BD = Behçet's disease; BID = twice daily; BMI = body mass index; cAMP = cyclic adenosine monophosphate; CPRD = Clinical Practice Research Database; CVD = cardiovascular disease; EAIR = event adjusted incidence rate; ECG = electrocardiogram; MACE = major adverse cardiovascular event; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term; PY = patient-years; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event

Note: Major adverse cardiac events were defined as TEAEs of sudden unwitnessed death, cardiovascular death (sudden cardiac death, death due to myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes), myocardial infarction, and nonfatal stroke. Potential MACE was defined as unstable angina requiring hospitalization, coronary revascularisation procedure, transient ischemic attack, rehospitalization for recurrent ischemia, embolic events, and deep vein thrombosis. An analysis of treatment-emergent tachyarrhythmia was conducted based on a search using the tachyarrhythmia broad scope SMQ terms.

Table 42. Important Potential Risk: Prenatal Embryo-fetal Loss and Delayed Fetal Development (Reduced Ossification and Fetal Weight) in Pregnant Women Exposed to Apremilast

Potential mechanisms	There is no clear mechanism on how embryo-fetal loss is triggered in humans. However, available literature data suggests that the mechanism may be different between mice and humans. While IL-6 contributes to normal trophoblast growth and placental development in humans, published data demonstrated that IL-6 is embryotoxic in mice, and PDE4 inhibitors, including apremilast, roflumilast, and cilomilast, have been shown to cause a dose-dependent elevation in IL-6 production from lipopolysaccharide-stimulated whole blood from mice and rats. Studies in monkeys showed that there is an increased risk of miscarriage or death of the unborn baby in animals given more than the dose of apremilast that would be taken by patients.
Evidence source(s) and strength of evidence	There are no adequate studies of apremilast in pregnant women, and it is not known whether apremilast will harm the unborn baby; however, nonclinical studies at high doses suggested an increased risk of miscarriage or death of the unborn baby.
Characterization of the risk	
Frequency	As of 20 March 2023, there have been a total of 21 cases of potential fetal exposure during pregnancy in females exposed to apremilast in prospective clinical trials.

The outcomes of these pregnancies are summarized below:

	Cumulative Prospective Clinical Trial Cases (N = 21) Timing of Exposure in Pregnancy			
Pregnancy Outcome	Before Conception	First Trimester	Second Trimester	Total
Elective termination (no fetal defects or unknown)	1	6	0	7
Live birth without congenital anomaly	3	6	1	10
Spontaneous abortion	0	1	0	1
Therapeutic abortion	0	1	0	1
Unknown	0	2	0	2
Total	4	16	1	21

No cases of reduced ossification or reduced fetal weight have been reported cumulatively. The majority of births reported from potential exposures are full term healthy infants.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 42. Important Potential Risk: Prenatal Embryo-fetal Loss and Delayed Fetal Development (Reduced Ossification and Fetal Weight) in Pregnant Women Exposed to Apremilast

Characterization of the risk (continued)	
Severity	Not applicable.
Reversibility	Not known
Long-term outcomes	Not known
Impact on quality of life	The potential impact to the patient of fetal loss and to the fetus of delayed development and reduced ossification is severe. However, there have been no such reports in clinical trials of apremilast.
Risk groups or risk factors	No specific group of women has been identified. In general, all women who can become pregnant are at risk.
Preventability	Apremilast is contraindicated in pregnancy (see the product label). Preclinical information on embryo-fetal development and information regarding use in pregnancy is provided in the product label.
Impact on the risk-benefit balance of the product	The potential impact to the patient of fetal loss and to the fetus of delayed development and reduced ossification is severe. However, there have been no such reports in clinical trials of apremilast.
Public health impact	The potential public health impact is considered to be low as the effect is only to the women who get pregnant while taking apremilast. Based on the most recently available estimates (2010) published by the European Commission, the rate of fetal loss in the EU 27 countries ranged from 1.5 to 4.3 per 1000 live births with gestation period of 28 weeks or greater and 4 to 8.9 per 1000 live birth overall (EURO-PERISTAT, 2013). Based on the most recently available estimates (2010) published by the European Commission, the rate of low birth weight live births (defined as birth weight less than 2500 g) ranged from 4% to > 9% of the EU 27 country population (EURO-PERISTAT, 2013). Based on the most recently available estimates (2005) published by Statistics Canada, fetal loss was experienced by 1 per 1000 women, while low birth weight live births (defined as birth weight < 2500 g) was 6% (Statistics Canada, 2014a; Statistics Canada, 2014b).

EU = European Union; IL = interleukin; PDE4 = phosphodiesterase 4

SVII.3.2 Presentation of the Missing Information

Table 43. Missing Information: Long-term Safety

Evidence source	The Long-term Benefits and Safety of Systemic Psoriasis Therapy (PsoBest) registry (complete); the British Society for Rheumatology Biologics Register in Psoriatic Arthritis (BSRBR-PsA) (ongoing), and the CPRD Data Analysis (complete).
Population in need of further characterization	Two additional pharmacovigilance studies assessing long-term efficacy and safety of apremilast are now complete. There is 1 more ongoing study of long-term safety data in the real-world setting. This study is described in Part III.2.

CPRD = Clinical Practice Research Database; BSRBR = British Society for Rheumatology Biologics Register; PsA = psoriatic arthritis

Part II: Module SVIII - Summary of the Safety Concerns

Table 44. Summary of Safety Concerns

Important identified risks	• Serious events of hypersensitivity • Suicidality • Serious events of depression
Important potential risks	• Vasculitis • Malignancies • Serious events of anxiety and nervousness • Serious infections including opportunistic infections and transmission of infections through live vaccines • MACE and tachyarrhythmia • Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast
Missing information	• Long-term safety

MACE = major adverse cardiovascular event

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 45.

Table 45. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Hypersensitivity	Serious events of hypersensitivity	To ensure that consistent and good quality follow-up data are obtained, to further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk.
Vasculitis	Vasculitis	To ensure that consistent and good quality follow-up data are obtained, to further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk.
Suicidality/Depression	Serious events of depression Suicidality	To ensure that consistent and good quality follow-up data are obtained, to further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk.
Core questions for follow-up of malignancies, and specific questions for multiple cancer types	Malignancies	To ensure that consistent and good quality follow-up data are obtained, to further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk.
Infection in general (including opportunistic infection abscess, soft tissue infections including necrotizing fasciitis)	Serious infections including opportunistic infections and transmission of infections through live vaccines	To ensure that consistent and good quality follow-up data are obtained, to further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk.
Cardiac arrhythmia and ECG changes Myocardial infarction Cerebrovascular accident (CVA)	MACE and tachyarrhythmia	To ensure that consistent and good quality follow-up data are obtained, to further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 45. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Pregnancy background (patient or partner of patient) Pregnancy follow-up (patient or partner of patient) Infant follow-up Pregnancy outcome and infant information	Prenatal embryo fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast.	To ensure that consistent and good quality follow-up data are obtained, to further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk.

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CVA = cerebrovascular accident; ECG = echocardiogram; MACE = major adverse cardiovascular event

III.2 Additional Pharmacovigilance Activities

Table 46. Category 1 to 3 Postauthorization Safety Studies

Study Short Name and Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
Apremilast PsA Registry in the UK – BSRBR-PsA (CC-10004-PSA-012) Safety Outcomes for Psoriatic Arthritis Patients Treated with Otezla in the British Society for Rheumatology Biologics Register in Psoriatic Arthritis (BSRBR-PsA). Category 3	Primary objective: • To evaluate the long-term safety of apremilast, a cohort of patients fulfilling the CASPAR in the BSRBR-PsA and treated with apremilast will be identified and incidence rates of the following AESIs will be estimated over a long-term apremilast study: Malignancies; Opportunistic and serious infections (defined as requiring hospitalisation, life threatening or resulting in death); Completed suicides and suicide attempts; MACE (including sudden cardiac death; death due to MI, heart failure, and stroke; death due to other cardiovascular causes; MI; and nonfatal stroke) and serious tachyarrhythmias; Vasculitis; Hypersensitivity, potentially life-threatening; and, Serious events of depression, anxiety and/or nervousness. Secondary objective: • To compare the event rates of AESIs between the exposed group (cohort treated with apremilast) and the non exposed groups (patients treated with non-apremilast treatments).	A prospective, longitudinal, multicentre study in a real-world cohort of patients. The study will involve retrospective analysis of data collected within the third-party registry BSRBR-PsA at predefined time points.	Patients in the UK who meet the CASPAR classification criteria for PsA with a score ≥ 3 points.	Protocol submission: 16 October 2018 (submission date) 1-year report submission: 23 June 2020 2-year report submission: 21 Jun 2021 3-year report submission: 07 June 2022 4-year report submission: 21 June 2023 5-year report submission: 24 June 2024 7-year report due: Q3 2026.

