EUROPEAN UNION RISK MANAGEMENT PLAN

Otezla® (apremilast)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	14.1
Date:	04 November 2021
Supersedes:	Version 13.0, dated 14 February 2020

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

RMP version number:	14.0 and 14.1
Data lock point of this RMP:	Data cut-off psoriatic arthritis studies: 01 March 2013 Data cut-off psoriasis studies: 11 January 2013 Data cut-off Behçet's disease study: 23 October 2018 Prenatal Embryo-fetal Loss and Delayed Fetal Development (Reduced Ossification and Fetal Weight) in Pregnant Women Exposed to Apremilast: 13 December 2018 Postmarketing data: 13 December 2018
Date of final sign-off:	04 November 2021
Rationale for submitting an updated RMP:	• Removal of completed category 3 postauthorization safety study: Apremilast Psoriasis Registry in the European Union (EU) – Long-term Benefits and Safety of Systemic Psoriasis Therapy (PsoBest) • Removal of completed category 3 postauthorization safety study: United Kingdom (UK) Clinical Practice Research Database (CPRD) Data Analysis for Psoriatic Arthritis (PsA) and Psoriasis • Transfer from Celgene to Amgen RMP template

Summary of significant changes in this RMP

The apremilast EU RMP has been transferred from the Celgene to the Amgen EU RMP template. A summary of other significant changes are provided in the table below.

Part/Module/Annex	Major Change(s)	Version Number and Date
Part I: Product(s) Overview	• Updated to show that the product is not subject to additional monitoring in the EU.	Version 14.0; 09 June 2021
Part II: Safety Specification		
SVII: Identified and Potential Risks	• Updated the missing information 'long-term safety' with status of the PsoBest study. • Updated the missing information 'long-term safety' with status of the UK CPRD study.	Version 14.0; 09 June 2021
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	• Removed the completed category 3 postauthorization safety study PsoBest. • Removed the completed category 3 postauthorization safety study UK CPRD. • Updated the status of the Safety Outcomes for Psoriatic Arthritis Patients Treated with Otezla in the British Society for Rheumatology Biologics Register in Psoriatic Arthritis (BSRBR-PsA) from planned to ongoing.	Version 14.0; 09 June 2021
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	• Removed the PsoBest study as an additional pharmacovigilance activity. • Removed the UK CPRD study as an additional pharmacovigilance activity.	Version 14.0; 09 June 2021
Part VI: Summary of the Risk Management Plan	• Updated per the changes listed above for Parts III and V.	Version 14.0; 09 June 2021

Part/Module/Annex	Major Change(s)	Version Number and Date
Part VII: Annexes		
Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	• Updated the category 3 postauthorization safety study PsoBest from ongoing to completed. • Updated the category 3 postauthorization safety study UK CPRD from ongoing to completed. • Updated the category 3 postauthorization safety study BSRBR-PsA from planned to ongoing.	Version 14.0; 09 June 2021
	• Added sequence numbers and submission dates of clinical study reports (CSRs) for PsoBest and UK CPRD.	Version 14.1; 04 November 2021
Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	• Removed the PsoBest study. • Removed the UK CPRD study.	Version 14.0; 09 June 2021
Annex 4: Specific Adverse Drug Reaction Follow-up Forms	• Replaced Celgene-headed follow-up questionnaires with Amgen-headed follow-up questionnaires.	Version 14.0; 09 June 2021
Annex 8: Summary of Changes to the Risk Management Plan Over Time	• Summary of changes to the risk management plan over time updated.	Version 14.0; 09 June 2021
	• Summary of changes to the risk management plan over time updated.	Version 14.1; 04 November 2021

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:	13.0
Approved with procedure:	EMEA/H/C/003746/II/0029
Date of approval (opinion date):	08 April 2020
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
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
CSR	clinical study report
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
GVP	Good Pharmacovigilance Practices
HCP	healthcare professional
hERG	human Ether à go-go-Related Gene

Term/Abbreviation	Explanation
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
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan

Term/Abbreviation	Explanation
RR	relative risk
SD	standard deviation
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
UK	United Kingdom
US	United States

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

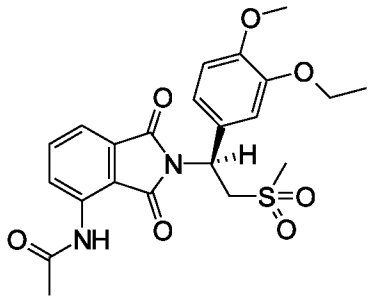
Active substance(s) (International Nonproprietary Name [INN] or common name)	Apremilast
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Phosphodiesterase (PDE) 4 Inhibitor ATC Code: L04AA32
Marketing authorization holder (MAH)	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Otezla®
Marketing authorization procedure	Centralized
Authorization Number(s)	EU/1/14/981/001; EU/1/14/981/002; EU/1/14/981/003
Brief description of the product	
Chemical class	Apremilast (N-[2-{(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl}-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl] acetamide, also called CC-10004) is a novel, orally available small molecule that specifically inhibits PDE4 and thus modulates multiple pro- and anti-inflammatory mediators. The chemical structure of the active pharmaceutical ingredient is: 

Table 1. Product(s) Overview

Brief description of the product (continued)	
Summary of mode of action	Apremilast, an oral small-molecule inhibitor of PDE4, 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.
Hyperlink to the Product Information (PI)	Link to apremilast PI on European Medicines Agency (EMA) website: https://www.ema.europa.eu/documents/product-information/otezla-epar-product-information_en.pdf
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	Not applicable

Table 1. Product(s) Overview

<table>
<tr><td>Dosage in the EEA

Current</td><td>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.
<u>Dose Titration Schedule</u>
<table>
<tr><td>Day 1</td><td colspan="2">Day 2</td><td colspan="2">Day 3</td><td colspan="2">Day 4</td><td colspan="2">Day 5</td><td colspan="2">Day 6 & Thereafter</td></tr>
<tr><td>AM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td></tr>
<tr><td>10 mg</td><td>10 mg</td><td>10 mg</td><td>10 mg</td><td>20 mg</td><td>20 mg</td><td>20 mg</td><td>20 mg</td><td>30 mg</td><td>30 mg</td><td>30 mg</td></tr>
</table>
AM = morning; PM = evening
Apremilast tablets should be swallowed whole.

Proposed
Not applicable</td></tr>
<tr><td>Pharmaceutical form(s) and strength(s)

Current (if applicable):</td><td>Apremilast is available as 10-, 20-, and 30-mg diamond shaped film-coated tablets containing microcrystalline cellulose National Formulary (NF)/European Pharmacopeia (Ph. Eur), lactose monohydrate NF/Ph. Eur, croscarmellose sodium NF/Ph. Eur, magnesium stearate, polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide red (E172), iron oxide yellow (E172, 20 and 30 mg only) and iron oxide black (E172, 30 mg only).</td></tr>
<tr><td>Proposed (if applicable):</td><td>Not applicable</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the European Union (EU)?</td><td>No</td></tr>
</table>

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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 PsA (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 (Helliwell and Wright, 2000; Wilson et al, 2009). • 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, 2012). The guidelines also suggest that glucocorticoids can be used as adjunctive therapy, but advise that their long-term use may lead to adverse events. • DMARD: methotrexate (MTX) and sulfasalazine. These are standard treatments for patients with polyarticular disease (Queiro-Silva et al, 2003) or with refractory oligoarticular disease (Pitzalis and Pipitone, 2000) before the occurrence of irreversible joint damage (Weaver, 2004). EULAR guidelines recommend that DMARDs should be used to treat patients who have active PsA with a potentially poor prognosis (Gossec et al, 2012). • Less commonly used DMARDs: cyclosporine, leflunomide, anti-malarial drugs (Pitzalis and Pipitone, 2000) and azathioprine (Menter et al, 2009).

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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)	• Biologic cytokine inhibitors: etanercept, adalimumab, infliximab, golimumab (all TNF blockers) and ustekinumab (an IL blocker [IL-12/23]; National Institute for Health and Care Excellence [NICE] Guidelines 2017; Gossec et al, 2012; Salvarani et al, 2006). EULAR guidelines recommend that TNF blockers are used for the treatment of PsA in patients that either cannot tolerate DMARDs, or for whom DMARD treatment has shown lack of efficacy (Gossec et al, 2012). However, the guidelines recommend treatment with TNF blockers for those with enthesitis and/or dactylitis after failure of non-specific anti-inflammatory therapy, since DMARDs have so far shown a lack of efficacy in this subgroup of the PsA population. TNF blockers may also be considered for use in those with axial disease before treatment with DMARDs. Following failure to respond to a biologic DMARD, treatment with another biologic DMARD, including alternative TNF blockers, should be considered (Gossec et al, 2016). Biologic cytokine inhibitors are also recommended for nail psoriasis (Coates et al, 2016). • Biologic cytokine inhibitors targeting the IL-12/23 and IL-17 pathway should be considered in patients with peripheral arthritis where conventional DMARDs are inadequate and TNF inhibitors are inappropriate (Gossec et al, 2016). • Targeted synthetic DMARDs, such as a PDE4 inhibitor, should be considered in patients with peripheral arthritis where conventional DMARDs are inadequate and biologic DMARDs are inappropriate (Gossec et al, 2016). • 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, EMA website 2013). • Glucocorticoids: local injections of glucocorticoids can be used as adjunctive therapy (Gossec et al, 2016).
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 polyarticular with or without distal interphalangeal involvement), enthesitis, dactylitis, spondylitis and/or sacroiliitis, as well as psoriatic nail disease (Ogdie and Weiss, 2015).

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

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 and Weiss, 2015; Ogdie et al, 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 (Han et al, 2006; Kaine et al, 2018). • 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).

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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; EU = European Union; EULAR = European League against Rheumatism; IL = interleukin; MTX = methotrexate; NICE = National Institute for Health and Care Excellence; NSAID = nonsteroidal anti-inflammatory drug; PDE = phosphodiesterase; PsA = psoriatic arthritis; PY = patient-years; SMR = standardized mortality rate; THIN = The Health Improvement Network; TNF = tumor necrosis factor; UK = United Kingdom; US = United States

Table 3. Summary of Epidemiology of Psoriasis

Incidence	• Estimates from an analysis of the CPRD reported that the incidence rate of psoriasis is 14 per 10 000 PY (Huerta et al, 2007).
Prevalence	• Psoriasis affects 1.5% to 3% of the general population in Europe (CHMP, 2004). Prevalence estimates from several large population-based studies were found with estimates ranging from 1.4% to 3.5%. The studies are summarized below: • A large cross-sectional study (N = 8416) conducted in Croatia in 1989 (Chandran and Raychaudhuri, 2010; Neimann et al, 2006; Plunkett and Marks, 1998) reported a prevalence of 1.55%. • An older questionnaire and examination-based study conducted on a sample (N = 2187) of the population of Lambeth, London in 1976 (Chandran and Raychaudhuri, 2010; Neimann et al, 2006; Plunkett and Marks, 1998) reported a prevalence psoriasis of 1.58% overall and moderate to severe psoriasis prevalence of 0.58%. • A large cross-sectional study (N = 8298) conducted in Sweden in 1980 (Chandran and Raychaudhuri, 2010; Neimann et al, 2006; Plunkett and Marks, 1998; Schäfer, 2006) reported a prevalence for psoriasis of 2.3%. The study only included children in grades 7 to 9 (aged approximately 13 to 15 years). • Two examination-based studies conducted in Northern (N = 897) and Southern (N = 1529) Germany between 1996 and 1997 (Chandran and Raychaudhuri, 2010; Schäfer, 2006) reported prevalence of psoriasis of 2.5% (Northern) and 3.5% (Southern). • A large population-based survey study (N = 14 667) conducted in Norway in 1985 (Chandran and Raychaudhuri, 2010; Schäfer, 2006) reported a prevalence of psoriasis of 4.8%. A subsequent population-based survey study (N = 10 576) also conducted in Norway in 1987 reported a lower prevalence of psoriasis of 1.4%. • A prevalence estimate from an analysis of the CPRD population (N = 114 521) between 1987 and 2002 (Gelfand et al, 2005) reported a prevalence of psoriasis of 1.52% (95% CI: 1.51-1.53). • By extrapolation from UK and US studies, it is estimated that more than 500 000 Canadians (approximately 1.7% of the population) have psoriasis. This affected population includes approximately 40 000 older individuals (≥ 70 years) and 20 000 children (≤ 10 years; Canadian Psoriasis Guidelines Committee, 2009).
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). • In a study conducted in Denmark in 1981 (Schäfer, 2006), prevalence in men was 3.2% and 2.5% in women.

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

Table 3. Summary of Epidemiology of Psoriasis

Demographics of population in the indication and risk factors for the disease (continued)	• 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).
Main existing treatment options	Moderate to Severe Psoriasis • Phototherapy, including PUVA and ultraviolet B phototherapy (Nast et al, 2012; Menter et al, 2009; Pathirana et al, 2009). • Conventional systemic therapies: MTX, cyclosporine and retinoids eg, acitretin (Nast et al, 2012; Menter et al, 2009; Pathirana et al, 2009). Systemic therapy with fumaric acid esters/fumarates is approved for use in Germany (Nast et al, 2012; Pathirana et al, 2009). • Biologic therapies: TNF-α blockers (adalimumab, etanercept and infliximab), IL-12/23p40 inhibitor (ustekinumab) and IL-17 inhibitors (secukinumab, ixekizumab); (Nast et al, 2018; NICE Guidelines 2018; Nast et al, 2012; Pathirana et al, 2009). • Targeted systemic therapies: PDE4 inhibitor (apremilast) (Nast et al, 2018).
Natural history of the indicated condition in the population including mortality and morbidity	• 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	• Infection (Haddad et al, 2016). • Suicide (Wu et al, 2017; Egeberg et al, 2016). • Metabolic syndrome (Augustin et al, 2010; Gisondi et al, 2007; Sommer et al, 2006). • Ischemic CVD (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 (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 (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 (Gowda et al, 2010; Takeshita et al, 2017). • Inflammatory bowel disease (ulcerative colitis and Crohn's disease) (Takeshita et al, 2017; Augustin et al, 2010; Gulliver, 2008).

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BMI = body mass index; CHMP = Committee for Medicinal Products for Human Use; CPRD = Clinical Practice Research Database; CVD = cardiovascular disease; HR = hazard ratio; IL = interleukin; MTX = methotrexate; NICE = National Institute for Health and Care Excellence; PDE4 = phosphodiesterase 4; PUVA = psoralen and ultraviolet-A light; 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 person-years 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. – IL10: 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.

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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

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).

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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; TNF = tumor necrosis factor; UK = United Kingdom; US = United States

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

Full details of the nonclinical safety data for apremilast are presented in Module 2.4 Nonclinical Overview.

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 or carcinogenic. 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-day 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 patients 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 patient 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 (standard deviation [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.

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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).	Small vessel cutaneous vasculitis was reported in 3 patients: 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 patient receiving apremilast 30 mg BID in Study PSA-005. Overall, there is no evidence of an increased risk of vasculitis with apremilast treatment.
	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.	Markedly abnormal laboratory test results (including liver function tests) among apremilast treated patients 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.

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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 postnatal 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 detected in the milk of lactating mice. A detailed discussion of the reproductive toxicity profile is provided in the nonclinical overview.	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 32).
• 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 patients showed QTc elevations of ≥ 450 or ≥ 470 msec, respectively, and few patients had a change from baseline of ≥ 60 msec. Dose dependent changes were not observed. The majority of these patients 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; 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; OATP = organic anion transporting polypeptide; PDE = phosphodiesterase; P-gp = permeability glycoprotein; PsA = Psoriatic arthritis

Part II: Module SIII - Clinical Trial Exposure

The data presented in this section for PsA are for four 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), and have a data cut-off of 01 March 2013. For psoriasis, data are provided for two Phase 3 studies CC-10004-PSOR-008 and CC-10004-PSOR-009 (hereafter referred to as PSOR-008 and PSOR-009), with a data cut-off of 11 January 2013. Pooled data are also provided for the PsA and psoriasis studies combined. The data presented in this section for BD are for one Phase 3 study CC-10004-BCT-002 (hereafter referred to as BCT-002), which has a database lock of 23 October 2018. Further details of the clinical studies included in this RMP are summarized in Table 6.

Table 6. Phase 3 Clinical Studies with Apremilast Included in the RMP

Indication	Study	Status
PsA	CC-10004-PSA-002 "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy and Safety of Two Doses of Apremilast (CC-10004) in Subjects with Active Psoriatic Arthritis"	Completed[a]
	CC-10004-PSA-003 "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy and Safety of Two Doses of Apremilast (CC-10004) in Subjects with Active Psoriatic Arthritis"	Completed[a]
	CC-10004-PSA-004 "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy and Safety of Two Doses of Apremilast (CC-10004) in Subjects with Active Psoriatic Arthritis and a Qualifying Psoriasis Lesion"	Completed[a]
	CC-10004-PSA-005 "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy and Safety Study of Two Doses of Apremilast (CC-10004) in Subjects with Active Psoriatic Arthritis who have not been Previously Treated with Disease Modifying Antirheumatic Drugs"	Completed[a]
Psoriasis	CC-10004-PSOR-008 "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of Apremilast (CC-10004) in Subjects with Moderate to Severe Plaque Psoriasis"	Completed[a]
	CC-10004-PSOR-009 "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Efficacy and Safety Study of Apremilast (CC-10004) in Subjects with Moderate to Severe Plaque Psoriasis"	Completed[a]
BD	CC-10004-BCT-002 "A Phase 3, Multicenter, Randomised, Double-blind, Placebo-controlled, Parallel-group study, followed by an Active-treatment Phase to Evaluate the Efficacy and Safety of Apremilast (CC-10004) in the Treatment of Subjects with Active Behçet's Disease"	Completed[b]

BD = Behçet's disease; CSR = clinical study report; PsA = psoriatic arthritis; Q = quarter; RMP = Risk Management Plan

[a] The CSR for this completed phase 3 study was submitted on 29 Jun 2018.

[b] The BCT-002 study also included an optional open-label extension period, which was available to subjects participating in Germany. Data from subjects enrolled in the extension period will be presented in a country-specific follow-up report to the final CSR, which will be provided to the German authorities (and others upon request) within 1 year after the last dose of apremilast in the extension period.

A total of 1945 patients who have received apremilast in the four phase 3 clinical studies in patients with PsA, 1184 patients who have received apremilast in the two phase 3 clinical studies in patients with psoriasis, and 207 patients who have received apremilast in the phase 3 clinical study in patients with BD, are included in the RMP. The phase 3 clinical studies of PsA, psoriasis and BD were designed with a placebo-controlled period and an active-treatment period. For these studies, data are presented for patients randomised to placebo at week 0 (ie, the start of the placebo-controlled period), and for all patients who received apremilast in either the placebo-controlled or active treatment periods (apremilast exposure period).

The duration of exposure to apremilast in the PsA phase 3 studies is provided in Table 7, in the psoriasis phase 3 studies is provided in Table 8, in the PsA and psoriasis phase 3 studies pooled is provided in Table 9, and in the BD phase 3 study is provided in Table 10.

Table 7. Duration of Exposure in Patients Exposed to Apremilast in Phase 3 Clinical Studies of Psoriatic Arthritis (Studies PSA-002, PSA-003, PSA-004 and PSA-005)

	Patients as Initially Treated at Week 0	Apremilast Patients 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)	0.96 (0.526)	0.97 (0.524)	0.97 (0.525)
Median	0.31	0.98	1.00	0.99
Range	≤ 0.01, 0.52	≤ 0.01, 2.49	≤ 0.01, 2.50	≤ 0.01, 2.50
Duration (n [%])				
≥ 1 day	671 (100.0)	972 (100.0)	973 (100.0)	1945 (100.0)
≥ 4 weeks	658 (98.1)	946 (97.3)	933 (95.9)	1879 (96.6)
≥ 8 weeks	633 (94.3)	910 (93.6)	901 (92.6)	1811 (93.1)
≥ 12 weeks	618 (92.1)	884 (90.9)	884 (90.9)	1768 (90.9)
≥ 24 weeks	153 (22.8)	790 (81.3)	817 (84.0)	1607 (82.6)
≥ 32 weeks	NA	673 (69.2)	696 (71.5)	1369 (70.4)
≥ 52 weeks	NA	467 (48.0)	495 (50.9)	962 (49.5)
≥ 78 weeks	NA	168 (17.3)	178 (18.3)	346 (17.8)
≥ 91 weeks	NA	79 (8.1)	85 (8.7)	164 (8.4)
≥ 104 weeks	NA	30 (3.1)	32 (3.3)	62 (3.2)

BID = twice daily; N/n = number of patients; NA = not applicable; PBO = placebo; SD = standard deviation