AESI = adverse event of special interest; BSRBR = British Society for Rheumatology Biologics Register; CASPAR = Classification of Psoriatic Arthritis; MACE = major adverse cardiac events; MI = myocardial infarction; PsA = psoriatic arthritis; UK = United Kingdom

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 47. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Dates
Category 3 - Required additional pharmacovigilance activities				
Apremilast PsA Registry in the UK – BSRBR-PsA (CC-10004-PSA-012) Safety Outcomes for Psoriatic Arthritis Patients Treated with Otezla in the British Society for Rheumatology Biologics Register in Psoriatic Arthritis (BSRBR-PsA) Ongoing	To collect long-term data on specified AESIs in real world setting.	• Serious events of hypersensitivity • Suicidality • Serious events of depression • Vasculitis • Malignancies • Serious events of anxiety and nervousness • Serious infections including opportunistic infections and transmission of infections through live vaccines • MACE and tachyarrhythmia • Long-term safety	Final protocol for BSRBR-PsA registry: Enrollment initiated: 1-year report submission date: 2-year report submission date: 3-year report submission date: 4-year report submission date: 5-year report submission date: 7-year report due date:	16 October 2018 Q4 2018 23 June 2020 21 June 2021 07 June 2022 21 June 2023 24 June 2024 Q3 2026

AESI = adverse event of special interest; BSRBR = British Society for Rheumatology Biologics Register; MACE = major adverse cardiac events; PsA = psoriatic arthritis; UK = United Kingdom

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing postauthorisation efficacy studies for apremilast.

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

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 48. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Serious events of hypersensitivity	Routine risk communication: SmPC Section 4.8 Undesirable effects Hypersensitivity included as an ADR. Patient information leaflet (PIL) Included as a possible side effect in Section 4. Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.3 Contraindications Contraindicated in patients with hypersensitivity to the active substance(s) or to any of the excipients. PIL Instruction not to take if the patient is allergic to apremilast or any of the other ingredients is included in Section 2. Other risk minimization measures beyond the PI: None

Table 48. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
Suicidality	Routine risk communication: SmPC Section 4.8 Undesirable effects Suicidal ideation and behaviour included as an ADR. PIL Included as a possible side effect in Section 4. Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 Special warnings and precautions for use Includes warnings regarding suicidal ideation and suicidal attempt. PIL Warnings regarding suicidal thoughts or behaviour are included in Section 2. Other risk minimization measures beyond the PI: None Legal status Apremilast is a prescription only medicinal product.
Serious events of depression	Routine risk communication: SmPC Section 4.8 Undesirable effects Depression included as an ADR. PIL Included as a possible side effect in Section 4. Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 Special warnings and precautions for use Includes warnings regarding depression. PIL Warnings regarding depression are included in Section 2. Other risk minimization measures beyond the PI: None Legal status Apremilast is a prescription only medicinal product.
Important Potential Risks	
Vasculitis	None
Malignancies	None

Table 48. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks (continued)	
Serious events of anxiety and nervousness	None
Serious infections including opportunistic infections and transmission of infections through live vaccines	None
MACE and tachyarrhythmia	None
Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: <u>SmPC</u> Section 4.3 Contraindications Contraindicated in pregnancy. Section 4.6 Fertility, pregnancy and lactation Includes information regarding use in pregnancy. Section 5.3 Preclinical safety data Includes preclinical information on embryo-fetal development. <u>PIL</u> Instructions not to take if the patient is or may be pregnant and information regarding use in pregnancy is included in Section 2. Other routine risk minimization measures beyond the PI: None <u>Legal status</u> Apremilast is a prescription only medicinal product.
Missing Information	
Long-term safety	None

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ADR = adverse drug reaction; MACE = MACE = major adverse cardiac events; PI = Product Information; PIL = Patient Information Leaflet; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimization Measures

There are no additional risk minimisation measures currently in place.

V.3 Summary of Risk Minimization Measures

Table 49. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Serious events of hypersensitivity	Routine risk minimization measures: SmPC • Contraindicated in those with hypersensitivity to apremilast (Section 4.3) and the risk of hypersensitivity is presented in Section 4.8. PIL • Includes advice not to take if allergic to apremilast in Section 2, and included in Section 4. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA
Suicidality	Routine risk minimization measures: SmPC • The risk of triggering suicide is discussed in Sections 4.4 and 4.8. PIL • Included in Sections 2 and 4 of the patient information. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA
Serious events of depression	Routine risk minimization measures: SmPC • The risk of depression is discussed in Sections 4.4 and 4.8. PIL • Included in Sections 2 and 4 of the patient information. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA

Table 49. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Vasculitis	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA
Malignancies	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA
Serious events of anxiety and nervousness	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA
Serious infections including opportunistic infections and transmission of infections through live vaccines	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA

Table 49. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
MACE and tachyarrhythmia	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA
Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast	Routine risk minimization measures: SmPC • Contraindicated in pregnancy (Section 4.3). Includes information regarding use in pregnancy (Section 4.6) and preclinical information on embryo-fetal development (Section 5.3). PIL • Includes information regarding use in pregnancy (including do not take if pregnant) in Section 2. Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: • None
Missing Information		
Long-term safety	Routine risk minimization measures: • None Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA

BSRBR = British Society for Rheumatology Biologics Register; MACE = MACE = major adverse cardiac events; PIL = Patient Information Leaflet; PsA = psoriatic arthritis; SmPC = Summary of Product Characteristics; UK = United Kingdom

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for apremilast is presented below.

Summary of Risk Management Plan for Otezla® (apremilast)

This is a summary of the risk management plan (RMP) for Otezla. The RMP details important risks of Otezla, how these risks can be minimized, and how more information will be obtained about Otezla's risks and uncertainties (missing information).

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

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

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

I. The Medicine and What it is Used for

Otezla is authorised for the following indications:

- Otezla, alone or in combination with disease modifying antirheumatic drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have an inadequate response or who have been intolerant to a prior DMARD therapy.
- Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis (PSOR) in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen, and ultraviolet-A light (PUVA).
- Otezla is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years and weighing at least 20 kg who are candidates for systemic therapy.
- Otezla is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

Otezla contains apremilast as the active substance and it is given by the oral route of administration.

Further information about the evaluation of Otezla's benefits can be found in Otezla's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/otezla.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

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

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

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

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of Important Risks and Missing Information

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

Important Identified and Potential risks, together with Missing Information, are summarized in the table below.

List of important risks and missing information	
Important identified risks	• Serious events of hypersensitivity • Suicidality • Serious events of depression
Important potential risks	• Vasculitis • Malignancies • Serious events of anxiety and nervousness • Serious infections including opportunistic infections and transmission of infections through live vaccines • Major adverse cardiac event (MACE) and tachyarrhythmia • Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast
Missing information	• Long-term safety

II.B. Summary of Important Risks

Important identified risk: Serious events of hypersensitivity	
Evidence for linking the risk to the medicine	This risk was identified during the clinical study setting. Events pertinent to the risk of serious events of hypersensitivity were observed during the clinical development programs for PsA and psoriasis. Hypersensitivity is listed as an uncommon side effect of roflumilast treatment (another phosphodiesterase 4 [PDE4] inhibitor), occurring in fewer than 1 in 100 people but more than 1 in 1000.
Risk factors and risk groups	General factors that increase the likelihood of experiencing a Type 1 hypersensitivity reaction include repeated exposure to the drug and a history of drug hypersensitivity, particularly if hypersensitivity occurred with a drug of the same chemical class (Lenz, 2007). Patient risk factors for hypersensitivity drug reactions include female gender, adulthood, human immunodeficiency virus (HIV) infection, concomitant viral infection, previous hypersensitivity to chemically related drug, asthma, use of beta blockers, specific genetic polymorphisms and the Caucasian race (Gomes and Demoly, 2005; Riedl and Casillas, 2003).
Risk minimization measures	Routine risk minimization measures: SmPC • Contraindicated in those with hypersensitivity to apremilast (Section 4.3) and the risk of hypersensitivity is presented in Section 4.8. Package Leaflet • Includes advice not to take if allergic to apremilast in Section 2, and included in Section 4. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Apremilast PsA Registry in the United Kingdom (UK) – British Society for Rheumatology Biologics Register in Psoriatic Arthritis (BSRBR-PsA) See Section II.C of this summary for an overview of the postauthorization development plan.