Table 8. Duration of Exposure in Patients Exposed to Apremilast in Phase 3 Clinical Studies of Psoriasis (Studies PSOR-008 and PSOR-009)

	Patients as Initially Treated at Week 0	Apremilast Patients as Treated
	PBO (N = 418)	30 mg BID (N = 1184)
Patient-Years		
Mean (SD)	0.28 (0.075)	0.95 (0.511)
Median	0.31	0.96
Range	≤ 0.01, 0.34	≤ 0.01, 2.17
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	854 (72.1)
≥ 52 weeks	NA	564 (47.6)
≥ 78 weeks	NA	197 (16.6)
≥ 91 weeks	NA	72 (6.1)
≥ 104 weeks	NA	24 (2.0)

BID = twice daily; N/n = number of patients; NA = not applicable; PBO = placebo; SD = standard deviation

Table 9. Duration of Exposure in Patients Exposed to Apremilast in Pooled Phase 3 Clinical Studies (Studies PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008 and PSOR-009)

	Patients as Initially Treated at Week 0	Apremilast Patients as Treated	
	PBO (N = 1089)	20 mg BID (N = 972)	30 mg BID (N = 2157)
Patient-Years			
Mean (SD)	0.32 (0.095)	0.96 (0.526)	0.96 (0.517)
Median	0.31	0.98	0.99
Range	≤ 0.01, 0.52	≤ 0.01, 2.49	≤ 0.01, 2.50
Duration (n [%])			
≥ 1 day	1089 (100.0)	972 (100.0)	2157 (100.0)
≥ 4 weeks	1055 (96.9)	946 (97.3)	2070 (96.0)
≥ 8 weeks	1010 (92.7)	910 (93.6)	2002 (92.8)
≥ 12 weeks	981 (90.1)	884 (90.9)	1956 (90.7)
≥ 24 weeks	153 (14.0)	790 (81.3)	1785 (82.8)
≥ 32 weeks	NA	673 (69.2)	1550 (71.9)
≥ 52 weeks	NA	467 (48.0)	1059 (49.1)
≥ 78 weeks	NA	168 (17.3)	375 (17.4)
≥ 91 weeks	NA	79 (8.1)	157 (7.3)
≥ 104 weeks	NA	30 (3.1)	56 (2.6)

BID = twice daily; N/n = number of patients; NA = not applicable; PBO = placebo; SD = standard deviation

Table 10. 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; N/n = number of patients; PBO = placebo; SD = standard deviation
[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.

Exposure by age group and gender is summarized for the PsA phase 3 studies in Table 11, for the psoriasis phase 3 studies in Table 12, for the pooled psoriasis and PsA phase 3 studies in Table 13, and for the BD phase 3 study in Table 14.

Table 11. Exposure by Age Group and Gender in Patients Exposed to Apremilast in Phase 3 Clinical Studies of Psoriatic Arthritis (Studies PSA-002, PSA-003, PSA-004 and PSA-005)

	Patients as Initially Treated at Week 0	Apremilast Patients 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)	1.00 (0.527)	0.95 (0.524)	0.98 (0.526)
Median	0.31	1.00	1.00	1.00
Range	≤ 0.01, 0.52	≤ 0.01, 2.49	≤ 0.01, 2.50	≤ 0.01, 2.50
Patient-Years, Females				
Mean (SD)	0.34 (0.109)	0.92 (0.524)	0.99 (0.524)	0.96 (0.525)
Median	0.31	0.94	1.00	0.98
Range	≤ 0.01, 0.49	≤ 0.01, 2.47	≤ 0.01, 2.48	≤ 0.01, 2.48

BID = twice daily; N/n = number of patients; PBO = placebo; SD = standard deviation

Table 12. Exposure by Age Group and Gender in Patients Exposed to Apremilast in Phase 3 Clinical Studies of Psoriasis (Studies PSOR-008 and PSOR-009)

	Patients as Initially Treated at Week 0	Apremilast Patients 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)	0.94 (0.502)
Median	0.31	0.94
Range	≤ 0.01, 0.34	≤ 0.01, 2.17
Patient-Years, Females		
Mean (SD)	0.27 (0.085)	0.99 (0.529)
Median	0.31	1.00
Range	≤ 0.01, 0.34	≤ 0.01, 2.16

BID = twice daily; N/n = number of patients; PBO = placebo; SD = standard deviation

Table 13. Exposure by Age Group and Gender in Patients Exposed to Apremilast in the Pooled Phase 3 Clinical Studies (Studies PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008 and PSOR-009)

	Patients as Initially Treated at Week 0	Apremilast Patients 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 patients; PBO = placebo

Table 14. Exposure by Age Group and Gender in Patients in Behçet's Disease Phase 3 Clinical Study BCT-002

	Patients 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; N/n = number of patients; PBO = placebo

Exposure by race and ethnic origin is summarised for the PsA phase 3 studies in Table 15, for the psoriasis phase 3 studies in Table 16, for the pooled psoriasis and PsA phase 3 studies in Table 17, and for the BD phase 3 study in Table 18.

Table 15. Exposure by Race and Ethnic Origin in Patients Exposed to Apremilast in Phase 3 Clinical Studies of Psoriatic Arthritis (Studies PSA-002, PSA-003, PSA-004 and PSA-005)

	Patients as Initially Treated at Week 0	Apremilast Patients 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	184.4	874.4	903.8	1778.2
Black	0.7	3.7	0.4	4.2
Asian	5.4	36.3	22.9	59.1
Patient-Years by Ethnicity				
Hispanic	5.1	20.7	24.5	45.2
Non-Hispanic	188.6	910.9	921.8	1832.7

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

Table 16. Exposure by Race and Ethnic Origin in Patients Exposed to Apremilast in Phase 3 Clinical Studies of Psoriasis (Studies PSOR-008 and PSOR-009)

	Patients as Initially Treated at Week 0	Apremilast Patients 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	1026.1
Black	3.2	32.7
Asian	5.9	52.6
Patient-Years by Ethnicity		
Hispanic	8.6	72.2
Non-Hispanic	107.9	1055.7

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

Table 17. Exposure by Race and Ethnic Origin in Patients Exposed to Apremilast in the Pooled Phase 3 Clinical Studies (Studies PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008 and PSOR-009)

	Patients as Initially Treated at Week 0	Apremilast Patients 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; N/n = number of patients; PBO = placebo

Table 18. Exposure by Race and Ethnic Origin in Patients in Behçet's Disease Phase 3 Clinical Study BCT-002

	Patients 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; N/n = number of patients; 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 19. 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)
All Phase 3 Studies (PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008, PSOR-009 and BCT-002)			
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. 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 19. 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)
All Phase 3 Studies (PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008, PSOR-009 and BCT-002) (continued)			
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.
All Phase 3 PsA and PSOR Studies (PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008 and PSOR-009)			
Hypersensitivity to the Active Substance or to any of the Excipients.	To ensure patient safety.	No	Hypersensitivity is an identified risk (not important). Treatment with apremilast is contraindicated in those with hypersensitivity to the active substance or any of the excipients (SmPC, Section 4.3).
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 19. 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)
All Phase 3 PsA and PSOR Studies (PSA-002, PSA-003, PSA-004, PSA-005, PSOR-008 and PSOR-009) (continued)			
Serum Creatinine ≥ 1.5 mg/dL (≥ 132.6 µmol/L)	To ensure patient safety.	No	Pharmacokinetic data are available for patients with mild, moderate or severe renal impairment. In patients 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 patients. In the PsA and psoriasis clinical studies, the safety profile observed in patients with mild renal impairment was comparable to that of patients 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 patients with moderate renal impairment have been treated with apremilast in clinical trials. In 8 patients 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 patients with mild and moderate renal impairment was complete after all patients 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 20. 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 13 December 2018, there have been a total of 24 cases of potential fetal exposure during pregnancy in female study patients treated with apremilast in apremilast 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	Not included in the clinical development program.
Patients with Hepatic Impairment	Not included in the clinical development program.
Population with Relevant Different Ethnic Origin	Apremilast exposure data by race and ethnic origin are presented in Table 15 for PsA, Table 16 for phase 3 studies of psoriasis, in Table 17 for pooled phase 3 studies of psoriasis and PsA, and in Table 18 for BD. In addition, apremilast was generally well tolerated in phase 2b Study PSOR-011 in patients with psoriasis and PsA in Japan. In this study, 241 Japanese patients were exposed to apremilast.
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 20. SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Other	**Pediatric Population:** Clinical development is ongoing. **Elderly Population:** A total of 285/3129 patients were ≥ 65 years of age in the pooled PsA and psoriasis studies, including 25 patients 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 patients in Studies PSA-002, PSA-003, and PSA-004 a total of 184 patients with PSA were ≥ 65 years, including 18 patients ≥ 75 years. No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients. Of the 1184 apremilast-treated patients in Studies PSOR-008 and PSOR-009, a total of 101 patients with psoriasis were ≥ 65 years, including 7 patients who were ≥ 75 years. No overall differences were observed in the efficacy and safety in elderly patients ≥ 65 years of age and younger adult patients. Of the 207 apremilast treated patients in Study BCT-002, 7 patients with BD were ≥ 65 years. No apparent overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients, although the number of patients ≥ 65 years was too small to allow for meaningful comparison.

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BD = Behçet's disease; PsA = psoriatic arthritis

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

Apremilast was approved in the US on 21 March 2014 (first global authorisation) as a treatment for adult patients with active PsA and on 23 September 2014 for adult patients with moderate to severe chronic plaque psoriasis. Apremilast was approved in the EU on 15 January 2015 for the treatment of adult patients with active PsA and adult patients with moderate to severe chronic plaque psoriasis. Apremilast was approved in the US on 19 July 2019 for the treatment of adult patients with oral ulcers associated with BD. Postmarketing exposure data are provided in the Periodic Safety Update Reports (PSURs).

SV.1.1 Method Used to Calculate Exposure

The patient exposure for the supplemental period represents the estimated number of unique patients exposed to apremilast during the supplemental period (21 March 2018 through 13 December 2018). The cumulative value for exposure represents the estimated number of unique patients exposed to the product from the international birth date (21 March 2014) through the data-lock point (13 December 2018).

It is important to note that the cumulative exposure represents the number of unique patients exposed to apremilast at least once, whereas the exposure during each reporting interval includes the total number of patients exposed to apremilast during the reporting interval by both new and repeat exposures. For example, a patient who is exposed initially during the previous interval for a reporting period may still be on treatment during the current reporting interval, and therefore, will be counted as an exposure in both reporting intervals. However, this patient is only counted once for the cumulative exposure.

Commercial exposure to apremilast for the supplemental period of 21 March 2018 through 13 December 2018 is approximately 147 420 patients. Estimated cumulative commercial exposure to apremilast from international birth date to data-lock point is approximately 358 544 unique patients.

Cumulative person-years exposure: Cumulative person-years exposure was calculated for apremilast. Using unique patient counts, and an average duration of therapy from claims data, the person-years exposure since launch until 20 March 2018 is 101 647 for the US. The total commercial exposure in the US is 226 428 (unique patients) for an

average of 0.44892 years per person. The total global exposure is 358 544 unique patients. Assuming the same apremilast regimen (30 mg BID), the global exposure by person-years is 160 957 person-years.

Expanded access/Named-patient program: Apremilast is available through an expanded access/named-patient program in territories where apremilast has not commercially launched. The estimated patient exposure is included in the clinical trials exposure.

Non-interventional studies: Patient exposure in all non-interventional studies and post-authorisation safety studies are included in commercial exposure.

SV.1.2 Exposure

The estimated cumulative commercial exposure to apremilast from all sources up to 13 December 2018 is approximately 358 544 unique patients.

A summary of worldwide commercial exposure by region is provided in Table 21.

Table 21. Summary of Worldwide Commercial Exposure from Launch to 13 December 2018

Region	Cumulative Exposure
US	226 428
EEA	84 421
Canada	9812
Japan	29 300
Australia/New Zealand	1011
ROW[a]	7572
TOTAL	358 544

EEA = European Economic Area, including the European Union, Iceland, Liechtenstein and Norway; ROW = rest of world; US = United States
[a] ROW includes countries and regions not otherwise specified in the table.

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 22. A description of the changes to the list of safety concerns in the approved RMPs is presented in Annex 8.

Table 22. 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 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 23. 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 24 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 25 for further details.
Serious Events of Depression	In clinical studies, uncommon cases of serious events of depression were reported with apremilast. Please see Table 26 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 27 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 28 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 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 29 for further details.

Table 23. 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 Daxas SmPC, 2018). In the apremilast clinical studies, the incidences of serious infections were comparable between the treatment groups. Please see Table 30 for further details.
MACE and Tachyarrhythmia	For roflumilast, cardiac disorders (palpitations) are listed as uncommon adverse reactions (Section 4.8 Daxas SmPC, 2018). In the apremilast clinical studies, the incidences of MACE or tachyarrhythmia were comparable between the treatment groups. Please see Table 31 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 32 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 33 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

Data for the 4 PsA phase 3 trials presented in the important identified and potential risks have a cut-off date of 01 March 2013. For the two phase 3 psoriasis studies, data are presented with a cut-off date of 11 January 2013. Data for the single BD phase 3 trial presented in the important identified and potential risks have a cut-off date of 23 October 2018. Where appropriate, data are presented for the placebo-controlled

period of the studies (weeks 0 to 16; 'as treated' population), and separately for the apremilast exposure period (which includes patients initially randomised to placebo who subsequently received apremilast). In addition to the phase 3 studies, supportive data are presented for phase 2 studies in PsA, psoriasis and rheumatoid arthritis where appropriate.

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

Table 24. 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	Events pertinent to the risk of serious events of hypersensitivity were observed during the clinical development programmes 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	For frequency of serious events of hypersensitivity see 'Seriousness/outcomes' below.
Seriousness/ outcomes	<u>Phase 3 PsA Studies</u> No serious adverse events pertaining to hypersensitivity were reported in patients treated with apremilast. However, during weeks 0 to 16, serious hypersensitivity was noted in 1/671 (0.1%) placebo treated patient. This subsequently resolved. <u>Phase 3 Psoriasis Studies</u> During weeks 0 to 16, 1/1184 (0.1%) apremilast treated patient (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 patients experienced serious adverse events of hypersensitivity. In the apremilast exposure period, a serious event of hypersensitivity was experienced by 1/1184 (0.1%) patient (PT: urticaria). The outcome of the serious adverse event was recovered/resolved. <u>Phase 3 BD study</u> During weeks 0 to 12, 1/103 (1.0%) placebo treated patient 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 patients experienced serious adverse events of hypersensitivity. In the apremilast exposure period, no serious adverse events of hypersensitivity were reported. <u>Other Studies</u> An event of anaphylactic reaction, reported in a patient treated with apremilast in a phase 2 psoriasis study, was not considered serious.

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

Table 24. Important Identified Risk: Serious Events of Hypersensitivity

Characterization of the risk (continued)	
Severity	Phase 3 PsA Studies During weeks 0 to 16, severe events of hypersensitivity were reported in 1/973 (0.1%) apremilast-treated patient in the 30 mg BID dose group (PT: urticaria) and 2/671 (0.3%) placebo-treated patients (PTs: urticaria and eczema); no patients in the 20 mg BID dose group experienced severe events of hypersensitivity. In the apremilast exposure period, events of severe hypersensitivity occurred in 2/1945 (0.1%) apremilast-treated patients (both in the 30 mg BID group; PTs: urticaria and eczema). During weeks 0 to 16, 2/972 (0.2%; PTs: urticaria and rash) and 1/973 (0.1%; PT: urticaria) apremilast-treated patients in the 20 mg BID and 30 mg BID groups, respectively, and 2/671 (0.3%; PTs: angioedema, dermatitis infected and urticaria) placebo-treated patients withdrew due to events of hypersensitivity. A total of 5/1945 (0.3%) patients in the apremilast exposure period withdrew as a result of events of hypersensitivity (3/972 [0.3%] and 2/973 [0.2%] apremilast-treated patients in the 20 mg BID [PTs: rash (2 patients) and urticaria (1 patient)] and 30 mg BID groups [PTs: rash erythematous (1 patient) and urticaria (1 patient)], respectively). Phase 3 Psoriasis Studies No severe events of hypersensitivity were reported during weeks 0 to 16. In the apremilast exposure period, severe events of hypersensitivity occurred in 1/1184 (0.1%) apremilast-treated patient (30 mg BID; PT: urticaria). During weeks 0 to 16, 1/1184 (0.1%) apremilast-treated patient (30 mg BID) withdrew due to an event of hypersensitivity (PT: dermatitis contact). No placebo-treated patients withdrew as a result of hypersensitivity. A total of 2/1184 (0.2%) patients in the apremilast exposure period withdrew as a result of events of hypersensitivity (30 mg BID; PTs: dermatitis contact and urticaria). Phase 3 BD Study No severe events of hypersensitivity were reported, and no patients withdrew as a result of hypersensitivity in Study BCT-002. Other Studies One patient who received apremilast 40 mg QD in a phase 2 study in the PsA population had drug interrupted and ultimately discontinued due to repeated hypersensitivity reactions. The patient had the first reaction (throat tightness, pruritus, urticaria) on study day 27 that resolved on study day 29. This patient was rechallenged twice and had similar reactions (urticaria, skin welts, pruritus, throat tightness, and rash). The patient's medical history included asthma, drug intolerance to sulfa products, and hypersensitivity to penicillin.

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

Table 24. Important Identified Risk: Serious Events of Hypersensitivity

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, 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).
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 was serious.
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.
Data source	Apremilast clinical trials (Module 2.7.4 of Marketing Authorization Application [MAA] and BCT-002 CSR).
Medical Dictionary for Regulatory Activities (MedDRA) Terms	An ad hoc list of PTs based on the MedDRA Version 19.0 Standardised MedDRA Query (SMQ) of hypersensitivity (narrow), mapped back to MedDRA Version 14.0, are listed in Annex 7 and are collectively referred to as hypersensitivity. The search criteria for this risk have been updated to be in line with the current PSUR search criteria.

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BD = Behçet's Disease; BID = twice daily; CSR = clinical study report; HIV = human immunodeficiency virus; MAA = Marketing Authorization Application; MedDRA = Medical Dictionary for Regulatory Activities; PsA = psoriatic arthritis; PT = Preferred Term; SMQ = Standardised MedDRA Query

Table 25. 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 PsA Studies During weeks 0 to 16, suicide/self-injury events were experienced by 2/1945 (0.1%) apremilast treated patients in the 20 mg BID group (PTs: suicidal ideation [1 patient] and suicide attempt [1 patient]) and no placebo treated patients. In the apremilast exposure period, there was an additional event of suicide attempt in the 30 mg BID group. Phase 3 Psoriasis Studies During weeks 0 to 16, suicide/self-injury events were experienced by 1/1184 (0.1%) apremilast treated patient (PT: suicide attempt). One patient (0.2%) randomized to placebo completed suicide. In the apremilast exposure period, no additional events of suicide/self-injury were reported. Phase 3 BD Study No patients in BD Study BCT-002 experienced events of suicidality. Other Studies In Study PSOR-005 (phase 2 study), a male patient randomized to the placebo group, was found dead with a pink complexion in his [redacted] on study day 84. Autopsy did not establish the cause of death in this potential suicide.
Seriousness/ outcomes	Phase 3 PsA Studies During weeks 0 to 16, serious suicide/self-injury events were experienced by 2/1945 (0.1%) apremilast-treated patients (PTs: suicide ideation [1 patient] and suicide attempt [1 patient]) and no placebo-treated patients. In the apremilast exposure period, serious events of suicide/self-injury were reported in 3 (0.2%) patients (ie, 1 additional patient compared with weeks 0 to 16). These serious adverse events were suicidal ideation (1 patient) and suicide attempt (2 patients). The events recovered/resolved with no sequelae. Phase 3 Psoriasis Studies During weeks 0 to 16, serious suicide/self-injury events were experienced by 1/1184 (0.1%) apremilast-treated patient (PT: suicide attempt). The outcome of the serious adverse event was recovered/resolved. One patient (0.2%) randomised to placebo completed suicide. In the apremilast exposure period, no additional events of suicide/self-injury were reported.

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

Table 25. Important Identified Risk: Suicidality

Characterization of the risk (continued)	
Seriousness/ outcomes (continued)	Phase 3 BD Study No patients in BD study BCT-002 experienced events of suicidality. Other Studies In Study PSOR-005 (Phase 2 study), a male patient randomised to the placebo group, was found dead with a pink complexion in his [redacted] on study day 84. Autopsy did not establish the cause of death in this potential suicide.
Severity	Phase 3 PsA Studies During weeks 0 to 16, a severe event of suicidal ideation was reported in 1/1945 (0.1%) apremilast-treated patient (20 mg BID group). This event led to the patient's withdrawal from treatment. In the apremilast exposure period, no additional severe events of suicide/self-injury were reported. Phase 3 Psoriasis Studies During weeks 0 to 16, no severe suicide/self-injury events were experienced by apremilast-treated patients. Overall, in the apremilast exposure period, severe suicide/self-injury events were reported in 1/1184 (0.1%) patient (PT: suicide attempt). A (non-severe) event of suicide attempt in a patient who received apremilast 30 mg BID resulted in withdrawal. Phase 3 BD Study No patients in BD study BCT-002 experienced events of 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.