Important identified risk: Suicidality	
Evidence for linking the risk to the medicine	Events pertinent to the risk of triggering suicide were observed during the clinical development programs for PsA and psoriasis. Suicidal thoughts (ideation) and behaviour are rare side effects of roflumilast treatment (another PDE4 inhibitor), occurring in fewer than 1 in 1000 people but more than 1 in 10 000.
Risk factors and risk groups	Suicide rates are twice as high in families of suicide victims (Fancher and Kravitz, 2007). Suicidal behaviour has a large number of complex underlying causes, including poverty, unemployment, loss of loved ones, arguments, breakdown of relationships, and legal or work-related problems. A family history of suicide, as well as alcohol and drug abuse, childhood abuse, social isolation and some mental disorders including depression and schizophrenia, also play a central role in a large number of suicides. Physical illness and disabling pain can also increase suicide risks. One study showed the risk of depression was higher in severe psoriasis compared with mild psoriasis, and higher in younger compared to older patients with psoriasis (Kurd et al, 2010).
Risk minimization measures	Routine risk minimization measures: SmPC • The risk of triggering suicide is discussed in Sections 4.4 and 4.8. Package Leaflet • Included in Sections 2 and 4 of the patient information. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA See Section II.C of this summary for an overview of the postauthorization development plan.

Important identified risk: Serious events of depression	
Evidence for linking the risk to the medicine	Events pertinent to the risk of serious events of depression were observed during the clinical development programs for PsA and psoriasis. Depression is listed as a rare side effect of roflumilast treatment (another PDE4 inhibitor), occurring in fewer than 1 in 1000 people but more than 1 in 10 000.
Risk factors and risk groups	One study showed that patients with psoriasis are at increased risk of depression compared to the general population (Kurd et al, 2010). The risk of depression was higher in patients with severe compared with mild psoriasis, and higher in younger compared to older patients with psoriasis. No risk groups or risk factors have been identified for patients with PsA beyond those described for psoriasis. Depression is typically measured using scores from psychometric instruments. Studies on depression among patients with BD show consistently higher depression scores regardless of instruments used when compared to patients without BD (de Oliveira Ribeiro et al, 2014; Taner et al, 2007; Gur et al, 2006). One study of Turkish patients with BD reported 45.5% of the study population experienced depression (Taner et al, 2007). Another study of Turkish patients with BD reported a prevalence of major depression in 17.8% of the study population and a prevalence of dysthymic disorder of 6.8% (Dursun et al, 2007). A small study of Turkish patients with BD showed that 32.3% of the study population experienced sadness related to their disease (Karlidag et al, 2003). A small study comparing patients with BD and controls using the Beck Suicide Inventory (BSI) showed a much higher BSI among the BD group (61.3) as compared to controls (30.4) (de Oliveira Ribeiro et al, 2014).
Risk minimization measures	Routine risk minimization measures: SmPC • The risk of depression is discussed in Sections 4.4 and 4.8. Package Leaflet • Included in Sections 2 and 4 of the patient information. Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Vasculitis	
Evidence for linking the risk to the medicine	Animal studies have shown that PDE4 inhibitors, including apremilast, roflumilast, and cilomilast, are pro-inflammatory in rodents, but not in monkeys or humans. Therefore, vasculitis has been included as an important potential risk for apremilast. In the apremilast clinical studies, small vessel cutaneous vasculitis was reported in 3 subjects. Two of these subjects participated in a rheumatoid arthritis study and the third subject participated in a PsA study.
Risk factors and risk groups	Risk factors in the general population include immune disorders, connective tissue diseases, infections, atherosclerotic cardiovascular diseases (CVDs), exposure to chemicals, medications, and malignancies. Behçet's disease is a chronic multisystem variable vessel vasculitis characterized by oral and genital ulcers, skin lesions, uveitis, arthritis, vascular, central nervous system, and gastrointestinal involvement (Cho et al, 2012; Keino and Okada, 2007) that requires long-term treatment.
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	Although there was no clear imbalance in the frequency of malignancies between apremilast and placebo treatment during the clinical development programs for PsA, psoriasis and BD, the duration of treatment was relatively short. Therefore, malignancies have been included as an important potential risk for apremilast. Many of the subjects who had events of malignancy in the clinical studies had risk factors such as a family history, history of prior skin cancer, or exposure to agents known to be associated with increased risk of cancer. In addition, most of these events were diagnosed in the first 6 months of starting treatment with apremilast, meaning it is unlikely that the occurrence of the malignancies is connected with apremilast.
Risk factors and risk groups	A systematic review of epidemiological studies in patients with psoriasis showed a small increased risk of some solid cancers in psoriasis, based on unadjusted estimates (Pouplard et al, 2013). However, confounding factors such as alcohol drinking and smoking may have contributed to the increase in risk seen in this population. A higher risk of non-melanoma skin cancer (NMSC), especially squamous cell carcinoma, was also shown. This was considered to be mainly due to previous exposure to psoralen and ultraviolet-A light (PUVA), cyclosporine, and possibly methotrexate. The incidence of malignancy in the patients with PsA is not thought to differ from that in the general population (Rohekar et al, 2008).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Serious events of anxiety and nervousness	
Evidence for linking the risk to the medicine	Anxiety is listed as an uncommon side effect of roflumilast treatment (another PDE4 inhibitor), occurring in fewer than 1 in 100 people but more than 1 in 1000, and nervousness is listed as a rare side effect of roflumilast treatment, occurring in fewer than 1 in 1000 people but more than 1 in 10 000. During the phase 3 PsA and psoriasis studies, serious events of anxiety and nervousness were reported in 2 subjects in the phase 3 PsA studies. Although these events can be associated with depression, anxiety and nervousness has been included in the RMP for apremilast as an Important Potential Risk specifically for serious events
Risk factors and risk groups	One study showed that patients with psoriasis are at increased risk of anxiety compared to the general population (Kurd et al, 2010). The risk of anxiety was similar in those with severe and mild psoriasis but was higher in younger compared to older patients with psoriasis (Kurd et al, 2010). No risk groups or risk factors have been identified for patients with PsA beyond those described for psoriasis. In a small study of Turkish patients with BD, 29.4% of the study population reported fear related to their disease (Karlidag et al, 2003). Another small study of Turkish patients with BD reported a prevalence of any anxiety disorder of 35.6% (Dursun et al, 2007).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Serious infections including opportunistic infections and transmission of infections through live vaccines	
Evidence for linking the risk to the medicine	It has been proposed that because apremilast can decrease the effects in the pro-inflammatory mediators, the response of the body to microorganisms may be compromised. During the clinical development program for PsA, psoriasis and BD, the incidence of infections was comparable between subjects treated with placebo and those treated with apremilast. The incidence of infections did not increase when subjects continued treatment with apremilast for a longer time. Despite this, because infections are an important potential risk for roflumilast (another PDE4 inhibitor) and because of the modulation of pro-inflammatory modulators by apremilast, serious infections including opportunistic infections and transmission of infections through live vaccines is considered an important potential risk for apremilast.
Risk factors and risk groups	Loss of skin integrity is associated with an increased risk of infections such as bloodstream infections (Emori and Gaynes, 1993). Since psoriasis causes loss of skin integrity, these patients are already at risk of these infections (Emori and Gaynes, 1993). In general, factors predisposing an individual to infection also include very young (≤ 1 year) or old (≥ 60 years) age, immunosuppressive chemotherapy, chronic lung disease (respiratory tract infections), female gender (urinary tract infection) and malnutrition (Emori and Gaynes, 1993).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: MACE and tachyarrhythmia	
Evidence for linking the risk to the medicine	The rate of major adverse cardiac events is higher in patients with psoriasis and PsA than in the normal population (Li et al, 2015; Mehta et al, 2011). The incidence of MACE during the clinical studies was similar between subjects treated with placebo and those treated with apremilast.
Risk factors and risk groups	Epidemiological studies have shown a high prevalence of CVD risk factors, including metabolic syndrome, cigarette smoking, obesity, hypertension, diabetes mellitus, insulin resistance and dyslipidemia, in patients with psoriasis (Horreau et al, 2013). The severity of psoriatic skin disease influences cardiovascular risk, (González-Gay et al, 2012), as does early onset of disease (Horreau et al, 2013). An increased (but low absolute) myocardial infarction risk has been reported in patients with psoriasis aged < 60 years (adjusted odds ratio 1.66; 95% confidence interval [CI]: 1.03-2.66) compared with patients without psoriasis (Brauchli et al, 2009).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA See Section II.C of this summary for an overview of the postauthorization development plan.