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

Table 25. Important Identified Risk: Suicidality

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.
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).
Data source	Apremilast clinical trials (Module 2.7.4 of MAA and BCT-002 CSR).
MedDRA terms	PTs listed within the MedDRA v14.0 SMQ of Suicide/self-injury SMQ (narrow) are collectively referred to as suicide/self-injury events.

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BD = ;Behçet's Disease; BID = twice daily; CSR = clinical study report; EAIR = exposure-adjusted incidence rate; HR = hazard ratio; MAA = Marketing Authorization Application; MedDRA = Medical Dictionary for Regulatory Activities; PsA = psoriatic arthritis; PT = Preferred Term; PY = patient-years; SMQ = Standardised MedDRA Query; UK = United Kingdom

Table 26. 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	For frequency of serious events of depression see 'Seriousness/outcomes' below.
Seriousness/ outcomes	Phase 3 PsA Studies During weeks 0 to 16, serious depression was experienced by 2/1945 (0.1%) apremilast treated patients (1 patient each from the apremilast 20 mg BID and 30 mg BID groups) and no placebo-treated patients. All events resolved without sequelae. In the apremilast exposure period, serious events of depression were reported in 2/1945 (0.1%) patients in the 20 mg BID group and 1 (0.1%) patient in the apremilast 30 mg BID group. All events resolved without sequelae. Phase 3 Psoriasis Studies During weeks 0 to 16, no serious events of depression were experienced by apremilast-treated patients. Overall, in the apremilast exposure period, a serious event of depression was reported in 1/1184 (0.1%) patient. The outcome of the serious adverse event was recovered/resolved. Phase 3 BD Study No patients in BD Study BCT-002 experienced serious events of depression.
Severity	Phase 3 PsA Studies During weeks 0 to 16, no severe events of depression were experienced by apremilast-treated or placebo-treated patients. Overall, 3/1945 (0.2%) apremilast-treated patients withdrew from the study due to depression (2 patients with PT depressed mood and 1 patient with PT depression). Overall, in the apremilast exposure period, a severe event of depression was reported in 1/1945 (0.1%) patient (apremilast 20 mg BID group). In total, 2 (0.1%) patients withdrew from the study due to depression (both in the apremilast 20 mg BID group).

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

Table 26. Important Identified Risk: Serious Events of Depression

Characterization of the risk (continued)	
Severity (continued)	Phase 3 Psoriasis Studies During weeks 0 to 16, no severe events of depression were experienced by apremilast-treated patients. In the apremilast exposure period, severe depression was reported in 1/1184 (0.1%) patient. Overall, 1 (0.1%) patient withdrew from the study due to depression. Phase 3 BD Study No patients in BD Study BCT-002 experienced serious events of depression.
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	Depression can have very little impact on the patient's quality of life to very severe impact, interfering with daily functioning, depending on the severity of the symptoms.
Public health impact	The potential public health impact varies depending on the event reported.

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

Table 26. Important Identified Risk: Serious Events of Depression

Data source	Apremilast clinical trials (Module 2.7.4 of MAA and BCT-002 CSR).
MedDRA terms	PTs listed within the MedDRA v14.0 SMQ of Depression (excl suicide and self-injury; SMQ [narrow]) are collectively referred to as depression events.

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BD = ;Behçet's Disease; BID = twice daily; BSI = Beck Suicide Inventory; CSR = clinical study report; MAA = Marketing Authorization Application; MedDRA = Medical Dictionary for Regulatory Activities; PsA = psoriatic arthritis; PT = Preferred Term; SMQ = Standardised MedDRA Query

Table 27. 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 patients. Two of these patients participated in a rheumatoid arthritis study and the third patient participated in a PsA study.
Characterization of the risk	
Frequency	Phase 3 PsA Studies One case of mild cutaneous vasculitis was reported in 1/1945 (0.1%) patient receiving apremilast 30 mg BID for approximately 1 year in Study PSA-005. Phase 3 Psoriasis Studies Vasculitis was not reported in the psoriasis clinical studies. Phase 3 BD Study Two cases of SMQ Vasculitis were reported in patients receiving apremilast 30 mg BID in Study BCT-002 (both PTs: Behçet's syndrome). Other Studies There were 2 patients 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).
Seriousness/ outcomes	No patients in the PsA or psoriasis phase 3 studies have reported a serious event of vasculitis. Both cases of vasculitis reported in Study BCT-002 (PT: Behçet's syndrome) were serious. One was reported to have resolved and the other resolved with sequelae. The event of cutaneous vasculitis in a patient who received apremilast 30 mg BID in Study RA-002 was serious, and was ongoing at the time of reporting.
Severity	No events of severe vasculitis were reported in the PsA or psoriasis phase 3 trials. One case of vasculitis reported in Study BCT-002 (PT: Behçet's syndrome) was severe and both cases resulted in study drug withdrawal. The event of cutaneous vasculitis in a patient who received apremilast 30 mg BID in Study RA-002 was severe and resulted in treatment discontinuation.

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

Table 27. Important Potential Risk: Vasculitis

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	Vasculitis can lead to mural destruction with haemorrhage, aneurysm formation, infarction, intimal-medial hyperplasia and subsequent stenosis causing tissue ischaemia (Carlson et al, 2005). The skin is often involved in vasculitis syndromes that range from localised and self-limited conditions to generalised and life-threatening symptoms involving multi-organ disease (Carlson et al, 2005).
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.
Data source	Preclinical toxicology studies conducted in PDE4 compounds including apremilast, and apremilast clinical trials (Module 2.7.4 of MAA and BCT-002 CSR).
MedDRA terms	PTs listed within the MedDRA v14.0 SMQ of Vasculitis (narrow) are collectively referred to as vasculitis.

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BD = Behçet's Disease; BID = twice daily; CSR = clinical study report; CVD = cardiovascular disease; MAA = Marketing Authorization Application; MedDRA = Medical Dictionary for Regulatory Activities; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term; SMQ = Standardised MedDRA Query

Table 28. 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 patients 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 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.
Characterization of the risk	
Frequency	<u>Phase 3 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 patients in the 20 mg BID and 30 mg BID treatment groups, respectively, and in 4/671 (0.6%) placebo-treated patients. In the apremilast exposure period, events of malignancies were experienced by 17/1945 (0.9%) patients treated with apremilast (8/972 [0.8%] and 9/973 [0.9%] patients in the 20 mg BID and 30 mg BID groups, respectively). <u>Phase 3 Psoriasis Studies</u> During weeks 0 to 16, events of malignancies were experienced by 10/1184 (0.8%) apremilast-treated patients (30 mg BID) and by 2/418 (0.5%) placebo-treated patients. In the apremilast exposure period, 17/1184 (1.4%) patients reported treatment-emergent adverse events (TEAEs) of malignancies. <u>Phase 3 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%) patients reported TEAEs of malignancies (PTs: breast cancer and endometrial cancer).
Seriousness/ outcomes	<u>Phase 3 PsA Studies</u> During weeks 0 to 16, serious events of malignancies were experienced by 2/972 (0.2%; PTs: breast cancer and T-cell lymphoma) and 1/973 (0.1%; PT: breast cancer) apremilast-treated patients in the 20 mg BID and 30 mg BID groups, respectively, and in 1/671 (0.1%; PT: prostate cancer) placebo-treated patient. An outcome of recovered/resolved was reported for the patient in the 30 mg BID group; outcomes of not recovered/not resolved were reported for the other 3 patients.

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

Table 28. Important Potential Risk: Malignancies

Characterization of the risk (continued)	
Seriousness/ outcomes (continued)	In the apremilast exposure period, serious events of malignancies were experienced by 7/1945 (0.4%) apremilast-treated patients (5/972 [0.5%; PTs: B-cell lymphoma, basal cell carcinoma, breast cancer, prostate cancer and T-cell lymphoma] and 2/973 [0.2%; PTs: breast cancer and splenic neoplasm malignancy unspecified] patients in the 20 mg BID and 30 mg BID groups, respectively). Outcomes of recovered/resolved were reported for 1 patient each in the 20 mg BID (PT: basal cell carcinoma) and 30 mg BID groups (PT: breast cancer); outcomes of not recovered/not resolved were reported for the other 5 patients. <u>Phase 3 Psoriasis Studies</u> During weeks 0 to 16, serious events of malignancies were experienced by 1/1184 (0.1%) apremilast-treated patient (30 mg BID; PT: uterine cancer) and 1/418 (0.2%) placebo-treated patient (PT: anal cancer). An outcome of not recovered/not resolved was reported for both serious adverse events. In the apremilast exposure period, serious events of malignancies were experienced by 5/1184 (0.4%) apremilast-treated patients (30 mg BID). An outcome of not recovered/not resolved was reported for 1 (0.1%) patient (PT: uterine cancer), with the outcome of recovered/resolved reported for 4 (0.3%) patients (PT: breast cancer [2 patients], renal cell carcinoma [1 patient] and squamous cell carcinoma of skin [1 patient]). <u>Phase 3 BD Study</u> No serious events of malignancies were reported during weeks 0 to 12 in the BD study BCT-002. In the apremilast exposure period, serious events of malignancies were experienced by 2/187 (1.1%) apremilast-treated patients (1/187 [0.5%; PTs: breast cancer and endometrial cancer]). Outcomes of resolved were reported for both patients.
Severity	<u>Phase 3 PsA Studies</u> During weeks 0 to 16, severe events of malignancies were reported in 1/972 (0.1%) and 1/973 (0.1%) apremilast-treated patients in the 20 mg BID and 30 mg BID dose groups (both PTs breast cancer), respectively, and in no placebo-treated patients. In the apremilast exposure period, severe events of malignancies occurred in 5/1945 (0.3%) apremilast-treated patients (3/972 [0.3%; PTs: B-cell lymphoma, basal cell carcinoma and breast cancer] and 2/973 [0.2%; PTs: breast cancer and splenic neoplasm malignancy unspecified] patients in the 20 mg BID and 30 mg BID groups, respectively). During weeks 0 to 16, 2/972 (0.2%) apremilast-treated patients in the 20 mg BID group (PTs: breast cancer and T-cell lymphoma) and 1/671 (0.1%) patient in the placebo group (PT: prostate cancer) withdrew due to events of malignancies; no patients withdrew due to events of malignancies in the 30 mg BID dose group.