Important potential risk: Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast	
Evidence for linking the risk to the medicine	There are no adequate studies of apremilast in pregnant women, and it is not known whether apremilast will harm the unborn baby; however, nonclinical studies at high doses suggested an increased risk of miscarriage or death of the unborn baby.
Risk factors and risk groups	No specific group of women has been identified. In general, all women who can become pregnant are at risk.
Risk minimization measures	Routine risk minimization measures: SmPC • Contraindicated in pregnancy (Section 4.3). Includes information regarding use in pregnancy (Section 4.6) and preclinical information on embryo-fetal development (Section 5.3). Package Leaflet • Includes information regarding use in pregnancy (including do not take if pregnant) in Section 2. Additional risk minimization measures: • None

Missing information: Long-term safety	
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Apremilast PsA Registry in the UK – BSRBR-PsA See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Otezla.

II.C.2. Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Apremilast PsA Registry in the UK – BSRBR-PsA (CC-10004-PSA-012)	To evaluate the long-term safety of apremilast, a cohort of patients fulfilling the CASPAR in the BSRBR-PsA and treated with apremilast will be identified and incidence rates of the following adverse event(s) of special interest (AESIs) will be estimated over a long-term apremilast study: Malignancies; Opportunistic and serious infections (defined as requiring hospitalisation, life threatening or resulting in death); Completed suicides and suicide attempts; MACE (including sudden cardiac death; death due to myocardial infarction, heart failure, and stroke; death due to other cardiovascular causes; myocardial infarction; and nonfatal stroke) and serious tachyarrhythmias; Vasculitis; Hypersensitivity, potentially life-threatening; and, Serious events of depression, anxiety and/or nervousness. Secondary objective: To compare the event rates of AESIs between the exposed group (cohort treated with apremilast) and the non exposed groups (patients treated with non-apremilast treatments).

PART VII: ANNEXES

Table of Contents

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

Follow-up Form Title	Version Number	Date of Follow-up Version
Hypersensitivity	Not applicable	11 May 2020
Suicidality/depression	Not applicable	11 May 2020
Vasculitis	Not applicable	11 May 2020
Malignancies	Not applicable	11 May 2020
Infection in general (including opportunistic infection, abscess, soft tissue infections including necrotizing fasciitis)	Not applicable	11 May 2020
Cardiac arrhythmia & ECG changes	Not applicable	11 May 2020
Myocardial infarction	Not applicable	11 May 2020
Cerebrovascular accident (CVA)	Not applicable	11 May 2020
Initial pregnancy questionnaire (mother)	1.1	11 January 2016
6 to 8 weeks post due date questionnaire (mother)	Not applicable	Not applicable
Six and twelve month infant questionnaire	Not applicable	Not applicable

AMGEN

Report of Suspected OTEZLA® Associated Adverse Event HYPERSENSITIVITY

Date of this Report (dd/mm/yyyy)

AER #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Amgen does not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

PATIENT INFORMATION

Patient Initials (Confidential)

Age at time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: lb kg

Event Date (dd/mm/yyyy)

Event Time (24 hr, ie, 14:30)

MEDICATION ADMINISTERED

☐ **Otezla**

Dose | Frequency | Route

Other Amgen Drug

Dose | Frequency | Route

Other Medications:

Co-Suspect Medications:

1. Describe the temporal relationship between the event(s) and the administration of suspect drug and circumstances surrounding the hypersensitivity reaction.

2. What kind of hypersensitivity was experienced (immediate, delayed, etc.), if confirmed?

3. What was the etiology of the hypersensitivity? Please provide rationale.

4. Was the patient previously exposed to the drug or a drug from the same class?

5. Does the patient have history of hypersensitivity reactions? ☐ Yes ☐ No If yes, to which medication?
   If yes, please describe the previous episodes. If they are drug-related, please indicate whether the patient already had a reaction to a product of the same class.

6. What was the final diagnosis for the hypersensitivity reaction?

7. Please check the types of specific symptoms observed:

- ☐ Fever, chills — Describe:
- ☐ Urticaria — Describe:
- ☐ Angioedema — Describe:
- ☐ Dizziness
- ☐ Dyspnea
- ☐ Bronchospasm
- ☐ Tachycardia — Indicate HR:
- ☐ Hypotension — Indicate systolic/diastolic BP:
- ☐ Shock — Describe:
- ☐ Renal dysfunction — Indicate laboratory values:
- ☐ Hepatic dysfunction — Indicate laboratory values:
- ☐ Pneumonitis/Interstitial lung disease — Describe:
- ☐ Others — Describe:

CONTINUED ON PAGE 2

AMGEN

Report of Suspected OTEZLA® Associated Adverse Event HYPERSENSITIVITY

Date of this Report (dd/mm/yyyy)	AER #

8. Please describe the kind of treatment administered (type, dose, and route of administration):

9. What was the outcome of the event?

10. Has this patient subsequently been re-exposed to the suspect drug? ☐ Yes ☐ No

11. If yes to above re-exposure question, did the event re-appear? ☐ Yes ☐ No

12. If yes (event re-appeared), at which dose? ☐ Same ☐ Different If the dose was different than before, please indicate:

13. If this patient was subsequently re-exposed was there any prophylaxis administered? ☐ Yes ☐ No If yes, what kind of prophylaxis?

14. Provide a complete list of concomitant medications including therapy start and stop date (please include dietary supplements and OTC):

Drug Name	**Indication for use**	**Start date** (dd/mm/yyyy)	**Stop date** (dd/mm/yyyy)

15. Has there been any recent change of any of these treatments? ☐ Yes ☐ No If yes, please describe:

16. Has any diagnostic workup been performed for this event? ☐ Yes ☐ No If yes, please describe:

REPORTER Name:
Address:
City:
Country:
State/Province:
Email:
Postal Code:
Phone: (+ country code)

Amgen
Office Fax:

Signature _____
Title _____ **Date** _____

CONTINUED FROM PAGE 1

AMGEN®

Report of Suspected OTEZLA® Associated Adverse Event SUICIDALITY/DEPRESSION

Date of this Report (dd/mm/yyyy)

AER #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Amgen does not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

PATIENT INFORMATION

Patient Initials (Confidential)

Age at time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: ☐ lb ☐ kg

Event Date (dd/mm/yyyy)

Event Time (24 hr, ie, 14:30)

MEDICATION ADMINISTERED

☐ **Otezla**

Dose | Frequency | Route

Other Amgen Drug

Dose | Frequency | Route

Other Medications:

Co-Suspect Medications:

MEDICAL HISTORY/RISK FACTORS (Check all that apply, provide dates and attach relevant reports)

1. Did the patient have any previous episodes of suicide attempts or ideation? ☐ Yes ☐ No If yes, please provide details:

2. Has the patient been hospitalized for similar events? ☐ Yes ☐ No If yes, please provide details:

3. Does the patient have a history of depression? ☐ Yes ☐ No If yes, provide information including start date of depression, treatments for depression:

4. If the patient has a history of depression, did the depression recently worsen? ☐ Yes ☐ No If yes, please explain:

5. Is the patient receiving any medications other than Otezla which have been associated with suicide attempts or ideation? ☐ Yes ☐ No
   If yes, please provide details:

6. Does the patient abuse alcohol or drugs? ☐ Yes ☐ No If yes, please explain:

7. Did the patient have any recent change in his/her social circumstances (job loss, family death, divorce, etc.)? ☐ Yes ☐ No If yes, please explain:

8. Please provide causality for suicidal ideation/attempt:
   ☐ Related to Otezla ☐ Not related to Otezla ☐ Other: please specify: _____ ☐ Unknown

TREATMENT DETAILS

9. Provide details of the treatment given for this episode:

REPORTER Name:

Address:

City State/ Prov.

Postal code: Country:

Phone Email:
(+ country code)

Signature

Title **Date**

Amgen
Office Fax:

AMGEN

Report of Suspected OTEZLA® Associated Adverse Event VASCULITIS

Date of this Report (dd/mm/yyyy)

AER #

PATIENT INFORMATION

Patient Initials (Confidential)

Age at time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: ☐ lb ☐ kg

Event Date (dd/mm/yyyy)

Event Time (24 hr, ie, 14:30)

MEDICATION ADMINISTERED

☐ **Otezla**

Dose | Frequency | Route

Other Amgen Drug

Dose | Frequency | Route

Other Medications: _____

Co-Suspect Medications: _____

SIGNS AND SYMPTOMS

1. Indicate type of vasculitis: ☐ small vessel ☐ medium vessel ☐ large vessel. Please provide details:

2. Please describe presenting signs and symptoms (cutaneous or systemic manifestations, visceral involvement):

3. Please provide description of cutaneous manifestations with extent/severity and localization of areas:

4. Were there any associated infections around this presentation? ☐ Yes ☐ No If yes, please specify type of infection, date, and treatment received:

DRUG INFORMATION / DECHALLENGE / RECHALLENGE

1. Provide time to onset of this event (after start of Otezla or duration of therapy). When did the vasculitis appear?

2. What action was taken with Otezla due to this event?
   - ☐ None
   - ☐ Permanently Discontinued Stop date: _____
   - ☐ Temporarily Interrupted Stop date: _____
   - ☐ Dose Reduced Date and dose: _____

3. If Otezla was discontinued, did the lesion(s) abate after discontinuation? ☐ Yes ☐ No

4. Was Otezla re-introduced? ☐ Yes ☐ No If yes, did the lesion(s) re-occur after re-introduction? ☐ Yes ☐ No Provide Otezla restart date and dosing:

5. Was the patient receiving treatment for vasculitis when Otezla was resumed? ☐ Yes ☐ No If yes, indicate the drug name with therapy dates:

6. Please provide concomitant medications:

Medication	Start date	Stop date	Dose/ frequency	Indication for use

7. Please provide causality for Vasculitis:

☐ Related to Otezla ☐ Not related to Otezla ☐ Other: please specify _____ ☐ Unknown

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AMGEN

Report of Suspected OTEZLA® Associated Adverse Event VASCULITIS

Date of this Report (dd/mm/yyyy)	AER #

WORKUP

1. Provide full biopsy report and/or supporting documentation for the diagnosis of vasculitis.

2. Provide CBC with eosinophils.

3. Include any results of serologic studies, blood cultures, sedimentation rate, chemistry panel, ANA, ANCA, rheumatoid factor, IgA anti phospholipid antibodies, total hemolytic complement, C3/C4, hepatitis panel, cryoglobulins, as appropriate.

4. Imaging studies: chest x-ray, visceral angiography as appropriate.

5. Provide status of underlying disease around onset of this event.

TREATMENT

1. Please provide treatment/intervention for the vasculitis. Specify drug names, route (oral, topical, IV) and administration dates.

2. Was a specialist consulted for further investigation? If so, please provide those findings.

MEDICAL HISTORY

1. Has patient had similar episodes of vasculitis before?

2. Please indicate whether or not the patient had a history of the following:

Rheumatoid arthritis	☐ Yes ☐ No	
SLE	☐ Yes ☐ No	
Sjögren syndrome	☐ Yes ☐ No	
Other Inflammatory disease	☐ Yes ☐ No	If yes, please specify _____
Past hypersensitivity reaction	☐ Yes ☐ No	
Intravenous drug use	☐ Yes ☐ No	
Blood transfusion	☐ Yes ☐ No	
Travel history	☐ Yes ☐ No	If yes, specify_____
Food or food additives reaction	☐ Yes ☐ No	
Henoch-Schönlein purpura	☐ Yes ☐ No	
Hepatitis	☐ Yes ☐ No	
HIV	☐ Yes ☐ No	
Other infection	☐ Yes ☐ No	If yes, please specify_____

REPORTER Name:
Address:
City:
Country:
Email:
Phone: (+ country code)
State/Province:
Postal Code:

Amgen
Office Fax:

Signature _____
Title _____ **Date** _____

CONTINUED FROM PAGE 1

AMGEN

Report of Suspected OTEZLA® Associated Adverse Event MALIGNANCIES

Date of this Report (dd/mm/yyyy)

AER #

PATIENT INFORMATION

Patient Initials (Confidential)

Age at time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: ☐ lb ☐ kg

Event Date (dd/mm/yyyy)

Event Time (24 hr, ie, 14:30)

MEDICATION ADMINISTERED

☐ **Otezla**

Dose | Frequency | Route

Other Amgen Drug

Dose | Frequency | Route

Other Medications: _____

Co-Suspect Medications: _____

CORE QUESTIONS FOR FOLLOW-UP OF MALIGNANCIES

1. Dates of treatment in regard to the event:

2. Dates of the underlying disease's diagnosis:

3. Is this the first time that the patient has been treated with Otezla? ☐ Yes ☐ No If no, please provide dates:_____

4. Previous history of malignancies (personal/familial) with estimated dates:

5. Underlying medical history and concomitant diseases:

6. Any previous chemotherapy rounds (dates, type) and /or radiotherapy (zone, duration, cumulative dose)?

7. Environmental exposure e.g. atmospheric pollutants/toxic chemicals (pesticides, herbicides, benzene, solvents); occupation/hobbies:

8. Tobacco, alcohol abuse:

9. Date of diagnosis of malignancy and date of first clinical symptoms:

10. Full biopsy reports with exact stage. If not available, please provide the detailed results:

11. Treatment of malignancy, provide details:

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AMGEN

Report of Suspected
OTEZLA® Associated Adverse Event
MALIGNANCIES

Date of this Report (dd/mm/yyyy)	AER #

RISK FACTOR INFORMATION FOR SPECIFIC TYPES OF CANCER

In addition to the Core Questions, specific information should be requested based on the risk factors for individual types of cancer.

Lung Cancer:

- ☐ Smoking history – length of time, number of cigarettes/day, age at starting, gender, product smoked and depth of inhalation
- ☐ Pre-existing pulmonary disease
- ☐ Family history of lung cancer
- ☐ Arsenic, asbestos, nickel, pesticides, radon or chromates exposure

Lymphoma:

- ☐ Medical conditions that compromise the immune system – HIV/AIDS, autoimmune diseases, diseases requiring immune suppressive therapy-organ transplant
- ☐ Infection with HIV, Epstein-Barr virus, Helicobacter pylori, hepatitis B or C, human T-lymphotrophic virus type I, Burkitt's lymphoma

Thyroid Cancer:

- ☐ Personal or family history of thyroid and/or autoimmune diseases – hypo or hyperthyroidism, goiter, benign thyroid nodules, Hashimoto's disease, Graves' disease
- ☐ Family history of familial medullary thyroid cancer, multiple endocrine neoplasia and familial adenomatous polyposis
- ☐ Living in iodine deficient area

Breast Cancer:

- ☐ Receptor status of the tumor – ER, PR, Her2/neu
- ☐ Age at onset of menses and age of menopause
- ☐ Number of pregnancies and age at first birth
- ☐ History of breastfeeding children
- ☐ Use of oral contraceptives or hormone replacement therapy
- ☐ Obesity
- ☐ Ethnic group, economic status and dietary iodine deficiency

Ovarian Cancer:

- ☐ Number of pregnancies and childbearing status
- ☐ History of hormone replacement therapy
- ☐ History of breast cancer

Uterine Cancer:

- ☐ Age at onset of menses and age of menopause
- ☐ Number of pregnancies
- ☐ Use of oral contraceptives
- ☐ Obesity

Colon Cancer:

- ☐ Family or personal history of adenomatous polyposis (FAP), Lynch syndrome (Hereditary nonpolyposis colorectal cancer)
- ☐ Diet high in red meat and animal fat, refined carbohydrates, low-fiber diet, and low overall intake of fruits and vegetables
- ☐ Obesity and sedentary habits
- ☐ Any history of inflammatory conditions of digestive tract - Chronic ulcerative colitis, Crohn's disease longer duration, greater extent of colon involvement

Anorectal Cancer:

- ☐ History of infection with human papillomavirus, chronic fistulas, irradiated anal skin, leukoplakia, lymphogranulomatoma venereum, condyloma acuminatum
- ☐ HIV status

Gastric Cancer:

- ☐ Diet rich in pickled vegetables, salted fish, salt, and smoked meats
- ☐ Helicobacter pylori infection
- ☐ Obesity
- ☐ Previous gastric surgery
- ☐ Pernicious anemia, adenomatous polyps, gastric ulcer
- ☐ Chronic atrophic gastritis
- ☐ Radiation exposure

Oesophageal Cancer:

- ☐ Genetic causes - tylosis (hyperkeratosis palmaris et plantaris)
- ☐ Alcohol use/smoking
- ☐ History of chronic or acute inflammation (e.g. GERD, Barrett's esophagus, caustic ingestion)Achalasia (esophageal motility disorder)
- ☐ Human papilloma virus
- ☐ Sclerotherapy
- ☐ Plummer-Vinson syndrome (dysphagia, associated with iron deficiency anemia)

Liver cancer:

- ☐ History of cirrhosis (including alcoholic, biliary cirrhosis), other chronic liver dysfunction
- ☐ Alcohol use
- ☐ Hepatitis B, C
- ☐ Hemochromatosis
- ☐ Indigestion of food contaminated with fungal aflatoxins (in subtropical regions)

Pancreatic Cancer:

- ☐ Smoking
- ☐ Obesity
- ☐ Diet (red meat)
- ☐ History of chronic pancreatitis or long-standing diabetes mellitus (primarily in women)
- ☐ Inherited predisposition hereditary pancreatitis, familial adenomatous poliposis)