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

Table 28. Important Potential Risk: Malignancies

Characterization of the risk (continued)	
Severity (continued)	A total of 3/1945 (0.2%) patients in the apremilast exposure period withdrew as a result of events of malignancies (all 3 patients were in the 20 mg BID group; PTs: B-cell lymphoma, breast cancer and T-cell lymphoma). Phase 3 Psoriasis Studies No severe events of malignancies were reported during weeks 0 to 16 in the psoriasis phase 3 studies. In the apremilast exposure period, severe events of malignancies were reported in 3/1184 (0.3%) apremilast-treated patients (30 mg BID; PTs: breast cancer [2 patients] and renal cell carcinoma [1 patient]). During weeks 0 to 16 in the phase 3 psoriasis studies, 2/1184 (0.2%) apremilast-treated patients (30 mg BID; PTs: squamous cell carcinoma of skin [1 patient] and uterine cancer [1 patient]) and 2/418 (0.5%) placebo-treated patients withdrew due to events of malignancies (PTs: squamous cell carcinoma of skin [1 patient] and anal cancer [1 patient]). A total of 4/1184 (0.3%) patients in the apremilast exposure period withdrew from the phase 3 studies due to events of malignancies (30 mg BID; PTs: squamous cell carcinoma of skin [2 patients], breast cancer [1 patient] and uterine cancer [1 patient]). Phase 3 BD Study During weeks 0 to 12 in phase 3 BD Study BCT-002, no apremilast-treated patients or placebo-treated patients experienced events of malignancies. A total of 1/187 (0.5%) patients in the apremilast exposure period had study drug withdrawn due to events of malignancies (PT: breast cancer).
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 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 on quality of life to significant morbidity and mortality.

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

Table 28. 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 patients 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 database 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 patients 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 patients 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).
Data source	Apremilast clinical trials (Module 2.7.4 of MAA and BCT-002 CSR).
MedDRA terms	Terms in the MedDRA Version 19.0 sub-SMQ of malignant tumours (narrow) and tumours of unspecified malignancy (narrow) were mapped to MedDRA Version 14.0 and an ad hoc list of MedDRA Version 14.0 PTs based on the Version 19.0 SMQ of malignant lymphoma (broad) are listed in Annex 7 and are collectively referred to as malignancies. The search criteria for this risk have been updated to be in line with the current PSUR search criteria.

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BD = ;Behçet's Disease; BID = twice daily; CPRD = Clinical Practice Research Database; CSR = clinical study report; EAIR = exposure-adjusted incidence rate; MAA = Marketing Authorization Application; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; NMSC = non-melanoma skin cancer; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term; PUVA = psoralen and ultraviolet-A light; PY = patient-years; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event

Table 29. 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 patients 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	For frequency of serious events of anxiety and nervousness see 'Seriousness/outcomes' below.
Seriousness/ outcomes	<u>Phase 3 PsA Studies</u> During weeks 0 to 16, serious events of anxiety and nervousness were experienced by 1/972 (0.1%) apremilast treated patient in the 20 mg BID group (PT of anxiety). No patients treated with 30 mg BID apremilast or placebo experienced a serious event of anxiety and nervousness. The event of anxiety was reported in a patient with a history of anxiety and depression, occurring after the patient'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 patient (20 mg BID group; PT of anxiety). The event resolved. <u>Phase 3 Psoriasis Studies</u> During weeks 0 to 16, no serious events of anxiety and nervousness were experienced by apremilast- or placebo-treated patients. Overall, in the apremilast exposure period, there were no serious events of anxiety and nervousness. <u>Phase 3 BD Study</u> No patients in BD study BCT-002 experienced events of serious anxiety and nervousness.

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

Table 29. Important Potential Risk: Serious Events of Anxiety and Nervousness

Severity	Phase 3 PsA Studies During weeks 0 to 16, no severe events of anxiety and nervousness were experienced by apremilast-treated or placebo-treated patients. In total, 1/972 (0.1%) patient treated with 20 mg BID apremilast and 1/671 (0.1%) patient treated with placebo withdrew from the study due to events of anxiety and nervousness (both PTs of anxiety); no patients treated with 30 mg BID apremilast during weeks 0 to 16 withdrew due to events of anxiety and nervousness. Overall, in the apremilast exposure period, a severe event of anxiety and nervousness was reported in 1/1945 (0.1%) patient (20 mg BID group; PT of anxiety). Overall, 3/1945 (0.2%) apremilast-treated patients withdrew due to the PT of anxiety (2 in the 30 mg BID group and 1 in the 20 mg BID group). Phase 3 Psoriasis Studies During weeks 0 to 16, no severe events of anxiety and nervousness were experienced by apremilast- or placebo-treated patients. Overall, in the apremilast exposure period, there were no severe events of anxiety and nervousness. During weeks 0 to 16 in the phase 3 psoriasis studies, 2/1184 (0.2%) apremilast-treated patients (30 mg BID) withdrew due to events of anxiety and nervousness (PTs: anxiety [1 patient] and generalised anxiety disorder [1 patient]). No placebo-treated patients in the phase 3 studies withdrew as a result of events of anxiety and nervousness. A total of 2/1184 (0.2%) patients in the apremilast exposure period withdrew due to events of anxiety and nervousness (30 mg BID; PTs: anxiety [1 patient] and generalised anxiety disorder [1 patient]). Phase 3 BD Study No patients in BD Study BCT-002 experienced events of serious anxiety and nervousness.
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.

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

Table 29. Important Potential Risk: Serious Events of Anxiety and Nervousness

Impact on the risk-benefit balance of the product	Anxiety and nervousness can have very little impact on the patient's quality of life to very severe impact, interfering with daily functioning, depending on the severity of the symptoms.
Public health impact	The potential public health impact varies depending on the event reported.
Data source	Apremilast clinical trials (Module 2.7.4 of MAA and BCT-002 CSR).
MedDRA terms	Primary PTs listed within the MedDRA v19.0 High Level Terms of Anxiety disorders NEC and Anxiety symptoms were mapped back to MedDRA Version 14.0: activation syndrome, agitation, agitation neonatal, anticipatory anxiety, anxiety, anxiety disorder, anxiety disorder due to a general medical condition, cardiac neurosis, generalised anxiety disorder, nervousness, neurosis, postpartum neurosis, stress, tension.

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BD = ;Behçet's Disease; BID = twice daily; CSR = clinical study report; MAA = Marketing Authorization Application; MedDRA = Medical Dictionary for Regulatory Activities; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term

Table 30. 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. PDE4 is a cAMP-specific PDE and the dominant PDE in inflammatory cells. 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 AMP 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 patients treated with placebo and those treated with apremilast. The incidence of infections did not increase when patients 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	For frequency of serious infections including opportunistic infections and transmission of infections through live vaccines see 'Seriousness/outcomes' below.
Seriousness/ outcomes	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 PsA Studies</u> Systemic opportunistic infection was identified in 1/671 (0.1%) patient in the placebo group. One event (urinary tract infection) was adjudicated as non-opportunistic non serious infection in 1/972 (0.1%) patient 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 patients (2/671; 0.9 per 100 PY) in the placebo group, 0.4% of patients (4/972; 0.4 per 100 PY) in the apremilast 20 mg BID group, and 0.6% of patients (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 30. Important Potential Risk: Serious Infections Including Opportunistic Infections and Transmission of Infections Through Live Vaccines

Characterization of the risk (continued)

Seriousness/ outcomes (continued)

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

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 patients were exposed to apremilast were included, regardless of when the apremilast exposure started.

Each patient was counted once for each applicable event type.

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

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

Table 30. Important Potential Risk: Serious Infections Including Opportunistic Infections and Transmission of Infections Through Live Vaccines

Characterization of the risk (continued)

Seriousness/ outcomes (continued)

	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

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 patients exposed to apremilast were included, regardless of when the apremilast exposure started.
Each patient was counted once for each applicable event type.
EAIR per 100 patient-years is 100 times the number (n) of patients reporting the event divided by patient-years (up to the first event start date for patients 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 patients. These patients were discontinued from the study.

Phase 3 BD Study

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

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

Severity

Phase 3 PsA Studies

Of the adjudicated events in apremilast-treated patients, 7 were severe and 4 resulted in discontinuation from the study.

During weeks 0 to 16, no patients withdrew due to opportunistic infection.

In the apremilast exposure period, a severe event of opportunistic infection was reported in 1/1945 (0.1%) patient. This was an event of herpes zoster.

There were no infections associated with the use of live vaccines.

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

Table 30. Important Potential Risk: Serious Infections Including Opportunistic Infections and Transmission of Infections Through Live Vaccines

Characterization of the risk (continued)	
Severity (continued)	Phase 3 Psoriasis Studies Of the adjudicated events in apremilast-treated patients, 4 were severe and 4 resulted in discontinuation from the study. During weeks 0 to 16, there were no severe events of opportunistic infections for apremilast-treated patients. During weeks 0 to 16 no patients withdrew due to opportunistic infection. In the apremilast exposure period, there were no severe events of opportunistic infections. No patients withdrew due to an opportunistic infection. There were no infections associated with the use of live vaccines. Phase 3 BD Study During weeks 0 to 12, severe events of serious infection were experienced by 0 apremilast-treated patients (30 mg BID) and 2 placebo-treated patients. In the apremilast exposure period, 2 patients reported severe TEAEs of serious infection. Study drug was withdrawn for 1 patient who experienced an event of SMQ Serious Infections incl. Opportunistic Infections and Transmission Through Live Vaccines (PT: vestibular neuronitis), which subsequently resolved with sequelae.
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 patients treated with placebo and those treated with apremilast. The incidence of infections did not increase when patients continued treatment with apremilast for a longer time.

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

Table 30. 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).
Data source	Apremilast clinical trials (Module 2.7.4 of MAA and BCT-002 CSR).
MedDRA terms	MedDRA v14.0 PTs listed in Annex 7 are collectively referred to as infection.