CONTINUED FROM PREVIOUS PAGE

AMGEN

Report of Suspected
OTEZLA® Associated Adverse Event
MALIGNANCIES

Date of this Report (dd/mm/yyyy)	AER #

RISK FACTOR INFORMATION FOR SPECIFIC TYPES OF CANCER (continued)

Renal Cancer (renal cell carcinoma):

- ☐ Smoking
- ☐ Obesity
- ☐ Hypertension
- ☐ Phenacetin-containing analgesics taken in large amounts
- ☐ History of renal transplantation:
- ☐ Exposure to radiopaque dyes, asbestos, cadmium, and leather tanning and petroleum products
- ☐ Inherited VHL disease (von Hippel-Lindau disease), Adult polycystic kidney disease, Tuberous sclerosis

Bladder Cancer:

- ☐ Smoking
- ☐ Industrial exposure to aromatic amines in dyes, paints, solvents, leather dust, inks, combustion products, rubber, and textiles
- ☐ Occupation - painting, driving trucks, and working with metal
- ☐ Prior spinal cord injuries with long-term indwelling catheters

Prostate Cancer:

- ☐ Ethnic group
- ☐ History of high-grade prostatic intraepithelial neoplasia (PIN)
- ☐ Genome changes-deletion of chromosome 3 and fusion of TMPRSS2 and ERG genes
- ☐ Testosterone level
- ☐ History of sexually transmitted diseases
- ☐ History of vasectomy
- ☐ History of exposure to cadmium
- ☐ History of genitor-urinary infections

Head and Neck Cancer:

- ☐ Smoking and alcohol use
- ☐ Prolonged sun exposure
- ☐ Exposure to Human papilloma virus (HPV) or Epstein-Barr virus (EBV)
- ☐ Ethnic group
- ☐ History of poor oral hygiene and/or poor nutrition
- ☐ Exposure to asbestos, wood dust, paint fumes or chemicals
- ☐ History of Gastroesophogeal reflux disease (GERD) or Laryngopharyngeal reflux disease (LPRD)

Brain Tumors (gliomas and menigiomas):

- ☐ Exposure to radiation
- ☐ Exposure to vinyl chloride, Pesticides
- ☐ Immune system disorders
- ☐ Hormone replacement therapy

Larynx Cancer:

- ☐ Smoking history, alcohol use
- ☐ Asbestos exposure
- ☐ Any activity requiring loud speech, exposure to sudden and frequent temperature changes
- ☐ Frequent hoarseness, frequent and persistent cough
- ☐ Persistently swollen neck glands
- ☐ Tonsillectomy and laryngeal surgery

Nasal and Paranasal Sinus Cancer:

- ☐ Woodworking, any dust/flour chronic exposure
- ☐ History of Infection with human papillomavirus (HPV)
- ☐ Smoking

Mouth and Oropharyngeal Cancer:

- ☐ Smoking
- ☐ Alcohol use
- ☐ History of poor oral hygiene
- ☐ Chronic mucosal/gum irritation / ill-fitting dentures
- ☐ Betel-Nut Chewing (Indian populations)
- ☐ History of syphilis or viral infections
- ☐ Impaired immunity – AIDS, transplant with anti-rejection drugs
- ☐ Precancerous mouth plaques – Leukoplakia or erythroplasia
- ☐ History of cancer of the aero-digestive tract

Melanoma:

- ☐ History of prolonged sun exposure (UV radiation) – severe blistering sunburns, frequent tanning, use of sunlamps and tanning booths
- ☐ History of living close to equator or at high elevation
- ☐ History of skin conditions – Dysplastic nevus, Xeroderma pigmentosum, nevoid basal cell carcinoma syndromes
- ☐ Skin type – fair (pale) skin – burns easily, freckles
- ☐ Eye color – blue, green or gray, Hair color – blond or red
- ☐ Use of medication causing sensitivity to sun – antibiotics, hormones, antidepressants,
- ☐ Immune system depression – AIDS, leukemias
- ☐ Exposure to arsenic, coal tar or creosote
- ☐ For eye localization: History of oculodermal melanocytosis or Dysplastic nevus syndrome
- ☐ Ethnic group
- ☐ History of prolonged sun exposure (UV radiation)

REPORTER Name:
Address:
City:
Country:
State/Province:
Email:
Postal Code:
Phone: (+ country code)

Amgen
Office Fax:

Signature _____
Title _____ **Date** _____

CONTINUED FROM PREVIOUS PAGE

AMGEN

Report of Suspected
OTEZLA® Associated Adverse Event
INFECTION IN GENERAL
(including opportunistic infection, abscess, soft tissue infections including necrotizing fasciitis)

Date of this Report (dd/mm/yyyy) | AER #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Amgen does not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

PATIENT INFORMATION

Patient Initials (Confidential) | Age at time of Event or Date of Birth: | Gender: ☐ Male ☐ Female | Weight: lb / kg

Event Date (dd/mm/yyyy) | Event Time (24 hr, ie, 14:30)

MEDICATION ADMINISTERED

☐ **Otezla**

Dose | Frequency | Route

Other Amgen Drug

Dose | Frequency | Route

Other Medications: _____

Co-Suspect Medications: _____

See specific questions targeted to opportunistic infections and specific questions targeted to necrotizing fasciitis on following pages.

1. Please provide the type and source of infection:

2. Does the patient have a history of recurrent infection? ☐ Yes ☐ No If yes, please explain:

3. Please provide the type and the stage of the patient's disease (specify) at the time of the onset of the event.:

4. Any history of bone marrow involvement, bone marrow transplantation or radiotherapy? If so, please provide approximate dates:

5. Please name any underlying condition(s) that may be relevant to the reported event, e.g. stage of disease, previous history of infection, neutropenia, exposure to monoclonal antibodies:

6. Please indicate one or more of the following: ☐ De novo infection ☐ Recurrent infection ☐ Relapse

7. If the patient was on infection prophylaxis, did he/she receive colony stimulating factors, antibiotics, etc.? ☐ Yes ☐ No
   If yes, please provide type and dates:

8. Please provide the following lab values at baseline, onset of the event (worst), and recovery:

Test	Range w/ Units	Baseline/ Date(prior to Otezla)	Worst/ Date	Recovery/ Date
WBC				
ANC				

9. Please provide relevant culture/serology results with dates:

10. Please provide any additional diagnostic test results/ laboratory values (Chest x-ray, CT scan, ultrasound, CBC, hemoglobin, RBC) including baseline, event onset and recovery values, with dates, for the **reported event**.

11. What treatments were given for the infection? Please include dates.

CONTINUED NEXT PAGE

AMGEN

Report of Suspected
OTEZLA® Associated Adverse Event
INFECTION IN GENERAL
(including opportunistic infection, abscess, soft tissue infections including necrotizing fasciitis)

Date of this Report (dd/mm/yyyy)	AER #

OPPORTUNISTIC INFECTIONS (*only if appropriate*)

1. Any suspicion or evidence of the following types of infections (incomplete list):

Viral:
- ☐ Epstein Barr virus (EBV)
- ☐ Hepatitis B (HBV)
- ☐ Cytomegalovirus (CMV)
- ☐ Herpes simplex (HSV)
- ☐ Varicella zoster virus (VZV)
- ☐ Progressive multifocal leukoencephalopathy (PML)

Protozoal:
- ☐ Pneumocystis carinii (PCP)
- ☐ Toxoplasmosis

Malignancies:
- ☐ Kaposi sarcoma (KS)

Fungal:
- ☐ Candidiasis
- ☐ Aspergillosis
- ☐ Histoplasmosis
- ☐ Cryptococcosis

Bacterial:
- ☐ Tuberculosis (TBC)
- ☐ Mycobacterium avium (MAI)
- ☐ Salmonellosis

2. If the answer to any of the above is yes, please indicate whether this diagnosis has been confirmed, and if so, how?

3. In case of suspected EBV and HBV, please provide test results in the table below:

Test	Baseline/ Date	Worst/ Date	Recovery/ Date
EBV viral load (PCR)			
EBER (Epstein Barr virus encoded RNA)			
HBsAg			
HBs Ab			
HBc Ab			
HBV DNA			
Hepatitis A			
Hepatitis C			
Hepatitis D			
Hepatitis E			
Transaminase			
Bilirubin			

4. Is there a history of hepatitis or does the event represent a new infection?

CONTINUED FROM PREVIOUS PAGE

AMGEN

Report of Suspected
OTEZLA® Associated Adverse Event
INFECTION IN GENERAL
(including opportunistic infection, abscess, soft tissue infections including necrotizing fasciitis)

Date of this Report (dd/mm/yyyy)	AER #

SOFT TISSUE INFECTIONS INCLUDING NECROTIZING FASCIITIS (*only if appropriate*)

1. Please provide the starting point of the soft tissue infection:

2. Please indicate if local precipitating event(s) causing NF has(ve) been identified at the starting site of occurrence and which ones (e.g. traumatic including surgery, minor invasive procedures [e.g. joint aspirations], and penetrating injuries [e.g. insect and animal bites] and nontraumatic including soft tissue burns):

3. If the suspect drug is an injectable form, please specify the route of administration: ☐ SC ☐ IV

4. If the route of administration of the suspect drug was SC, please specify if the starting point of the soft tissue infection was at the injection site:

5. Please specify if any of the below risk factor has been identified:

☐ Diabetes
☐ Chronic disease, if yes, specify: _____
☐ Immunosuppressive drugs (including corticosteroids)
If yes, specify:_____
☐ Malnutrition
☐ Age > 60 years
☐ Peripheral vascular disease
☐ Alcohol /drug abuse, if yes, specify:_____
☐ Renal failure
☐ Obesity
☐ Recent childbirth
☐ Recent infection with rash (e.g. varicella)
☐ Recent stay in health care facility
☐ Recent dental work
☐ Others, if yes, specify:_____

6. Please provide the identified infectious causative pathogen and source of identification (e.g. skin or blood culture/serology results with dates):

7. Please provide any additional diagnostic test results if available (eg scan; MRI; skin biopsy; muscle biopsy):

8. Please provide additional lab data including:

Test	Range w/ Units	Baseline/ Date*(prior to Otezla)*	Worst/ Date	Recovery/ Date
CPK MM				
CPK				
lactate				
BUN				
Creatinine				
Glucose				
INR				
PT				
D- Dimer				
Serum C-reactive protein				

9. Please provide treatment of the infection including local procedures (e.g. surgery):

10. Please provide post-surgery pathology results including also cultures from deep specimen samples during the intervention:

11. Patient's hobbies (e.g. fishing, weightlifting/heavy workout/gardening):

REPORTER Name:
Address:
City:
Country:
Email:
Phone: (+ country code)
State/Province:
Postal Code:

Amgen
Office Fax:

Signature _____
Title _____ **Date** _____

CONTINUED FROM PREVIOUS PAGE

AMGEN®

Report of Suspected OTEZLA® Associated Adverse Event CARDIAC ARRHYTHMIA & ECG CHANGES

Date of this Report (dd/mm/yyyy)

AER #

PATIENT INFORMATION

Patient Initials (Confidential)

Age at time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: ____ lb ____ kg

Event Date (dd/mm/yyyy)

Event Time (24 hr, ie, 14:30)

MEDICATION ADMINISTERED

☐ **Otezla**

Dose | Frequency | Route

Other Amgen Drug

Dose | Frequency | Route

Other Medications: _____

Co-Suspect Medications: _____

1. Type of arrhythmia/ECG change:

2. Clinical signs and symptoms, if present (if none please state):

3. Start date (dd/mm/yyyy):_____ Stop date (dd/mm/yyyy):_____

4. Does this patient have a relevant cardiac history? ☐ Yes ☐ No If yes, please specify in box below.

   Does this patient have a history of cardiac risk factors (e.g. hypertension, hyperlipidemia, hypercholesterolemia, diabetes, sepsis, obesity, smoking, renal disease, cardiorespiratory problems)?

Medical History (Diagnosis)	Onset Date /Duration

5. Please provide all relevant concomitant medications, including antiemetics (use separate sheet if necessary)

Medication	Indication	Start date	End date	Dose/Route/Frequency

6. Please provide the available results of the diagnostic workup (use separate sheet if necessary)

Test	Baseline		Event Onset / Worst		Recovery / Latest	
	Date	Results	Date	Results	Date	Results
EKG findings						
Echocardiogram						
Chest x-ray						
Holter, Stress Test						

CONTINUED ON PAGE 2

AMGEN®

Report of Suspected
OTEZLA® Associated Adverse Event
CARDIAC ARRHYTHMIA & ECG CHANGES

Date of this Report (dd/mm/yyyy)	AER #

7. Please provide the available results of the diagnostic workup (always ask for the results of serum potassium and magnesium studies – use separate sheet if necessary)

Laboratory Testing	Reference Range	At Baseline		At Event Onset / Worst		Recovery / Latest	
		Date	Value	Date	Value	Date	Value
CPK CPK-MB							
Troponin							
RBC							
Hemoglobin							
Metabolic Panel (specify)							
Serum potassium							
Serum magnesium							
Phosphorus							
Calcium							
Uric acid							
Creatinine							
BUN							

8. Please describe specific treatments and interventions of the arrhythmia:

9. Please provide outcome for arrhythmia/ECG changes:
   - ☐ Recovered
   - ☐ Recovered with sequelae: Please specify sequelae: _____
   - ☐ Not recovered
   - ☐ Death
   - ☐ Unknown

10. Please provide causality for arrhythmia/ECG changes:
   - ☐ Related to Otezla
   - ☐ Not related to Otezla
   - ☐ Other: please specify _____
   - ☐ Unknown

REPORTER Name:
Address:
City:
Country:
Email:
Phone: (+ country code)
State/Province:
Postal Code:

Amgen
Office Fax:

Signature _____
Title _____ **Date** _____

CONTINUED FROM PAGE 1

AMGEN®

Report of Suspected OTEZLA® Associated Adverse Event MYOCARDIAL INFARCTION

Date of this Report (dd/mm/yyyy)

AER #

PATIENT INFORMATION

Patient Initials (Confidential)

Age at time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: lb kg

Event Date (dd/mm/yyyy)

Event Time (24 hr, ie, 14:30)

MEDICATION ADMINISTERED

☐ **Otezla**

Dose | Frequency | Route

Other Amgen Drug

Dose | Frequency | Route

Other Medications:

Co-Suspect Medications:

1. Did the patient have a history of cardiac disease such as coronary artery disease, myocardial infarction, arrhythmia, or congestive heart failure? Please provide the onset dates of diagnosis.

2. Please provide any risk factors for the myocardial infarction (hyperlipidemia, hypercholesterolemia, obesity, hypertension, COPD, renal disease, diabetes, sepsis, substance abuse, sedentary lifestyle, immobility, dehydration, etc.).

3. Please provide the following laboratory data: serial CPK and MB, troponin, BNP, Blood cell counts, Hgb, Hct, electrolytes including Mg, and Ca. Please include baseline, worst, and recovery values and dates drawn.

4. Please provide the following diagnostic results including the baseline and the most recent EKG, echocardiogram, stress test, and cardiac catheterization, if available.

5. Please provide the treatment and interventions that were administered due to the myocardial infarction.

CONTINUED ON PAGE 2

AMGEN®

Report of Suspected
OTEZLA® Associated Adverse Event
MYOCARDIAL INFARCTION

Date of this Report (dd/mm/yyyy)	AER #

6. Please provide RELEVANT concomitant medications including indications, dosage, and therapy dates. Please include erythropoietin and thromboprophylactic medications and others as appropriate.

7. Please provide concurrent events/circumstances surrounding the MI.

8. Did the patient have a history of chest pain?

9. Was the patient receiving thromboprophylaxis? If yes, which type and dose?

10. Did the patient have a history of thromboembolic events? If yes, please specify type.

REPORTER Name:
Address:
City:
Country:
Email:
Phone: (+ country code)
State/Province:
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Signature _____
Title _____ **Date** _____

CONTINUED FROM PAGE 1

AMGEN®

Report of Suspected OTEZLA® Associated Adverse Event CEREBROVASCULAR ACCIDENT (CVA)

Date of this Report (dd/mm/yyyy) | AER #

PATIENT INFORMATION

Patient Initials (Confidential) | Age at time of Event or Date of Birth: | Gender: ☐ Male ☐ Female | Weight: ☐ lb ☐ kg

Event Date (dd/mm/yyyy) | Event Time (24 hr, ie, 14:30)

MEDICATION ADMINISTERED

☐ **Otezla**

Dose | Frequency | Route

Other Amgen Drug

Dose | Frequency | Route

Other Medications: _____

Co-Suspect Medications: _____

1. Please characterize the cerebrovascular accident: ☐ ischemic ☐ hemorrhagic ☐ unknown

2. Please provide details surrounding the CVA (shock, infection, thromboembolic event, status of underlying cardiac disease, etc.)

3. Please provide CBC and blood pressure at baseline (prior to receiving Otezla therapy) and at time of CVA.

4. Please provide relevant diagnostic imaging results (EEG, CT, MRI, PET, etc.) or other (Doppler, EKG) including dates and results.