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BD = ;Behçet's Disease; BID = twice daily; cAMP = cyclic adenosine monophosphate; CSR = clinical study report; EAIR = event adjusted incidence rate; IL = interleukin; MAA = Marketing Authorization Application; MedDRA = Medical Dictionary for Regulatory Activities; PDE4 = phosphodiesterase 4; PsA = psoriatic arthritis; PT = Preferred Term; PY = patient-years; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; TNF = tumor necrosis factor

Table 31. 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 patients 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 PsA Studies</u> Events were adjudicated as MACE in 0% of patients (0/671) in the placebo group, 0.3% of patients (3/972; 0.3 per 100 PY) in the apremilast 20 mg BID group, and 0.1% of patients (1/973; 0.1 per 100 PY) in the apremilast 30 mg BID group. Events were adjudicated as potential MACE in 0.1% of patients (1/671; 0.4 per 100 PY) in the placebo group, 0.6% of patients (6/972; 0.6 per 100 PY) in the apremilast 20 mg BID group, and 0.4% of patients (4/973; 0.4 per 100 PY) in the apremilast 30 mg BID group. Tachyarrhythmia TEAEs were reported in 0.1% of patients in the placebo group, 0.4% of patients in the apremilast 20 mg BID group, and 0.5% of patients 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 TEAEs 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 Psoriasis Studies</u> Events were adjudicated as MACE in 0.2% of patients (1/418; 0.9 per 100 PY) in the placebo group and 0.5% of patients (6/1184; 0.5 per 100 PY) in the apremilast 30 mg BID group. Five of the 6 apremilast treated patients 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 31. Important Potential Risk: MACE and Tachyarrhythmia

Characterization of the risk (continued)	
Frequency (continued)	Events were adjudicated as potential MACE in 0.2% of patients (1/418; 0.9 per 100 PY) in the placebo group and 0.8% of patients (9/1184; 0.8 per 100 PY) in the apremilast 30 mg BID group. Eight of the 9 patients 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 TEAEs were reported in 0.2% of patients in the placebo group and 0.6% of apremilast 30 mg BID patients as treated. Based on EAIR per 100 PY there was no evidence of an increased incidence of tachyarrhythmia TEAEs 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>Phase 3 BD Study</u> No events were adjudicated as MACE in Study BCT-002. During weeks 0 to 12, tachyarrhythmia TEAEs were reported in 1/103 (1.0%) patients in the placebo group and no apremilast 30 mg BID treated patients. Based on EAIR per 100 PY there was no evidence of an increased incidence of tachyarrhythmia TEAEs 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).
Seriousness/ outcomes	<u>Phase 3 PsA Studies</u> All events of MACE and potential MACE reported in the phase 3 PsA studies were considered serious. In the apremilast exposure period, tachyarrhythmia serious adverse events were reported in no patients in the placebo group, 1 patient in the apremilast 20 mg BID group, and 2 patients in the apremilast 30 mg BID group. <u>Phase 3 Psoriasis Studies</u> All events of MACE and potential MACE reported in the phase 3 psoriasis studies were considered serious. In the apremilast exposure period, serious events of tachyarrhythmia were reported in 1 patient in the placebo group, and no patients in the apremilast 30 mg BID group. <u>Phase 3 BD Study</u> No serious SMQ MACE and tachyarrhythmia TEAEs were reported during weeks 0 to 12 or during the apremilast exposure period.

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

Table 31. Important Potential Risk: MACE and Tachyarrhythmia

Characterization of the risk (continued)	
Severity	Phase 3 PsA Studies In the apremilast exposure period, severe MACE and potential MACE were experienced by no patients in the placebo group, 7 patients in the apremilast 20 mg BID group and 1 patient in the apremilast 30 mg BID group. In this period, 5 patients in the apremilast 20 mg BID group and 2 patients in the apremilast 30 mg BID group discontinued. Severe tachyarrhythmia was reported in 1 patient in the apremilast 30 mg BID group. One patient in the apremilast 20 mg BID group discontinued due to an event of tachyarrhythmia. Phase 3 Psoriasis Studies In the apremilast exposure period, severe MACE and potential MACE were experienced by 1 patient in the placebo group, and 10 patients in the apremilast 30 mg BID group. In this period, 1 patient in the placebo group and 5 patients in the apremilast 30 mg BID group were withdrawn. No patients had events of severe tachyarrhythmia. One patient in the placebo group discontinued due to an event of tachyarrhythmia. Pooled Phase 3 Studies Three patients discontinued treatment due to tachyarrhythmia and 1 patient required dose reduction. Phase 3 BD Study There were no events of MACE or tachyarrhythmia leading to discontinuation of apremilast, and no severe events of MACE or tachyarrhythmia.
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).

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

Table 31. Important Potential Risk: MACE and Tachyarrhythmia

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 patients treated with placebo and those treated with apremilast. The cardiac disorders described above may impact the quality of life of patients. The impact varies from minimal to physical limitations and death.
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).

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

Table 31. Important Potential Risk: MACE and Tachyarrhythmia

Public health impact (continued)	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).
Data source	Apremilast clinical trials (Module 2.7.4 of MAA and BCT-002 CSR).
MedDRA terms	MedDRA v14.0 PTs listed in Annex 7 are collectively referred to as MACE. The PTs listed within the MedDRA v14.0 SMQ broad scope are collectively referred to as tachyarrhythmia.

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AHA = American Heart Association; BD = ;Behçet's Disease; BID = twice daily; BMI = body mass index; CSR = clinical study report; CVD = cardiovascular disease; EAIR = event adjusted incidence rate; ECG = electrocardiogram; MAA = Marketing Authorization Application; MACE = major cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; 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 32. 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 13 December 2018, there have been a total of 24 cases of potential fetal exposure during pregnancy in female study patients treated with apremilast in apremilast interventional clinical trials. The outcomes of these pregnancies are summarized below:

	Timing of Exposure in Pregnancy (N = 24)		
Pregnancy Outcome	Before Conception	First Trimester	Grand Total
Elective termination (no fetal defects or unknown)	2	6	8
Therapeutic abortion	0	1	1
Live birth without congenital anomaly	3	8	11
Spontaneous abortion	0	1	1
Unknown	0	2	2
Ongoing	1	0	1
Grand Total	6	18	24

There were no fetal defects, ectopic pregnancies or congenital anomalies reported in any patient who became pregnant while being exposed to apremilast/blinded therapy. There was 1 instance of spontaneous abortion reported in a female patient receiving active apremilast treatment. The 11 live births reported to date with female patients exposed to apremilast were full term healthy infants.

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

Table 32. 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)	
Seriousness/ outcomes	All live births reported to date with female patients exposed to apremilast therapy or in partners of male patients exposed to apremilast therapy were full term healthy infants (see 'Frequency').
Severity	All live births reported to date with female patients exposed to apremilast therapy or in partners of male patients exposed to apremilast therapy were full term healthy infants (see 'Frequency').
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).
Data source	Apremilast clinical trials (Module 2.7.4 of MAA and BCT-002 CSR); 5-year license renewal data and preclinical studies.
MedDRA terms	Preferred terms listed within the MedDRA v14.0 SMQ of pregnancy and neonatal topics; sub SMQs of Foetal disorders, Neonatal disorders, Normal pregnancy conditions and outcomes, Termination of pregnancy and risk of abortion.

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CSR = clinical study report; EU = European Union; IL = interleukin; MAA = Marketing Authorization Application; MedDRA = Medical Dictionary for Regulatory Activities; PDE4 = phosphodiesterase 4; SMQ = Standardised MedDRA Query

SVII.3.2 Presentation of the Missing Information

Table 33. 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 Table 35.

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

Part II: Module SVIII - Summary of the Safety Concerns

Table 34. 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 cardiovascular event

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance activities are described in the Pharmacovigilance System Master File and the Drug Safety's Standard Operating Procedures, in accordance with Good Pharmacovigilance Practices (GVP) and local requirements.

In addition to expedited reporting, Amgen vigilantly undertakes follow-up on all ADRs, including serious ADRs that are provided to health authorities to ensure that all details of the case are captured for clinical evaluation. This includes efforts to obtain all relevant information and to establish the final outcome of the ADRs. Emerging potential safety signals can be detected by periodic and if appropriate, cumulative evaluation of the ADRs.

For events of special interest, materials and tools (such as event-specific questionnaires) have been developed to ensure that consistent and good quality follow-up information is obtained. All event specific questionnaires for apremilast are included in Annex 4 of the RMP.

Specific Adverse Reaction Follow-up Questionnaires

Event specific questionnaires for the collection of adverse event and follow-up data have been developed for the risks of: Vasculitis; Suicidality; Serious events of depression; Malignancies; Serious infections including opportunistic infections and transmission of infections through live vaccines; MACE and tachyarrhythmia; and, Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast. These questionnaires have been developed to ensure that consistent and good quality follow-up data are obtained. The forms are provided in Annex 4 of the RMP.

III.2 Additional Pharmacovigilance Activities

Postmarketing Surveillance Studies

Apremilast PsA Registry in the UK – British Society for Rheumatology Biologics Register in Psoriatic Arthritis (BSRBR-PsA)

A disease registry in the UK for PsA collects further data in the real-world setting. The primary objective of this apremilast PsA registry is:

To evaluate the long-term safety of apremilast, a cohort of patients fulfilling the CASPAR in the British Society for Rheumatology Biologics Register in Psoriatic Arthritis

(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.

The secondary objective is to compare the event rates of the AESIs between the exposed group (cohort treated with apremilast) and the non-exposed groups (patients treated with non-apremilast treatments).

The BSRBR-PsA is a specific PsA registry. This registry will be internationally recognised. The BSRBR-PsA protocol was first submitted to Pharmacovigilance Risk Assessment Committee (PRAC) on 27 March 2017, with the final protocol submitted on 16 October 2018.

The study will run for 7 years starting with the first patient recruited. Enrollment in the BSRBR-PsA registry started in Quarter 4 (Q4) 2018, data collection (follow-up) will end Q2 2025 and the final report of study results (Year 7, cumulative) will be completed Q2 2026. The registry is planned to cover 80 sites including an estimated total of 2500 enrolled patients with PsA. The exposure follow-up period for the evaluation of AESIs will be from the initiation of treatment to either first observation of an AESI, patient switching therapy, loss to follow up, or end of study. However, data collection will continue for all patients until end of study. All patients will be followed up annually until the end of the study (Year 7).

For the specified AESIs, this registry collects adverse events and serious adverse events. Annual progress reports will be communicated to the relevant health authorities as part of the PSUR, with a final report of study results produced at the end of the study (Year 7).

Table 35. Apremilast PsA Registry in the UK – BSRBR-PsA

Study Short Name and Title	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).	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.	Final protocol for BSRBR-PsA registry: 16 Oct 2018. Approved protocol submitted with Sequence 0059. Enrollment initiated: Q4 2018. 1-year report submission date: 23 Jun 2020. Final report of study results (Year 7, cumulative): available Q2 2026. Proposed submission date: Q3 2026.

Long-term Efficacy and Safety Studies

Long-term Follow-up

All additional pharmacovigilance studies assessing long-term efficacy and safety of apremilast are now complete. As discussed in RMP Version 8.0, a long-term study was completed previously, and a final CSR submitted (CC-10004-PSOR-010; Annex 9 of RMP Version 8.0). This study followed up patients for 2 years and provided data on malignancies, long-term safety and long-term efficacy to evaluate apremilast. Several additional long-term studies (CC-10004-PSA-002, -003, -004 and CC-10004-PSOR-008, -009) were reported as completed in RMP Version 10.0, with CSR submission pending. These CSRs have now been submitted alongside the CSR for the remaining study which is now complete (CC-10004-PSA-005; Annex 2). The CSRs for Studies CC-10004-PSA-002, -003, -004, -005 and CC-10004-PSOR-008, -009 were submitted on 29 June 2018. The Apremilast Psoriasis Registry in Germany – Long-term Benefits and Safety of Systemic Psoriasis Therapy (PsoBest) registry and the UK CPRD data analysis for PsA and psoriasis study are both complete, and the CSRs will be submitted with RMP version 14.0. Together, these studies involved patient follow up for up to 5 years and provide additional data on malignancies and long-term safety.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 36. (Table Part III.1) Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due 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 will be available: Proposed submission date: 3-year report will be available: Proposed submission date: 4-year report will be available: Proposed submission date: 5-year report will be available: Proposed submission date: 6-year report will be available: Proposed submission date: 7-year report will be available: Proposed submission date:	16 Oct 2018 Q4 2018 23 Jun 2020 Q1 2021 Q2 2021 Q1 2022 Q2 2022 Q1 2023 Q2 2023 Q1 2024 Q2 2024 Q1 2025 Q2 2025 Q2 2026 Q3 2026

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 37. (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 37. (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 37. (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:** **SmPC** **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. **PIL** 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 **Legal status** Apremilast is a prescription only medicinal product.
Missing Information	
Long-term safety	None

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V.2 Additional Risk Minimization Measures

There are no additional risk minimisation measures currently in place.

V.3 Summary of Risk Minimization Measures

Table 38. (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 38. (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 38. (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

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 to or who have been intolerant to a prior DMARD therapy.
- Otezla is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to, 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 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	In the phase 3 PsA studies, serious adverse events of hypersensitivity were reported in no apremilast treated patients and 1/671 (0.1%) placebo treated patient during weeks 0 to 16. In the phase 3 psoriasis studies, serious adverse events of hypersensitivity (Preferred Term: urticaria) were reported in 1/1184 (0.1%) apremilast treated patient each during weeks 0 to 16and over 5 years of apremilast treatment in long-term extension studies, and in no placebo treated patients. In phase 3 BD Study BCT-002, serious adverse events of hypersensitivity were reported in 1/103 (1.0%) placebo-treated patient during weeks 0 to 12. No events were reported in patients treated with apremilast.
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: <u>SmPC</u> • Contraindicated in those with hypersensitivity to apremilast (Section 4.3) and the risk of hypersensitivity is presented in Section 4.8. <u>PIL</u> • 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) – 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	No mechanism by which apremilast may trigger suicide has been identified. In the phase 3 PsA studies, nonfatal suicide/self-injury events were experienced by 2/1945 (0.1%) apremilast treated patients and no placebo treated patients during weeks 0 to 16, and an additional event of suicide attempt was reported over 5 years of apremilast treatment in long-term extension studies. In the phase 3 psoriasis studies, suicide/self injury events were experienced by 1/1184 (0.1%) apremilast treated patient, and 1 patient (0.2%) randomised to placebo died due to suicide. In Study PSOR-005 (phase 2 study), a male patient randomised to the placebo group, was found dead with a pink complexion in his [redacted] on study day 84. Autopsy did not establish the cause of death in this potential suicide. No patients in phase 3 BD study BCT-002 experienced events of suicidality.
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. PIL • 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	No mechanism by which apremilast may result in serious events of depression has been identified. In the phase 3 PsA studies, serious depression was experienced by 2/1945 (0.1%) apremilast treated patients and no placebo treated patients during weeks 0 to 16, and serious events of depression were reported in 3/1945 (0.2%) patients over 5 years of apremilast treatment in long-term extension studies. In the phase 3 psoriasis studies, no serious events of depression were experienced by apremilast treated patients during weeks 0 to 16, and a serious event of depression was reported in 1/1184 (0.1%) patient over 5 years of apremilast treatment in long-term extension studies. No patients in phase 3 BD study BCT-002 experienced serious events of depression.
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. PIL • 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	The phosphodiesterase (PDE) 4 inhibitors, including apremilast, have been shown to produce inflammatory perivascular histopathological changes in rodent studies. With apremilast, vasculitis has only been observed in rodents. No mechanism by which apremilast may cause vasculitis has been identified. In the apremilast phase 3 PsA clinical studies, small vessel cutaneous vasculitis was reported in 1/1945 (0.1%) apremilast treated patient (none in the phase 3 psoriasis studies). Two cases of Standardised Medical Dictionary for Regulatory Activities Query (SMQ) Vasculitis were reported in patients receiving apremilast 30 mg twice daily (BID) in Study BCT-002 (both Preferred Terms (PTs): Behçet's syndrome).
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.
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	No mechanism by which apremilast may cause malignancy has been identified. In the phase 3 PsA studies, malignancies were experienced by 4/1945 (0.2%) apremilast treated patients and 4/671 (0.6%) placebo treated patients during weeks 0 to 16, and by 17/1945 (0.9%) patients over 5 years of apremilast treatment in long term extension studies. In the phase 3 psoriasis studies, events of malignancies were experienced by 10/1184 (0.8%) apremilast treated patients and 2/418 (0.5%) placebo treated patients during weeks 0 to 16, and by 17/1184 (1.4%) patients over 5 years of apremilast treatment in long term extension studies. In phase 3 BD study BCT-002, no events of malignancy were experienced during weeks 0 to 12. In the apremilast exposure period, 2/187 (1.1%) patients reported treatment-emergent adverse events (TEAEs) of malignancy (PT: breast cancer and endometrial cancer). Many of the patients 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.
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	No mechanism by which apremilast may cause anxiety and nervousness has been identified. In the phase 3 PsA studies, serious events of anxiety and nervousness were experienced by 1/972 (0.1%) apremilast treated patient and no placebo treated patients during weeks 0 to 16, and by 1/1945 (0.1%) patient over 5 years of apremilast treatment in long term extension studies. No serious events of anxiety and nervousness were experienced by any patients during the phase 3 psoriasis studies or the phase 3 BD study BCT-002.
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.
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	Apremilast works intracellularly to modulate a network of pro-inflammatory and anti inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP) specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of tumour necrosis factor (TNF) alpha (α), interleukin (IL) 23, IL-17 and other inflammatory cytokines. Cyclic AMP 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. In the phase 3 PsA studies, events were adjudicated as non-opportunistic serious infections in 0.3% of patients in the placebo group, 0.4% of patients in the apremilast 20 mg BID group, and 0.6% of patients in the apremilast 30 mg BID group. In the phase 3 psoriasis studies, events were adjudicated as non-opportunistic serious infection in 0.5% of patients in the placebo group and 0.9% of patients in the apremilast 30 mg BID group. In phase 3 BD study BCT-002, events of serious infection were experienced by 0 apremilast treated patients (30 mg BID) and 2/103 (1.9%) placebo treated patients during weeks 0 to 12, and 2 patients in the apremilast exposure period. During the clinical development programme for PsA and psoriasis, the incidence of infections was comparable between patients treated with placebo and those treated with apremilast. The incidence of infections did not increase when patients continued treatment with apremilast for a longer time.
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	No mechanism by which apremilast may cause cardiac events has been identified. In the phase 3 PsA studies, events were adjudicated as MACE in 0% of patients in the placebo group, 0.3% of patients in the apremilast 20 mg BID group, and 0.1% of patients in the apremilast 30 mg BID group. Tachyarrhythmia TEAEs were reported in 0.1% of patients in the placebo group, 0.4% of patients in the apremilast 20 mg BID group, and 0.5% of patients in the apremilast 30 mg BID group during weeks 0 to 16. In the phase 3 psoriasis studies, events were adjudicated as MACE in 0.2% of patients in the placebo group and 0.5% of patients in the apremilast 30 mg BID group. During weeks 0 to 16, SMQ tachyarrhythmia TEAEs were reported in 0.2% of patients in the placebo group and 0.6% of apremilast 30 mg BID patients as treated. No events were adjudicated as MACE in Study BCT-002. During weeks 0 to 12, tachyarrhythmia TEAEs were reported in 1/103 (1.0%) patients in the placebo group and no apremilast 30 mg BID treated patients. The rate of MACE is higher in patients with psoriasis and PsA than in the normal population (Li et al, 2015; Mehta et al, 2011). The incidence of these events during the clinical studies was similar between patients 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 dyslipidaemia, 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 is no clear mechanism on how embryo-fetal loss is triggered in humans. However, 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. 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. As of 13 December 2018, there have been a total of 24 cases of potential fetal exposure during pregnancy in female study patients treated with apremilast in apremilast interventional clinical trials. There were no fetal defects, ectopic pregnancies or congenital anomalies reported in any patient who became pregnant while being exposed to apremilast/blinded therapy. There was 1 instance of spontaneous abortion reported in a female patient receiving active apremilast treatment. The 11 live births reported to date with female patients exposed to apremilast in clinical trials were full term healthy infants.
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). PIL • 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 Classification of Psoriatic Arthritis (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

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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 #

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:

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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:
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 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 Medications:

Other Amgen Drug

Dose | Frequency | Route

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:

Amgen
Office Fax:

REPORTER Name:

Address:

City State/ Prov.

Postal code: Country:

Phone Email:
(+ country code)

Signature

Title **Date**

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:

CONTINUED ON NEXT 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

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)

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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 (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:
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 INFECTION IN GENERAL

(including opportunistic infection, abscess, soft tissue infections including necrotizing fasciitis)

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: _____

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

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:
Postal Code:

Amgen
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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:
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Country:
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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.