Test	**Date** (dd/mm/yyyy)	**Results**
Electroencephalogram (EEG)		
Computed Tomography (CT) scan		
Magnetic Resonance Imaging (MRI)		
Positron Emission Tomography (PET) scan		
Others (specify): _____		

5. Please provide pertinent medical history including risk factors.

History/Risk Factors	**Yes**	**No**	**Comments**
Previous CVA	☐	☐	
Atrial fibrillation	☐	☐	
Arrhythmia,specify: _____	☐	☐	
Renal disease	☐	☐	
Hypertension	☐	☐	
Diabetes	☐	☐	
High cholesterol	☐	☐	
Tobacco use	☐	☐	
Substance abuse	☐	☐	
Others (specify): _____	☐	☐	

CONTINUED ON PAGE 2

AMGEN®

Report of Suspected
OTEZLA® Associated Adverse Event
CEREBROVASCULAR ACCIDENT (CVA)

Date of this Report (dd/mm/yyyy)	AER #

6. Please clarify if the patient was using or was exposed to any **anticoagulants/thromboprophylaxis** prior to CVA. ☐ Yes ☐ No ☐ Unknown
If yes, please provide specific anticoagulants/thromboprophylaxis used prior to CVA and therapy dates.

Drug Name	**Indication**	**Start date** (dd/mm/yyyy)	**Stop date** (dd/mm/yyyy)

7. Please provide **concomitant drugs** including drug names, indications, and therapy dates. ☐ None ☐ Unknown

Drug Name	**Indication**	**Start date** (dd/mm/yyyy)	**Stop date** (dd/mm/yyyy)

8. Please provide the treatment/intervention measures:

9. Please provide outcome for CVA:

☐ Recovered
☐ Recovered with sequelae: Please specify sequalae: _____
☐ Not recovered
☐ Unknown

10. Please provide causality for CVA:

☐ Related to Otezla
☐ Not related to Otezla
☐ Other: please specify: _____
☐ Unknown

REPORTER Name:
Address:
City:
Country:
Email:
Phone: (+ country code)
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Amgen
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Title _____ **Date** _____

CONTINUED FROM PAGE 1

AMGEN

Safety Database # _____

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER)

You may return completed form to Amgen Office Fax or Email: _____

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other_____ Parent exposed to product? ☐ Mother ☐ Father

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the patient sign the *Authorization for Release of Pregnancy Related Medical Information*? ☐ Yes ☐ No

Section 2 – Mother Current Pregnancy Information

Mother's Initials: _____

Date of birth: (if permitted to provide by local laws) _____ Day Month Year

Date of last menstrual period: _____ Day Month Year

Age: _____ years

Number of fetuses_____

Estimated date of delivery: _____ Day Month Year

Relevant Laboratory Tests & Procedures

Test Name	Test Date (dd/mm/yr)	Test Result

Section 3 – Mother Prenatal Medication History

Please list all medications (prescription and over-the-counter [include vitamins, herbal medications, etc.) and vaccines, taken by the **mother within 3 months prior to or during pregnancy**.

Amgen Product Used	Dose	Route (e.g. oral, subq)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Weeks of Pregnancy When Drug Taken (e.g. wk 28–wk 32)	Indication for Treatment
Resumed (if applicable)							
Amgen Product Lot Number _____ ☐ Lot Number Not Known							

List any other medications used within 3 months prior to or during the pregnancy

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Safety Database # _____

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER) *continued*

Section 4 – Pregnancy Complication and Adverse Event Information

If the **mother** experienced any pregnancy complications (e.g. preeclampsia, gestational diabetes, placenta previa, etc.) please complete the following:

Pregnancy Complication or Adverse Event	**Date the Complication or Event Started** (dd/mm/yy)	**Date the Complication or Event Resolved** (dd/mm/yr)	**Outcome** (for example: resolved, not resolved, unknown, other, etc.)

Section 5 – Mother Relevant Medical History

Please provide pertinent medical history:

☐ hypertension ☐ seizure ☐ diabetes ☐ difficulty conceiving ☐ asthma ☐ thyroid dysfunction ☐ other_____

Please describe any additional factors that may have an impact on the outcome of this pregnancy, including relevant medical or family history, mother's occupation, illnesses during pregnancy etc. Please specify other disorders including familial birth defects/genetic/chromosomal disorders, etc.:

Section 6 – Mother Previous Obstetrical (Pregnancy) History

Please provide the number of pregnancies after treatment with an Amgen product was initiated. Include the pregnancy outcome for each of these pregnancies and any additional relevant details:

Number of pregnancies and outcome details:

☐ Normal healthy baby: _____

☐ Stillbirth: _____

☐ Baby with birth defect: _____

☐ Outcome unknown: _____

_____

☐ Miscarriage: _____

☐ Abortion (induced for medical reason): _____

_____

_____

☐ Abortion (induced for non-medical [voluntary] reason):

_____

☐ Other (specify outcome) or any significant additional information:

Safety Database # _____

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER) *continued*

Section 7 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (check the appropriate box below):

☐ Live birth
☐ Number of infants_____(1: single, 2: twins, etc.)
(If multiple births: Please provide all information for each infant in the additional information text box below:)

If live birth: Gender: ☐ Male ☐ Female

Length: _____ cm/inches Birth weight: _____ gram/lb

Head circumference: _____cm/inches

Did the baby have any complications/medical problems/ congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information on the medical problem:

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
☐ Due to health issue (mother or baby)
☐ For voluntary reason
☐ Other (please specify):_____

Please confirm if there were there any tests done or results given for the baby/fetus? ☐ Yes ☐ No
If yes, please provide the details below.

Additional Information on pregnancy outcome and/or test/results:

Section 8 – Reporter Signature (can be digital or manual)

Signature of person completing questionnaire: _____ Date: _____
Please print name: _____
Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs.
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:
Name _____ Phone ( ) _____ Fax ( ) _____
Email _____Address _____ City _____
State/Province _____ Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:
Name _____ Phone ( ) _____ Fax ( ) _____
Email _____Address _____ City _____
State/Province _____ Zip/Postal Code _____

Health Care Provider for the child:
Name _____ Phone ( ) _____ Fax ( ) _____
Email _____Address _____ City _____
State/Province _____ Zip/Postal Code _____ Country _____

Safety Database # _____

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)

You may return completed form to Amgen Office Fax or Email:
Fax (888) 814-8653 or Emailsvc-ags-in-us@amgen.com

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other _____

Any change in the reporter contact information? ☐ Yes ☐ No If yes, please provide updated contact information:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

Section 2 – Mother Prenatal Medication History

Please provide any additional medication information for medicines used during your pregnancy not previously reported. For example, if you resumed or discontinued the Amgen Product or any other medications during the pregnancy (include vitamins, folic acid, herbal medications, and vaccines).

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 3 – Mother Pregnancy Complications and/or Adverse Event Information Not Previously Reported

Pregnancy Complication or Adverse Event (e.g. preeclampsia, gestation diabetes)	Date the Complication or Event Started (dd/mm/yy)	Date the Complication or Event Resolved (dd/mm/yr)	Outcome (for example: resolved, not resolved, unknown, other, etc.)

AMGEN

Safety Database # _____

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER) *continued*

Section 4 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (please check the appropriate box below)

☐ Live birth
- ☐ Number of infants_____(1: single, 2: twins, etc.)
  (If multiple births: Please provide all information for each infant in the additional information text box below:)

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
- ☐ Due to health issue (mother or baby)
- ☐ For voluntary reason
- ☐ Other (please specify):_____

If live birth: Gender: ☐ Male ☐ Female

Length: _____cm/inches Birth weight: _____gram/lb Head circumference: _____cm/inches

Did the baby have any complications/medical problems/congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information below.

Additional Information on pregnancy outcome:

Section 5 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

AMGEN

Safety Database #

Health Care Provider for the child:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

Mother Safety Database # _____

Infant Safety Database # _____

AMGEN®

SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

You may return completed form to Amgen Office Fax or Email:

_____

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Father ☐ Health Care Professional (HCP) ☐ Other_____

Section 2 – Infant Healthcare Provider (HCP) Information

May Amgen contact the HCP for medical information regarding your child? ☐ Yes ☐ No

If yes, please provide contact information:

Name _____ Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province Zip/Postal Code Country

List any other medications/drugs (include vitamins and over-the-counter medications taken by the child)

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Has the infant had any abnormal screening tests? ☐ Yes ☐ No If yes, please explain:

Has the infant followed growth curves and developmental milestones as expected for chronological age?

☐ Yes ☐ No If no, please explain:

Has the infant had any illnesses or persistent health problems? ☐ Yes ☐ No If yes, please explain:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____Date: _____

Mother Safety Database #	
Infant Safety Database #	

AMGEN®

Please print name: _____ Title and specialty if HCP _____

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable.