EU-RISK MANAGEMENT PLAN FOR BIMZELX® (BIMEKIZUMAB)

160mg/mL pre-filled syringe or pre-filled pen

Version 1.12

Date: 01 Nov 2023 20231101-rmp-v1.12 RTN-003637

ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 1.12

Data lock point for this RMP: 15 Nov 2022 (for hidradenitis suppurativa [HS] data)

Date of final sign off: 01 Nov 2023

Rationale for submitting an updated RMP: Responses to D90 Request for Supplementary Information (RSI) on the extension of indication in patients with HS (Procedure EMEA/H/C/005316/II/0020)

Summary of significant changes in this RMP: Revised wording for HS indication, addition of HS to PS0038, updated milestone dates for HS0005

This RMP is based upon version EU RMP v1.10, which is under evaluation.

Other RMP version under evaluation:

Version number: EU RMP v1.11 (addition of information related to 2 new 320mg/2mL presentations)

Submission on: 06 Sep 2023

Procedure number: EMEA/H/C/005316/X/0021

Version number: EU RMP v1.10 (HS procedure)

Submission on: 21 Jun 2023

Procedure number: EMEA/H/C/005316/II/0020

Details of the currently approved RMP:

Version number: 1.9

Approved with procedure: EMEA/H/C/005316/IB/0019

Date of approval (opinion date): 26 Jun 2023

Qualified Person for Pharmacovigilance (QPPV) name: Bart Teeuw

QPPV signature: Please see the electronic signature of the EEA QPPV or his deputy on the last page of this module.

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LIST OF ABBREVIATIONS

AE	adverse event
ADR	adverse drug reaction
AS	ankylosing spondylitis
ASAS-EULAR	Assessment of spondyloarthritis international Society and the European Alliance of Associations for Rheumatology
axSpA	axial spondyloarthritis
bDMARD	biological disease-modifying antirheumatic drug
BSA	body surface area
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CSR	clinical study report
EAM	extra-articular manifestation
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU GVP	European Union Good Pharmacovigilance Practice
EULAR	European Alliance of Associations for Rheumatology
FcRn	neonatal Fc receptor
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
IBD	inflammatory bowel disease
Ig	immunoglobulin
IGA	Investigator's Global Assessment
IL	interleukin
IL-17RA	interleukin-17 receptor A
IMP	investigational medicinal product
iv	intravenous
JAKi	janus-kinase inhibitor
LPLV	last patient last visit
mAb	monoclonal antibody
MACE	major adverse cardiovascular event
MTX	methotrexate
nr-axSpA	non-radiographic axial spondyloarthritis

NSAID	non-steroidal anti-inflammatory drug
OLE	open label extension
PASI	Psoriasis Area and Severity Index
PDE4	phosphodiesterase 4
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	psoriatic arthritis
PSO	psoriasis
py	participant/person-years
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
QPPV	Qualified Person responsible for Pharmacovigilance
r-axSpA	radiographic axial spondyloarthritis
RMP	Risk Management Plan
sc	subcutaneous(ly)
SFU	safety follow-up
SIB	suicidal ideation and behavior
SmPC	summary of product characteristics
SNDS	Système National de Données de Santé
SpA	spondyloarthritis
TNF	tumor necrosis factor
tsDMARD	targeted synthetic disease-modifying antirheumatic drug

PART I: PRODUCT(S) OVERVIEW

Table 1: Product overview

Active substance(s) (INN or common name)	Bimekizumab
Pharmacotherapeutic group(s) (ATC code)	Immunosuppressants, interleukin inhibitors L04AC21
Marketing Authorization Applicant	UCB Pharma S.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Bimzelx
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class**: Bimekizumab is a humanised IgG1 mAb produced by recombinant DNA technology
	Summary of mode of action: Inhibition of the activity of cytokines IL-17A and IL-17F
	Important information about its composition: Produced by recombinant DNA technology in a Chinese hamster ovary cell line. No other materials of animal origin are used in the manufacturing process.
Hyperlink to the Product Information	Module 1.3.1 SmPC, Labeling and Package Leaflet

Table 1: Product overview

Indication(s) in the EEA	Current: **Psoriasis** Bimekizumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. **Psoriatic arthritis:** Bimekizumab, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more DMARDs. **Axial spondyloarthritis:** Non-radiographic axial spondyloarthritis Bimekizumab is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging who have responded inadequately or are intolerant to non-steroidal anti-inflammatory drugs. Ankylosing spondylitis (radiographic axial spondyloarthritis) Bimekizumab is indicated for the treatment of adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy.
	Proposed: Bimekizumab is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy.

Table 1: Product overview

Dosage in the EEA	Current: Psoriasis: The recommended dose for adult patients with plaque psoriasis is 320mg (given as 2 subcutaneous injections of 160mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter. For some patients with plaque psoriasis (including psoriatic arthritis with coexistent moderate to severe psoriasis) and a bodyweight ≥120kg who did not achieve complete skin clearance at week 16, 320mg every 4 weeks after week 16 may further improve treatment response. Psoriatic arthritis: The recommended dose for adult patients with active psoriatic arthritis is 160mg (given as 1 subcutaneous injection of 160mg) every 4 weeks. For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, the recommended dose is the same as for plaque psoriasis (320mg [given as 2 subcutaneous injections of 160mg each] at Week 0, 4, 8, 12, 16 and every 8 weeks thereafter). After 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to160mg every 4 weeks can be considered. Axial spondyloarthritis (non-radiographic axial spondyloarthritis and ankylosing spondylitis): The recommended dose for adult patients with axial spondyloarthritis is 160 mg (given as 1 subcutaneous injection) every 4 weeks.
	Proposed: The recommended dose for adult patients with hidradenitis suppurativa is 320 mg (given as 2 subcutaneous injections of 160mg each) every 2 weeks up to Week 16 and every 4 weeks thereafter.
Pharmaceutical form(s) and strength(s)	Current: Solution for injection in pre-filled syringe. Each pre-filled syringe contains 160mg bimekizumab in 1mL. Solution for injection in a pre-filled pen. Each pre-filled pen contains 160mg bimekizumab in 1mL.
	Proposed: Not Applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC=Anatomical Therapeutic Chemical; DMARD=disease-modifying antirheumatic drug; DNA=deoxyribonucleic acid; EEA=European Economic Area; IgG=immunoglobulin G; IL=interleukin; INN=International non-proprietary name; mAb=monoclonal antibody; SmPC=summary of product characteristics; RMP=risk management plan

PART II: SAFETY SPECIFICATION

PART II: MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

1 PSORIASIS

1.1 Incidence

The incidence of PSO in Europe is variable, with reported annual estimates of 98 per 100,000 person-years (PYs) in Sweden, 120 per 100,000 PYs in the Netherlands, 140 per 100,000 PYs in the UK, 200 per 100,000 in Denmark and 230 per 100,000 PYs in Italy (Egeberg et al, 2017; Parisi et al, 2013; Archier et al, 2012). A study of UK based data Clinical Practice Research Datalink reported that the unadjusted prevalence of PSO increased steadily from 2.3% (2297 cases per 100,000 PYs) in 1999 to 2.8% (2815 cases per 100,000 PYs) in 2013, however, age and gender adjusted PSO incidence declined from 159 cases per 100,000 PYs (95% confidence interval [CI] 155–164) in 1999 to 129 cases per 100,000 PYs (95% CI 126, 133) in 2013 (Springate et al, 2017).

1.2 Prevalence

The prevalence of PSO varies across European studies depending upon patient population and varying case ascertainment methods (Griffiths et al, 2017). Table 1–1 shows a range of prevalence estimates from recent European literature.

Table 1–1: PSO prevalence estimates in Europe from observational literature

Country	Date of Estimate	Estimate	Author date
Sweden	2010	1.2%	Löfvendahl et al, 2014
UK	2010	2.2%	Seminara et al, 2011
Denmark	2017	2.2%	Egeberg et al, 2017
Spain	2013	2.3%	Ferrándiz et al, 2014
Germany	2011	2.0% – 3.5%[a]	Augustin et al, 2011
UK	2013	2.8%	Springate et al, 2017
Italy	2008	2.9%	Saraceno et al, 2008
France	2009	5.2%	Wolkenstein et al, 2009
Norway	2016	8.0%	Modalsli et al, 2016

[a]Augustin et al, 2011 is a systematic review of multiple German studies

Psoriasis affects approximately 3% of the US adult population (Rachakonda et al, 2014; Kurd and Gelfand, 2009), and its onset can begin at any age (Augustin et al, 2011). There is limited published literature on the epidemiology of PSO in Japan. Existing literature shows an estimated prevalence of 0.34% and the incidence is unknown (Kubota et al, 2015). A systematic review of the global epidemiology of PSO conducted in 2016 reported that prevalence estimates in Asian

countries including Japan are generally lower than those seen in Europe although risk factors including cardiovascular disease are similar (Michalek et al, 2017).

It is important to note that estimates of PSO incidence and prevalence generally include all subtypes of PSO. Plaque PSO is the most common form of the disease; therefore, reported estimates of the magnitude of this condition are likely weighted heavily by this subtype (Feldman et al, 2018; Feldman et al, 2015; Yeung et al, 2013; Ahlehoff et al, 2011; Christophers et al, 2010; Gisondi et al, 2007; Gelfand et al, 2006).

1.2.1 Demographics of the PSO population – age, gender, ethnic origin and risk factors for the disease

Onset can occur at any age, although PSO is less common before 9 years of age (Parisi et al, 2013). Psoriasis is reported to affect 0.5–1% of children in Europe, with reports of increasing prevalence over time. As of 2011 the reported incidence of pediatric PSO was 40.8 per 100,000 PYs with a median age of onset between 7 and 10 years (Napolitano et al, 2016). There is generally a trend of increasing incidence with age up to 39 years, a reduced incidence between 40-49 years, and a second peak at around 50-59 years or 60-69 years, followed by a decreased incidence toward the end of life. There is evidence of genetic differences in patients with early onset PSO, specifically strong association with Class I human leukocyte antigen alleles, which are not found in later onset PSO (Pezzolo et al, 2019; Parisi et al, 2013). Incidence peaks occur approximately 3-5 years earlier in women than in men, but PSO is generally believed to be equally common in men and women (Al et al, 2017; Gudjonsson and Elder, 2007). Both the incidence and prevalence of PSO are higher among Caucasians and a recent systematic review has reported that PSO most often occurs in individuals of European ancestry, followed by black and Hispanic individuals (Kaufman and Alexis, 2018; Crow, 2012). A systematic review investigating genetic differences in different subpopulations found that PSO is less common among Asians, Aborigines, Andean-Indians, Alaskans, Canadians, and Native Americans living in the US (Oka et al, 2012).

Available evidence suggests that the development of the disease is jointly influenced by genetic predisposition and environmental factors (Gran et al, 2020). A meta-analysis of genome-wide association studies identified 15 new PSO-associated susceptibility loci that are involved in innate host-defense, including several proteins engaged in the tumor necrosis factor (TNF), interleukin (IL)-23 and IL-17 signaling pathways (Tsoi et al, 2012).

Other risk factors including smoking, stress, extreme temperatures, drug reaction, and infections have been shown to be associated with onset or exacerbation of disease (Naldi, 2004). Both the incidence and prevalence of PSO are higher among those living in higher latitudes (Crow, 2012). A systematic review reported that smoking was an independent risk factor for the development of PSO, and that smoking may exacerbate existing PSO symptoms (Armstrong et al, 2014). Studies have identified psychological or emotional stress as contributors to the development of disease and the exacerbation of PSO through their role in dysregulating hypothalamic-pituitary-adrenal axis activity (Evers et al, 2010; Malhotra and Mehta, 2008). Seasonal variation may also impact development of PSO, where low humidity during the winter has been suggested to worsen PSO, through thickening of the epidermis and stimulation of inflammatory mediator production (Balato et al, 2013). Exposure to certain drugs such as lithium, beta-blockers, and antimalarials, can also incite the development of PSO or exacerbate disease (Balak and Hajdarbegovic, 2017; Fry and Baker, 2007). Microbial infections may also exacerbate pre-

existing chronic plaque PSO, as well as be responsible for the onset of disease (Fry and Baker, 2007).

1.2.2 The main existing treatment options

Therapy for patients with PSO varies per the severity of disease. Limited or mild disease is often treated with topical therapies, such as corticosteroids and vitamin D analogs, fumarates, and retinoids. Patients with more severe disease are often treated with photochemotherapy, ciclosporin, methotrexate (MTX), apremilast (a small molecule inhibitor of phosphodiesterase 4 [PDE4]) or biologic agents. Each therapy has unique characteristics that contribute to benefits and risks of treatment, as summarized below based on the most recent treatment guidelines (Stiff et al, 2018; Armstrong et al, 2017; Nast et al, 2015). Topical steroids (eg, triamcinolone, mometasone, clobetasol, betamethasone, hydrocortisone) are generally used as first-line treatment of PSO. High-strength steroids are typically reserved for use on the arms and legs. Areas such as the face and skin folds (eg, axillary and inguinal regions) are usually treated with a low potency steroid. Chronic use of potent topical steroids can lead to tachyphylaxis and corticosteroid-related side effects, such as skin atrophy and fragility, and is generally discouraged. Topical vitamin D analogs (eg, calcipotriol and tacalcitol) are commonly used to treat mild to moderate PSO and work best among patients with mild disease. They are safe but lack efficacy for many moderate to severe patients. Details of the recommended treatment guidelines were published in 2015 through a combined effort from the European Dermatology Forum, the European Association for Dermatology and Venereology and the International Psoriasis Council (Nast et al, 2015).

Phototherapy is a frequent option for patients with mild, moderate, and moderate to severe PSO, but the inconvenience of multiple treatment visits and varying efficacy limits its use. The use of photosensitizing agents, such as 8-methoxypsoralen, followed by ultraviolet A exposure (so-called, photochemotherapy or phototherapy) has proven to be effective in extensive forms of the disease (Henseler et al, 1981; Parrish and Jaenicke, 1981). However, phototherapy is associated with an increased risk of skin carcinoma (Archier et al, 2012).

Systemic immunosuppressants, such as ciclosporin and MTX, are used to treat patients with moderate to severe PSO. Toxicity concerns are limitations to this treatment regimen and include nausea, vomiting, diarrhea, oral ulcers, loss of appetite, low blood counts, infection, and hepatotoxicity and/or nephrotoxicity. Apremilast, an oral small molecule PDE4 inhibitor, is indicated for patients with moderate to severe plaque PSO who are candidates for phototherapy or systemic therapy. The most common adverse events (AEs) for apremilast are diarrhea, nausea, and headache (Bianchi et al, 2016), with loss of efficacy and AEs cited as the main reasons for treatment discontinuation (Del Alcazar et al, 2020; Zeb et al, 2019).

Biologics including, but not limited to, TNFα inhibitors and IL inhibitors (eg, IL-17 and IL-23), are available treatment options for patients with moderate to severe PSO who are candidates for systemic therapy. These products are injected subcutaneously (sc) or delivered via intravenous (iv) infusion, and while effective, not all patients respond to current therapies and loss of response often can occur over time (Piaserico et al, 2014; Menter et al, 2011). Key safety concerns associated with the use of these biologic treatments include an increased risk of developing serious infections and malignancies; however, the associated risks vary across the different classes of biologic treatments.

1.3 Natural history of PSO, including mortality and morbidity

Psoriasis is a common chronic inflammatory disease characterized by a series of linked cellular changes in the skin: hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and infiltration of T lymphocytes, neutrophils, and other types of leucocytes in affected skin. Various types of PSO exist including plaque, guttate, inverse, pustular, and erythrodermic. It is estimated that approximately 80% of PSO patients have mild to moderate disease while 20% of patients have more severe PSO, which either affects greater than 5% of body surface area (BSA) or is located on high-impact areas including scalp, genitals, hands, and nails (Menter et al, 2008). Plaque PSO (PSO vulgaris) is the most common, comprising approximately 80% to 90% of all cases (Hsu et al, 2012; Nast et al, 2012). The disease usually manifests as raised, well-demarcated, erythematous oval plaques with adherent silvery scales (Nestle et al, 2009). The scalp is the most frequently and earliest affected area of the body in both pediatric and adult PSO patients (Merola et al, 2018). Classic PSO vulgaris commonly presents on the elbows, knees and scalp, and may remain localized or become generalized (Lowes et al, 2007). Though the pathophysiology of PSO is not fully understood, the importance of T-cells and inflammatory cytokines has been demonstrated by the clinical benefit provided by therapies directed at these targets (Nestle et al, 2009; Krueger and Ellis, 2005).

Psoriasis has a wide range of phenotypic manifestations, believed to be a result of multiple genetic risk factors, triggering environmental agents, and stochastic factors. The development of psoriatic arthritis (PsA) is a sequela to the development of PSO in approximately 30% of patients (Oliveira et al, 2015; Christophers et al, 2010). Early onset PSO, with onset before 40 years and peak onset at 16-22 years of age, comprises 70% of all psoriatic patients. Late-onset PSO which occurs at or after 40 years has a peak onset between 57 and 60 years (Gudjonsson and Elder, 2007).

Psoriasis can contribute to significant morbidity including physical, psychological, social and overall wellbeing (Feldman et al, 2018; Feldman et al, 2015; Yeung et al, 2013; Ahlehoff et al, 2011; Gelfand et al, 2006). Psoriasis in specific areas such as face, scalp, and genitals have been reported to be particularly detrimental to psychological and social health (Merola et al, 2016). A recent meta-analysis of observational studies identified an increased risk of mortality associated with PSO (Dhana et al, 2019), and some comorbidities such as cardiovascular disease have been shown to increase with disease severity and may increase mortality risk in part due to shared inflammatory pathways (Takeshita et al, 2017; Yeung et al, 2013).

1.4 Important co-morbidities

Epidemiology of important comorbidities in PSO population is summarized in Table 1–2.

Table 1–2: Summary of epidemiology of important comorbidities in the PSO population

Comorbidity	Incidence/prevalence/association
PsA	The derived global, pooled prevalence of PsA among patients with PSO based on a meta-analysis of only good quality (N=134) observational and clinical studies according to the Newcastle-Ottawa Scale, was 18.1% (95% CI 16.6%, 19.6%) (Alinaghi et al, 2019). The incidence of PsA among patients with PSO ranged from 0.27 in non-selected population-based studies in the US and the UK (Love et al,

Table 1–2: Summary of epidemiology of important comorbidities in the PSO population

	2012; Wilson et al, 2009) to 2.7 in Canada (Eder et al, 2016) per 100 PYs. The prevalence has been reported to increase with progression of disease, with greater prevalence observed among patients with more extensive skin disease (Scher et al, 2019).
Cardiovascular disease	Global observational studies estimate the incidence of MACE amongst PSO patients at 0.28 to 0.65 per 100 PYs (Ogdie et al, 2015; Papp et al, 2015). A meta-analysis of observational studies found that compared to controls, severe psoriasis is associated with an increased risk of several poor cardiovascular outcomes, including cardiovascular mortality (risk ratio 1.39 [95% CI 1.11, 1.74]), myocardial infarction (risk ratio 1.70 [95% CI 1.32, 2.18]), and stroke (risk ratio 1.56 [95% CI 1.32, 1.84]) (Armstrong et al, 2013).
Metabolic syndrome	Data from THIN reported that 34% of PSO patients had metabolic syndrome compared with 26% of controls (Langan et al, 2012). This study reported increasing prevalence of metabolic syndrome with increasing BSA of affected PSO patients. A meta-analysis of metabolic syndrome in PSO observational studies identified prevalence estimates ranging from 0.2% to 66% among 35 studies (Singh et al, 2017a). The methodology and source population varied considerably in the primary articles in the meta-analysis which lead to this large variation, however, the prevalence of metabolic syndrome was consistently higher among PSO patients compared to control patients, with an overall summary odds ratio of 2.14 (95% CI 1.84, 2.48).
Inflammatory bowel disease	EU-based studies of PSO patients have reported a prevalence of Crohn's disease of 0.7% and prevalence of ulcerative colitis of 0.8% (Eppinga et al, 2017; Radtke et al, 2017). A higher incidence rate has been reported to be associated with more severe PSO (Egeberg et al, 2016a). A systematic review and meta-analysis reported a risk ratio of 2.53 (95% CI 1.65, 3.89) for Crohn's disease and a risk ratio of 1.71 (95% CI 1.55, 1.89) for ulcerative colitis comparing PSO patients to controls (Fu et al, 2018).
Depression	Prevalence of depression in patients with PSO ranges from 2.1 to 33.7% compared to 0 to 22.7% in unaffected controls (Wu et al, 2017). Pooled analysis from a meta-analysis estimated a prevalence of 28% (95% CI 22, 34), with a pooled odds ratio of 1.57 (95% CI 1.40, 1.76) comparing PSO patients to controls when basing depression on ICD codes (Dowlatshahi et al, 2014).
Suicidality	Data from a systematic literature review and meta-analysis reported a pooled odds ratio for suicidal ideation among patients with PSO of 2.05 (95% CI 1.54, 2.74) (Singh et al, 2017b). Specific rates vary by data source and definition. More severe PSO and younger age were reported to be associated with a greater likelihood of suicide.
Liver disease	Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver conditions from the simple steatosis to steatohepatitis (non-alcoholic steatohepatitis), with the risk to evolve to cirrhosis and hepatocellular carcinoma. In a meta-analysis of 7 population- and clinical based case-control studies that were considered low to moderate quality and, for the most part, did not adjust for potential confounding factors, such as metabolic syndrome, NAFLD was found to

Table 1–2: Summary of epidemiology of important comorbidities in the PSO population

	be more prevalent among patients with versus without PSO (pooled odds ratio, 2.15 [95% CI, 1.57-2.94]) (Candia et al, 2015). The odds ratio for NAFLD among patients with severe PSO was 2.07 (95% CI, 1.59-2.71) versus patients with mild PSO. Population- and clinic-based studies published to date report a significantly greater prevalence of NAFLD in patients with PSO than in controls without PSO (17-66% vs 8-35%) (Fiore et al, 2018; Carrascosa et al, 2017; Oliveira et al, 2019). Heterogeneity can be attributed to differences in diagnosis, age, case source, inclusion/ exclusion of hepatotoxic agents etc. (Awosika et al, 2018).
Hyperlipidemia	Twenty of 25 population- and clinic-based studies included in a systematic literature review reported that PSO was significantly associated with dyslipidemia, with odds ratios for dyslipidemia ranging from 1.04 to 5.55 (Ma et al, 2013). The odds ratio for dyslipidemia among patients with severe PSO was 1.36-5.55 versus 1.10-3.38 for patients with mild PSO (based on 3 studies). Four studies reported significantly increased odds ratios of 1.20-4.98 for hypertriglyceridemia (≥ 150 mg/dL) in PSO. One cohort study found a significantly higher incidence of hyperlipidemia among patients with PSO (hazard ratio 1.17; 95% CI 1.11-1.23).
Hypertension	Results of a meta-analysis of 16 population- and clinic based adjusted-for-covariates studies in Asia (N=5), the EU (N=10) and South-America (N=1), indicated that PSO was associated with an increased risk of hypertension compared to those without PSO (odds ratio 1.43; 95% CI 1.25–1.64) (Duan et al, 2020). Stratification by severity showed a significant association in patients with severe PSO (odds ratio 1.13; 95% CI 1.03–1.25), while there was no association in patients with mild PSO (odds ratio 1.09; 95% CI 0.98–1.22). High heterogeneity was attributed to the difference in diagnostic criteria for hypertension and PSO, instruments for measuring blood pressure, case source, etc.
Diabetes	Analysis of electronic health records in Wales identified that 11.9% of PSO patients had a history of diabetes compared to 7.8% of controls (Cooksey et al 2018). The prevalence of diabetes was 4.8% in mild PSO patients and 6.0% for severe PSO patients in an analysis of the UK's CPRD data (Edson-Heredia et al 2015).

BSA=body surface area; CI=confidence interval; CPRD=Clinical Practice Research Datalink; ICD=International classification of diseases; MACE=major adverse cardiovascular events; N=number; NAFLD=non-alcoholic fatty liver disease; PsA=psoriatic arthritis; PSO=psoriasis; PY=persons-years; THIN=The Health Improvement Network

Other comorbidities identified in the literature for which there is conflicting or minimal data include renal disease (Yeung et al, 2013), chronic obstructive pulmonary disease, and peptic ulcer disease (Takeshita et al, 2017). Additionally, there is evidence suggesting a small increased risk of certain malignancies, including non-melanoma skin cancers among patients with PSO (Pouplard et al, 2013). Some of the increased risk is believed to be due to exposure to common conventional PSO treatments including methotrexate, phototherapy, and immunosuppressants, including ciclosporin (Pouplard et al, 2013). The burden of comorbidities increases with increasing disease severity (Yeung et al, 2013). Some comorbidities including cardiovascular disease are thought to have shared inflammatory pathways, cellular mediators, genetic susceptibility, and common risk factors to PSO (Takeshita et al 2017).

2 PSORIATIC ARTHRITIS

2.1 Incidence

A meta-analysis of 28 studies evaluating the prevalence and incidence of PsA estimated that the study-specific incidence rate of PsA ranged from 3.0 to 41.3 cases every 100,000 PYs, albeit with high inter-study heterogeneity (I2 index 98.1%). The study also reported a pooled PsA incidence rate of 8.3 (95% CI: 4.1-16.7) every 100,000 PY (Scotti et al, 2018). The incidence of PsA in the general population is approximately 6.0-8.0 per 100,000 in most European countries (Karmacharya et al, 2021a). In a population-based study, the overall age- and sex-adjusted annual incidence of PsA per 100,000 population was 8.5 (95% CI: 7.2-9.8); incidence was higher in males (9.3, 95% CI: 7.4-11.3) than females (7.7, 95% CI: 5.9-9.4). The incidence of PsA varies across the globe: Greece 3.02; Czech-republic 3.60; Israel 10.9; Canada 13-15; Finland 23.10, and Norway 43.10 per 100,000 PY. The study also presented that the overall incidence trend was stable from 2000-2017 in some countries like Canada, and Israel, while some countries reported steady increase in incidence rate such as Denmark and Taiwan (Karmacharya et al, 2021b).

2.2 Prevalence

The reported prevalence of PsA ranges from 0.1% to 1% in the general population around the world (Karmacharya et al, 2021a). Results from a systematic review and meta-analysis of 28 studies reported study-specific prevalence rates of PsA between 20 to 670 cases per 100,000 subjects, with high inter-study heterogeneity (I2 index 99.3%). Additionally, the random effect pooled PsA prevalence rate was 133 per 100,000 subjects (95% CI: 107-164 per 100,000 subjects) (Scotti et al, 2018). The prevalence estimates ranged from 6 per 100,000 in a study using International Classification of Disease-9 codes to 25 per 100,000 in studies using self-reported diagnosis of PsA in the US, while it ranged from 50 to 210 per 100,000 in Turkey and Sweden, respectively. However, Asian countries reported low prevalence: 0.1, 2 and 4 per 100,000 in Japan, China and Taiwan, respectively (Karmacharya et al, 2021b). A retrospective cohort study of 4490 patients with PsA in Israel, reported a doubling of the prevalence rate of PsA from 2006 to 2015 (from 0.073% to 0.153%) with an overall crude prevalence rate of 0.153% (95% CI: 0.149-0.158) (Eder et al, 2018).

2.3 Demographics of the target population in the PsA indication – age, gender, racial, and/or ethnic origin and risk factors for the disease

Studies have reported increases in the mean age at diagnosis of PsA in both males and females, with modest increases in incidence among females, specifically in the age range of 40-59 years (Karmacharya et al, 2021b). A study including data from health insurance companies in Germany (between Jan 2009 and Dec 2012) estimated that the age-specific and sex specific incidence of PsA showed a continuous increase with rising age until it peaked slightly before the age of 60 and declined thereafter. The age-standardised incidence for PsA ranged from 15.46 per 100 000 individuals (95% CI 14.85 to 16.01 per 100 000 PY) to 17.31 per 100 000 individuals (95% CI 16.54 to 18.01 per 100 000 PY) in men (2009–2011). Similarly, the age-standardised

incidence in females changed over this period from 17.19 per 100 000 PY (95% CI 16.63 to 17.70 PY) to 19.54 per 100 000 PY (95% CI 18.84 to 20.25 per 100 000 PY) (Deike et al, 2021).

Certain PSO-related factors such as PSO severity and nail lesions, a family history of PSO or PsA, environmental factors such as physical/emotional stress, trauma and infections, smoking and alcohol use/abuse are thought to play a role in the development of PsA (Karmacharya et al, 2021a). Other factors responsible for an increased risk included geographic region, ethnicity, higher prevalence of obesity, hyperlipidemia, and smoking (Karmacharya et al, 2021b; Scher et al, 2019).

2.4 The main existing treatment options

The current literature elucidates substantial variability in persistence, discontinuation, adherence, reinitiating, and switching patterns among the different biologic and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) treatment options for PsA patients (Murage et al, 2022).

Different international and national recommendations are developed for the management of patients with PsA, such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and the European League Against Rheumatism (EULAR) recommendations. According to EULAR recommendations, management of PsA comprises of TNF inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), tsDMARDs, and biological DMARDs (bDMARDs) including originator or biosimilar TNF inhibitors, anti-IL-12/23, and anti-IL-17 agents (Ogdie et al, 2020).

For stiffness and pain, NSAIDs are the first-line recommended treatment (van der Heijde et al, 2017). Local glucocorticoid injections can be considered as adjunctive therapy in PsA; however, its use is limited for shorter duration due to risk of flare on withdrawal. Physiotherapy and MTX are part of initial treatment approaches in patients with PsA; however, treatment can be limited due to adverse event of hepatotoxicity (Mease et al, 2019). Patients can be switched to sulfasalazine, leflunomide, and cyclosporine, if MTX is contraindicated or has already failed (Gossec et al, 2020; Gottlieb and Merola, 2021). In patients who show structural damage, high erythrocyte sedimentation rate/C-reactive protein, dactylitis or nail involvement, treatment with csDMARD is recommended (Gossec et al, 2020). Patients who showed an inadequate response to at least 1 csDMARD are initiated on a bDMARD TNF inhibitor (Gossec et al, 2020). If insufficient response to TNF inhibitors, then bDMARDs targeting IL-12/23 or IL-17 axis may be considered. In patients with peripheral arthritis and an inadequate response to at least 1 csDMARD and at least 1 bDMARD, or when a bDMARD is considered not appropriate (non-adherence to injections or a strong patient preference for an oral drug), a janus kinase inhibitor (JAKi, such as tofacitinib) may be considered. In patients with mild disease, and an inadequate response to at least 1 csDMARD, in whom neither bDMARD nor a JAKi is appropriate, PDE4i (such as apremilast) may be considered (Gossec et al, 2020). Patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or glucocorticoids are treated with bDMARDs (Kaeley et al, 2018). Key safety events associated with the use of these biologic treatments included an increased risk of developing serious infections and malignancies; however, the associated risks vary across the different classes of biologic treatments.

2.5 Natural history of PsA, including mortality and morbidity

Approximately 23-30% of patients with PSO develop PsA and around 67% of PsA patients have a history of PSO. While studies have shown that the prevalence of PsA is increased among patients with severe PSO, it varies between 6 and 39%.

Classified as a potentially erosive disease, approximately 50% of patients exhibit structural damage and functional impairment due to involvement of joints, entheses, or spine. About 25%-70% of patients with PsA showed axial involvement, while 5% showed exclusive axial involvement. Patients with PsA show heterogeneous characteristics including enthesitis, dactylitis (sausage digit), nail changes, and peripheral arthritis, alone or in combination with one another. Common symptoms of axial PsA include morning back/neck stiffness, neck or back pain which improved with activity, while worsening due to inactivity or limited mobility. Psoriatic arthritis is diagnosed by physical examination and imaging (eg, sacroiliitis, spinal ossifications). Sacroiliitis a common feature of axial PsA (25%-50% of patients) and worsens with time; 37% and 52% of patients develop grade 2 or higher sacroiliitis within 5 and 10 years, respectively. In sacroiliitis, patients presented with alternating pain over the sacroiliac joint/buttock, with the pain typically lasting longer than 20 minutes and being worse during the second half of the night (Gottlieb and Merola, 2021; Koolae 2013).

Patients with axial PsA and uveitis were more likely to be HLA-B27 positive (Brown et al, 2020). A study reported that severe skin PSO ($p=0.041$) and younger age at PsA onset ($p<0.001$) were associated with developing sacroiliitis (Haroon et al, 2017). Psoriatic arthritis is frequently associated with metabolic disorders including obesity, metabolic syndrome, and diabetes mellitus (Dal Bello et al, 2020), alongside other comorbidities such as uveitis (6%-7%) and inflammatory bowel disease (11%) (Halling et al, 2017; Jadon et al, 2017). Patients with axial PsA had significantly impaired physical function and quality of life ($p<0.001$) due to worse pain, resulting in decreased work productivity and significantly higher proportions of missed work time (10.0% vs 3.3%), overall work impairment (32.3% vs 16.8%) and overall activity impairment (37.0% vs 18.1%; $p<0.001$ for all) (Gottlieb and Merola, 2021).

Recent studies suggest that there is no increased risk of mortality among patients with PsA (Ogdie et al, 2017; Ogdie et al, 2015; Arumugam and McHugh, 2012; Buckley et al, 2010). Ogdie et al, (2017) assessed the cause of death-specific hazard ratios among thousands of PsA patients and found no significant increased risk of death due to cardiovascular disease, respiratory disease, malignancy, or infection compared with that in age- and sex-adjusted controls.

2.6 Important comorbidities

Table 2-1: Summary of epidemiology of important comorbidities in the PsA population

Comorbidity	Incidence/prevalence/association
Cardiovascular comorbidity	A registry analysed cases with a diagnosis of RA, SpA or PsA and controls (matched for age, gender, general practitioner practice and diagnosis date) and showed that the while RA patients had a higher 3-year incidence of CVD than controls ($p<0.035$), the PsA cohort had a non-statistically significant doubling of the 3-year incidence of cardiovascular disease burden compared with controls. In

Table 2-1: Summary of epidemiology of important comorbidities in the PsA population

	the PsA cohort, the average incidence (per 1000 PY) of CVD was 0.11, while the 3- year incidence of CVD (per 1000 PY) was 20.29 vs controls (10.98) (Stouten V et al, 2021). A cross-sectional study including patients with PsO, PsA and without PSO or PsA revealed that the incidence rate (per 1000 PY) of CVD events and all-cause mortality (composite endpoint) was 16.22 (95% CI; 10.46-25.14) in patients with PsA compared to 13.29 (95% CI; 12.74-13.86) in the non-PSO/PsA patients. After adjusting for sex, age, smoking, BMI, family history of coronary artery disease, dyslipidemia, hypertension, diabetes and comorbidity score, the adjusted HR for CVD events and all-cause mortality was 1.25 (95% CI: 0.80-1.94, p=0.33) for patients with PsA (Tinggaard et al, 2021). A meta-analysis of 11 observational studies, comprising of 32,973 patients with PsA, reported a 43% increased risk of cardiovascular diseases when compared with the general population (pooled OR 1.43; 95% CI: 1.24-1.66). The study also reported an increased risk of incident cardiovascular events by 55% (pooled OR 1.22-1.96) and morbidity risks for myocardial infarction, cerebrovascular diseases, and heart failure were increased by 68%, 22%, and 31%, respectively (pooled OR 1.68 [95% CI: 1.31-2.15], pooled OR 1.22 [95% CI: 1.05-1.41], and pooled OR 1.31 [95% CI: 1.11-1.55], respectively) (Polachek et al, 2017).
Metabolic syndrome	In a cross-sectional study of 319 patients (AS=153; PsA=166), metabolic syndrome was present in 43% of PsA and 19% of AS ($p < 0.001$). A BMI > 23 (OR: 3.7), female gender (OR range: 3.8-3.9), and the number of syndesmophytes or ankylosis (OR: 1.1) were associated with metabolic syndrome among PsA patients. High proportions of all metabolic syndrome components, including increased waist circumference ($p = 0.001$), elevated blood pressure ($p < 0.001$), elevated fasting glucose ($p < 0.001$), elevated triglycerides ($p = 0.01$), and decreased HDL cholesterol ($p = 0.016$) are associated with PsA when compared to AS (Petcharat et al, 2021). A systematic literature review including 18 articles with PsA patients estimated that 23.5% to 62.9% of PsA patients have metabolic syndrome (Urruticoechea-Arana A et al, 2022).
Hyperlipidemia	Studies have shown that dyslipidemia is significantly more prevalent in PsA compared with PSO, and PsA patients have worse atherogenic lipid profiles than patients with PSO (Gupta et al 2021). A single-center study showed that dyslipidemia was more common in PsA than in PSO (28% versus 13.5%, OR 2.5, 95% CI: 1.7-3.3) (Queiro et al, 2019). Another study from a tertiary care center found higher odds of hyperlipidemia in patients with PsA compared with PSO (OR 15.94, 95% CI 1.64–154.80) (Su, 2020). A study from the MarketScan claims database showed a higher incidence of hyperlipidemia in PsA compared with controls (Incidence rate ratio 1.10, 95% CI 1.04–1.17) (Karmacharya et al, 2021c, Radner et al, 2017).
Diabetes	The overall prevalence of DM in patients with PsA ranges from 6.1 to 20.2%; the prevalence rate of DM in PsA cohorts are reported as 11.3-20.2%, 18.6%, 15.3%, 9.2–13.8%, 6.1% in North America, Hong Kong, Israel, Spain, and UK, respectively. The risk was higher in PsA compared with subjects without PsA (OR, 1.48 in Israel and 9.27 in Hong Kong). Prevalence of DM was higher in females in PsA 18.7% (10.3% in the control group) with OR 1.60 (95% CI: 1.02–2.52), while males had the same prevalence (11.2%) in both PsA and control groups (OR 0.71,

Table 2-1: Summary of epidemiology of important comorbidities in the PsA population

	95% CI 0.42-1.22) (Dal Bello et al, 2020). A cohort study comprising of 408 patients reported that the prevalence of T2D was 7.8% in PsA, compared to 4.4% in controls. The multivariate logistic regression model including age, disease duration, and BMI as covariates revealed that increasing age (OR, 1.079; p = 0.006) and BMI (OR, 1.188; p = 0.011) but not PsA duration were predictors for T2D (Ciaffi J et al, 2022).
Inflammatory bowel disease	In a meta-analysis of 2 cohort studies matched for age and sex, the relative risk of CD was 2.74 (95% CI: 1.41-5.32; $I^2 = 0\%$) and the relative risk of UC was 1.74 (95% CI: 0.72-4.17; $I^2 = 34\%$) in patients with PsA (Fu et al., 2018). A case-control study reported the OR of CD as 2.20 (95% CI: 1.59-3.03) and UC as 1.91 (95% CI: 1.21-3.00) in 3,161 age- and sex-matched patients with PsA (Fu et al, 2018). The pooled prevalence for IBD in a meta-analysis was 3.3% (95% CI: 1.5-7.1, $I^2 = 97\%$), UC was 0.9% (95% CI: 0.6-1.5, $I^2=91\%$) and CD was 1.1% (95% CI: 0.6-1.9, $I^2=95\%$), with high inter-study heterogeneity independent of age, sex, year of publication, geography, or bias score (Pittam et al, 2020). Charlton et al studied cases of PsA matched (for age, sex and general practice) to patients with PSO without PsA and the general population. The incidence rate (per 10,000 PY) of all IBD among patients with PsA was 7.68 (5.18 to 10.96) compared to 4.58 (3.55 to 5.81) in the general population and 4.63 (3.59 to 5.88) in the PSO cohort. The incidence of CD in patients with PsA was 4.09 (95% CI: 2.34 to 6.65) compared to 1.71 in the general population (95% CI: 1.11 to 2.52) and 1.52 (0.95 to 2.30) in the PSO cohort (Charlton et al, 2018).
Depression	The incidence rate ratio of depression in patients with PsA was 1.22 (95% CI: 1.16-1.29) in a retrospective cohort study (Wu et al, 2017). Result of a meta-analysis reported a higher risk of developing depression than controls with ≥80% higher odds for depression, but with high inter-study heterogeneity (I^2 99%) for age, disease severity, duration of study and other characteristics (Zhao et al, 2020a). A real-world study including 208 patients with PsA showed that depression was prevalent in 62 (29.8%) and was closely correlated with disease activity and physical function impairment (Lai et al, 2022).
Suicidality	Data from a retrospective cohort of PsA patients (PSO patients with concomitant PsA; n= 13,959) reported 10 suicidal behavior events with an incidence of 9.95 per 100,000 PY (95% CI: 4.77-18.29; p=0.20) (Wang et al, 2020). Another retrospective cohort study showed that the HR for death by suicide in PsA was 3.03 (95% CI: 1.56-5.90) (Ogdie et al, 2017). The adjusted incidence rate ratios in a population-based cohort study in PsA for suicidal ideation were 0.70 (95% CI: 0.29-1.72); for suicide attempt: 1.28 (95% CI: 0.93-1.77), (Wu et al, 2017). Specific rates vary by data source and definition. More severe PsA and younger age were reported to be associated with a greater likelihood of suicide.
Liver disease	Nonalcoholic fatty liver disease encompasses a spectrum of liver conditions from simple steatosis to steatohepatitis (non-alcoholic steatohepatitis), with the risk to evolve to cirrhosis and hepatocellular carcinoma. In PsA, Zhao et al, reported a pooled prevalence of liver disease of 2.9% (95% CI: 0.7-6.4), with high inter-study heterogeneity (I^2 99%) (Zhao et al, 2020b). The incidence of liver abnormalities (per 10,000 PY) in patients with PsA was reported

Table 2-1: Summary of epidemiology of important comorbidities in the PsA population

	as 18.41 with systemic therapies, while the incidence of mild and moderate liver diseases (per 1000 PY) were demonstrated as 2.39 (95% CI: 1.95-2.91) and 0.51 (95% CI: 0.32-0.77), respectively (Gelfand et al, 2021; Ogdie et al, 2018). Heterogeneity can be attributed to differences in diagnosis, age, case source, inclusion/ exclusion of hepatotoxic agents etc (Awosika et al, 2018). Additionally, pre-existing insulin resistance, which favors the accumulation of lipids in the liver leading to nonalcoholic fatty liver disease, has not been accounted for in most studies.
Malignancy	An incidence rate of 2.45 per 100 PY was reported for any type of cancer in patients with PsA (Kaine et al, 2019) and the prevalence of cancer in patients with PsA ranges from 0.19% to 6.32% (Fernández-Carballido et al, 2020; Vaengebjerg et al, 2020; Shah et al, 2017). The prevalence of metastatic cancer ranges from 0.1% to 1.4% in patients with PsA (Fernández-Carballido et al, 2020; Redeker et al, 2020). A meta-analysis of observational cohort studies reported that the prevalence of overall cancer in the PsA group was 5.74% (95% CI: 3.64-8.28) with an incidence of 6.44 per 1000 PY (95% CI: 4.80-8.32). Of the included studies, none found a significant association between PsA and cancer overall (RR 1.02, 95% CI: 0.97-1.08) (Vaengebjerg et al, 2020).

AS=ankylosing spondylitis; BMI=body mass index; CD=Crohn's disease; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; DM=diabetes mellitus; HR=hazard ratio; IBD=inflammatory bowel disease; OR=odds ratio; PsA=psoriatic arthritis; PSO=psoriasis; PY=persons-years; RA=rheumatoid arthritis; RR=relative risk; SpA=spondyloarthritis; T2D=type 2 diabetes mellitus; UC=ulcerative colitis

3 AXIAL SPONDYLOARTHRITIS

3.1 Incidence

Axial spondyloarthritis is an umbrella term that includes both ankylosing spondylitis (AS), also called radiographic axSpA (r-axSpA, diagnosed with definite radiographic damage of the sacroiliac joints), and non-radiographic axSpA (nr-axSpA, where there is no definitive radiographic damage on the sacroiliac joints) (Sieper and Poddubnyy, 2021; Wallman et al, 2015). Incidence data for nr-axSpA are scarce as this condition was poorly defined prior to development of Assessment of SpondyloArthritis international Society criteria in 2009 (Bohn et al, 2018; Sieper and Poddubnyy, 2017). The incidence of AS/r-axSpA varies considerably; estimates for the incidence range from 0.44 in Iceland to 7.3 cases per 100,000 person years in the US and northern Norway and 15 per 100,000 person years in Ontario, Canada (Bohn et al, 2018). A systematic review of 24 publications estimated an overall incidence rate of AS as 4.8 per 100,000 PYs (Alamanos et al, 2021).

3.2 Prevalence

The estimated prevalence of AS/r-axSpA ranges from 0.05% to 1.5% (Bohn et al, 2018; Sieper and Poddubnyy 2017; Curtis et al, 2016). Data are limited on the prevalence of nr-axSpA. A multinational study found that among patients with inflammatory back pain, 29% met criteria for nr-axSpA, with variation in the prevalence by geographic region (36% in Asia and 16% in Africa) (Burgos-Varga et al, 2016). It is estimated that the proportion of patients that present with nr-axSpA is similar to that of patients diagnosed with AS/r-axSpA; thus, the total

population of patients with axSpA is at least double the proportion reported for AS/r-axSpA (Baraliakos and Braun, 2015). Recent studies have reported the prevalence of AS ranging from 9 to 30 per 10000 in the general population (Wang and Ward, 2018). Citera et al, reported that the regional pooled prevalence of spondyloarthritis (SpA; including AS, PsA and undifferentiated SpA) worldwide was in the range 0.20% (95% CI: 0.00-0.66) in South-East Asia to 1.61% (95% CI: 1.27-2.00) in the Northern Arctic communities. The estimated SpA prevalence in South/Latin America, was estimated at 0.52% (95% CI: 0.10-1.25), and was similar to that of Europe (0.54%; 95% CI: 0.36-0.78) (Citera et al, 2021). The wide geographical difference in the prevalence of SpA was reported to be due to difference in prevalence of human leukocyte antigen-B27 antigen (López-Medina and Moltó, 2018).

3.3 Demographics of axSpA population – age, gender, racial, and/or ethnic origin and risk factors for the disease

Axial spondyloarthritis is a disease that usually starts in the third decade of life, with about 80% of patients developing the first symptoms before the age of 30 and less than 5% of patients being older than 45 at the start of the disease (Sieper and Braun 2014). While nr-axSpA appears to be equally present in women and men, studies have highlighted a male predominance in r axSpA. However, evidence show that women and men may experience axSpA differently (Chimenti et al, 2021; Wright et al, 2020).

High background prevalence of Human leukocyte antigen (HLA)-B27, in some regions such as Northern Europe and among the native peoples of the circumpolar arctic and subarctic regions of Eurasia and North America, is reported to be associated with higher rates of axSpA. In contrast, the near absence of axSpA in southern Africa and the low rates in Japan is linked to low HLA B27 prevalence (Sieper and Poddubnyy 2017; Navarro-Compán, 2021).Other factors such as fatigue can contribute to morbidity in AS, as it impacts quality of life at young age in patients with SpA. Human leukocyte antigen-B27 presence is associated with a higher prevalence of uveitis and cardiac involvement, thus is one of the strongest risk factors for AS.

3.4 The main existing treatment options

The treatment options in axSpA are tailored according to the patient need and disease severity. Under non-pharmacological interventions exercise, increased patient awareness and smoking cessation are the key therapeutic modalities (Dougados, 2020; Kiltz et al, 2020). The recommendations from the Assessment of spondyloarthritis international Society and the European Alliance of Associations for Rheumatology, (ASAS-EULAR) stated that patients should be educated about axSpA and benefits of physical exercise on a regular basis and stop smoking; physical therapy should be encouraged (Dougados, 2020; Molto et al, 2021).

The cornerstone of pharmacological intervention in axSpA are non-steroidal anti-inflammatory drugs (NSAIDs). The ASAS-EULAR recommend use of NSAIDs at the maximum dose. In an observational study of 627 patients with axSpA, 92.8% had received NSAIDs; which significantly decreased over time, to 73% patients after 3 years ($p<0.001$) (Molto et al, 2017). There is no evidence for the usefulness of DMARDs, including sulfasalazine and methotrexate, to treat axial disease; however, sulfasalazine may be considered in patients with peripheral disease (Sieper, 2014). Intra-articular corticosteroids may be used for sacroiliac or peripheral joint inflammation whereas systemic corticosteroids in general are of little benefit. Patients with active AS who are intolerant of or have inadequately responded to NSAIDs or those in whom

NSAIDs are contraindicated, have approved treatment options such as tumor necrosis factor-α inhibitors (van der Heijde, 2017; Ward et al, 2016). Tumor necrosis factor-α inhibitors were found to be effective at both early and later stage of disease in patients with or without structural damage at the sacroiliac joint level. Additionally, IL 17A inhibitors (secukinumab, ixekizumab) were also found to be effective in axSpA with an added advantage of being effective in case of concomitant skin PSO as well (Dougados, 2020). Janus kinase inhibitors (tofacitinib and upadacitinib) have been recently approved for treatment of patients with active AS (Navarro Compán et al, 2021).

3.5 Natural history of axSpA

Spondyloarthritis is currently classified as predominantly axial, affecting the spine, pelvis, and thoracic cage or predominantly peripheral (Robinson et al, 2021). In the axial subgroup, a distinction is made between patients with definitive radiographic structural damage on the sacroiliac joint and those without radiographic evidence, AS/r-axSpA, and nr-axSpA, respectively (Sieper and Poddubnyy, 2017; Wallman et al, 2015). Approximately 10% patients with nr-axSpA progress to AS/r-axSpA within 2 years and 26-59% progress to AS/r-axSpA within 10 years of symptoms (Burgos-Varga et al, 2016; Robinson 2021). These conditions share common pathophysiology and symptomatology.

The hallmark feature of axSpA is low back pain and stiffness (Sieper and Poddubnyy, 2017; Taurog et al, 2016; Wallman et al, 2015). Clinically recognized structural damage can take years of pain and inflammation to develop, resulting in delayed and/or missed diagnoses (Sieper and Poddubnyy, 2017; Wallman et al, 2015). Prolonged inflammation causes progression from no spinal abnormalities to skeletal changes that limit range of motion and cause disability (Taurog et al, 2016). Inflammatory lesions are visible through magnetic resonance imaging before structural damage can be observed with radiographs (van Tubergen, 2015; Wallman et al, 2015).

Arthritis and enthesitis are amongst the most common peripheral manifestations, occurring in up to 50% of patients with axSpA (Robinson 2021; Sieper and Poddubnyy, 2017). These manifestations are predominantly found in the lower limbs, frequently in an asymmetrical fashion. Peripheral enthesitis usually manifests with pain, stiffness and/or tenderness. In axSpA, axial inflammation (synovitis and enthesitis) leads to irreversible structural damage and both can limit the mobility of the spine (Navarro-Compán, 2021). Extra-articular manifestations (EAMs) are common and important systemic features of axSpA, the most common being acute anterior uveitis, inflammatory bowel disease (IBD) and PSO. The prevalence of EAMs is broadly similar in r-axSpA and nr-axSpA, except for acute anterior uveitis prevalence that is higher in r-axSpA than nr-axSpA. EAMs contribute to the disease burden and add a layer of complexity to the management of axSpA (de Winter et al, 2016; Derakshan et al 2020).

Literature on mortality among patients with axSpA is limited to the patients with AS/r-axSpA . Additionally, studies show an increase in the mortality rate between AS/r-axSpA patients and the general population (Exarchou et al, 2015; Bakland et al, 2011). Studies by Bakland et al, (2011) and Exarchou et al, (2015) reported cardiovascular disease as the most frequent cause of death. Exarchou et al, (2015) noted that spinal trauma was more commonly reported as an intermediate cause of death among AS patients than with controls. Wysham et al, (2017) analyzed in-hospital mortality among patients with AS/r-axSpA using data from the US Nationwide Inpatient Sample; the primary diagnosis most frequently observed was sepsis and c-spine fracture. Adjusted odds ratios (aORs) were reported; c-spine facture with spinal cord injury and sepsis had the highest

relative risk of in-hospital death with aORs of 13.43 (95% CI 8.0 to 22.6) and 7.63 (95% CI 5.6 to 10.4), respectively (Wysham et al, 2017).

3.6 Important comorbidities

Table 3-1: Summary of epidemiology of important comorbidities in the axSpA population

Comorbidity	Incidence/prevalence/association
Cardiovascular disease	A recent meta-analysis of 16 studies by Kim and Choi reported a significantly higher risk of myocardial infarction in AS (RR: 1.49; 95% CI: 1.34-1.66) than in the general population (Kim and Choi, 2021). Similar results were reported from the data of a Swedish cohort followed from 2006-2012 where the standardized incidence ratios for acute coronary syndrome and stroke were higher in patients compared to the general population (4.3 and 5.4/1,000 PYs compared to 3.2 and 4.7, respectively) (Bengtsson et al, 2017).
Metabolic syndrome	Results from the ASAS-COMOSPA study estimated the prevalence of diabetes as 8.8% in patients with axSpA, alongside a high frequency of metabolic syndrome according to the NCEP-ATP III (frequency: 45.8 vs. 10.9% in the controls) (Toussirot 2021). In a cross-sectional study of 319 patients, metabolic syndrome was present in 19% of AS ($p < 0.001$). Regression analysis identified that body mass index > 23 (OR: 9.1) and age > 40 (OR: 4.3) were risk factors associated with metabolic syndrome (Petcharat et al, 2021).
Inflammatory bowel disease	In a multivariable analysis of 4 parallel case-control studies, the OR for AS and IBD was 5.46 (95% CI: 4.12-7.23) (Meer et al, 2022). Another study reported that IBD was more frequent among patients with axSpA than controls (30% versus 16%; OR: 2.5 [95% CI: 1.1 to 5.7]; p=0.036) after adjusting for age and sex (Wallman et al, 2020).
Liver disease	A meta-analysis of 119427 patients with axSpA reported a prevalence of 2.9% (95% CI, 0.7-6.4) for liver disease, with high inter-study heterogeneity (I^2 99%) for age, disease severity, duration of the study and other characteristics (Zhao et al, 2020).
Hyperlipidemia	A meta-analysis of 36 studies reported that the pooled prevalence of hyperlipidaemia was 16.8% (95% CI 10.1, 24.7, I2 100%) (Zhao et al, 2020).
Malignancy	A meta-analysis comprising of 119427 patients with axSpA reported that the pooled OR of cancer in patients with axSpA was 1.22 (95% CI 1.01 to 1.47) compared to the control group (Zhao et al, 2020).

AS=ankylosing spondylitis; ASAS-COMOSPA=Assessment of Spondyloarthritis international Society-COMOrbidities in SPondyloArthritis; ASCVD=atherosclerotic cardiovascular disease; axSpA=axial spondyloarthritis; CI=confidence interval; IBD=inflammatory bowel disease; N=number; NCEP ATP III= US National Cholesterol Education Programme Adult Treatment Panel III; OR=odds ratio; PY=persons-years; RR=relative risk

4 HIDRADENITIS SUPPURATIVA

4.1 Incidence

The incidence of HS in Europe is not well reported. Annual estimates are available for Germany and the UK with 10 per 100,000 PYs in Germany as of 2017 and 28 per 100,000 PYs in the UK from 1996-2013 (Pinter et al, 2020; Ingram et al, 2018). The UK study used Clinical Practice Research Datalink data and reported that the unadjusted incidence of HS appeared to be stable over time (30 per 100,000 PYs in 1996 and 30 per 100,000 PYs in 2013).

4.2 Prevalence

The prevalence of HS varies across European studies depending upon patient population and varying case ascertainment methods (Jfri et al, 2021) and is estimated between 0.10-0.54% for diagnosed HS. Some studies have shown higher prevalence estimates of up to 1.0% (Prens et al, 2022; Revuz et al, 2008; Jemec et al, 1996). However, these estimates have limited reliability as they were based on self-reported diagnosis of HS, not confirmed by a physician. Table 4–1 shows a range of prevalence estimates from recent European literature.

Table 4–1: HS prevalence estimates in Europe from observational literature

Country	Date of Estimate	Estimate	Author date
Germany	2010	0.03%	Kirsten et al, 2020
Italy	2010	0.05%	Fania et al, 2017
Italy	2009-2013	0.06%	Bettoli et al, 2016
Germany	2012-2017	0.07%	Pinter et al, 2020
Portugal	2000-2014	0.08%	Santos et al, 2017
Germany	2010-2012	0.09%	Schneider-Burrus et al, 2021
Sweden	2001-2014	0.14%	Killasli et al, 2020
France	2005	0.15%	Richard et al, 2018
Germany	2014-2017	0.30%	Kirsten et al, 2021
UK	2013	0.54%	Ingram et al, 2018

HS affects approximately 0.1% of the US adult population (Shahi et al, 2014; Garg et al, 2017), and its onset typically occurs between puberty and age 30 (Garg et al, 2017). One published literature in Japanese on the prevalence of HS in Japan was retrieved. The analysis was performed using JMDC claims database and the estimated prevalence was 0.0039% for diagnosed HS in 2015-2016 (Terui et al, 2019). Existing literature for South Korea shows an estimated prevalence of 0.06% in 2013 and the incidence is unknown (Lee et al, 2018). A systematic review of the global epidemiology of HS conducted in 2018 reported that prevalence estimates in Asia-Pacific countries are generally lower than those seen in Europe (Phan et al, 2020).

4.2.1 Demographics of the population in the proposed indication – age, gender, ethnic origin and risk factors for the disease

Symptom onset in HS typically occurs between puberty and age 30. A US study identified the highest age-specific incidence of HS to be among patients aged 18 to 29 years when looking at the one-year incidence from October 2015 to October 2016 (Garg et al, 2017). Average age at symptom onset ranged from 18 to 26 years of age across European studies (Bettoli et al, 2019; Canoui-Poitrine et al, 2009; Chiricozzi et al, 2018; Molina-Leyva et al, 2020). In an international HS study across 24 countries, average age at onset was 24.7 years (Saunte et al, 2015). Women have also been shown to have a younger age at disease onset than men (Saunte et al, 2015; Omine et al, 2020; Bettoli et al, 2016); for example, in a Japanese study, median age at symptom onset for women was 20 years of age while it was 36 years for men (Omine et al, 2020). Risk factors for adolescent-onset of HS (between 10 and 21 years of age) include female sex and family history of HS (Molina-Leyva et al, 2019).

Average age at diagnosis of HS ranged from 28 to 32 years of age, which resulted in a mean delay in diagnosis between 5 to 11 years. In an international HS study across 24 countries, the average diagnostic delay was 7.2 years (Saunte et al, 2015). Diagnostic delay among patients with HS is the result of both a patient's delay in first seeking care after symptom onset as well as subsequent provider and/or system-related delays that may cause a lag between first visit and receipt of a diagnosis. This can be seen in data from the same international study, which demonstrated that the diagnostic delay was partly explained by the fact that patients spent, on average, 2.3 years with symptoms before first physician contact and then saw an average of 3.9 physicians before receiving a diagnosis. The majority of patients (73%) reported a diagnostic delay of more than two years in length from the first onset of symptoms. Women and patients with moderate or severe disease were more likely to experience a delay greater than two years (Saunte et al, 2015).

Women are also more likely to develop HS than men (Garg et al, 2017), which is seen in the international study (59% female) and in the first national Italian registry (60% female) (Bettoli et al, 2016; Saunte et al, 2015). Women comprise an even higher proportion of patients with HS in studies published from the US (range: 71-81%). This female predominance is also observed among pediatric patients with HS (Garg et al, 2018c). In contrast to the female predominance of HS in the United States and Europe, there is a consistent male predominance among patients with HS in East Asia (72.4% male) (Omine et al, 2020).

White patients account for the majority of patients represented in the literature. However, the prevalence of HS is disproportionally high among African Americans in the US in both adult and pediatric patient populations (Garg et al, 2018; Garg et al, 2017; Vaidya et al, 2017). African-American patients with HS have also been shown to experience more severe disease compared to non-African American patients with HS (Soliman et al, 2019).

Genetic susceptibility is one of the most commonly recognized risk factors in HS. In a study of patients with HS across 24 countries worldwide, 24% of patients with HS had a family history of this condition (Saunte et al, 2015). Family history of HS is less common in Japan (~2-4%) than in the United States and Europe (Omine et al 2020; Hayama et al, 2020). Patients with early-onset HS (before 13 years of age) are also more likely to report a family history of HS (56%) when compared to patients with HS without early onset disease (i.e., onset at or after 13 years of age; 34%), according to findings from the Netherlands (Deckers et al, 2015).

Hormones and smoking (nicotine) are also risk factors for HS, which may be due to their effects on the follicular epithelium (von Laffert et al, 2011). The association between HS and smoking status is well established in the literature and the majority of patients with HS are smokers (Bettoli et al, 2016; Revuz et al, 2008). The role of hormones in HS is supported by the typical onset of the disease after puberty and the improvement of symptoms observed with antiandrogen treatment (Kraft et al, 2007). HS disproportionally impacts women of childbearing age, yet the relationship between HS symptoms over a woman's life course and during times of hormonal transition is inconsistent. The majority of patients with HS represented in the literature are classified as either overweight or obese with a range of mean body mass index (BMI) from 26 (Canoui-Poitrine et al, 2009) to 34 kg/m2 (Reddy et al, 2019). As with smoking, it is not clear whether excess weight is a causal risk factor for HS or a consequence of disease.

4.2.2 The main existing treatment options

Pharmacological, procedural, and surgical interventions are heavily dependent on the severity of HS, which is primarily assessed by the extent of skin involvement and the presence of secondary lesions. Clinical grading of HS severity using Hurley staging (Hurley, 1989) is universally recommended across international treatment guidelines for HS, which have been proposed by a variety of international working groups and organizations throughout North America and Europe (Ingram et al, 2019; Alikhan et al, 2019a, 2019b; Zouboulis et al, 2019)

While the international treatment guidelines are consistent in terms of the referenced studies and case reports supporting efficacy for HS-related treatment modalities, inconsistencies are apparent between recommendations (Hendricks et al, 2019). There is widespread agreement on first-line agents, which generally include topical and systemic antibiotics for mild-to-moderate disease (Hurley stages I and II) and biologics for more severe forms of HS (Hurley stages II and III). However, second and third-line therapeutic recommendations vary significantly across guidelines, which may be due to the fact that large-scale robust clinical trials determining efficacy in HS are lacking for these agents. Pharmacological interventions with consistent recommendations across guidelines for HS include topical clindamycin, tetracyclines, combination clindamycin and rifampin therapy, and adalimumab; the majority of these have been evaluated for efficacy among patients with HS through randomized clinical trials. Other recommended treatments include intralesional corticosteroids to treat acute HS flares, retinoids as a second- or third-line therapy, as well as hormonal therapies (finasteride, spironolactone, metformin) which may serve as effective monotherapies and adjunctive treatment for HS in women with comorbidities, such as hyperandrogenism, diabetes, or polycystic ovary syndrome. International treatment guidelines endorse biologics for the treatment of Hurley stage II and III disease unresponsive to systemic antibiotic therapies. Notably, adalimumab (TNF-α inhibitor) is the only first-line biologic therapy for HS recommended across all guidelines, with infliximab (TNF-α inhibitor) endorsed as a second-line option in many of the guidelines.

International procedural and surgical recommendations for HS are inconsistent across guidelines, with the exception of surgical excision, which has been regarded as an effective intervention in HS (Hendricks et al, 2019). As a general rule of thumb, European-based guidelines place less emphasis on the use of procedural and surgical interventions in HS compared with North American guidelines. Intense pulsed light therapy and photodynamic therapy have been suggested as a potential therapy in HS for patients with Hurley stage II and III with variable results (Hendricks et al, 2019). Laser therapy is also recommended for use in Hurley stage II and

III disease (Hendricks et al, 2019). Incision and drainage is recommended as a surgical modality for relieving pain linked to acute, isolated HS lesions (Danby et al, 2015). However, since lesions are likely to reoccur, it should not be considered as a long-term treatment. Deroofing is recommended as a surgical approach for recurrent nodules and sinus tracts in localized lesions of mild disease or in Hurley stage II and III disease (Hendricks et al, 2019). Excision, and particularly wide excision, is recommended for the management of chronic and widespread Hurley stage III (Danby et al, 2015).

4.3 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Hidradenitis suppurativa is a chronic, inflammatory, and recurrent skin condition characterized by painful, deep-seated, and inflamed lesions typically located in the intertriginous areas of the body (e.g., axillae, inguinal, and anogenital regions) (Zouboulis et al, 2015). Distribution across disease severity varies based on the patient population/data source with patient samples drawn from specialty care centers skewed towards more severe disease. Most patients have mild or moderate disease with the majority typically having moderate disease, though severe disease has been reported in 4 to 28 percent of patients (Canoui-Poitrine et al, 2019; Molina-Leyva et al, 2020). Risk factors for more severe disease include higher BMI/obesity (Bettoli et al, 2016; Omine et al, 2020), diabetes (Hayama et al, 2020; Bettoli et al, 2016), and duration of disease (Bettoli et al, 2016; Omine et al, 2020). Disease activity usually manifests itself as flares or painful boils, however the frequency of flares and factors related to flares are not well understood due to the heterogeneous nature of HS. Common aggravating factors include sweating due to heat or exercise, stress or fatigue, and tight clothing or other sources of friction, or menstruation for female patients (von der Werth et al, 2000).

The visible manifestations of disease among patients with HS impact interpersonal relationships, self-esteem, and perception of self-image and public image, resulting in depression and embarrassment. HS can progress to become a debilitating skin disease with disfiguring scarring; as a result, it has the highest negative impact on patients' quality of life among all assessed dermatological conditions (Zouboulis 2015).

Hidradenitis suppurativa is associated with significant comorbidity burden regardless of age, sex, racial, and disease severity group (Reddy et al, 2019; Kimball et al, 2018). Based on the current body of evidence, the US and Canadian Hidradenitis Suppurativa Foundations recommend providers screen for a variety of metabolic (metabolic syndrome, diabetes), psychiatric (depression, anxiety), and inflammatory/immune-related conditions (inflammatory bowel disease, autoinflammatory syndrome, inflammatory arthropathy) as well as polycystic ovary syndrome and tobacco abuse (Garg et al, 2022).

The risk mortality among patients with HS is uncertain. One US study has reported that patients with HS are at higher odds of all-cause death than patients without HS. Predictors of mortality among patients with HS included older age, male sex, ever smoking status, and Charlson Comorbidity Index score (Reddy et al, 2019). Another study from Denmark reported a higher risk of all-cause mortality among HS patients compared to matched controls (adjusted incidence rate ratio 1.35 (95% CI 1.15-1.59)) (Egeberg et al, 2016).

4.4 Important co-morbidities

The epidemiology of selected important comorbidities in the HS population (Garg et al, 2022) is summarized in Table 4–2.

Table 4–2: Summary of epidemiology of important comorbidities in the HS population

Comorbidity	Incidence/prevalence/association
Acne vulgaris/conglobata	Higher prevalence of acne vulgaris/conglobata among patients with HS compared to control individuals was observed across 4 studies, with the prevalences ranging from 4.5% to 15.2% The odds of having acne vulgaris/conglobata were 1.77 to 5.07 times greater in patients with HS than control individuals (Wertenteil et al, 2019; Ingram et al 2018; Lee et al. 2018; Kimball et al, 2018).
Anxiety disorder	In a meta-analysis, the prevalence of generalized anxiety disorder among patients with HS was approximately 5% (Machado et al, 2019) Larger retrospective clinical and administrative database studies have also described higher prevalences and likelihoods of anxiety among patients with HS compared to control individuals (Kimball et al, 2018; Huilaja et al, 2018)
Cardiovascular disease	**Myocardial infarction (MI)** The prevalence of a history of MI in patients diagnosed with HS ranged from 0.9% in the USA to 2.3% in Germany and Denmark. The incidence of MI in patients diagnosed with HS was measured in three large studies and ranged from 1.52/kpy in Denmark (Andersen et al, 2020) to 2.9/kpy in Israel (Kridin et al, 2022) and the USA (Reddy et al, 2020). The US study also reported an incidence rate of 4.0/kpy in HS patients who were on a biologic medication. An unadjusted relative risk of 1.37 (95% CI) (1.35-1.39) for an acute MI was estimated in a large study in Denmark (Andersen et al, 2020). Hazard ratios for a new MI ranged from 1.21 (1.12-1.32) in the USA (Reddy et al, 2020) and 1.33 (1.04-1.68) in Israel (Kridin et al, 2022). The latter study reported a doubled risk in women compared to men. The risk was about 7% higher in patients on a biologic medication in the USA study. **Coronary artery disease (CAD)** A study in Germany with 1,760 HS patients reported that 9.9% had CAD (Pinter et al., 2020). A study in Denmark reported an incidence of 2.21/kpy for CAD (Andersen et al, 2020), and a Taiwanese study reported 21.3/kpy (Hung et al, 2019). However, the Taiwan study used a wider definition of the disease, also including angina pectoris. Patients with HS in Denmark had an unadjusted relative risk of CAD of 1.23 (1.21-1.24) compared to patients without HS (Andersen et al, 2020). A study in Taiwan reported an HR of 2.72 (1.63-4.56) for CAD (Hung et al, 2019). A study in Finland, comparing against patients with Psoriasis, reported an HR of 1.29 (1.06-1.59) (Tiri et al, 2019). Co-occurrence was measured in a German study (Pinter et al, 2020), reporting an OR of 1.24 (1.05-1.46).

Table 4–2: Summary of epidemiology of important comorbidities in the HS population

	Congestive heart failure (CHF) The prevalence of CHF ranged from 1.0% to 1.3% in two USA studies (Kimball et al., 2018, Kohorst et al., 2022).
Depression	The prevalence of depression in HS populations is as high as 26%, as estimated in a UK study. The adjusted odds of depression among patients with HS is 1.69 ((95% CI, 1.62–1.77) times that of control populations (Ingram et al, 2018). The prevalence of depression may be greater among patients with a higher Hurley stage (Onderdijk et al, 2013).
Diabetes mellitus	A higher prevalence of DM among patients with HS compared to control individuals was observed across several studies, with prevalences ranging from 7.1% to 24.8% (Ingram et al, 2018; Kimball et al, 2018; Shalom et al, 2015; Shlyankevich et al, 2014; Garg et al, 2018a; Miller et al, 2014). In 2 meta-analyses of 12 and 7 studies, the unadjusted pooled odds of DM among patients with HS were 2.17 (95% CI, 1.9–2.6) (Phan et al, 2019) and 2.8 (95% CI, 1.8–4.3) (Bui et al, 2018) times that of control individuals, respectively.
Dyslipidemia	A higher prevalence of dyslipidemia among patients with HS compared to control individuals was observed across 4 studies, with prevalences ranging from 3.3% to 45.3% (Ingram et al, 2018; Lee et al, 2018; Kimball et al, 2018; Shlyankevich et al, 2014). Adjusted odds of dyslipidemia among patients with HS ranged from 1.4 to 4.1 times that of control individuals (Ingram et al, 2018; Lee et al, 2018; Kimball et al, 2018).
Hypertension	Patients with HS had significantly higher prevalence of hypertension in 6 of 8 total studies addressing this relationship, with aORs ranging from 1.2 to 2.1 (Ingram et al, 2018; Lee et al, 2018; Kimball et al, 2018; Shalom et al, 2015 ; Shlyankevich et al, 2014; Sabat et al, 2012; Miller et al, 2014; Kwa et al, 2017) In these studies, the prevalence of hypertension among patients with HS ranged from 7.8% to 56.3%. In 1 of these studies, the risk of hypertension was lower in patients with HS (OR, 0.7; 95% CI 0.6–0.7] than control individuals, although data from this study were limited to single inpatient admissions and may not have included past comorbidity information (Kwa et al, 2017).
Inflammatory bowel disease (IBD)	The prevalence of IBD in patients with HS varies, ranging from 1.4% in a single-center study in the USA (Cices et al, 2017) to 6.6% in a tertiary referral center in Denmark (Jørgensen et al, 2020). The prevalence of CD ranged from 0.21% in a claims database study from Korea (Lee et al, 2018) to 4.3% in a tertiary referral center in Denmark (Jørgensen et al, 2020). The prevalence of UC ranged from 0.2% in an electronic medical record database from the UK (Ingram et al, 2018) to 2.6% in a tertiary referral center in Denmark (Jørgensen et al, 2020). Two studies showed that patients with more severe HS had higher prevalences of CD, but not of UC (Jørgensen et al, 2020, Kimball et al, 2018). All studies that also reported prevalences in the non-HS population showed that these were lower than in the HS population. Two studies reported incidence rates for IBD in patients diagnosed with HS, which were 0.59, 0.97 and 0.13 /kpy for CD, UC and unspecified IBD, respectively, in a population-based study in Denmark (Egeberg et al, 2017a), and

Table 4–2: Summary of epidemiology of important comorbidities in the HS population

	1.16, 2.26 and 3.06/kpy in a claims database study in the USA (Schneeweiss et al, 2022). Both studies showed 30-50% lower incidence rates in the non-HS population. The associations between HS and IBD confirmed the earlier observations that both prevalence and incidence are higher in people with HS than in those without HS. Patients with HS had between 2-4 times higher odds of having IBD or its components CD and UC, compared to patients without HS (Cices et al, 2017, Egeberg et al, 2017a, Garg et al, 2018b, Hua et al, 2021, Ingram et al, 2018, Lee et al, 2018, Schneeweiss et al, 2022). Only two studies estimated the risk for new-onset IBD. The study in Denmark (Egeberg et al, 2017a) with 7,732 patients with HS showed statistically significant increased risks of HS for CD (HR 2.19; 95% CI, 1.44-3.34]), UC (HR 1.63; 95% CI, 1.18-2.27), but not for unspecified IBD (HR 2.07; 95% CI, 0.86-5.00) which is likely due to the low number (5) of new unspecified IBD cases, while for CD and UC there were 22 and 36 new cases, respectively. The claims database study from the USA (Schneeweiss et al, 2019) showed significantly increased risks of IBD (HR 2.21; 95% CI, 1.63–3.00), CD alone (HR 2.70, 95% CI 1.69–4.32), and UC alone (HR 2.30; 95% CI 1.61– 3.28).
Metabolic syndrome	Higher prevalence of metabolic syndrome among patients with HS compared to control individuals were observed across 5 studies, with prevalence ranging from 10.4% to 50.6% (Shalom et al, 2015; Sabat et al, 2012, Miller et al, 2014; Gold et al, 2014; Loo et al, 2018). The pooled adjusted odds of metabolic syndrome among patients with HS ranged from 1.8 to 2.2 times that of control individuals (Phan et al, 2019; Tzellos et al, 2015, Rodríguez-Zuñiga et al, 2019).
Polycystic ovary syndrome	In a cross-sectional analysis involving 23,000 women with HS, the prevalence of PCOS was 9.0%, compared to 2.9% in control individuals. Women with HS had twice the adjusted odds of having PCOS (aOR, 2.14; 95% CI, 2.04–2.24) (Garg et al, 2018c). In other retrospective database studies evaluating various comorbid outcomes, the prevalences of PCOS among women with HS ranged from 0.8% to 4%. Across these studies, women with HS had 1.2 to 13.4 times the odds of having PCOS compared to control individuals (Ingram et al, 2018; Kimball et al, 2018, Phan et al, 2019)
Psoriasis	In EU based studies, prevalence estimates of psoriasis in patients with HS range from 6.4 -7% (Kjaersgaard et al, 2020; Kirsten et al, 2020). In an US-based study using MarketScan data the estimated prevalence of psoriasis was 2.2% and higher than in patients without HS (0.3%) (Schneeweiss et al, 2020).
Suicidality	Evidence from European national registries indicate higher incidence of completed suicide among patients with HS. A survey study performed in the EU and USA in 2017 and 2019 with 1,299 patients with HS who filled out the questionnaire estimated a prevalence of suicidal ideation of 7.9% (95% CI, 3.1-5.3) and suicidal attempts of 4.2% (95% CI, 3.1-5.3) (Garg et al, 2020). A Danish study in 2008-2012 used national registries to study completed suicides in 7,732 patients with HS (Thorlacius et al, 2018). They found an incidence rate of 0.29 (95% CI, 0.16-0.53) completed suicides /1,000 person-years. Compared

Table 4–2: Summary of epidemiology of important comorbidities in the HS population

	with the general population, patients with HS had an increased risk of completed suicide (HR 2.42; 95% CI, 1.07-5.45]). A Finnish registry-based study found that the risk of suicide in patients with HS was almost three times greater compared to patients with psoriasis (HR 2.8; 95% CI, 1.7-4.5). However, the increased risk was only seen in women (HR 2.53, 95% CI, 1.36-4.71) and not in men (HR 0.70, 95% CI, 0.34-1.42). These estimates were not adjusted for confounders (Tiri et al, 2018).

aOR=adjusted odds ratio; CAD=coronary artery disease; CD=Crohn's disease; CHF=congestive heart failure; CI=confidence interval; DM=diabetes mellitus; HR= hazard ratio; HS=hidradenitis suppurativa; IBD=inflammatory bowel disease; kpy= thousand person-years; MI=myocardial infarction; OR=odds ratio; PCOS=polycystic ovary syndrome; UC=ulcerative colitis.

Other comorbidities that should be screened for include, obesity, spondyloarthritis, sexual dysfunction, and Down syndrome (Garg et al, 2022).

PART II: MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

Bimekizumab is a monoclonal immunoglobulin (Ig) G1 potently and selectively inhibiting the activity of IL-17A and IL-17F in human and Cynomolgus monkey. The Cynomolgus monkey was considered the only pharmacologically relevant species to assess toxicity of bimekizumab. Key safety findings from nonclinical studies and relevance to human usage are presented below:

1.1 Toxicity

1.1.1 Single and multiple dose toxicity studies

Bimekizumab was well tolerated in the Cynomolgus monkey, when administered by intravenous (iv) or subcutaneous (sc) routes at doses up to 200mg/kg/week for up to 26 weeks. Exposure was as expected for an IgG1 and was maintained throughout the treatment phase. There were generally no clinical signs, no effects on blood pressure or electrocardiography, no effects on body weight, no changes in clinical pathology, including neutrophil counts, or blood immunophenotyping, no alteration of the response to immunization with keyhole limpet haemocyanin, no effects on organ weights and no histopathological changes that could be ascribed to the test item.

Some monkeys developed findings varying from one study to the other, all considered to be related to exaggerated pharmacology and a consequence of decreased muco-epidermal immunity

- Infectious enteritis with *Balantidium coli* identified (single dose study at 10mg/kg: 4/8 animals; none at lower or higher dose),
- Infectious enteritis with no pathogen identified – leading to early termination of animal (single dose at 10mg/kg: 1/8 animals and 26-week study 50mg/kg/week: 2/10 animals),
- Increased load or incidence of *Balantidium coli* in cecum and large intestine (8-week studies, at 20mg/kg/week and higher doses: 0/4 control animals vs 8/24 bimekizumab-treated animals positive in the study with bimekizumab alone; increased load of protozoa in presence or absence of adalimumab in the study where bimekizumab was co-administered with adalimumab),
- Abscess with *Staphylococcus aureus* (8-week study and 26-week study, 200mg/kg/week),
- Superficial dermatitis with increased skin load of gram-positive cocci (mainly *Staphylococcus aureus*) in the 26-week toxicity study at 50mg/kg/week (6/12 animals) or 200mg/kg/week (12/12 animals); increased incidence of skin findings in the enhanced pre- and postnatal development study (8/16 control animals, vs 9/16 animals given 20mg/kg/week and 11/16 animals given 50mg/kg/week).

Relevance to human: All microorganism-related findings are reflecting decreased muco-epidermal immunity and the increased risk of infection in humans. None of the pathogen-related changes are directly translatable to human because of different microorganism flora and different specificity and sensitivity to pathogens between humans and nonhuman primates. Superficial dermatitis may be a consequence of skin colonization by specific bacteria. Conversely, it may possibly be due to selective neutralization of IL-17A and IL-17F by bimekizumab, leading to an

overproduction of other inflammatory cytokines and inducing a paradoxical inflammation and a secondary change of skin flora.

1.1.2 Carcinogenicity

No carcinogenicity study was conducted as there is no suitable in vitro/in vivo model for carcinogenicity studies, however an extensive assessment was performed on the carcinogenic potential of prolonged inhibition of IL-17A and IL-17F with bimekizumab and summarized in a carcinogenicity assessment document.

There are conflicting data in the literature about the role of IL-17 in tumorigenesis. On one hand, IL-17 may have a role in early tumor formation, tumor proliferation, metastasis, and chemoresistance: IL-17 expression is up-regulated in a wide range of advanced tumor types and there are direct and indirect evidences of a role of IL-17 in tumor growth promotion; IL-17A has been shown to attract myeloid-derived suppressor cells to the tumor microenvironment, to promote neutrophil and macrophage recruitment to tumor sites, to have a positive effect on angiogenesis. Therefore, bimekizumab, by neutralizing IL-17A and IL-17F, could theoretically be protective against tumors.

On the other hand, IL-17 can promote an antitumor cytotoxic response through CD8+ cytotoxic T cells and natural killer cells. Hence, bimekizumab might theoretically have a deleterious effect by reducing immune surveillance.

Interleukin-17F is generally less potent than IL-17A and is not reported to recruit leukocytes or to promote angiogenesis with few data available reporting a clear role of IL-17F in carcinogenesis or tumor progression.

Relevance to human: The carcinogenic risk of bimekizumab is not expected to be significantly different from that of IL-17A inhibitors such as secukinumab or ixekizumab and clinical experience has not demonstrated a specific risk for these drugs. The effects of IL-17 may depend on the specific tumor microenvironment and tumor/immune cell phenotype in each individual. It is also possible that the T-helper 17 role varies according to cancer cause, type, location, and stage of the disease. However, no meaningful impact on key anti-tumor immune defense mechanisms has been noticed in toxicity studies with bimekizumab.

1.1.3 Reproductive toxicology

A 26-week toxicity study was conducted in sexually mature Cynomolgus monkeys with weekly sc doses of 50 or 200mg/kg. Bimekizumab did not impair reproductive endpoints evaluated, ie, menstrual cycle in females, semen quality, spermatic staging, and testis size in males, and histopathology of reproductive organs in both sexes.

Enhanced peri- and postnatal development study: The peri- and postnatal development of Cynomolgus monkeys was evaluated in a study where pregnant females were given weekly sc bimekizumab doses of 20 or 50mg/kg/week from Gestation Day 20 until parturition. After delivery, infants were kept for 6 months and evaluated for potential abnormalities, development, usual toxicity parameters and immune system development.

The doses selected for this study were lower than in the 26-week toxicity study to limit the risk of infections, that may impair the interpretation of the study endpoints.

The treatment with bimekizumab was well tolerated and resulted in sustained exposure in maternal animals during the entire treatment phase and comparable exposure in mothers and corresponding infants 1 week after birth. Exposure in infants was high enough to neutralize IL-17A and IL-17F for several months. No effects on toxicology parameters, pregnancy duration, parturition, infant survival and development were observed at an exposure ratio of 24-fold for Cmax and 27-fold for the AUC corresponding to a clinical dose of 320mg every 4 weeks. In addition, no effects on the development of the immune system of the infants were noted based on blood immunophenotyping, response to immunization and examination of lymphoid organs.

Relevance to human: Cynomolgus monkeys present a physiology of reproduction and parturition very close to that of humans.

The study design does not allow the evaluation of the implantation phase since treatment starts once pregnancy is confirmed. Since IgGs only marginally cross the placenta during the first trimester of pregnancy, fetuses are not or weakly exposed during embryogenesis and therefore, no teratogenicity is expected. However, expression of the neonatal Fc receptor (FcRn) allowed progressive placenta transfer after the first trimester so that exposure 1 week after birth was similar in maternal animals and infants suggesting a substantial in utero exposure during the development of major systems, including the immune system. Under the conditions of the study design, results did not indicate direct or indirect AE risks with respect to pregnancy, teratogenicity, embryonic/fetal development, parturition, or postnatal development in humans.

1.1.4 Genotoxicity

No genotoxicity studies were conducted as monoclonal antibodies (mAbs) do not interact with deoxyribonucleic acid or chromosomes.

1.1.5 Local tolerance

Local tolerance was evaluated as part of repeat dose toxicity studies. No macroscopic changes were seen at the iv or sc injection site in these studies.

1.2 Safety pharmacology

No specific safety pharmacology studies were conducted, cardiovascular parameters were included in repeat dose toxicology studies.

No effects on electrocardiogram parameters and waveform or morphology were seen, there were no effects on heart rate or blood pressure after single or repeat dose in the 8-week study or in the 26-week study.

Bimekizumab, due to its mechanism of action, is not expected to affect central nervous system or respiratory function. Therefore, no formal evaluation was conducted but detailed clinical evaluation during the course of the toxicity study would have caught any important treatment-related effects.

PART II: MODULE SIII: CLINICAL TRIAL EXPOSURE

Psoriasis: Bimekizumab studies in study participants with moderate to severe PSO were combined for the purpose of pooled safety analyses.

- Pool S1 summarizes the safety data for study participants who received study medication during the Initial Treatment Periods of the two Phase 3 studies: PS0009 (bimekizumab and placebo arms only) and PS0013. This pool summarizes the safety of bimekizumab versus placebo through Week 16.
- Pool S2 is the most comprehensive safety pool and was designed to investigate long-term exposure and safety data in all bimekizumab-treated study participants with moderate to severe PSO. Data from all blinded Phase 2 and Phase 3 studies and their respective extension studies (including interim data for PS0008 [up to Week 52], PS0009 & PS0013 [up to Week 56]; data up to the cut-off of 01 Nov 2019 for PS0014; and final data from completed studies PS0010, PS0011, PS0016, and PS0018) were combined in this pool. Note that although the Initial and Maintenance Treatment Periods in PS0008, PS0009, and PS0013 are completed, a small number of study participants were ongoing in the Safety Follow-Up (SFU) Period at the time of the cut-off date for the submission. Available data from the SFU Periods of each study were also included in Pool S2.

  All study participants exposed to bimekizumab during any of these 8 studies were included in this pool. All safety data collected during exposure to bimekizumab were included (ie, Initial Treatment Period, Maintenance Treatment Period, and open label extension [OLE] data were combined).

For the clinical trial exposure in this section, safety treatment group “Phase 2/3 bimekizumab Total” in Pool S2 is utilized (ISS Section 4.1.2).

Psoriatic arthritis: Bimekizumab studies in participants with PsA were combined for the purpose of pooled safety analyses.

- Pool SP1 summarizes safety data for study participants who received at least one dose of investigational medicinal product during the Initial Treatment Periods of the 2 Phase 3 placebo-controlled studies (PA0010 and PA0011). This pool summarizes the safety data of bimekizumab compared to placebo through Week 16.
- Pool SP2 represents the most comprehensive set of safety data from the Phase 2/3 studies for bimekizumab in active PsA. It summarizes the safety of bimekizumab over extended dosing, including during open-label periods in the PsA population. Pool SP2 consists of study participants who received at least 1 dose of bimekizumab in the following:
  - Completed Phase 2 studies PA0008 and PA0009
  - Completed 52-week Phase 3 study PA0010 (including all data up through SFU Period, database lock 27 Jul 2022)
  - Completed Phase 3 study PA0011 (including all SFU data from this study, database lock 04 Mar 2022)
  - Ongoing OLE study PA0012 (all safety data entered as of the designated cut-off date [20 May 2022, the last Week 52 visit in PA0010])

For the clinical trial exposure in this section, the "bimekizumab Total" treatment group is utilized which includes data from all study participants treated with any bimekizumab regimen during the Phase 2 and Phase 3 studies PA0008, PA0009, PA0010, PA0011, and PA0012 (PsA ISS Section 4.1.2).

Axial spondyloarthritis: Bimekizumab studies in study participants with axSpA (AS and nr-axSpA) were combined for the purpose of pooled safety analyses.

- Pool SA1 summarizes safety data for study participants who received study medication during the Initial Treatment Periods of the 2 Phase 3 placebo-controlled studies (AS0010 and AS0011). This pool summarizes the safety data of bimekizumab compared to placebo through Week 16.
- Pool SA2 represents the most comprehensive set safety data from the Phase 2/3 studies for bimekizumab in axSpA (including AS and nr-axSpA). It summarizes the safety of bimekizumab over extended dosing, including during open-label periods in the axSpA population. Pool SA2 consists of study participants who received at least 1 dose of bimekizumab in the following:
  - Completed Phase 2 studies AS0008 and AS0013
  - 52-week Phase 3 studies AS0010 and AS0011
  - All safety data entered into the OLE studies AS0009 and AS0014 databases as of the designated clinical cut-off date (04 Jul 2022).

  For clinical trial exposure "bimekizumab Total" treatment group is utilized which includes data from all study participants treated with any bimekizumab regimen during the Phase 2 and Phase 3 studies AS0008, AS0009, AS0010, AS0011, AS0013, and AS0014 (axSpA ISS Section 4.1.2).

Hidradenitis suppurativa: Bimekizumab studies in study participants with HS were combined for the purpose of pooled safety analyses.

- Pool S1 was defined for the purpose of summarizing the safety of bimekizumab compared to placebo through Week 16 in the HS population. Pool S1 consists of study participants who received at least 1 full or partial dose of study medication (bimekizumab or placebo) during the Initial Treatment Period of the Phase 3 placebo-controlled studies HS0003 and HS0004.
- Pool S3 was defined to summarize the safety of bimekizumab over all studies conducted in HS, including the OLE study. Pool S3 consists of study participants who received at least 1 full or partial dose of bimekizumab in the Phase 2 study, HS0001, or in the Phase 3 studies HS0003, HS0004, and HS0005 (note that per the study designs, any study participant receiving bimekizumab in HS0005 should have already received bimekizumab in HS0003 or HS0004).

  All study participants exposed to bimekizumab during any of the 4 studies were included in this pool. All safety data collected during exposure to bimekizumab were included (ie, Initial Treatment Period, Maintenance Treatment Period, and OLE data were combined).

For the clinical trial exposure in this section, safety treatment group "Phase 2/3 bimekizumab Total" in Pool S3 is utilized (HS ISS Section 4.1.3). The Phase 2/3 bimekizumab Total treatment

group includes data from all study participants treated with any bimekizumab regimen during the Phase 2 and Phase 3 studies (HS0001, HS0003, HS0004, and HS0005).

Table 1 presents the study participant exposure to bimekizumab in PSO clinical trials by duration.

Table 1: Duration of exposure (PSO)

Duration of exposure	Study participants (%)	Participant-years
>0 months	1789 (100%)	
≥4 months	1603 (89.6%)	
≥8 months	1399 (78.2%)	
≥12 months	1073 (60.0%)	
≥16 months	237 (13.2%)	
≥20 months	14 (0.8%)	
≥24 months	0	
Total person time		1830.4 participant-years

PSO=psoriasis
Data source: PSO Integrated Summary of Safety Data Table 4.2.1.1 cut off 01 Nov 2019

Table 2 presents the study participant exposure to bimekizumab in PsA clinical trials by duration.

Table 2: Duration of exposure (PsA)

Duration of exposure	Study participants (%)	Participant-years
>0 months	1413 (100%)	
≥4 months	1347 (95.3%)	
≥8 months	1276 (90.3%)	
≥12 months	1147 (81.2%)	
≥16 months	986 (69.8%)	
≥20 months	817 (57.8%)	
≥24 months	709 (50.2%)	
Total person time		2664.0 participant-years

PsA=psoriatic arthritis
Data source: PsA Integrated Summary of Safety Data Table 4.2.1.1 cut off 27 July 2022

Table 3 presents the study participant exposure to bimekizumab in axSpA clinical trials by duration.

Table 3: Duration of exposure (axSpA)

Duration of exposure	Study participants (%)	Participant-years
>0 months	928 (100%)	
≥4 months	890 (95.9%)	
≥8 months	845 (91.1%)	
≥12 months	715 (77.0%)	
≥16 months	590 (63.6%)	
≥20 months	532 (57.3%)	
≥24 months	495 (53.3%)	
Total person time		2241.1 participant-years

axSpA=axial spondyloarthritis
Data source: axSpA Integrated Summary of Safety Data Table 4.2.1.1 (Pool SA2) cut off 04 Jul 2022

Table 4 presents study participant exposure to bimekizumab in HS clinical trials by duration.

Table 4: Duration of exposure (HS)

Duration of exposure	Study participants (%)	Participant-years
>0 months	1041 (100%)	
≥4 months	893 (85.8%)	
≥8 months	765 (73.5%)	
≥12 months	630 (60.5%)	
≥16 months	478 (45.9%)	
≥20 months	284 (27.3%)	
≥24 months	113 (10.9%)	
Total person time		1296.8 participant-years

HS=hidradenitis suppurativa
Data source: HS Integrated Summary of Safety Data Table 4.3.1; cut off 15 Nov 2022

Table 5 presents study participant exposure to bimekizumab in PSO clinical trials by age group and gender.

Table 5: Exposure by age group and gender (PSO)

Age group	Study participants		Participant-years	
	Male	Female	Male	Female
<18 years	0	0	0	0
18 to <40 years	451	202	456.83	206.11

Table 5: Exposure by age group and gender (PSO)

Age group	Study participants		Participant-years	
	Male	Female	Male	Female
40 to <65 years	695	288	710.05	297.67
≥ 65 years	106	47	110.10	49.65
Total	1252	537	1277.0	553.4

PSO=psoriasis
Data source: PSO Integrated Summary of Safety Data Table 4.2.2 and Table 4.2.3 cut off 01 Nov 2019

Table 6 presents study participant exposure to bimekizumab in PsA clinical trials by age group and gender.

Table 6: Exposure by age group and gender (PsA)

Age group	Study participants		Participant-years	
	Male	Female	Male	Female
<40 years	187	150	371.51	281.80
40 to <65 years	413	493	799.09	923.27
≥ 65 years	75	95	129.27	159.02
Total	675	738	1299.9	1364.1

PsA=psoriatic arthritis
Data source: PsA Integrated Summary of Safety Data Table 4.2.4 and Table 4.2.3; cut off 27 July 2022

Table 7 presents study participant exposure to bimekizumab in axSpA clinical trials by age group and gender.

Table 7: Exposure by age group and gender (axSpA)

Age group	Study participants		Participant-years	
	Male	Female	Male	Female
<40 years	375	97	918.62	185.97
40 to <65 years	281	142	752.08	308.47
≥65 years	16	17	36.58	39.36
Total	672	256	1707.3	533.8

axSpA=axial spondyloarthritis
Data source: axSpA Integrated Summary of Safety Data Table 4.2.3 and Table 4.2.4 (pool SA2) cut off 04 Jul 2022

Table 8 presents study participant exposure to bimekizumab in HS clinical trials by age group and gender.

Table 8: Exposure by age group and gender (HS)

Age group	Study participants		Participant-years	
	Male	Female	Male	Female
<40 years	272	376	358.9	447.0
40 to <65 years	166	209	214.4	255.6
≥65 years	9	9	9.5	11.4
Total	447	594	582.8	714.0

HS=hidradenitis suppurativa
Data source: HS Integrated Summary of Safety Data Table 4.3.3 and Table 4.3.4; cut off 15 Nov 2022

Table 9 presents study participant exposure to bimekizumab in PSO clinical trials by dose.

Table 9: Exposure by dose (PSO)

Dose of exposure	Study participants	Participant-years
Bimekizumab 320mg Q4W	1556	1285.8
Bimekizumab 320mg Q8W[a]	510	295.9
Bimekizumab Total[b]	1789	1830.4

PSO=psoriasis; Q4W=every 4 weeks; Q8W=every 8 weeks
[a] Bimekizumab 320mg Q8W was utilized only in the Phase 3 studies
[b] Bimekizumab Total provides exposure to all doses and frequencies of bimekizumab in Phase 2 and 3 studies (including bimekizumab 64mg, 160mg, 320mg loading dose followed by 160mg, 320mg, and 480mg)
Study participants who received both bimekizumab 320mg Q4W and bimekizumab 320mg Q8W are included in the population count and participant-years of both treatment groups, but only once in the bimekizumab Total group.
Data source: PSO Integrated Summary of Safety Data Table 4.2.1.1 and Table 4.2.1.2 cut off 01 Nov 2019

Table 10 presents study participant exposure to bimekizumab in PsA clinical trials by dose.

Table 10: Exposure by dose (PsA)

Dose of exposure	Study participants	Participant-years
Bimekizumab 160mg Q4W	1407	2590.8
Bimekizumab Total[a]	1413	2664.0

PsA=psoriatic arthritis; Q4W=every 4 weeks
[a] Bimekizumab Total provides exposure to all doses and frequencies of bimekizumab in Phase 2 and 3 studies (in PA0008 some participants also received bimekizumab 160mg, 160mg Q4W with a 320mg loading dose at Baseline, and bimekizumab 320mg Q4W, in all other PsA studies included in pool SP2, the only bimekizumab dose utilized was 160mg Q4W).
Data source: PsA Integrated Summary of Safety Data Table 4.2.1.1 cut off 27 July 2022

Table 11 presents study participant exposure to bimekizumab in axSpA clinical trials by dose.

Table 11: Exposure by dose (axSpA)

Dose of exposure	Study participants	Participant-years
Bimekizumab 160mg Q4W	848	2034.4
Bimekizumab Total[a]	928	2241.1

axSpA=axial spondyloarthritis; Q4W=every 4 weeks

[a] Bimekizumab Total provides exposure to all doses and frequencies of bimekizumab in Phase 2 and 3 studies (in Phase 2 study AS0008, participants also received bimekizumab 16mg Q4W, 64mg Q4W, 320mg Q4W, and in AS0013 participants also received bimekizumab 160mg Q2W and 320mg Q4W; in all other axSpA studies included in pool SA2, the only bimekizumab dose utilized was 160mg Q4W).

Data source: axSpA Integrated Summary of Safety Data Table 4.2.1.1 (pool SA2) cut off 04 Jul 2022

Table 12 presents study participant exposure to bimekizumab in HS clinical trials by dose.

Table 12: Exposure by dose (HS)

Dose of exposure	Study participants	Participant-years
Phase 3 bimekizumab 320mg Q2W[a]	823	729.4
Phase 2/3 bimekizumab 320mg Q2W[b]	869	754.5
Phase 3 bimekizumab 320mg Q4W[c]	650	544.1
Phase 2/3 Bimekizumab Total	1041	1296.8

HS=hidradenitis suppurativa; Q2W=every 2 weeks; Q4W=every 4 weeks

[a] Includes exposure to bimekizumab 320mg Q2W in Phase 3 studies HS0003, HS0004, and HS0005

[b] Includes exposure to bimekizumab 320mg Q2W in Phase 2 and 3 studies HS0001, HS0003, HS0004, and HS0005

[c] Includes exposure to bimekizumab 320mg Q4W in Phase 3 studies HS0003, HS0004, and HS0005

Note: Study participants who received bimekizumab in both a feeder study (HS0003 or HS0004) and in the extension study (HS0005) are counted only once.

Data source: HS Integrated Summary of Safety Data Table 4.3.1; cut off 15 Nov 2022

Table 13 presents study participant exposure to bimekizumab in PSO clinical trials by ethnic origin.

Table 13: Exposure by ethnic origin (PSO)

Ethnic origin	Study participants	Participant-years
Black	26	27.5
White	1468	1527.5
Asian	260	240.3
Other	35	35.1
Total	1789	1830.4

PSO=psoriasis

Data source: PSO Integrated Summary of Safety Data Table 4.2.2 cut off 01 Nov 2019

Table 14 presents study participant exposure to bimekizumab in PsA clinical trials by ethnic origin.

Table 14: Exposure by ethnic origin (PsA)

Ethnic origin	Study participants	Participant-years
Black	7	12.6
White	1352	2576.5
Asian	42	59.6
Total[a]	1413	2664.0

PsA=psoriatic arthritis
[a] Note that the total also includes the "Other" ethnic origin category that comprises 12 participants.
Data source: PsA Integrated Summary of Safety Data Table 4.2.3 and Table 4.2.1.1; cut off 27 July 2022

Table 15 presents study participant exposure to bimekizumab in axSpA clinical trials by ethnic origin.

Table 15: Exposure by ethnic origin (axSpA)

Ethnic origin	Study participants	Participant-years
Black	3	6.1
White	825	2104.7
Asian	84	100.1
Total[a]	928	2241.1

axSpA=axial spondyloarthritis
[a] Note that the total also includes the "Other" ethnic origin category that comprises 16 participants.
Data source: axSpA Integrated Summary of Safety Data Table 4.2.1.1 and Table 4.2.3 (pool SA2) cut off 04 Jul 2022

Table 16 presents study participant exposure to bimekizumab in HS clinical trials by ethnic origin.

Table 16: Exposure by ethnic origin (HS)

Ethnic origin	Study participants	Participant-years
Black	116	131.8
White	831	1046.3
Asian	41	61.0
Other [a]	48	51.2
Total [b]	1041	1296.8

HS=hidradenitis suppurativa
[a] Other group includes American Indian/Alaska Native (3 participants), Native Hawaiian or Other Pacific Islander (2 participants), and other/mixed (43 participants).

Table 16: Exposure by ethnic origin (HS)

[b] Study participant total includes 5 participants with missing race.
Data source: HS Integrated Summary of Safety Data Table 2.3.1, Table 4.3.1, and Table 4.3.3; cut off 15 Nov 2022

PART II: MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Exclusion criteria in pivotal clinical studies within the development programme are discussed in Table 1–1:

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Pediatrics (patients under 18 years of age)	
Reason for exclusion	Considering the proposed indication and GCP, it is a standard practice to initiate studies in the adult patient population. There are no adequate data on use of bimekizumab in pediatric patients.
Is it considered to be included as a missing information	No
Rationale	Pediatric studies are ongoing under separate PIPs (EMEA-002189-PIP01-17-M02) for PSO and are planned under separate PIPs (EMEA-002189-PIP04-20) for hidradenitis suppurativa and JIA (EMEA-002189-PIP03-19). No efficacy and safety data in study participants under 18 years are available yet. Use in pediatrics is not considered a part of the proposed indication population. There is no anticipated risk of off label use in pediatrics. Thus, use in pediatrics is not considered a missing information as per EU GVP module V rev 2.
Pregnancy	
Reason for exclusion	There are no adequate data on the use of bimekizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development. As a precautionary measure, it is preferable to avoid the use of bimekizumab during pregnancy. Moreover, physiological changes during pregnancy can influence main study outcome measures including disease activity.
Is it considered to be included as a missing information	Yes
Breastfeeding	
Reason for exclusion	Human IgGs are known to be excreted in breast milk during the first few days after birth, and decrease to low concentrations soon afterwards; consequently, a risk to the breastfed infant during this period cannot be excluded. It is unknown whether bimekizumab is excreted in human milk. Only a small fraction of plasma IgG is present in mature breast milk. Hence, the amount of bimekizumab excreted in milk is likely to be very limited.

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Is it considered to be included as a missing information	Yes
Live vaccination	
Reason for Exclusion	Live vaccines are currently not recommended during treatment with any immunomodulator drug and consequently, study participants were not allowed to receive concurrent administration of live vaccines during clinical studies with bimekizumab. No clinical data are available on the immunological response to live vaccinations or the potential for transmission of infection by live vaccines.
Is it considered to be included as a missing information	No
Rationale	The Warning and precaution (Section 4.4) in the SmPC of bimekizumab states that live vaccines should not be given in patients treated with bimekizumab. Routine risk minimization measure and pharmacovigilance activities are considered adequate for this topic and as such no additional pharmacovigilance or risk minimization measures beyond routine are required. Thus, in line with EU-GVP module V rev 2, administration of live vaccines is not considered a missing information for bimekizumab.
Hypersensitivity (to bimekizumab or any of the excipients)	
Reason for Exclusion	All monoclonal antibodies could potentially be associated with hypersensitivity reactions, including anaphylactic events.
Is it considered to be included as a missing information	No
Rationale	Serious hypersensitivity reactions are considered as an important potential risk for bimekizumab.
Clinically important active infection such as TB, or recent history of other serious or significant opportunistic infection	
Reason for Exclusion	As an immunomodulating biologic agent, bimekizumab might be associated with an increased risk for infections.
Is it considered to be included as a missing information	No

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Rationale	Clinical data are not suggestive of significant immunosuppressant activity of bimekizumab; the majority of the infections observed in the clinical program were mild to moderate, resolved, and did not lead to study drug discontinuation. In the PSO, PsA, axSpA, and HS programs, no study participant on bimekizumab developed active TB. Use of bimekizumab is contraindicated in patients with clinically important active infections (eg, active tuberculosis). Serious infections are considered an important identified risk for bimekizumab.
Concurrent acute or chronic hepatitis B or C or HIV	
Reason for Exclusion	Preclinical studies have shown a significant role of IL-17 and IL-17-producing cells in the inflammatory response in chronic hepatitis B and its progression to liver fibrosis (Bao et al, 2017; Paquissi 2017; Wang et al, 2010). Based on the available published data, the risk of reactivation of hepatitis B and C with anti-IL-17 molecules in chronic diseases is considered low (Piaserico et al, 2019; Winthrop et al, 2018); however, such patients were excluded from studies as a precautionary measure as reactivations have been seen with biologic immunomodulators (with a different mechanism of action). In HIV infection, presence of underlying (latent) virus reservoir might be associated with an increased risk of opportunistic infections. Furthermore, to reduce potential interference of concurrent antiviral and other therapies with the safety analyses in the study, those with a history of acute or chronic hepatitis B or C or HIV infection were excluded from participation.
Is it considered to be included as a missing information	No
Rationale	The Warning and precaution (Section 4.4) in the SmPC of bimekizumab states that "Caution should be exercised when considering the use of bimekizumab in patients with a chronic infection or a history of recurrent infection. Treatment with bimekizumab must not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated." Routine risk minimization measures and pharmacovigilance activities are considered adequate for this topic and as such no additional pharmacovigilance or risk minimization measures beyond routine are required. Moreover, serious infections are already considered as an important identified risk. Thus, in line with EU-GVP module V rev 2, concurrent acute or chronic hepatitis B or C or HIV is not considered a missing information for bimekizumab.
Active symptomatic Crohn's disease or ulcerative colitis	

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Reason for exclusion	Some studies with IL-17 inhibitors have shown no benefit or even worsening of symptoms in patients with active inflammatory bowel disease. Cases of new or exacerbations of Crohn's disease and ulcerative colitis have been reported with IL-17 blockade.
Is it considered to be included as a missing information	No
Rationale	Inflammatory bowel disease (Crohn's disease and ulcerative colitis) is considered an important identified risk for bimekizumab.
Active suicidal ideation, moderately severe or severe major depression	
Reason for Exclusion	Patients with PSO are at increased risk for depression, anxiety and suicidality compared to the general population (Kurd et al, 2010). Hagberg et al (2016a) used CPRD data to conclude that rates of depression are higher in patients with PsA compared to non-PsA patients. Data from a systematic review and meta-analysis conducted by Singh et al (2017b) showed patients with PSO were twice as likely to consider suicide than the general population. Additionally, PSO was significantly associated with both attempted and completed suicide. A meta-analysis by Zhao et al (2018) estimated that the pooled prevalence of mild depressive symptoms in patients with axSpA (AS and nr axSpA) was 38%, and that for moderate/severe depression (defined as HADS score ≥11) it was 15%. Although data are limited, rates of depression and suicidality in PsA and axSpA are comparable to those in PSO (Sheahan et al, 2017). Patients with HS are at increased risk for depression, anxiety, and other psychiatric conditions compared to the general population (Huilaja et al, 2018; Shavit et al, 2015). Evidence from European national registries indicate higher incidence of completed suicide among patients with HS. A Danish study in 2008-2012 used national registries to study completed suicides in 7,732 patients with HS and found an incidence rate of 0.29 (95% CI: 0.16, 0.53) completed suicides/1,000 person-years (Thorlacius et al, 2018). Study participants were excluded if they had a history of a suicide attempt within the 5 years prior to the Screening Visit or presence of active suicidal ideation in the last month. Such study participants are generally not considered appropriate candidates for participation in a blinded controlled clinical trial for which improvement in major neuropsychiatric conditions such as depression or suicidality is not a primary endpoint. Study participants with a history of suicide attempt more than 5 years ago were allowed to enroll into the bimekizumab Phase 3 studies after evaluation by a mental healthcare practitioner.
Is it considered to be included as a missing information	No

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Rationale	T helper 17 cells and IL-17A contribute to glial activation and neuroinflammation and their presence at inflammatory sites in the brain has a deleterious effect (Cipollini et al, 2019; Ye et al, 2019). Mounting evidence suggests that inflammation is involved in suicidal behavior. Holmes et al (2018) confirmed the evidence of increased microglial activation in the anterior cingulate cortex during a moderate to severe major depressive episode. Furthermore, inflammatory cytokines may serve as mediators of both environmental and genetic factors that contribute to the development of depression (Felger and Lotrich 2013). Transfer of immunoglobulins (including IgG1 and thus bimekizumab) across the blood brain barrier is expected to be very minimal and while it may increase under inflammatory conditions, the effect would theoretically be beneficial, by decreasing chronic inflammation. At the time of submission in the bimekizumab development program in PSO, no completed suicide or suicidal attempt were reported in study participants on bimekizumab. One event reported under bimekizumab was adjudicated as suicidal ideation; this individual case was confounded by schizoaffective disorder- bipolar type and medical history of suicide attempt. The incidence rate of adjudicated SIB was very low (0.1 per 100 participant-years) with no evidence of increased rates compared to the background population. No particular trend in event type was identified in the Psychiatric disorders SOC or from ongoing neuropsychiatric monitoring through questionnaires during studies. In the bimekizumab development program in PsA, the incidence rate of adjudicated SIB was very low (0.1 per 100 participant-years [95% CI: 0.0, 0.3]) with no evidence of increased rates compared to the background population. In the bimekizumab development program in axSpA, the incidence rate of adjudicated SIB was very low (0.1 per 100 participant-years) with no evidence of increased rates compared to the background population. In the bimekizumab development program in HS, the exposure adjusted incidence rate of adjudicated SIB was 0.5 per 100 participant-years [95% CI: 0.2, 1.1]) with no evidence of increased rates compared to the background population. No trend was identified in overall psychiatric disorders or from ongoing monitoring during studies considering psychiatric comorbidities in the HS population. No completed suicide occurred under bimekizumab in the HS development program. Currently there is no evidence to suspect a causal relationship between bimekizumab and development of suicidal ideation and behavior, and evidence from published literature supports a possible beneficial effect of IL-17 inhibition in CNS disorders characterized by neuroinflammation.
Active malignancy or recent history of malignancy or a history of lymphoproliferative disease	

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Reason for exclusion	Recent history of malignancy or active malignancy could have interfered with the interpretation of the safety profile of bimekizumab and prevented study participants from completing the study. In addition, immunomodulatory compounds may theoretically interfere with the pathogenesis of malignancy.
Is it considered to be included as a missing information	No
Rationale	No meaningful impact on key anti-tumor immune-defense mechanisms or signaling has been noticed in toxicity studies with bimekizumab. A comprehensive carcinogenicity assessment report concluded that the carcinogenic risk of bimekizumab is not expected to be significantly different from that of IL-17A inhibitors. In line with other IL-17 inhibitors, malignancy is considered an important potential risk for bimekizumab.
Recent myocardial infarction or stroke (last 6 months)	
Reason for exclusion	Recent history of myocardial infarction or stroke could have interfered with the interpretation of the safety profile of bimekizumab. The underlying medical history of a recent myocardial infarction or stroke could have prevented the study participants from being able to complete the study.
Is it considered to be included as a missing information	No
Rationale	In line with other IL-17 inhibitors, MACE is considered an important potential risk for bimekizumab.
Severe hepatic impairment or severe renal impairment	
Reason for exclusion	Good clinical practice and also to reduce potential interference with the safety analyses in the study.
Is it considered to be included as a missing information	No

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Rationale	The renal elimination of an intact IgG monoclonal antibody (and thus of bimekizumab), is expected to be low and of minor importance (Wang et al, 2008). Similarly, IgGs are mainly eliminated via intracellular catabolism and hepatic impairment is not expected to influence their clearance (Wang et al, 2008), including that of bimekizumab. Hence hepatic or renal impairment is not expected to alter the pharmacokinetics of bimekizumab. Although no formal hepatic impairment study has been conducted, in order to assess the impact on the pharmacokinetics of bimekizumab, liver markers ALT and bilirubin were tested as potential covariates on clearance and were not found to be significant covariates. Similarly, based on population pharmacokinetic analyses, serum creatinine levels, or creatinine clearance did not have a meaningful impact on bimekizumab clearance of study participants. Thus, the safety and efficacy of bimekizumab is not expected to differ in patients with severe hepatic or severe renal impairment.
White blood cell count, neutrophil or lymphocyte abnormalities • White blood cell count $<3.00x10^3/\mu L$ • Absolute neutrophil count $<1.5x10^3/\mu L$ • Lymphocyte count <500 cells/μL	
Reason for exclusion	Interleukin-17 plays a significant role in regulating lymphocyte recruitment and lymphopoeisis. Bimekizumab is known to lower neutrophil counts and is an immunomodulator with potential to lower WBC counts
Is it considered to be included as a missing information	No
Rationale	Among hematology variables that contribute to cytopenia, the percentage of study participants with shifts from normal at baseline to low post-baseline minimum values was generally small across all treatment groups with no dose-related trend. None of the patients with Grade 3 or 4 lymphopenia or neutropenia had reports of concurrent serious infections. Serious infections as a possible consequence of neutropenia is considered as an important identified risk for bimekizumab.

ALT=alanine aminotransferase; AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; CNS=central nervous system; CPRD=clinical practice research datalink; EU-GVP=European Union Good Pharmacovigilance Practice; GCP=Good Clinical Practice; HADS=Hospital anxiety and depression scale; HIV=human immunodeficiency virus; HS=hidradenitis suppurativa; IgG=immunoglobulin G; IL=interleukin; JIA=juvenile idiopathic arthritis; MACE=major adverse cardiovascular events; nr-axSpA=non-radiographic axial spondyloarthritis; PIP=paediatric investigation plan; PsA=psoriatic arthritis; PSO=psoriasis; rev=revision; SIB=suicidal ideation and behavior; SmPC=Summary of product characteristics; SOC=System Organ Class; TB=tuberculosis; TEAE=treatment-emergent adverse event; WBC=white blood cell

2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 3–1 provides an overview of exposure in special populations typically under-represented in clinical trial development programmes.

Table 3–1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Pregnant women were not included in the clinical development program. PSO: As of the cut off (01 Nov 2019), 7 pregnancies were reported after maternal exposure to bimekizumab. PsA: As of the cut off (27 Jul 2022), 4 pregnancies were reported after maternal exposure to bimekizumab. axSpA: As of the cut off (04 July 2022), no pregnancies were reported after maternal exposure to bimekizumab. HS: As of the cut off (15 Nov 2022), 8 pregnancies were reported after maternal exposure to bimekizumab. The review of those cases did not identify any trend of abnormal pregnancy outcome compared to what is expected in this patient population.
Breastfeeding women	Not included in the clinical development program

Table 3–1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	See Part II SIII, Tables 13-16

axSpA=axial spondyloarthritis; HS=hidradenitis suppurativa; PsA=psoriatic arthritis; PSO=psoriasis

PART II: MODULE SV: POSTAUTHORIZATION EXPERIENCE

1 POSTAUTHORIZATION EXPOSURE

1.1 Method used to calculate exposure

A conservative approach was adopted by assuming that all patients receive complete dosage regimens at the time of treatment. Patient exposure is estimated using the available UCB sales data from international birth date (20 Aug 2021) to 31 Jan 2023 for the cumulative time interval. Note that sales data are only available to UCB on a month-to-month basis.

The Standard Monthly Dose is assumed to be 160mg according to the company core data sheet. For calculation purposes, a year is defined as 12 months. Patient exposure is calculated with the following formula:

$$\text{Patient-years} = \frac{\text{total amount of product distributed/ Standard Monthly Dose}}{\text{12 months in year}}$$

1.2 Exposure

The total amount of product sold is CCI [redacted] mg cumulatively, as derived from the UCB sales data. According to this methodology, the patient exposure to bimekizumab is estimated as approximately CCI [redacted] patient-years cumulatively from 20 Aug 2021 to 31 Jan 2023. Exposure calculations by age, gender, route of administration, or dosage cannot be estimated using the available sales data.

The breakdown of the exposure by region is presented for the cumulative time interval in Table 1 .

Table 1: Cumulative patient exposure by region (01 Aug 2021 to 31 Jan 2023)

Region	Country	Patient-years cumulatively
EEA	CCI [redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Table 1: Cumulative patient exposure by region (01 Aug 2021 to 31 Jan 2023)

Region	Country	Patient-years cumulatively
	CCI [redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	Total EEA	**3209**
Asia Pacific	CCI [redacted]	[redacted]
	[redacted]	[redacted]
	Total Asia Pacific	**600**
Europe (non-EEA)	CCI [redacted]	[redacted]
	[redacted]	[redacted]
	Total Europe (non-EEA)	**695**
Middle East and Africa	CCI [redacted]	[redacted]
	[redacted]	[redacted]
	Total Middle East and Africa	**105**
US and Canada	CCI [redacted]	[redacted]
	[redacted]	[redacted]
Total		CCI [redacted]

EEA=European Economic Area
Patient-years data is rounded to the nearest whole number.

PART II: MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Based on the characteristics, target population of this drug, and analysis of cases retrieved from the UCB Global Safety database, there is no evidence to suggest the potential for drug abuse or misuse of bimekizumab.

PART II: MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Table 1–1: Risks not considered important and reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks not considered important	Justification for non-inclusion in list of safety concerns
Dermatitis and eczema	Dermatitis and eczema is a risk with minimal clinical impact on patients (in relation to the severity of the indication treated). In the bimekizumab PSO program, the vast majority of events seen were mild to moderate and nonserious. Serious forms of dermatitis possibly associated with hypersensitivity reactions are captured under the important potential risk of 'serious hypersensitivity reactions' (Part II SVII, Section 1.2). Dermatitis and eczema are included as common ADRs (SmPC Section 4.8)
Injection site reaction	Although injection site reactions are causally associated with bimekizumab administration, these injection site reactions are well characterized. They were reported as nonserious events, mild to moderate in severity, without leading to product discontinuation. The events were local injection site reactions without systemic involvement, and they resolved. Injection site reactions appear to be generally tolerable, and do not warrant additional clinical actions to minimize the risk. They are considered to have minimal public health and benefit risk impact. Injection site reactions are included as common ADRs (SmPC Section 4.8)
Nonserious infections	This is a known risk associated with the mode of action and does not have an important impact on the risk-benefit profile and does not meet the criteria for important risk per the EU-GVP module V rev2 definition. Upper respiratory tract infections and fungal infections were the most frequently observed TEAEs. The vast majority of the infections observed in the clinical program of bimekizumab were nonserious, local, mild to moderate in intensity, manageable with standard of care and did not lead to study drug discontinuation. Gastrointestinal infections, particularly gastroenteritis, have also been reported in association with bimekizumab. This is considered to have minimal public health and benefit-risk impact. Serious infections are considered an Important identified risk (Part II SVII, Section 1.2) Infections and infestations are included in the list of ADRs in SmPC Section 4.8 (Upper respiratory tract infections as very common ADRs; Oral candidiasis, Tinea infections, Ear infections, Herpes simplex infections, Oropharyngeal candidiasis, Gastroenteritis, and Folliculitis as common ADRs; and Mucosal and cutaneous candidiasis (including oesophageal candidiasis) and Conjunctivitis as uncommon ADRs).

Table 1–1: Risks not considered important and reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks not considered important	Justification for non-inclusion in list of safety concerns

ADR=adverse drug reaction; EU-GVP=European Union Good Pharmacovigilance Practice; PSO=psoriasis; rev=revision; RMP=Risk Management Plan; SmPC=summary of product characteristics; TEAE=treatment-emergent adverse event

Other events of interest not included in list of safety concerns for bimekizumab:

Suicidal ideation and behavior:

Amongst the molecules approved for use in patients with PSO with similar mode of action, suicidal ideation and behavior (SIB) is included as an important potential risk in the EU-RMP for an IL-17 receptor A (IL-17 RA) antagonist and for one of the IL-17 A inhibitor molecules. Per European Union Good Pharmacovigilance Practice (EU GVP) module V revision 2, if an important identified or potential risk common to other members of the pharmacological class is not thought to be an important identified or important potential risk with the concerned medicinal product, the evidence to support this should be provided and discussed. Thus, a justification for non-inclusion of SIB in the list of safety concerns for bimekizumab is provided.

Patients with PSO are at increased risk for depression, anxiety, and suicidality compared to the general population (Kurd et al, 2010). Data from a systematic review and meta-analysis conducted by Singh et al (2017b) showed patients with PSO were twice as likely to consider suicide than the general population. Additionally, PSO was significantly associated with both attempted and completed suicide. Across the currently available literature, studies assessing suicidality and depression among patients with PSO use a variety of methods and outcome definitions resulting in a wide range of estimates. In patients with PSO, rates of suicidal ideation range from <1.0% to 17.0% (Kurd et al, 2010; Dalgard et al, 2015) and depression ranges from 9.0% to 39.8% (Egeberg et al, 2016b; Dowlatshahi et al, 2014).

Given the association of suicidal ideation and depression in the PSO population, UCB conducted robust surveillance of suicidality:

- Questionnaires were used for proactive screening and monitoring of suicidality (electronic Columbia-Suicide Severity Scale) and depression/anxiety (Hospital Anxiety and Depression Scale in Phase 2 studies) and depression (Patients' Health Questionnaire-9 in Phase 3 studies) in alignment with the US Food and Drug Administration recommendations to prospectively monitor neuropsychiatric events using validated instruments.
- All programmatically-identified treatment-emergent AEs (including all fatal cases) and abnormal monitoring scale scores meeting threshold criteria for withdrawal were sent to the independent Neuropsychiatric Adjudication Committee Chair for review and potential escalation to the Committee for adjudication.

In the PSO Phase 3 studies with bimekizumab, participants with a history of suicidality were not excluded from participation, unless they had a suicide attempt within the last 5 years or active

suicidal ideation in the last month; as these participants are generally not considered appropriate candidates for enrollment in blinded controlled studies.

No completed suicide or suicidal attempt was reported in study participants on bimekizumab in the PSO development program. As of the data lock point of this RMP, one event reported under bimekizumab was adjudicated as suicidal ideation; this individual case was confounded by schizoaffective disorder- bipolar type and medical history of suicide attempt. The incidence rate of adjudicated SIB under bimekizumab was very low (0.1 per 100 participant-years) with no evidence of increased rates compared to the background population. No particular trend in event type was identified in the Psychiatric disorders System Organ Class or from ongoing neuropsychiatric monitoring through questionnaires during studies.

T-helper17 cells and IL-17A contribute to glial activation and neuroinflammation and their presence at inflammatory sites in the brain has a deleterious effect (Cipollini et al, 2019; Ye et al, 2019). Mounting evidence suggests that inflammation is involved in suicidal behavior. Holmes et al (2018) confirmed the evidence of increased microglial activation in the anterior cingulate cortex during a moderate to severe major depressive episode. Furthermore, inflammatory cytokines may serve as mediators of both environmental and genetic factors that contribute to the development of depression (Felger and Lotrich, 2013). Transfer of immunoglobulins (including IgG1 and thus bimekizumab) across the blood brain barrier is expected to be minimal and while it may increase under inflammatory conditions, the effect would theoretically be beneficial by decreasing chronic neuroinflammation.

Currently there is no evidence to suspect a causal relationship between bimekizumab and development of SIB, and evidence from published literature supports a possible beneficial effect of IL-17 inhibition in CNS disorders characterized by neuroinflammation. Thus, SIB does not meet the definition of important potential risk for bimekizumab per EU GVP module V (revision 2) and is not included in the summary of safety concerns for bimekizumab.

1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table 1–2: Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks	
Serious infections	
Risk-benefit impact	Interleukin-17A and IL-17F play a role in protection against mucoepidermal immunity by a variety of pathogens and inhibition of IL-17 may increase susceptibility of infection during the period of exposure (Ishigame et al, 2009). A small but persistent increased risk of serious infection has been identified across a range of IL-17 inhibitors authorised for treatment of PSO. Serious infection was added as an important identified risk as a class effect for IL-17 inhibitors. Infections were amongst the most commonly observed TEAE in the clinical trials of bimekizumab. In the SmPC, clinically important active infections (eg, active tuberculosis) are included as a contraindication (SmPC Section 4.3) and information is also included in SmPC Section 4.4 and SmPC Section 4.8 to minimise the risk of serious infections. Serious infections may require medical intervention to be treated, often requiring hospitalization. Serious infections are thus included as an important identified risk consistent with the IL-17 inhibitor class.

Table 1–2: Risks considered important for inclusion in the list of safety concerns in the RMP

Important potential risks	
Serious hypersensitivity reactions	
Risk-benefit impact	All monoclonal antibodies could potentially be associated with hypersensitivity reactions, including anaphylactic/anaphylactoid events. From the nonclinical and clinical study program analysis there is evidence to suggest a causal relationship between bimekizumab and certain hypersensitivity events, such as dermatitis and eczema, which are mostly nonserious, mild to moderate and not leading to drug discontinuation. No cases of anaphylactic reactions related to bimekizumab were observed in the clinical program. Anaphylactic reactions are severe, potentially life-threatening allergic reactions. Serious hypersensitivity reactions may need immediate medical intervention and/or hospitalization. Hypersensitivity to the active substance or to any of the excipients is included as a contraindication (SmPC Section 4.3) and a warning and precaution to minimize the risk is also included in SmPC Section 4.4. Serious hypersensitivity reactions are considered an important potential risk with bimekizumab.
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	
Risk-benefit impact	In accordance with observations from clinical programs with other IL-17 inhibitors and as an expected comorbidity for the psoriasis patient population, new onset IBD (ulcerative colitis) was observed in clinical studies with bimekizumab in PSO. Exacerbation or new onset of Crohn's disease and ulcerative colitis were observed in bimekizumab treated patients during clinical studies in other indications under development. With the limited number of cases seen in the clinical development program a causal association of bimekizumab with occurrence of IBD cannot be established. However, due to the potential involvement of the IL-17 pathway in the pathogenesis, it is not possible to rule out the potential of increased risk for IBD. A study evaluating high doses of bimekizumab in study participants with active moderate to severe ulcerative colitis (UC0011 - EudraCT: 2016-000420-26) was terminated early (at the recommendation of the DMC) based on an imbalance in TEAEs and SAEs together with an observed increase in clinical signs of ulcerative colitis. The observed increase in clinical symptoms suggestive of ulcerative colitis was not reflected in similar changes in the variables that objectively measured disease activity (total Mayo scores, endoscopy, and histopathology assessments). The total Mayo scores did not indicate an objective worsening of the underlying condition, although the number of study participants that had endoscopy was too small to enable definitive conclusions. Inflammatory bowel disease is a chronic disease potentially impacting the quality of life of patients and requiring long-term management. Inflammatory bowel disease can be debilitating and sometimes leads to life-threatening complications. Inflammatory bowel disease (Crohn's disease and ulcerative colitis) is thus considered as important potential risk. Information related to IBD is described in SmPC Section 4.4 (Special warnings and precautions for use) and SmPC Section 4.8 (Undesirable effects).
Major adverse cardiovascular events (MACE)	

Table 1–2: Risks considered important for inclusion in the list of safety concerns in the RMP

Risk-benefit impact	Psoriasis is associated with increased prevalence of cardiovascular risk factors including smoking, limited physical activity, obesity, diabetes, hypertension, and hyperlipidemia (Parisi et al, 2015). The combined presences of these risk factors are collectively known as metabolic syndrome. In addition, PSO patients have an increased risk of vascular inflammation and MACE (defined as myocardial infarction, stroke and cardiovascular related death) beyond that attributable to known cardiovascular risk factors (Egeberg et al, 2017; Gelfand et al 2006). Based on the available preclinical data for bimekizumab, there is no evidence to indicate an increased risk of MACE. In the clinical studies, the exposure adjusted incidence rate of MACE in the bimekizumab PSO program is similar to other IL-17 inhibitors and in line with the expected incidence in the treated patient population. No increased risk of MACE was associated with bimekizumab treatment beyond that attributable to the potential underlying risk with PSO. However, MACE remains a theoretical risk for biologic immunomodulators and is considered as an important potential risk for other IL-17A inhibitors or IL-17 RA antagonist molecules. Further patient exposure is needed to completely evaluate the risk of MACE with bimekizumab. Major adverse cardiovascular events are serious in nature, patients may be hospitalized for treatment (including surgical interventions) and disability or death may occur. Thus, MACE is included as an important potential risk for bimekizumab.
Malignancy	
Risk-benefit impact	Immunosuppressors can increase the risk for some specific cancers, such as lymphomas, nonmelanoma skin cancers, Kaposi sarcomas and hepatocarcinoma (Bugelski et al, 2010). Interleukin-17, with its pro-inflammatory properties, may play a dual role in cancer, serving either as a promoter or antitumor factor, possibly dependent on the cellular source. In some studies IL-17 has been demonstrated to promote an antitumor cytotoxic T cell and NK response leading to tumor regression. Alternatively, IL-17 has been postulated to have a role in early tumor formation, tumor proliferation, metastasis, and chemoresistance by facilitating angiogenesis, recruiting MDSC and neutrophils, and inhibiting apoptosis. Carcinogenic potential of prolonged inhibition of IL-17A and IL-17F with bimekizumab was assessed in a carcinogenicity assessment document. The report concludes that the effects of IL-17 may depend on the specific tumor microenvironment and tumor/immune cell phenotype in each individual. It is also possible that Th17 role vary according to cancer cause, type, location, and stage of the disease. However, no strong impact on immune function/status has been noticed in toxicity studies with bimekizumab. The carcinogenic risk of bimekizumab is not expected to be significantly different from that of IL-17A inhibitors. Based on bimekizumab's clinical data there is no evidence to suggest an increased risk of malignancy among patients receiving bimekizumab compared to placebo, however, the clinical data is limited by duration of exposure to detect malignancy as an adverse reaction. Malignancies are often serious, needing chronic medical intervention. Hospitalization is often required in order to provide appropriate treatment (medication and/or procedure). Malignancies have a potential for a severe outcome and death.

Table 1–2: Risks considered important for inclusion in the list of safety concerns in the RMP

	Malignancy is thus considered an important potential risk for bimekizumab in line with other IL-17 inhibitor molecules and immunomodulating drugs.
Missing information	
Use during pregnancy and lactation	
Risk-benefit impact	No effects of bimekizumab have been observed on pregnancy and parturition in Cynomolgus monkeys, or on fetal, and peri-and postnatal development of infant monkeys. There are no adequate data on the use of bimekizumab in pregnant women. Women of childbearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment (SmPC Section 4.6). It is unknown whether bimekizumab is excreted in human milk. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from bimekizumab therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. Use during pregnancy and lactation is thus considered missing information.
Long-term safety data	
Risk-benefit impact	Limited data are currently available on long term use (beyond 60 weeks) in adult patients with moderate to severe plaque PSO. Long-term use of bimekizumab is currently under investigation in the OLE study PS0014 (up to 144 weeks in addition to the exposure in respective feeder studies) (EudraCT #2016-003427-30) and in study PS0015 (up to 144 weeks) (EudraCT #2017-003784-35).

DMC=data monitoring committee; IBD=inflammatory bowel disease; IL=interleukin; IL-17RA=interleukin-17 receptor A; MACE=major adverse cardiovascular events; MDSC=myeloid derived suppressor cells; NK=natural killer cells; OLE=open label extension; PSO=psoriasis; RMP=Risk Management Plan; SAE=serious adverse event; SmPC=summary of product characteristics; TEAE=treatment-emergent adverse event; Th=helper T cells

2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns were identified or reclassified as part of this updated RMP.

3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

PSO: Data from the initial placebo-controlled period (Pool S1) and for the combined Initial, Maintenance, and OLE study Periods (Pool S2) from the PSO clinical development program are provided for characterization of the risks.

PsA: Data from the initial placebo-controlled period, through Week 16 (Pool SP1) and for the combined Initial, Maintenance, and OLE Treatment Periods with the available data at the time of the designated cut-off date (Pool SP2) from the PsA clinical development program are provided for characterization of risks.

axSpA: Data from the initial placebo-controlled period, through Week 16 (Pool SA1) and for the combined Initial, Maintenance, and OLE Treatment Periods with the available data at the time of

the designated cut-off date (Pool SA2) from the axSpA clinical development program are provided for characterization of risks.

HS: Data from the initial placebo-controlled period through Week 16 (Pool S1) and for the combined Initial, Maintenance, and OLE study Periods (Pool S3) from the HS clinical development program are provided for characterization of the risks.

3.1 Presentation of important identified risks and important potential risks

3.1.1 Important identified risks

Important identified risks with bimekizumab treatment are characterised in Table 3–1 and Table 3–2.

Table 3–1: Important identified risk: Serious infections

Potential mechanisms	Bimekizumab is a humanised IgG1 mAb (produced by recombinant DNA technology) that selectively and potently inhibits the activity of both IL-17A and IL-17F isoforms in vitro. A potential risk of infections is associated with any immunomodulatory biologic agent. Interleukin-17A and IL-17F play a role in the protection against mucoepidermal infection by a variety of pathogens and inhibition of IL-17 may increase susceptibility to infection during the period of exposure (Ishigame et al, 2009).
Evidence source(s) and strength of evidence	Serious infections are considered as an important identified risk as a class effect for IL-17 inhibitors.
Characterization of the risk	Frequency: **PSO:** In Pool S1, the incidence of SAEs in the SOC of Infections and infestations in the Initial Treatment Period was low (2 study participants [0.3%]; EAIR: 1.0/100 py [95% CI: 0.1, 3.5]) in the bimekizumab 320mg Q4W group. Two serious infections (enterovirus infection and pneumonia) were reported in 1 study participant each (0.1%; EAIR: 0.5/100 py [95% CI: 0.0, 2.7]). Both TEAEs resolved. No study participant reported serious infections while receiving placebo. In Pool S2, the incidence of SAEs in the SOC of Infections and infestations in the Combined Initial, Maintenance, and OLE Treatment Period was also low (25 study participants [1.4%]; EAIR: 1.4/100 py [95% CI: 0.9, 2.0] in the Phase 2/3 bimekizumab Total group). There were no opportunistic infections reported with bimekizumab in the PSO studies other than localized mucocutaneous fungal events (all but 1 were nonserious), which are expected per mechanism of action and were classified as opportunistic by internal company conventions. There were no cases of active TB among bimekizumab-treated study participants. **PsA**: In Pool SP1, the incidence of SAEs in the SOC of Infections and infestations in the Initial Treatment Period was low (3 study participants [0.4%]; EAIR: 1.4/100 py [95% CI: 0.3, 4.0]) in the bimekizumab 160mg Q4W group. Two

Table 3–1: Important identified risk: Serious infections

	serious infections of pneumonia were reported in 2 study participants (0.3%; EAIR: 0.9/100 py [95% CI: 0.1, 3.3]) and 1 serious infection of bronchitis was reported in 1 study participant (0.1%; EAIR: 0.5/100 py [95% CI: 0.0, 2.5]). All 3 SAEs resolved or are resolving. No study participant reported serious infections while receiving placebo. In Pool SP2, the incidence of SAEs in the SOC of Infections and infestations in the Combined Initial, Maintenance, and OLE Treatment Period was also low (30 study participants with 32 infections [2.1%]; EAIR: 1.1/100 py [95% CI: 0.8, 1.6] in the bimekizumab Total group). There were no opportunistic infections reported with bimekizumab in the PsA studies other than localized mucocutaneous fungal events (all but 1 were nonserious), which are expected per mechanism of action and were classified as opportunistic by internal company conventions. There were no cases of active TB among bimekizumab-treated study participants. **axSpA**: In Pool SA1, the incidence of SAEs in the SOC of Infections and infestations in the Initial Treatment Period was low: 1 study participant (0.3%; EAIR: 0.9/100 py [95% CI: 0.0, 5.1]) in the bimekizumab 160mg Q4W group was reported with a serious infection of hepatitis A and 1 study participant (0.4%; EAIR: 1.4/100 py [95% CI: 0.0, 7.6]) in the placebo group was reported with a serious viral infection. In Pool SA2, the incidence of SAEs in the SOC of Infections and infestations in the Combined Initial, Maintenance, and OLE Treatment Period was also low (31 study participants [3.3%] reported 36 serious infections; EAIR: 1.4/100 py [95% CI: 1.0, 2.0] in the bimekizumab Total group). Opportunistic infections reported with bimekizumab in the axSpA studies were all localised mucocutaneous fungal events, with the exception of 2 nonserious herpes viral infections (herpes zoster considered not related to bimekizumab and herpes oesophagitis considered related to bimekizumab). **HS:** In Pool S1, the incidence of SAEs in the SOC of Infections and infestations during the Initial Treatment Period was low (1 study participant [0.1%]; EAIR: 0.4/100 py [95% CI: 0.0, 2.1]) in the bimekizumab Total group. One serious infection of cellulitis was reported in the 320mg Q2W group (0.2%; EAIR: 0.6/100 py [95% CI: 0.0, 3.2]), which resolved. No study participant reported serious infections while receiving placebo. In Pool S3, the incidence of SAEs in the SOC of Infections and infestations in the Combined Initial, Maintenance, and OLE Treatment Periods was also low in the Phase 2/3 bimekizumab Total group (22 study participants [2.1%] with 25 events; EAIR: 1.7/100 py [95% CI: 1.1, 2.6]). There were no opportunistic infections reported with bimekizumab in the HS studies other than localized mucocutaneous fungal events (all but 2 [oropharyngeal candidiasis and genital candidiasis] were nonserious), which are

Table 3–1: Important identified risk: Serious infections

	expected per mechanism of action and were classified as opportunistic by internal company conventions. There were no cases of active TB among bimekizumab-treated study participants. Severity: **PSO:** In Pool S1, of the 2 serious infections reported, the event of enterovirus infection was severe in intensity, and the event of pneumonia was moderate. In Pool S2, of the 25 serious infections reported, 9 were moderate in intensity and 16 were severe. None of the serious infections led to a fatal outcome. **PsA**: In Pool SP1, 2 serious infections were severe in intensity (1 event of pneumonia and 1 event of bronchitis) and 1 serious infection of pneumonia (reported as Covid pneumonia) was moderate in intensity. In Pool SP2, of the 32 serious infections reported in 30 study participants, 2 infections were mild, 18 were moderate, and 12 were severe in intensity. None of the serious infections led to a fatal outcome. **axSpA**: In Pool SA1, both serious infections reported were moderate in intensity. In Pool SA2, of the 36 serious infections reported, 3 were mild, 22 were moderate, and 11 were severe in intensity. None of the serious infections led to a fatal outcome. **HS:** In Pool S1, the serious infection of cellulitis was of severe intensity. In Pool S3, of the 25 serious infections reported, 7 were moderate and 18 were severe in intensity. Reversibility: **PSO:** In Pool S1, the outcome of both TEAEs of serious infections was resolved. In Pool S2, the outcome of 24 of the 25 serious infections was resolved; the outcome of the remaining event was resolved with sequelae. **PsA**: In Pool SP1, the outcome of all 3 TEAEs of serious infections was resolved or resolving at the time of data cut-off. In Pool SP2, the outcome of 29 of the 32 serious infections was resolved; the outcomes of the remaining 3 events were resolved with sequelae (postoperative wound infection), resolving (gangrene), and not resolved (infective bursitis) at the time of data cut-off. **axSpA**: In Pool SA1, the outcome of both TEAEs of serious infections was resolved. In Pool SA2, the outcome of 33 of the 36 serious infections was resolved and 3 resolved with sequelae. **HS:** In Pool S1, the outcome of the serious TEAE of cellulitis was. In Pool S3, of the 25 serious infections reported, 19 had resolved, 1 had resolved with sequelae, 3 were resolving, and 1 was not resolved (cellulitis) at the time of the data cut-off; in addition, 1 case reported as possible CNS infection had a fatal outcome (PT: central nervous system infection).

Table 3–1: Important identified risk: Serious infections

	Long term outcome/ impact on quality of life: Serious infections may require medical intervention to be treated, often requiring hospitalization. No long-term effect is expected after resolution of the serious infection.
Absolute risk	**PSO**: In the current literature, the risk of serious infection is overall higher in patients with PSO compared to the general population, including but not limited to pneumonia, staphylococcus, herpes, respiratory tract, abdominal, and skin infections (Takeshita et al, 2017). A Dutch cohort study of 25,742 PSO patients, reported that the incidence of serious infection in PSO was twice as high as in the non-PSO population (908 vs 438 events/100,000 person years) (Wakkee et al, 2011). When adjusting for PSO treatment including biologics, PSO was found to be independently associated with an increased risk of serious infection (HR: 1.54 [95% CI: 1.44-1.65]). This demonstrates that beyond any increased risk due to biologic treatment, having PSO was associated with 1.54 times the risk of serious infection compared to patients without PSO. Respiratory tract, abdominal, and skin infections were the most commonly reported infections. In the bimekizumab PSO development program, the incidence rate of serious infections was low (1.4/100 py) and, in line with expectations for the study population, events were mostly related to skin (cellulitis, abscess), ear infections, and the gastrointestinal tract. All serious infections were resolved (1 erysipelas resolved with sequela of edema) and in the vast majority, treatment with bimekizumab was resumed following event resolution. **PsA**: A cohort study of patients with PSO or PsA estimated that after adjustment of propensity scores, there was no evidence of increased risk of serious infections with IL-17, as compared to either TNF-α (HR=0.89, 95% CI 0.48-1.66) or IL-12/23 (HR=1.12, 95% CI 0.62-2.03). However, IL-23/23 were associated with a lower risk of infections than TNF-α (HR=0.59, 95% CI 0.39-0.90) (Li et al, 2019). The Psoriasis Longitudinal Assessment and Registry enrolled 4315 PsA patients and reported an incidence rate of serious infections as 2.0 per 100 py. The most commonly reported serious infections were cellulitis (n=25) and pneumonia (n=24). (Ritchlin et al, 2019). A retrospective study reported that the incidence rate of serious infections was 2.6 (95% CI: 1.9-3.7) per 100 py. Age was reported to be a confounding factor for increased risk of serious infections in the study (Porrua et al, 2021). In the bimekizumab PsA development program, the incidence rate of serious infections was low (1.1/100 py) and, in line with expectations for the study populations. **axSpA**: A meta-analysis including data from 25 randomized clinical trials revealed that the risk of serious infections was increased numerically (non-statistically significant) in patients with AS and nr-axSpA treated with biologics compared with controls (odds ratio: 1.42; 95% CI: 0.58-3.47); there was no significant effect of biologics on serious infections in patients with AS (p=0.29) and nr-axSpA (p=0.89) (Wang et al, 2018a). In the bimekizumab axSpA development program, the incidence rate of serious infections was low (1.4/100 py).

Table 3–1: Important identified risk: Serious infections

	HS: In the current literature, there are no robust observational studies on the background risk of serious infections in general HS patient population. The only reported information on serious infections comes from 5 small cohort studies with patients undergoing treatment for HS, 4 studies with a biologic (Elis et al, 2020; Esme et al, 2022; Marzano et al, 2020; Odorici et al, 2022) ranging from 11 to 389 patients, and 1 study with 98 patients treated with retinoids (Bouwman et al, 2022). Besides the low number of patients, none of the studies used a comparator group. Therefore, no information on the relative risk of serious infections in HS patients comparing with other populations is available. While there is no apparent increased risk of serious infections with bimekizumab as compared to the background risk in the treated populations, a small but persistent increased risk of serious infections has been identified with IL-17 inhibitors. Serious infection is considered an important identified risk as a class effect for IL-17 inhibitors.
Risk factors and risk groups	**PSO:** Increasing age, diabetes mellitus, smoking, significant infection history, and PSO treatment were each associated with an increased risk of serious infections (Kalb et al, 2015). Treatment with biologics or small molecules may increase risk of serious infection in PSO patients, with variability by the mechanism of action (Siegel and Winthrop 2019). **PsA**: Increasing age, prednisone use, PGA scores of 4 or 5 at the time closest to the reported event, history of infection, diabetes, chronic pulmonary comorbidity, and total duration of bDMARD use can potentially contribute to the risk of development of serious infections (Celkys et al, 2020, Ritchlin et al, 2019). Comorbidity Index (risk increased with increasing score), and annual average number of csDMARD prescriptions are significantly associated with increased risk of hospitalization for infections in patients with PsA (Quartuccio al, 2019). Empirical evidence for risk of serious infections with biologic use in PsA is variable (Li 2019, Malik et al, 2018). **axSpA**: Annual average number of csDMARD prescriptions and time to first biological drug prescription are significantly associated with increased risk of hospitalization for infections in patients with AS (Quartuccio et al, 2019). The use of biologics among patients with AS and nr-axSpA are not significantly associated with an increased risk of serious infection (Wang et al, 2018b). **HS**: Patients with HS have multiple potential risk factors for serious and antibiotic-resistant infections, including epidermal disruption from suppurating lesions and erosions; treatment with immunosuppressants, topical agents and/or oral antibiotics; and comorbidities such as diabetes that are independently associated with infections (Lee et al, 2020; Bettoli et al, 2019).
Preventability	Use of bimekizumab is contraindicated in patients with clinically important active infections (eg, active tuberculosis) (SmPC Section 4.3). Caution should be exercised when considering the use of bimekizumab in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur (SmPC Section 4.4). Information on serious infections is also provided in SmPC Section 4.8 (Undesirable effects).

Table 3–1: Important identified risk: Serious infections

Impact on risk-benefit balance of the product	The majority of TEAEs of infections observed with bimekizumab were mild to moderate and were resolved with standard of care treatment. Risk of serious infections has been considered in the overall benefit-risk assessment with the benefit-risk balance remaining positive. Routine and additional pharmacovigilance activities will be implemented to monitor this risk (see Part III, Table 3-1). Clinically important active infections (eg, tuberculosis) are considered a contraindication (SmPC Section 4.3) and risk of infection is included in the warnings and precautions for use (SmPC Section 4.4). Information on serious infections is also provided in SmPC Section 4.8 (Undesirable effects). Risk minimization activities are discussed in Part V, Table 3-1.
Public health impact	No significant public health impact is expected. Per real world evidence data, PSO, PsA, axSpA, and HS are found to be independently associated with an increased risk of serious infection.

AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; bDMARD=biologic disease-modifying antirheumatic drug; CI=confidence interval; csDMARD=conventional synthetic disease-modifying antirheumatic drug; DNA=deoxyribonucleic acid; EAIR=exposure adjusted incidence rate; HR=hazard ratio; HS=hidradenitis suppurativa; IgG1=immunoglobulin G1; IL=interleukin; mAb=monoclonal antibody; nr-axSpA=non-radiographic axial spondyloarthritis; OLE=open-label extension; PGA=physician's global assessment; PsA=psoriatic arthritis; PSO=psoriasis; py=participant-years; Q2W=every 2 weeks; Q4W=every 4 weeks; SAE=serious adverse event; SOC=System Organ Class; SmPC=summary of product characteristics; TB=tuberculosis; TEAE=treatment-emergent adverse event; TNF=tumor necrosis factor

Data sources: PSO: Integrated Summary of Safety Data Table 5.1.3 and Table 5.2.3; PsA Integrated Summary of Safety Data Table 5.1.3, Table 5.2.3, Table 5.1.9.1.3, Table 5.2.9.1.3, Listing 2.1.1, Listing 2.1.2, Listing 2.2.1, Listing 2.2.2; axSpA Integrated Summary of Safety Data Table 5.1.3, Table 5.2.3, Table 5.1.9.1.3, Table 5.2.9.1.3, Listing 2.1.2, Listing 2.2.2, Listing 2.1.5.1.2, Listing 2.2.5.1.2; HS: Integrated Summary of Safety Data Table 5.1.9.1.1, Table 5.3.3, Table 5.3.9.1.1, Table 5.3.14.1.2, Table 5.3.16.1.1, Table 5.1.18.1.1, Table 5.3.9.1.3, Listing 2.1.2, Listing 2.3.1, Listing 2.3.2, Listing 2.3.5.1.2.

Table 3–2: Important identified risk: Inflammatory bowel disease (Crohn's disease and ulcerative colitis)

Potential mechanisms	The current literature is not conclusive. Common genetic and inflammatory pathways have been implicated in PSO and IBD, which includes CD and UC. (Takeshita et al, 2017). Data have shown that ribonucleic acid transcripts for IL-17A and IL-17F are upregulated in the inflamed mucosa of IBD patients (Galvez, 2014). It has been postulated that IL-17 and T-helper 17 cells might have protective rather than pro-inflammatory roles in the intestine which may explain the lack of response to IL-17 inhibitors in IBD and potential for worsening of existing disease (Akiyama and Sakuraba, 2021). Inflammatory bowel disease has been intrinsically linked to axSpA as an extra-musculoskeletal manifestation of the disease. The overlap between axSpA and IBD is well established, and epidemiological studies have consistently shown a strong association between these diseases. Epidemiological studies have shown a significant association between HS and IBD; the conditions also share common clinical manifestations, genetic susceptibility, and immunologic features. In addition, T helper type 17 cells, interleukin-23, and tumor necrosis factor have been implicated in both HS and IBD pathogenesis, (Egeberg et al, 2017).
Evidence source(s) and strength of evidence	This risk is based on a safety evaluation performed including pharmacoepidemiological background incidence and prevalence rates of IBD, comparison of data from other IL-17 inhibitors, and review of bimekizumab clinical data (including the study UC0011 - EudraCT # 2016-000420-26).

Characterization of the risk	Frequency: TEAEs coded to the HLT of "Colitis (excl infective) were used for characterization of risk of IBD events in PSO program. **PSO**:In Pool S1, one study participant (0.1%; EAIR: 0.5/100 py [95% CI: 0.0, 2.7]) in the bimekizumab 320mg Q4W group reported a TEAE of IBD (PT: Ulcerative colitis). No study participants in the placebo group reported an IBD TEAE. In Pool S2, no additional TEAEs of IBD were reported in any treatment group compared with Pool S1 (<0.1%; EAIR: 0.055/100 py [95% CI: 0.001, 0.304]). Gastrointestinal events of interest were adjudicated by an expert committee who performed independent medical review of all potential IBD adverse events reported during bimekizumab clinical studies for UCB. Events adjudicated as definite or probable IBD were used for characterization of risk of IBD events in the PsA, axSpA, and HS indications. **PsA**: In Pool SP1, no study participants in the bimekizumab 160mg Q4W or placebo groups reported a TEAE that was adjudicated as a definite or probable IBD TEAE. In Pool SP2, 7 study participants (0.5%) in the bimekizumab Total group reported 8 TEAEs that were adjudicated as definite or probable IBD TEAEs (EAIR 0.3/100 py [95% CI: 0.1, 0.5]), including 3 study participants with 4 definite IBD events (ulcerative colitis in 1 study participant; enteritis and inflammatory bowel disease in 1 study participant, and microscopic colitis in 1 study participant), and 4 study participants with a probable IBD event each (colitis in 1 study participant and diarrhoea in 3 study participants). **axSpA**: In Pool SA1, 2 study participants (0.6%; EAIR 1.8/100 py [95% CI: 0.2, 6.7]) in the bimekizumab 160mg Q4W group reported a TEAE that was adjudicated as a definite or probable IBD TEAE (PTs: Crohn's disease [definite] and Ulcerative colitis [probable]). One study participant (0.4%; EAIR 1.4/100 py [95% CI: 0.0, 7.6]) in the placebo group reported a TEAE that was adjudicated as definite or probable IBD TEAE (PT: Ulcerative colitis [definite]). In Pool SA2, 17 study participants (1.8%; EAIR 0.8/100 py [95% CI: 0.4, 1.2]) in the bimekizumab Total group reported 29 TEAEs that were adjudicated as a definite or probable IBD TEAE. Events reported in 2 or more study participants and adjudicated as a definite IBD TEAE were Crohn's disease (4 study participants) and Ulcerative colitis (5 study participants). Events reported in 2 or more study participants and adjudicated as a probable IBD TEAE were Crohn's disease and diarrhoea (2 study participants each). **HS:** In Pool S1, 4 study participants (0.5%; EAIR: 1.5/100 py [95% CI: 0.4, 3.9]) reported 5 events that were adjudicated as definite or probable IBD: 3 participants in the bimekizumab 320mg Q4W group (1.1%; EAIR: 3.5/100 py [95% CI: 0.7, 10.2]) with 1 event each (2 with diarrhoea, 1 with colitis microscopic), and 1 participant in the bimekizumab 320mg Q2W group (0.2%; EAIR: 0.6/100 py [95% CI: 0.0, 3.2]) with 2 events (colitis ulcerative and proctitis). In Pool S3, 8 study participants in the Phase 2/3 bimekizumab total group (0.8%; EAIR: 0.6/100 py [95% CI: 0.3, 1.2]) reported 16 events that were adjudicated as definite or probable IBD (3 events of Crohn's disease, 5 events of diarrhoea, 4 events of colitis ulcerative, 2 events of colitis microscopic, 1 event of proctitis, and 1 event of abdominal pain).

Table 3–2: Important identified risk: Inflammatory bowel disease (Crohn's disease and ulcerative colitis)

	Severity: **PSO:** The event of UC was moderate. **PsA**: In Pool SP2, of the 8 TEAEs that were adjudicated as definite or probable IBD TEAEs, 1 event of was mild (diarrhoea), 6 events were moderate (ulcerative colitis, inflammatory bowel disease, microscopic colitis, colitis, and 2 events of diarrhoea) and 1 event was severe (enteritis). **axSpA**: In Pool SA1, 1 event of definite or probable IBD in the bimekizumab 160mg Q4W group was severe, and 2 events (1 each in the placebo and bimekizumab 160mg Q4W groups) were moderate in intensity. In Pool SA2, of the 29 TEAEs that were adjudicated as a definite or probable IBD TEAE, 7 were mild, 18 were moderate, and 4 were severe in intensity. **HS:** In Pool S1, of the 5 events that were adjudicated as definite or probable IBD, 3 events were mild, 1 event was moderate, and 1 event was severe. In Pool S3, of the 16 events that were adjudicated as definite or probable IBD, 8 were mild, 6 were moderate, and 2 were severe in intensity. Reversibility: **PSO**: The event of UC was not resolved. **PsA**: In Pool SP2, of the 8 TEAEs that were adjudicated as definite or probable IBD TEAEs, 7 events were resolved (ulcerative colitis, enteritis, microscopic colitis, colitis, and 3 events of diarrhoea) and 1 event was not resolved (inflammatory bowel disease) at the time of data cut-off. **axSpA**: In Pool SA1, 1 event of definite or probable IBD in the placebo group was resolving and 2 events (both in the bimekizumab 160mg Q4W group) had resolved with sequelae at the time of data cut-off. In Pool SA2, of the 29 TEAEs that were adjudicated as a definite or probable IBD TEAE, 15 resolved, 4 resolved with sequelae, and 10 had not resolved at the time of data cut-off. **HS:** In Pool S1, all 5 events that were adjudicated as definite or probable IBD were resolved. In Pool S3, of the 16 events that were adjudicated as definite or probable IBD, 10 were resolved, 1 was resolving, and 5 were not resolved at the time of the data cut-off (2 events of Crohn's disease, 2 events of colitis ulcerative, and 1 event of abdominal pain).
	Long term outcome/ impact on quality of life: The IBD symptoms may have a substantial impact on patients' lives and quality of life, potentially requiring treatment with chronic immunomodulators, biologics, or surgical interventions (Ghosh and Mitchell, 2007).

Absolute risk	**PSO:** Several studies have observed increased prevalence and incidence of IBD among patients with PSO compared to patients without PSO. EU-based studies of PSO patients have reported a prevalence of IBD (UC and CD combined) from 0.7% to 1.6% (Li et al, 2013; Eppinga et al, 2017) compared to a prevalence in the general population of up to 0.5% (Molodecky et al, 2012). Prevalence estimates from a medical record review of 1669 PSO patients from a large medical center in the Netherlands reported that 1.6% of PSO patients had comorbid IBD, specifically 0.7% CD and 0.8% UC (Eppinga et al, 2017). In a US prospective cohort study among 2755 female patients with self-reported PSO, incidence rates were 0.03 per 100 patient-years for CD and 0.01 per 100 patient-years for UC (Li et al, 2013). New-onset or exacerbation of IBD has been reported in patients treated with IL-17 inhibitors, although causality has not been fully established and longer-term studies are needed to fully evaluate the risk (Fieldhouse et al, 2020). Based on these observations with the class of IL-17 inhibitors, study participants with active IBD were excluded from study participation. Study participants with a history of IBD were allowed to participate in bimekizumab studies as long as they had no active symptomatic disease at Screening or Baseline. Overall, there was no evidence of an increased risk of IBD with bimekizumab in the PSO development program with a single case of IBD (new onset colitis ulcerative [EAIR: 0.055/100 py]) reported. **PsA**: A cohort study reported that the incidence rate (IR per 10,000 py) for IBD among patients with PsA was 7.68 (95% CI: 5.18 to 10.96) compared to 4.58 in the general population (95% CI: 3.55 to 5.81). The IR of CD in patients with PsA was 4.09 (95% CI: 2.34 to 6.65) compared to 1.71 in the general population (95% CI: 1.11 to 2.52). The adjusted RR of CD was 2.96 (95% CI: 1.46 to 6.00) and 3.60 (95% CI: 1.83 to 7.10) for the general population and PSO cohorts and for UC was 1.30 (95% CI: 0.66 to 2.56) and 0.98 (95% CI: 0.50 to 1.92), respectively. The adjusted models accounted for smoking status, BMI and PSO severity on the index date. (Charlton et al, 2018). A meta-analysis reported the pooled prevalence for IBD as 3.3% (95% CI: 1.5-7.1, I2 = 97%), UC as 0.9% (95% CI: 0.6-1.5, I2 = 91%) and CD as 1.1% (95% CI: 0.6-1.9, I2 = 95%), albeit with a high inter-study heterogeneity independent of age, sex, year of publication, geography or bias score (Pittam et al, 2020). The incidence of IBD in study participants treated with bimekizumab was not increased beyond expected background rates of IBD in PsA populations. **axSpA**: Using data from the IBM MarketScan Research Databases, a study demonstrated that the prevalence of IBD was 6.05% and 0.60% in patients with AS and the general population, respectively. The 1-year incidence rate of IBD was 0.52% in the overall inflammatory disease cohort (AS cohort: 1.73%; PSO without PsA cohort: 0.39%; PSO or PsA cohort: 0.50%; AS, PsA, or PSO cohort: 0.54%) and in the general population was 0.25% (Hudesman et al, 2020). The studies pertaining to the incidence and prevalence of IBD in nr-axSpA are limited. The incidence of IBD in study participants treated with bimekizumab was not increased beyond expected background rates of IBD in axSpA populations. **HS**: The prevalence of IBD in patients with HS varied in the literature, ranging from 1.4% in a single-centre study in the USA (Cices et al, 2017) to 6.6% in a

Table 3–2: Important identified risk: Inflammatory bowel disease (Crohn's disease and ulcerative colitis)

	tertiary referral centre in Denmark (Jørgensen et al, 2020). The prevalence of CD ranged from 0.21% in a claims database study from Korea (Lee et al, 2018) to 4.3% in a tertiary referral centre in Denmark (Jørgensen et al, 2020). The prevalence of UC ranged from 0.2% in an electronic medical record database from the UK (Ingram et al, 2018) to 2.6% in a tertiary referral centre in Denmark (Jørgensen et al, 2020). Two studies showed that patients with more severe HS had higher CD prevalences vs those with less severe HS (Jørgensen et al, 2020: Hurley stage 1=0%, stage 2=5.6% and stage 3=6.7%); (Kimball et al, 2018: mild=0.8%, severe=1.4%). An association between HS severity and prevalence was not demonstrated with UC in the same studies (Kimball et al, 2018; Jørgensen et al, 2020). Two studies reported incidence rates for IBD in patients diagnosed with HS, which were 0.59, 0.97, and 0.13 /1,000 py) for CD, UC, and unspecified IBD, respectively, in a population-based study in Denmark (Egeberg et al, 2017), and 1.16, 2.26, and 3.06/1,000 py in a claims database study in the USA (Schneeweiss et al, 2019). Patients with HS had between 2 to 4 times higher odds of having IBD or its components CD and UC, compared to patients without HS (Cices et al, 2017, Egeberg et al, 2017, Garg et al, 2018, Hua et al, 2021, Ingram et al, 2018, Lee et al, 2018, Schneeweiss et al, 2022). Only 2 studies estimated the risk for new-onset IBD. The study in Denmark (Egeberg et al, 2017) showed a 2.2 times higher risk of CD and a 1.6 times higher risk of UC. The claims database study from the USA (Schneeweiss et al, 2019) showed a 2.2 times higher risk of IBD, 2.7 times higher risk of CD and 2.3 times higher risk of UC. Overall, the incidence of IBD was slightly higher in the bimekizumab HS development program compared with the background rate in a similar HS population. However, the low number of events and the thorough evaluation and identification of potential events by the adjudication committee, make comparison with published background rates challenging.

Table 3–2: Important identified risk: Inflammatory bowel disease (Crohn's disease and ulcerative colitis)

Risk factors and risk groups	**PSO:** Risk of IBD in PSO patients increases with severity of disease and systemic medication usage. Cancer, obesity, and cardiovascular disease may also be risk factors of IBD in PSO patients (Lee et al, 2019; Radtke et al, 2017; Takeshita et al, 2017; Vlachos et al, 2016; Molodecky et al, 2012; Loftus Jr, 2004). **PsA**: Risk of IBD in PsA increases with environmental risk factors such as smoking, infections, high doses of NSAIDs, and genetic predisposition (Schreiber et al, 2019, Charlton et al, 2018). Previous failure of a TNF antagonist has also been associated with exacerbations and less disease control (Schreiber et al, 2019). **axSpA**: Risk of IBD in axSpA increases with environmental risk factors such as smoking, infections, genetic predisposition, previous failure of a TNF antagonist, and high doses of NSAIDs (Schreiber et al, 2019; Fragoulis 2019). People in the older age group (≥65 years) and those with comorbidity of cancer also have a higher risk for IBD (Wang et al, 2020). **HS**: A study in the USA reported adjusted Odds Ratios for HS (vs non-HS) for CD (Garg et al, 2018) in subgroups, by testing effect modification. Sex significantly altered the Odds Ratios of CD, with men having a higher risk than women. They also found higher risk in older patients, higher in non-obese patients than in obese patients, and higher in non-smokers than in smokers.
Preventability	Cases of new or exacerbations of IBD have been reported with bimekizumab. Bimekizumab is not recommended in patients with IBD. If a patient develops signs and symptoms of IBD or experiences an exacerbation of pre-existing IBD, bimekizumab should be discontinued and appropriate medical management should be initiated (SmPC Section 4.4). Consistent with the IL-17 inhibitor class, information regarding IBD is also included in SmPC Section 4.8.
Impact on risk-benefit balance of the product	Risk of IBD (including CD and UC) has been considered in the overall benefit-risk assessment with benefit-risk balance remaining positive. Routine and additional pharmacovigilance will be implemented to monitor this risk (see Part III, Table 3-1). Inflammatory bowel disease is included in Warnings and precautions for use (SmPC Section 4.4) and Undesirable effects (SmPC Section 4.8). Risk minimization activities are discussed in Part V, Table 3-1.
Public health impact	Because of low overall incidence of IBD-related adverse events the potential public health impact is considered low.

Table 3–2: Important identified risk: Inflammatory bowel disease (Crohn's disease and ulcerative colitis)

AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; CD=Crohn's disease; CI=confidence interval; EAIR=exposure adjusted incidence rate; EudraCT= European Union Drug Regulating Authorities Clinical Trials Database; HLT=High Level Term (MedDRA); HS=hidradenitis suppurativa; IBD=inflammatory bowel disease; IL=interleukin; IR=incidence rate; nr-axSpA=non radiographic axial spondyloarthritis; NSAID=non-steroidal anti-inflammatory drug; PsA=psoriatic arthritis; PSO=psoriasis; PT=Preferred Term; py=participant-years; Q2W=every 2 weeks; Q4W=every 4 weeks; SmPC=summary of product characteristics; TEAE=treatment-emergent adverse event; TH=T-helper; TNF=tumor necrosis factor; UC=ulcerative colitis
Data sources: PSO: Integrated Summary of Safety Data Table 5.1.9.8.1 and 5.2.9.8.1; PsA Integrated Summary of Safety Data Table 5.1.9.6.2, Table 5.2.9.6.2, Listing 2.2.5.6.1; axSpA Integrated Summary of Safety Data Table 5.1.9.6.2, Table 5.2.9.6.2, Listing 2.1.5.6.1, and Listing 2.2.5.6.1; HS: Table 5.1.9.6.2, Table 5.3.9.6.2, Table 5.3.16.4, Listing 2.1.5.6.1, Listing 2.3.5.6.1

3.1.2 Important potential risks

Important potential risks with bimekizumab treatment are characterised in Table 3–3 , Table 3–4, and Table 3–5.

Table 3–3: Important potential risk: Serious hypersensitivity reactions

Potential mechanisms	Two types of allergic reactions, IgE and non-IgE mediated, appear to be associated with monoclonal antibody administration. The non-IgE reactions are triggered by IgGs or IgMs. The IgE-mediated reactions triggers histamine release from basophils and mastocytes, whereas the IgG/IgM will trigger cytokine release from neutrophils, monocytes, and macrophage and/or complement activation, and/or activation of basophils and mastocytes.
Evidence source(s) and strength of evidence	All monoclonal antibodies could potentially be associated with hypersensitivity reactions, including anaphylactic/anaphylactoid events. Data to evaluate safety concerns derive from clinical studies.

Characterization of the risk	Frequency: **PSO**:In Pool S1, there were no serious hypersensitivity reactions. In Pool S2, in the Phase 2/3 bimekizumab Total group, 3 study participants (0.2%; EAIR: 0.2/100 py [95% CI: 0.0, 0.5]) experienced a serious hypersensitivity reaction: anaphylactic shock, dermatitis atopic, and circulatory collapse in 1 study participant each. The TEAE of anaphylactic shock was reported as 'anaphylactic shock due to insect sting' and considered unrelated to bimekizumab. The TEAE of circulatory collapse was not related to hypersensitivity but an unrelated post-surgical complication. The event atopic dermatitis (reported 414 days after first exposure to bimekizumab) was attributed to an environmental factor. **PsA**: In Pool SP1, there were no serious hypersensitivity reactions. In Pool SP2, in the bimekizumab Total group, 1 study participant (<0.1%; EAIR 0.0/100 py [95% CI: 0.0, 0.2]) experienced a serious hypersensitivity reaction of dermatitis, considered unrelated to bimekizumab. **axSpA**: In Pools SA1 and SA2, there were no reports of serious hypersensitivity reactions. **HS**: In Pool S1, there were no serious hypersensitivity reactions. In Pool S3, 1 study participant (<0.1%; EAIR: 0.1/100 py [95% CI: 0.0, 0.4]) in the Phase 2/3 bimekizumab Total group experienced a serious hypersensitivity reaction: rash pustular, considered related to bimekizumab (reported as medication induced generalized pustular rash, with onset 154 days after the first exposure to bimekizumab and 14 days since the last bimekizumab dose); the event led to discontinuation of bimekizumab. Severity: **PSO**: In Pool S1, there were no serious hypersensitivity reactions. In Pool S2, the event of dermatitis atopic was moderate, and the events of anaphylactic shock and circulatory collapse were severe. **PsA**: In Pool SP1, there were no serious hypersensitivity reactions. In Pool SP2, the event of dermatitis was moderate. **axSpA**: In Pools SA1 and SA2, there were no reports of serious hypersensitivity reactions. **HS**: In Pool S1, there were no serious hypersensitivity reactions. In Pool S3, the event of rash pustular was of moderate intensity. Reversibility: **PSO:** In Pool S1, there were no serious hypersensitivity reactions. In Pool S2, the event of circulatory collapse was fatal; the events of dermatitis atopic and anaphylactic shock were resolved. **PsA**: In Pool SP1, there were no serious hypersensitivity reactions. In Pool SP2, the event of dermatitis was resolving at the time of data cut off. **axSpA**: In Pools SA1 and SA2, there were no reports of serious hypersensitivity reactions.

Table 3–3: Important potential risk: Serious hypersensitivity reactions

	HS: In Pool S1, there were no serious hypersensitivity reactions. In Pool S3, the event of rash pustular was resolving at the time of data cut-off.
	Long term outcome: No long-term outcome is expected after resolution of hypersensitivity reactions.
	Impact on quality of life: For severe or life-threatening hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalized for treatment. Generally, patients recover when their hypersensitivity reaction is treated.
Absolute risk	Bimekizumab is considered to have a low risk of immunogenicity given the humanized status of the molecule, the identical antigen-binding domains, and the soluble nature of its targets. Despite its low risk for immunogenicity, the potential for bimekizumab as a monoclonal antibody to elicit hypersensitivity reactions exists. In the bimekizumab development programs in PSO, PsA, axSpA and HS, no anaphylactic reactions related to bimekizumab were seen. Cutaneous hypersensitivity events were observed, the vast majority were mild to moderate.
Risk factors and risk groups	Risk groups include patients who have hypersensitivity to the active substance or to any of the excipients.
Preventability	Use of bimekizumab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients (SmPC Section 4.3). Serious hypersensitivity reactions including anaphylactic reactions have been observed with IL-17 inhibitors. If a serious hypersensitivity reaction occurs, administration of bimekizumab should be discontinued immediately and appropriate therapy initiated (SmPC Section 4.4).
Impact on risk-benefit balance of the product	Risk of serious hypersensitivity reactions has been considered in the overall benefit-risk assessment with benefit-risk balance remaining positive. Routine and additional pharmacovigilance will be implemented to monitor serious hypersensitivity reactions (see Part III, Table 3-1). Hypersensitivity is included in contraindication (SmPC Section 4.3) and Warnings and Precautions (SmPC Section 4.4). Risk minimization activities are discussed in Part V, Table 3-1.
Public health impact	Since most hypersensitivity (and related) events reported with bimekizumab were nonserious, and the difference of incidence rates between bimekizumab and placebo were small, the potential public health impact is considered low.

axSpA=axial spondyloarthritis; CI=confidence interval; EAIR=exposure adjusted incidence rate; HS=hidradenitis suppurativa; Ig=immunoglobulin; IL=interleukin; Q2W=every 2 weeks; PsA=psoriatic arthritis; SmPC=summary of product characteristics; PSO=psoriasis; py=participant years; TEAE=treatment-emergent adverse event
Data sources: PSO: Integrated Summary of Safety Data Table 5.1.9.9.1.2 and 5.2.9.9.1.2. PsA Integrated Summary of Safety Data Table 5.1.9.7.1.2, Table 5.2.9.7.1.2, Listing 2.2.2, Listing 2.2.5.7.1; axSpA Integrated Summary of Safety Data Table 5.1.9.7.1.2, Table 5.2.9.7.1.2. HS: Table 5.1.9.7.1.2, Table 5.3.9.7.1.1, Table 5.3.9.7.1.2, Table 5.3.9.7.2.1, Table 5.3.18, Listing 2.1.5.7.1, Listing 2.3.5.7.1, Listing 2.3.5.7.2

Table 3–4: Important potential risk: Major adverse cardiovascular events

Potential mechanisms	Psoriasis as well as PsA, axSpa, and HS are multisystem, inflammatory conditions associated with increased risk for CV comorbidities. The role of IL-17 in the modulation of endothelial cell activation is still poorly understood. Evidence suggests that modifying underlying inflammation in PSO may reduce CVD risk (assigning a pro-atherogenic role of IL-17 in atherosclerosis) (Lockshin et al, 2018). Observational studies have shown that when systemic inflammation is driving CV disease risk, then systemic treatment with methotrexate and biologic drugs may reduce elevated risk of MACE (Jindal and Jindal, 2018). Other preclinical research data show conflicting results regarding contributions of IL-17 to the development of atherosclerosis.
Evidence source(s) and strength of evidence	Data to evaluate safety concerns derive from clinical studies, comparison of data from other IL-17 inhibitors, and pharmacoepidemiological background incidence and prevalence rates.
Characterization of the risk	Frequency: **PSO:** In Pool S1, the incidence of any adjudicated MACE in the Initial Treatment Period was low in the bimekizumab 320mg Q4W group (cardiac arrest in 1 study participant [0.1%]; EAIR: 0.5/100 py [95% CI: 0.0, 2.7]). No adjudicated MACE TEAE was reported in the placebo group. In Pool S2, TEAEs that were adjudicated as MACE were reported in 12 study participants (0.7%; EAIR: 0.657/100 py [95% CI: 0.339, 1.147]) in the Phase 2/3 bimekizumab Total group. The following TEAEs adjudicated as MACE were reported for 2 or more study participants: myocardial infarction (4 study participants, 0.2%), acute myocardial infarction (3 study participants, 0.2%), and cerebral infarction (2 study participants, 0.1%). All the adjudicated MACE occurred in study participants with multiple CV risk factors (including significant cardiac/metabolic history, smoking history, high BMI). **PsA**: In Pool SP1, no adjudicated MACE TEAEs were reported in the bimekizumab 160mg Q4W or placebo groups. In Pool SP2, 11 TEAEs that were adjudicated as MACE were reported for 10 study participants (0.7%; EAIR 0.4/100 py [95% CI: 0.2, 0.7]) in the bimekizumab Total group. The following TEAEs adjudicated as MACE were reported for 2 or more study participants: acute myocardial infarction (2 study participants [0.1%]) and ischaemic stroke (3 study participants [0.2%]). All the adjudicated MACE occurred in study participants with multiple CV risk factors (including significant cardiac/metabolic history, smoking history, high BMI). **axSpA**: In Pool SA1, no adjudicated MACE TEAE was reported in the bimekizumab 160mg Q4W or in the placebo groups. In Pool SA2, 7 TEAEs that were adjudicated as MACE were reported in 5 study participants (0.5%; EAIR 0.2/100 py [95% CI: 0.1, 0.5]) in the bimekizumab Total group. The following 7 TEAEs adjudicated as MACE were reported for 1 study participant each (0.1%): coronary artery stenosis; acute myocardial

Table 3–4: Important potential risk: Major adverse cardiovascular events

	infarction; cardiac arrest; cerebrovascular accident; and cardio-respiratory arrest, ventricular fibrillation, and dyspnoea in the same study participant. All the adjudicated MACE occurred in study participants with multiple CV risk factors (including significant cardiac/metabolic history, smoking history, high BMI). **HS:** In Pool S1, there were no TEAEs that were adjudicated as MACE in the Initial Treatment Period. In Pool S3, the incidence of TEAEs adjudicated as MACE in the Combined Initial, Maintenance, and OLE Treatment Periods was low in the Phase 2/3 bimekizumab Total group (4 study participants [0.4%] with 4 events; EAIR: 0.3/100 py [95% CI: 0.1, 0.8]). The following TEAEs adjudicated as MACE were reported for 1 participant (<0.1%) each: cardiac failure congestive, acute coronary syndrome, cerebral infarction, and ruptured cerebral aneurysm. All the adjudicated MACE occurred in study participants with multiple CV risk factors (including significant cardiac/metabolic history, smoking history, high BMI). Overall, across indications, the incidence of adjudicated MACE with bimekizumab is within expected range and comparable to background incidence (see absolute risk). <u>Severity</u>: **PSO:** In Pool S1, the event of cardiac arrest was severe. In Pool S2, of the 12 TEAEs adjudicated as MACE, 10 were severe and 2 were moderate. **PsA**: In Pool SP2, of the 11 TEAEs adjudicated as MACE, 9 were severe and 2 were moderate. **axSpA**: In Pool SA1, no adjudicated MACE TEAE was reported. In Pool SA2, of the 7 TEAEs adjudicated as MACE, 1 was moderate and 6 were severe in intensity. **HS:** In Pool S1, there were no TEAEs that were adjudicated as MACE in the Initial Treatment Period. In Pool S3, all 4 TEAEs adjudicated as MACE were severe in intensity. <u>Reversibility</u>: **PSO**: In Pool S1, the event of cardiac arrest was fatal. In Pool S2, all TEAEs adjudicated as MACE resolved, with the exception of the fatal event of cardiac arrest mentioned above, a fatal event of cardiopulmonary failure, and an event of myocardial infarction which resolved with sequelae. **PsA**: In Pool SP2, of the 11 TEAEs adjudicated as MACE, 5 resolved, 2 resolved with sequelae (myocardial infarction and cerebral haemorrhage), 1 was resolving at the time of data cut-off (monoparesis), 2 were fatal (acute myocardial infarction

Table 3–4: Important potential risk: Major adverse cardiovascular events

	and sudden death), and for 1 TEAE (cerebrovascular accident), the outcome was unknown. **axSpA**: In Pool SA1, no adjudicated MACE TEAE was reported. In Pool SA2, of the 7 TEAEs adjudicated as MACE, 3 resolved, 2 were fatal (cardiac arrest and cardio-respiratory arrest), and 2 had an unknown outcome (ventricular fibrillation and dyspnoea in the participant with the fatal cardio-respiratory arrest). **HS**: In Pool S1, there were no TEAEs that were adjudicated as MACE in the Initial Treatment Period. In Pool S3, all TEAEs adjudicated as MACE were resolved, with the exception of the fatal event of cardiac failure congestive.
	Long term outcome /Impact on quality of life: This condition may vary from mild to severe cases and is often related to an insidious underlying cardiovascular disorder. It may be fatal in some cases. Quality of life is greatly affected.

Absolute risk	**PSO:** Psoriasis is associated with increased prevalence of cardiovascular risk factors including smoking, limited physical activity, obesity, diabetes, hypertension, and hyperlipidemia (Parisi et al, 2015). Global observational studies estimate the incidence of MACE overall amongst PSO patients at 0.28 to 0.65 per 100 person-years (Ogdie et al, 2015; Papp et al, 2015). In the PSO Phase 3 studies with bimekizumab, participants with stable CV disease were not excluded from study participation, unless they had a recent (<6 months) myocardial infarction or stroke. As expected for a moderate to severe PSO population, CV disease and CV disease risk factors were common in study participants at Baseline. Human in vitro and mouse in vivo data from literature suggest a pro-thrombotic role for IL-17A and IL-17F. Also, a large majority of studies suggest that IL-17A inhibition is protective in preclinical atherosclerosis models, mainly apoE deficient and LDLr deficient mice. Observational studies have shown that if systemic inflammation is driving CVD risk then systemic treatment with methotrexate and biologic drugs may reduce elevated risk of MACE (Jindal and Jindal, 2018). Twelve cases of adjudicated MACE (0.7%; EAIR: 0.657/100 py) were seen in the Phase 2/3 bimekizumab Total group, of which 2 resulted in a fatal outcome. All the adjudicated MACE occurred in study participants with multiple CV risk factors (including significant cardiac/metabolic history, smoking history, high BMI); none was assessed related to bimekizumab by the Investigators. Most of the study participants continued in the study (or later enrolled in OLE studies) without any significant AEs. In the PSO development program, there was no evidence of an increased risk of MACE with bimekizumab when compared to the background rates observed in the moderate to severe PSO population. The observed rates were also consistent with those seen in patients with PSO treated with biologics with similar mechanisms of action. No increased risk of MACE was associated with bimekizumab treatment beyond that attributable to the potential underlying risk with PSO. **PsA**: A Danish cohort study reported the incidence rate (per 1,000 person-years) for any MI and first time MI as 4.07 (95% CI 3.49 to 4.76) and 3.40 (95% CI: 2.86 to 4.04), respectively, in patients with PsA (Egeberg et al, 2017). A meta-analysis reported that the RR of stroke (based on studies adjusting for age and sex) was significantly increased in PsA (RR=1.33, 95% CI: 1.22 to 1.45) (Liu et al, 2021). A cohort study reported higher incidences of composite major CV disease (9.96 [n=118] vs 7.36 [n=1001]; p<0.0001), composite CV risk factors (31.94 [n=603] vs 24.32 [n=3307]; p<0.0001) and CV death (1.22 [n=23] vs 0.71 [n=97]; p=0.0191) in patients with PsA compared to patients with PSO vulgaris. The incidence of stroke (0.9 [n=17] vs 0.64 [n=77]; p=0.194) and MI (0.85 [n=16] vs 0.86 [n=117]; p=0.9539) were not significantly different among patients with PsA and PSO vulgaris (Oh et al, 2017). In the PsA development program, there was no evidence of an increased risk of MACE with bimekizumab when compared to the background rates observed in the PsA population. No increased risk of MACE was associated with bimekizumab treatment beyond that attributable to the potential underlying risk with PsA.

Table 3–4: Important potential risk: Major adverse cardiovascular events

	axSpA: Bengtsson et al, 2017 reported standardized incidence rates of 5.4, 5.9, and 5.7 stroke events per 1000 person-years at risk for AS, PsA, and undifferentiated SpA, compared to 4.7 in the general population. The age- and sex-adjusted hazard ratios were reported to be significantly increased in AS (1.25, 95% CI; 1.06 to 1.48), and PsA (1.34, 95% CI 1.22 to 1.48) and non-significantly in undifferentiated SpA 1.16 (95% CI 0.91 to 1.47) compared to the general population cohort (Bengtsson et al, 2017). A recent meta-analysis of population-based studies demonstrated a significantly higher risk of MI (RR: 1.52; 95% CI: 1.29 to 1.80) and stroke (RR: 1.21; 95% CI: 1.0 to 1.47) in patients with SpA (including AS, PsA, and undifferentiated SpA) compared with the general population (Kim and Choi, 2021). No increased risk of MACE was associated with bimekizumab treatment beyond that attributable to the potential underlying risk with axSpA. **HS:** The incidence of MI in patients with HS was measured in three large studies and ranged from 1.52/1,000 py in Denmark (Andersen et al, 2020) to 2.9/1,000py in Israel (Kridin et al, 2022) and the USA (Reddy et al, 2020). The US study also reported an incidence rate of 4.0/1,000 py in HS patients on biologic medication. These three studies showed a 1.2 to 1.4 times higher risk of an MI in patients with HS compared to non-HS patients. The estimated incidence of a CVA was 1.3/1,000 py in Israel (Kridin et al, 2022), 4.1/1,000 py in the USA (Reddy et al, 2020), and 6.7/1,000 py in Taiwan (Hung et al, 2019, who used a more inclusive definition of a CVA). The Reddy study reported an incidence of 3.6/1,000 py in the subgroup of patients on biologic medication. The studies from Israel and Taiwan reported a lower, not statistically significant risk of CVA in patients with HS compared to non-HS patients. Still, the study from the USA reported a 1.2 times higher risk of CVA (95% CI 1.14 to 1.31) in HS vs non-HS patients. A cohort study in the US with 226 patients with HS and 678 age/sex-matched controls reported a 2 times higher risk of cardiovascular/cerebrovascular-related death in HS patients, but this was not statistically significant (Kohorst et al, 2022). In the HS development program, there was no evidence of an increased MACE risk with bimekizumab when compared to the expected background rate for the study population.

Table 3–4: Important potential risk: Major adverse cardiovascular events

Risk factors and risk groups	**PSO**: The increased CV risk in PSO patients is partly due to the association with factors that are known predictors of cardiovascular risk including hyperlipidemia, obesity, hypertension, and diabetes. In addition, PSO patients have an increased risk of vascular inflammation and MACE (defined as myocardial infarction, stroke, and cardiovascular related death) beyond that attributable to known cardiovascular risk factors (Egeberg et al, 2017; Gelfand et al, 2006). Observational studies have shown that if systemic inflammation is driving CVD risk then systemic treatment with methotrexate and biologic drugs may reduce elevated risk of MACE (Jindal and Jindal, 2018). Some clinical trials of IL-12/23 inhibitors have reported elevated risk of major cardiovascular events, however; a recent review across 38 RCTs found no statistically elevated risk (Rungapiromnan et al, 2017; Parisi et al, 2015). **PsA**: The risk of developing CV events is driven by traditional CV risk factors; however, the level of disease activity and the extent of systemic inflammatory factors and chronic recurring inflammation are predictors of CV events (Zheng et al, 2022, Eder et al, 2016). Independent predictors for any CV event include hypertension, diabetes, dactylitic digits and erythrocyte sedimentation rate in women (Eder et al, 2016). Alongside traditional CV risk factors, such as diabetes, dyslipidemia, and smoking, markers of PsA disease activity, including polyarthritis, dactylitis, extensive skin psoriasis, and elevated inflammatory markers, have been associated with clinical CV events (Karmacharya et al, 2021c, Ogdie et al, 2015). Results from a real-world study revealed that patients receiving phototherapy, biologic, and methotrexate were not associated with a statistically significant effect of MACE when compared to those who had not received any systemic treatment, however, cyclosporine and mixed conventional systemic cohorts had a higher MACE risk (Hong et al, 2021). Analysis of a large database revealed that despite small overall number of MACEs, the risk of MACEs was greater for PsA new users of IL-12/23 and IL-17 as compared to TNF inhibitors (Vegas et al, 2022). **axSpA**: Inflammation, disease activity or its severity are well-recognized factors for accelerated atherosclerosis in axSpA, along with traditional CV risk factors such as smoking, hypertension, obesity, diabetes, and dyslipidemia (Toussirot et al, 2021). **HS**: Studies have shown higher prevalence of metabolic syndrome among patients with HS (Shalom et al, 2015; Miller et al, 2014; Gold et al, 2014) as well as increased risks for certain associated comorbidities such as hypertension, diabetes mellitus, and dyslipidemia (Garg et al, 2022; Shalom et al, 2015). In addition, obesity and smoking are CV risk factors that are associated with HS (Garg et al, 2022). Mediation analyses in an EMR-based study in the USA revealed that age, sex, and race all significantly modified the association between HS and risk of the combined outcome of MI or CVA, while adjusting for cardiovascular risk factors (Reddy et al, 2020). Women had a higher risk than men. Patients <50 years of age had an increased risk, compared to non-HS patients, but in older patients, this was not the case anymore. African-Americans had the lowest risk of the different ethnic groups.

Table 3–4: Important potential risk: Major adverse cardiovascular events

Preventability	Psoriasis, PsA, axSpA, and HS populations include a high proportion of patients with various CV risk factors. Lowering the inflammation burden in these patients could potentially prevent CV events.
Impact on risk-benefit balance of the product	MACE has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine and additional pharmacovigilance activities are in place to monitor this risk (see Part III, Table 3-1).
Public health impact	The incidence of adjudicated MACE with bimekizumab is within expected range for the population treated with biologics and comparable to background incidence, thereby no additional impact to public health is foreseen.

AE=adverse event; AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; apoE=apolipoprotein E; BMI=body mass index; CI=confidence interval; COX-2=cyclooxygenase 2; COPD=chronic obstructive pulmonary disease; CV=cardiovascular; CVA=cerebrovascular accident; CVD=cardiovascular disease; EAIR=exposure adjusted incidence rate; EMR=electronic medical record; HS=hidradenitis suppurativa; IBD=inflammatory bowel disease; IL=interleukin; LDLr=low density lipoprotein receptor; MACE=major adverse cardiovascular events; MI=myocardial infarction; OLE=open-label extension; PsA=psoriatic arthritis; PSO=psoriasis; py=participant-year; Q2W=every 2 weeks; Q4W=every 4 weeks; RCT=randomized clinical trials; TEAE=treatment-emergent adverse event; TNF=tumor necrosis factor
Data sources: PSO: Integrated Summary of Safety Data Table 5.1.9.5.1 and 5.2.9.5.1; PsA Data sources: Integrated Summary of Safety Data Table 5.1.9.3.1, Table 5.2.9.3.1, Listing 2.2.5.3.1; axSpA Integrated Summary of Safety Data Table 5.1.9.3.1, Table 5.2.9.3.1, Listing 2.1.5.3.1, Listing 2.2.5.3.1; HS: Table 5.1.9.3.1, Table 5.3.9.3.1, Table 5.3.16.3, Listing 2.3.5.3.1.

Table 3–5: Important potential risk: Malignancy

Potential mechanisms	Interleukin-17, with its pro-inflammatory properties, plays a dual role in cancer, serving either as a promoter or antitumor factor. On the one hand, by facilitating angiogenesis and egress of tumor cells from the primary focus, IL-17 promotes tumor growth. On the other hand, IL-17 promotes an antitumor cytotoxic T cell response leading to tumor regression. Immunomodulation and exposure to UV radiation may add to the risk of developing certain malignancies (especially skin cancers)
Evidence source(s) and strength of evidence	Data to evaluate safety concerns derive from clinical studies, comparison of data from other IL-17 inhibitors, and pharmacoepidemiological background incidence and prevalence rates.
Characterization of the risk	Frequency: **PSO:** In Pool S1, the incidence of malignant tumor TEAEs was low. One study participant in the bimekizumab 320mg Q4W group (0.1%; EAIR: 0.5/100 py [95% CI: 0.0, 2.7]) experienced a TEAE of basal cell carcinoma. One study participant in the placebo group (0.6%; EAIR: 1.9/100 py [95% CI: 0.0, 10.8]) experienced a TEAE of oesophageal adenocarcinoma. In Pool S2, the incidence of malignant tumor TEAEs reported during the Combined Initial, Maintenance, and OLE Treatment Period in the Phase 2/3 bimekizumab Total group (15 study participants [0.8%]; EAIR: 0.8/100 py [95% CI: 0.5, 1.4]) was also low. Malignant tumor TEAEs reported in the Phase 2/3

Table 3–5: Important potential risk: Malignancy

	bimekizumab Total group are basal cell carcinoma (7 study participants [0.4%]), colon cancer (2 study participants [0.1%]), gastric cancer, anal squamous cell carcinoma, acute myeloid leukaemia, squamous cell carcinoma [in 1 participant who also experienced basal cell carcinoma], squamous cell carcinoma of lung, squamous cell carcinoma of skin, and keratoacanthoma (1 study participant [<0.1%] each). **PsA**: In Pool SP1, the incidence of malignant tumor TEAEs was low. One study participant in the placebo group (0.2%; EAIR 0.8/100 py [95% CI: 0.0, 4.3]) experienced a TEAE of breast cancer stage I. One study participant each in the placebo group (0.2%; EAIR 0.8/100 py [95% CI: 0.0, 4.3]) and in the bimekizumab 160mg Q4W group (0.1%; EAIR 0.5/100 py [95% CI: 0.0, 2.5]) experienced a TEAE of basal cell carcinoma. In Pool SP2, the incidence of malignant tumor TEAEs reported during the Combined Initial, Maintenance, and OLE Treatment Period in the bimekizumab Total group was also low (20 malignant tumor TEAEs in 17 study participants [1.2%]; EAIR: 0.6/100 py [95% CI: 0.4, 1.0]). Malignant tumor TEAEs reported in the bimekizumab Total group were basal cell carcinoma (5 study participants [0.4%]), and breast cancer, colon cancer, endometrial cancer stage I, recurrent gastric cancer, chronic lymphocytic leukaemia, chronic lymphocytic leukaemia stage 0, squamous cell carcinoma, ovarian cancer, prostate cancer, malignant melanoma in situ, papillary thyroid cancer, and uterine cancer (1 study participant [<0.1%] each). **axSpA**: In Pool SA1, no malignant tumor TEAE was reported in the bimekizumab 160mg Q4W or placebo groups. In Pool SA2, the incidence of malignant tumor TEAEs reported during the Combined Initial, Maintenance, and OLE Treatment Periods in the bimekizumab Total group was low (6 study participants [0.6%]; EAIR: 0.3/100 py [95% CI: 0.1, 0.6]). Malignant tumor TEAEs reported in the bimekizumab Total group (1 study participant [0.1%] each) were breast cancer, clear cell renal cell carcinoma, lung neoplasm malignant, superficial spreading melanoma stage I, basal cell carcinoma, and testicular seminoma (pure). **HS**: In Pool S1, the incidence of malignant tumor TEAEs reported during the Initial Treatment Period was low (1 study participant [0.1%]; EAIR: 0.4/100 py [95% CI: 0.0, 2.1] in the bimekizumab Total group). One TEAE of breast cancer was reported in the 320mg Q2W group (0.2%; EAIR: 0.6/100 py [95% CI: 0.0, 3.2]), which had not resolved at the time of data cut-off. No study participant reported a malignancy TEAE while receiving placebo. In Pool S3, the incidence of malignant tumor TEAEs reported during the Combined Initial, Maintenance, and OLE Treatment Periods in the Phase 2/3 bimekizumab Total group was also low (9 study participants [0.9%] with 9 events; EAIR: 0.7/100 py [95% CI: 0.3, 1.3]). Malignant tumor TEAEs reported in the Phase 2/3 bimekizumab Total group were adrenal gland cancer, breast cancer, intraductal proliferative breast lesion, Hodgkin's disease, squamous cell carcinoma of the tongue, clear cell renal cell carcinoma, basal cell carcinoma, keratoacanthoma, and papillary thyroid cancer (1 study participant [<0.1%] each) Severity:

Table 3–5: Important potential risk: Malignancy

	PSO: In Pool S1, the event of basal cell carcinoma in the bimekizumab 320mg Q4W group was moderate. The event of esophageal adenocarcinoma in the placebo group was severe. In Pool S2, four events (2 events of basal cell carcinoma, 1 event of anal squamous cell carcinoma, and 1 event of squamous cell carcinoma) were mild, 7 events were moderate (5 events of basal cell carcinoma, 1 event of gastric cancer, and 1 event of keratoacanthoma), and 5 events were severe (1 event each of squamous cell carcinoma, squamous cell carcinoma of the tongue, acute myeloid leukaemia, squamous cell carcinoma of the lung, and colon cancer). None of the malignancies in study participants on bimekizumab resulted in a fatal outcome. **PsA**: In Pool SP1, the event of breast cancer stage I in the placebo group was moderate. The 2 events of basal cell carcinoma in the placebo and bimekizumab 160mg Q4W group were mild. In Pool SP2, of the 20 TEAEs reported, 7 events were mild (5 events of basal cell carcinoma, 1 event of chronic lymphocytic leukaemia, and 1 event of prostate cancer), 7 events were moderate (colon cancer, basal cell carcinoma, squamous cell carcinoma, breast cancer, uterine cancer, and 2 events of papillary thyroid cancer), and 6 events were severe (malignant melanoma in situ, chronic lymphocytic leukaemia stage 0, colon cancer, ovarian cancer, recurrent gastric cancer, and endometrial cancer stage I). **axSpA**: In Pool SA1, no malignant tumor TEAE was reported in the bimekizumab 160mg Q4W or placebo groups. In Pool SA2, 1 event was mild (superficial spreading melanoma stage I), 3 events were moderate (basal cell carcinoma, clear cell renal cell carcinoma, and breast cancer), and 2 events were severe (lung neoplasm malignant and testicular seminoma [pure]). None of the malignancies in study participants on bimekizumab resulted in a fatal outcome. **HS**: In Pool S1, the TEAE of breast cancer was of severe intensity. In Pool S3, of the 9 malignant tumor TEAEs reported, 1 event was mild (keratoacanthoma), 2 events were moderate (squamous cell carcinoma of the tongue and basal cell carcinoma), and 6 events were severe in intensity (intraductal proliferative breast lesion, adrenal gland cancer, breast cancer, clear cell renal cell carcinoma, papillary thyroid cancer, and Hodgkin's disease). None of the malignancies in study participants on bimekizumab resulted in a fatal outcome. <u>Reversibility</u>: **PSO**: In Pool S1, the event of basal cell carcinoma in the bimekizumab 320mg Q4W group resolved. The event of esophageal adenocarcinoma in the placebo group was fatal. In Pool S2, eight events resolved (5 events of basal cell carcinoma, 1 event each of squamous cell carcinoma, squamous cell carcinoma of skin, and keratoacanthoma). Four events (2 events of basal cell carcinoma and 1 event each of colon cancer and gastric cancer) were not resolved; 2 events (squamous cell

Table 3–5: Important potential risk: Malignancy

	carcinoma of lung and colon cancer) were resolving. The event of acute myeloid leukaemia was resolved with sequelae, and the outcome of the event of anal squamous cell carcinoma was unknown). **PsA**: In Pool SP1, the event of breast cancer stage I in the placebo group and the event of basal cell carcinoma in bimekizumab 160mg Q4W group both resolved. The event of basal cell carcinoma in the placebo group did not resolve at the time of data cut-off. In Pool SP2, of the 20 TEAEs reported, 15 events resolved (2 events of colon cancer, 6 events of basal cell carcinoma, 2 events of papillary thyroid cancer, and 1 event each of malignant melanoma in situ, squamous cell carcinoma, breast cancer, endometrial cancer stage I, and prostate cancer), 2 events were resolving (uterine cancer and chronic lymphocytic leukaemia) and 3 events did not resolve (chronic lymphocytic leukaemia stage 0, ovarian cancer, and recurrent gastric cancer) at the time of data cut-off. **axSpA**: In Pool SA1, no malignant tumor TEAE was reported in the bimekizumab 160mg Q4W or placebo groups. In Pool SA2, 3 events were resolved (basal cell carcinoma, clear cell renal cell carcinoma, and superficial spreading melanoma stage I), 1 event was resolving (lung neoplasm malignant), and 2 events were not resolved (testicular seminoma [pure] and breast cancer) at the time of data cut-off. **HS**: In Pool S1, the TEAE of breast cancer had not resolved by the time of data cut-off. In Pool S3, of the 9 malignant tumor TEAEs reported, 3 were resolved (squamous cell carcinoma of the tongue, keratoacanthoma, and papillary thyroid cancer) and 6 had not resolved by the time of data cut-off (adrenal gland cancer, breast cancer, Hodgkin's disease, intraductal proliferative breast lesion, clear cell renal cell carcinoma, and basal cell carcinoma).
	Long term outcome/ Impact on quality of life: Malignancies have a potential for a severe outcome and death. The impact for a reduced quality of life is high in many cases.
Absolute risk	**PSO:** Estimates of malignancy in the PSO population vary by geographic location and type of malignancy, ranging from 5 to 29 per 1,000 person-years in the current literature (Takeshita et al, 2017). Several studies have reported an increased risk of non-melanoma skin cancer in patients with PSO and especially in patients who have received psoralen and UV-A (PUVA) therapy. Pouplard et al (2013) reported an increased risk of squamous cell carcinoma (SIR=5.3, 95% CI: 2.63 to 10.71) and basal cell carcinoma (SIR=2.00, 95% CI: 1.83 to 2.20) in PSO. Two retrospective cohort studies examined the severity of PSO disease and/or treatment in relation to cancer incidence (Kimball et al, 2015; Lee et al, 2012). These studies found a trend in the incidence of all cancers, with lymphoma, melanoma, and non-melanoma skin cancer associated with increased PSO disease severity, as defined by treatment. Interleukin-17, with its pro-inflammatory properties, may play a dual role in cancer, serving either as a promoter or antitumor factor, possibly dependent on the cellular source.

Table 3–5: Important potential risk: Malignancy

	In the bimekizumab PSO development program, there was no overall trend in the type or incidence of malignancies observed with bimekizumab that might indicate an increased risk compared to the background rate in the study population. Malignancies were observed across the different treatment groups at low incidence rates in the Pool S2 Phase 2/3 bimekizumab Total group (EAIR: 0.8/100 py). No malignancy was considered drug-related by the Investigator. None of the malignancies in study participants on bimekizumab resulted in a fatal outcome. **PsA**: In a systematic review and meta-analysis of observational cohort studies, the prevalence of overall cancer in the PsA group was reported as 5.74% (95% CI 3.64 to 8.28) with an incidence of 6.44 per 1,000 py (95% CI 4.80 to 8.32) and the prevalence of site-specific cancer ranged from 0.19% (95% CI 0.09 to 0.31) for lymphoma to 3.59% (95% CI 1.67 to 6.21) for keratinocyte cancer. Of the included studies, none found a significant association between PsA and cancer overall (RR: 1.02, 95% CI 0.97 to 1.08). PsA was significantly associated with an increased risk of breast cancer. The remaining cancer types either had too few studies for analysis or no association was seen (Vaengebjerg et al, 2020). In a prospective study, the most common malignancies observed in patients with PsA were skin (30/1413), breast (21/1413), and hematological (20/1413). Standardized incidence ratio for malignancy in patients with the psoriatic disease was 0.83 (95% CI 0.68 to 1.00). Skin cancer was the only specific cancer in patients with psoriatic disease that had a higher incidence than the general population with SIR 3.37 (95% CI 1.84 to 5.66). In this long-term prospective follow-up of patients with PsA and PSO without arthritis (cutaneous PSO), the overall malignancy risk was not found to be higher than the general population, while skin cancer increased (Polachek et al, 2021). **axSpA**: A meta-analysis showed that AS is associated with a 14% (pooled RR 1.14; 95% CI 1.03 to 1.25) increase in the overall risk for malignancy. Compared to controls, patients with AS are at a specific increased risk for malignancy of the digestive system (pooled RR 1.20; 95% CI 1.01 to 1.42), multiple myelomas (pooled RR 1.92; 95% CI 1.37 to 3.69) and lymphomas (pooled RR 1.32; 95% CI 1.11 to 1.57) (Deng et al, 2016). Meta-analyses on patients with SpA (including axSpA and peripheral SpA) treated with biologics indicate no elevated incidence of malignancy with biologics (Alghamdi et al, 2021, Kwan et al, 2020). A study showed an increased risk of malignancy in patients with SpA (including axSpA and peripheral SpA) treated with biologics compared to placebo (Peto OR 2.49, 95% CI 1.61 to 3.87, p <0.001). However, the short period of exposure in the included RCTs is a major limitation. In axSpA, the higher risk was associated with TNF receptor-Fc fusion protein compared to placebo (Peto OR 7.18, 95% CI 1.21 to 42.69, p=0.030) (Man et al, 2021). **HS**: A study in the USA (Kimball et al, 2018) reported cutaneous malignancies in 6.3% of HS patients and non-cutaneous ones in 4.4%, while this was 1.5% and 2.3% in matched non-HS patients. Another study in the USA reported a prevalence of 9.0% for all malignancies, excluding cutaneous malignancies (Reddy et al, 2019). A survey study in The Netherlands reported a prevalence of self-reported malignancies of 6.6% in patients with HS (Prens et al, 2022). A study in the USA reported an incidence rate of 278/100,000 py for squamous cell carcinoma and 303/100,000 py for basal cell carcinoma (Ashrafzadeh et al,

Table 3–5: Important potential risk: Malignancy

	2020). A study in South Korea reported an incidence of malignancies of 358/100,000 py in HS (Jung et al, 2020). A significantly increased risk was found for 6 out of 29 malignancies (oral cavity and pharyngeal, non-melanoma skin, prostate, central nervous system, and Hodgkin lymphoma) in patients with HS than in non-HS patients. The risk of HS for overall malignancies was 1.3 times higher than in non-HS patients. In the bimekizumab HS development program, malignancies were observed at a low incidence in the Phase 3 bimekizumab total group in Pool S3 (0.9%; EAIR: 0.7/100 py) and with no trend in type of malignancies or an increased incidence of malignancies in the bimekizumab treated study participants. No case was fatal, and Investigators considered all but 1 case as not related to bimekizumab. Overall, in the bimekizumab PSO, PsA, axSpA, and HS development programs, there was no overall trend in the type or incidence of malignancies observed with bimekizumab that might indicate an increased risk compared to the background rate in the study population. Malignancies were observed across the different treatment groups at low incidence rates in the PSO, PsA, axSpA, and HS programs (in the PSO Pool S2 Phase 2/3 bimekizumab Total group EAIR: 0.8/100 py; in the PsA Pool SP2 bimekizumab Total group EAIR: 0.6/100 py; in the axSpA Pool SA2 bimekizumab Total group EAIR: 0.3/100 py; in the HS Pool S3 bimekizumab group EAIR: 0.7/100 py). No malignancy was considered drug-related by the Investigator in the PSO and axSpA programs. Of the 20 malignancy TEAEs reported in the PsA program, 3 events (malignant melanoma in situ, chronic lymphocytic leukemia stage o, and ovarian cancer) were considered drug-related by the Investigator. One of the malignancies (squamous cell carcinoma of the tongue) was considered related to bimekizumab in the HS program (as assessed by the Investigator). None of the malignancies in study participants on bimekizumab resulted in a fatal outcome.
Risk factors and risk groups	**PSO**: Several mechanisms may contribute to the increased risk of cancer among patients with PSO, including chronic inflammation and impaired immunosurveillance associated with the disease itself. Other factors, such as treatment with certain pharmacologic agents or behavioral factors including smoking and alcohol consumption may also contribute to risk independently. A large meta-analysis showed that risk factors of cancer in PSO patients included alcohol and cigarette use, phototherapy, and disease severity (Pouplard et al, 2013). Two retrospective cohort studies examined severity of PSO disease and/or treatment in relation to cancer incidence (Kimball et al, 2015; Lee et al, 2012). These studies found a trend in the incidence of all cancers, lymphoma, melanoma, and non-melanoma skin cancer associated with increased PSO disease severity defined by treatment. **PsA**: The increased risk of cancers in PsA could be driven by the chronic inflammatory nature of the disease itself and the requirement for long-term therapy with immunosuppressive agents and/or phototherapy. An increased risk of cancer can also be attributed to a more severe form of PsA which requires more long-term use and high-cumulative dose of immunosuppressants. Although data on the risk of cancer for the different therapeutic domains in PSA are variable, patients treated with csDMARDs are reported to present with increased cancer risk, but not those treated with biological therapies (Woo et al, 2020; Hagberg et

Table 3–5: Important potential risk: Malignancy

	al, 2016b; Luo et al, 2019; Vaengebjerg et al, 2020; Costa et al, 2016; Fagerli et al, 2019). **axSpA**: Chronic inflammation in patients with AS can drive the risk of developing malignancies. Evidence suggests that Asian populations, but not American or European populations, have a higher risk of malignancy (Deng et al, 2016). A recent meta-analysis has indicated no overall elevated risk of malignancy among SpA patients (including axSpA and peripheral SpA) treated with biologics (Kwan et al, 2020). **HS:** The chronic inflammation and immune dysregulation present in patients with HS, as well as genetic and environmental factors, increase the risk of developing different cancers (Lapins et al, 2001). The survey study in The Netherlands reported a higher prevalence of self-reported malignancies in men (7.8%) than in women (6.1%) (Prens et al, 2022). A study in the USA found that men with HS had 1.4 times higher odds of having squamous cell carcinoma, while this was 1.1 times in women (Hua et al, 2021). Whites had significantly increased risk, but this was not the case for other ethnic groups.
Preventability	Early detection and prompt treatment has a significant impact on progression of disease and treatment success.
Impact on risk-benefit balance of the product	Malignancy has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive. Routine and additional pharmacovigilance activities are in place to monitor this risk (see Part III, Table 3-1).
Public health impact	Because of the low overall incidence of malignancies and related adverse events (which was in line with the background rate of malignancies in the treated patient population), the potential public health impact is considered low.

AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; CI=confidence interval; csDMARD=conventional synthetic disease-modifying antirheumatic drugs; EAIR=exposure adjusted incidence rate; HS=hidradenitis suppurativa; IL=interleukin; OLE=open-label extension; OR=odds ratio; PsA=psoriatic arthritis; PSO=psoriasis; py=participant years; Q2W=every 2 weeks; Q4W=every 4 weeks; RCT=randomized clinical trial; RR=relative risk; SIR=standardized incidence ratio; SpA=spondyloarthritis; TEAE=treatment-emergent adverse event; TNF=tumor necrosis factor; UV=ultraviolet
Data sources: PSO: Integrated Summary of Safety Data Table 5.1.9.4 and 5.2.9.4; PsA Integrated Summary of Safety Data Table 5.1.9.2.2, Table 5.2.9.2.2, Listing 2.1.5.2.2, Listing 2.2.5.2.2; axSpA Integrated Summary of Safety Data Table 5.1.9.2.2, Table 5.2.9.2.2, Listing 2.1.5.2.2, Listing 2.2.5.2.2; HS: Table 5.1.9.2.2, Table 5.1.18.2, Table 5.3.9.2.2, Table 5.3.16.2, Listing 2.1.5.2.2, Listing 2.3.5.2.2.

3.2 Presentation of the missing information

3.2.1 Use during pregnancy and lactation

Evidence source:

There are no adequate clinical data from the use of bimekizumab in pregnant women. Although, animal studies do not indicate direct or indirect AE risks with respect to pregnancy,

teratogenicity, embryonic/fetal development, parturition, or postnatal development; the potential risk for humans is unknown.

It is unknown whether bimekizumab is excreted in human milk. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from bimekizumab therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Population in need of further characterization:

The safety and efficacy of bimekizumab use during pregnancy and lactation is not established.

3.2.2 Long-term safety data

Evidence source:

Limited data are currently available on the long-term use of bimekizumab in adult patients with moderate-to-severe PSO.

For PsA, long-term safety data are available for up to 152 weeks (from 183 study participants who enrolled into the long-term extension study of Phase 2b PA0009). This Phase 2b extension study was completed and confirmed the safety conclusions from Phase 2b study that long-term treatment with bimekizumab 160mg Q4W was well tolerated in adult study participants with PsA.

In axSpA, 255 patients were enrolled in the ongoing Phase 2 OLE trial (total duration of 4 years) at the data cut-off; an interim analysis at 3 years of bimekizumab exposure showed that long-term treatment with bimekizumab 160mg Q4W was well tolerated in adult study participants with active AS.

In HS, 653 participants (at the time of the 15 Nov 2022 data cutoff) were enrolled in the ongoing Phase 3 OLE trial (total duration of 100 weeks) following completion of Week 48 of the feeder studies; an interim analysis in a limited sub-population of 25 Japanese participants showed that long-term treatment (up to 1 year) with bimekizumab was well-tolerated in adult study participants with moderate to severe HS.

Population in need of further characterization:

The long-term use of bimekizumab in adult patients with moderate-to-severe chronic plaque PSO is under investigation in OLE study PS0014 (up to 144 weeks in addition to the exposure in respective feeder studies, with an additional 48 weeks exposure in the United States and Canada) (EudraCT number: 2016-003427-30) and the study PS0015 (up to 144 weeks, with an additional 48 weeks exposure in the United States and Canada) (EudraCT number: 2017-003784-35).

The long-term use of bimekizumab in adult patients with PsA is further under investigation in OLE study PA0012 (up to 140 weeks in addition to the exposure in respective feeder studies) (EudraCT number: 2018-004725-86).

The long-term use of bimekizumab in adult patients with axSpA is further under investigation in OLE study AS0014 (up to 112 weeks in addition to the exposure in respective feeder studies) (EudraCT number: 2019-004163-47).

The long-term use of bimekizumab in adult patients with HS is further under investigation in OLE study HS0005 (up to 100 weeks in addition to the exposure in the respective feeder studies) (EudraCT number: 2020-004179-42).

PART II: MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Table 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serious infections
	Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
Important potential risks	Serious hypersensitivity reactions
	Major adverse cardiovascular events
	Malignancy
Missing information	Use during pregnancy and lactation
	Long-term safety data

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION STUDIES)

1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

- Specific adverse reaction follow-up questionnaires for safety concerns: None
- Other forms of routine pharmacovigilance activities: In addition to AE reporting and standard signal detection practices, there will be continued surveillance for AEs of interest in post-marketing safety data and throughout the ongoing studies across all indications in the bimekizumab development program.

2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

2.1 PS0038: Bimekizumab Real-World Outcomes Study

Study short name and title

Bimekizumab real-world outcomes study

Rationale and study objectives

The primary purpose of this study will be to evaluate any potential increase in the risk of safety outcomes of interest in bimekizumab exposed PSO, PsA, axSpA, and HS patients compared to PSO, PsA, axSpA, and HS patients exposed to other biologics indicated for moderate-to-severe PSO, PsA, axSpA, and HS except for any other anti-IL-17 biologics (eg, anti-TNF, anti-IL-23) in the real-world setting.

Study design

The proposed study is an observational cohort study of PSO, PsA, axSpA, and HS patients who are new users of bimekizumab and new users of other biologics indicated for moderate-to-severe PSO, PsA, axSpA, and HS except for any other anti-IL-17 biologics (eg, anti-TNF, anti-IL-23).

UCB proposes to use large, well-documented US and EU healthcare databases to mitigate challenges related to recruitment, data quality, and sustainability, and to reach the necessary sample size for the analysis in a timely manner. The safety outcomes of interest will include but are not limited to major cardiovascular events (MACE), malignancy, serious infections, IBD, and serious hypersensitivity reactions.

Study population

Adult patients with moderate to severe plaque PSO, PsA, axSpA, and HS who are new users of biologic treatments (ie, use of a drug of the same class of the specific treatment of interest in the 180 days before treatment start) among commercially insured patients in the US, and patients included in the national French Système National des Données de Santé (SNDS).

Milestones

Protocol submission: Draft protocol for PSO submitted on 16 Dec 2022, final CHMP opinion received on 30 Mar 2023. Protocol amendment 1, to include PsA and axSpA patients in the study, has been submitted to the Agency on 01 Sep 2023 (Procedure

EMEA/H/C/005316/MEA/002.3) and is under review at time of this RMP internal approval. Revised protocol, to include HS patients in the study, to be submitted within 3 months after approval of HS indication in the EU.

Interim reports submission: Two standalone interim reports will be submitted in the following 2 fixed milestones: Q3 2027 and Q3 2030. Progress updates (including number of patients enrolled and exposed, and latest available results) will be provided in periodic safety update reports as per European union reference date list.

Final reports submission: 31 Dec 2034

2.2 PS0036: Bimekizumab pregnancy exposure and outcomes registry

Study short name and title

Bimekizumab pregnancy exposure and outcomes registry

Rationale and study objectives

The objective of this study is to assess maternal, fetal, and infant outcomes among women who become pregnant while exposed to bimekizumab relative to the outcomes in 2 frequency matched comparator populations. The primary analysis will be a comparison of the birth prevalence of major structural defects in live born infants between the bimekizumab-exposed cohort and the disease comparison cohort. Additional outcome variables will be to evaluate the potential effect of bimekizumab exposure on other adverse pregnancy outcomes including, but not limited to, spontaneous abortion, elective termination, stillbirth, preterm delivery, and infant outcomes including small for gestational age, pattern of 3 or more minor structural defects, postnatal growth (to 1 year of age), developmental concerns (at approximately 1 year of age), and serious infections (up to 1 year of age).

Study design

Prospective, observational study of pregnancy outcomes in participants enrolled in 3 cohort groups and an exposure series group.

Study population

Pregnant women exposed to bimekizumab for PSO, or another condition for which bimekizumab has an approved indication, during pregnancy and pregnant women with PSO, or another condition for which bimekizumab has an approved indication, who are not exposed to bimekizumab or any other anti-IL-17-biologics during pregnancy (disease-matched comparison group), and pregnant women not diagnosed with any condition for which bimekizumab has an approved indication and not exposed to bimekizumab or any other anti-IL-17 biologics during pregnancy (non-disease comparison group).

Milestones

Protocol submission: Draft protocol submitted on 25 Nov 2021, final CHMP opinion received on 30 Mar 2023.

Annual recruitment report: 01 Jun 2024 and annually thereafter until recruitment close

Interim feasibility assessment: End of third year from the start of recruitment

Final reports submission: 31 Dec 2034

2.3 PS0037: An observational cohort study to evaluate bimekizumab exposure during pregnancy

Study short name and title

An observational cohort study to evaluate bimekizumab exposure during pregnancy.

Rationale and study objectives

The primary objective is to assess adverse pregnancy and infant outcomes, more specifically major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, preterm birth, and infant infections, in women exposed to bimekizumab during pregnancy compared to women exposed to other biologics indicated for moderate-to-severe PSO, PsA, axSpA, or any condition for which bimekizumab has an approved indication except for any other anti-IL-17 biologics (eg, anti-TNF, anti-IL-23) during pregnancy using a cohort study design with data from a large electronic health database.

Study design

An observational cohort study using the US administrative claims database CCI to compare the risk of specified pregnancy and neonatal outcomes among 2 cohorts (women with PSO, PSA, axSpA, or any other condition for which bimekizumab is indicated exposed to bimekizumab during pregnancy and women with the same indications exposed to other biologics except for any other anti-IL-17 biologics [eg, anti-TNF, anti-IL-23] during pregnancy). As a secondary study objective, this study will compare the risks of these outcomes in pregnancies exposed to bimekizumab to the risk in pregnancies not exposed to oral or injected prescription treatments for PSO in women with PSO. Where feasible, the secondary objective will also include indication-specific risk analyses for PsA, axSpA, or any other condition for which bimekizumab has an approved indication.

Study Population

The study population will include the pregnant women meeting inclusion criteria and the infants linked to the qualifying pregnancies. In most analyses, pregnant women must be continuously enrolled during the 90-day period preceding the first day of the last menstrual period through 30 days following end of pregnancy. Linked infants must be continuously enrolled until at least 30 or 90 days after birth from the qualifying pregnancies, depending on the outcome and will be followed for 30 days (small for gestational age, preterm birth), 90 days (congenital malformations), or until whichever of the following events occurs first: infection, end of continuous enrollment, or until 365 days after their estimated birth date (infant infections). The population will be restricted to pregnant women with PSO, PsA, axSpA, or any other condition for which bimekizumab has an approved indication, with or without exposure to bimekizumab.

Milestones

Protocol submission: Draft protocol for PSO submitted on 25 Nov 2021, endorsed 10 Nov 2022; protocol amendment 1, to include PsA, axSpA and any other condition for which bimekizumab has an approved indication, has been submitted to the Agency on 31 Aug 2023 (Procedure EMEA/H/C/005316/MEA/004.2) and is under review at time of this RMP internal approval.

Progress report (Phase 1 – monitoring of bimekizumab use during pregnancy): 31 Dec 2024 (Annually until 50 bimekizumab-exposed pregnant women are identified).

Interim report (Phase 2 – causal inference analysis): Annually after end of Phase 1

Final reports submission: 31 Jun 2035

2.4 PS0014

Study short name and title

PS0014 (EudraCT Number: 2016-003427-30) is a multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO.

Rationale and study objectives

The primary objective of the study is to assess the long-term safety and tolerability of bimekizumab administered sc in adult study participants with moderate to severe chronic plaque PSO who complete 1 of the Phase 3 feeder studies (PS0008 [EudraCT#2016-003392-22], PS0009 [EudraCT#2016-003425-42], and PS0013 [EudraCT#2016-003426-16]) (Cohort A) and includes an additional open-label cohort (Cohort B) in Japan to allow direct enrolment of study participants with moderate to severe chronic PSO, generalized pustular PSO, and erythrodermic PSO.

The safety concerns, including serious infection, serious hypersensitivity reactions, MACE, malignancy, and IBD, are listed as safety topics of interest in the PS0014 study protocol.

Study design

PS0014 Cohort A includes 2 periods, a Treatment Period (144 weeks) and a Safety Follow-Up (SFU) period (20 weeks after the final dose of investigational medicinal product [IMP]). Study participants receive IMP (bimekizumab 320mg every 4 weeks [Q4W] or bimekizumab 320mg every 8 weeks [Q8W]) based on their treatment regimen and PSO Area and Severity Index (PASI) response in the feeder study. At Week 48 (or at the next scheduled clinic visit after implementation of Protocol Amendment #3 if the participant had already completed the Week 48 visit), the dose regimen is changed to bimekizumab 320mg Q8W for all participants, based on available pooled data from the Phase 3 feeder studies. Following the implementation of the country-specific Protocol Amendment 3.3 (addition of a 48-week open-label treatment period) in Canada and the US, PS0014 is prolonged by an open-label extension (OLE) 2 Period, during which eligible participants are invited to continue or reinitiate bimekizumab treatment for an additional 40 weeks and are followed in a second SFU Period of 20 weeks after the final dose of IMP (SFU2 Period), as appropriate.

Study population

The Cohort A study population consists of adult study participants (>18 years of age) who have completed 1 of the Phase 3 feeder studies and had an initial diagnosis of moderate to severe chronic PSO (PASI ≥12, BSA affected by PSO≥10%, and Investigator's Global Assessment [IGA] score ≥3 [on a 5-point scale]). Study participants must have achieved a PASI50 response by the designated time in the feeder study to be eligible for PS0014.

Milestones

First protocol submission to EU national Health Authorities: 25 Jul 2018

Interim report submission: 15 Aug 2023

Final report submission: 31 Dec 2024

2.5 PS0015

Study short name and title

PS0015 (EudraCT Number: 2017-003784-35) is a multicenter, randomized, double-blind, secukinumab-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO.

Rationale and study objectives

The primary objective of this study is to compare the efficacy of bimekizumab administered sc for 16 weeks versus secukinumab at achieving complete clearance (PASI100) in study participants with moderate to severe chronic plaque PSO. Efficacy and safety of bimekizumab compared with secukinumab will be evaluated in a double-blind manner during 48 weeks of treatment.

The OLE period will allow collection of long-term efficacy and safety data from eligible study participants on open-label bimekizumab for an additional 96 weeks.

The safety concerns, including serious infection, serious hypersensitivity reactions, MACE, malignancy, and IBD, are listed as safety topics of interest in the PS0015 study protocol.

Study design

For each study participant, the study lasts a maximum of up to 165 weeks. The study has a Screening Period of 2 to 5 weeks, followed by a double-blind Treatment Period of 48 weeks comparing secukinumab 300mg Q4W versus bimekizumab 320mg (either Q4W through Week 48 or Q4W for 16 weeks followed by Q8W treatment). After completion of the Week 48 assessments, study participants will be allowed to enroll in the OLE Period (96 weeks). During this period, all study participants receive bimekizumab 320mg Q4W or bimekizumab 320mg Q8W based on their treatment regimen and PASI response in the double-blinded treatment period. At Week 64 (or at the next scheduled clinic visit after implementation of Protocol Amendment 5), the bimekizumab dose level is changed to Q8W for all study participants through Week 144. A SFU Period is planned 20 weeks after the final dose of IMP. Following the implementation of Protocol Amendment 5.3 in Canada and amendment 5.4 in the US (addition of a 48-week open-label treatment period), PS0015 is prolonged by an open-label extension (OLE) 2 Period, during which eligible participants are invited to continue or reinitiate bimekizumab treatment for an additional 40 weeks and are followed in a second SFU Period of 20 weeks after the final dose of IMP (SFU2 Period), as appropriate.

Study population

Adult study participants with a diagnosis of moderate to severe PSO (PASI≥12 and BSA ≥10% and IGA score ≥3 [on a 5-point scale]) who are candidates for secukinumab, or for systemic PSO therapy and/or phototherapy.

Milestones

First protocol submission to EU national Health Authorities: 25 Apr 2018

Interim report submission: 31 Jan 2023

Final reports submission: 31 Jul 2024

2.6 PA0012

Study short name and title

PA0012 (EudraCT number: 2018-004725-86) is a multicenter, OLE study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of study participants with active PsA.

Rationale and study objectives

The primary objective of this study is to assess the long-term safety and tolerability of bimekizumab over a period of up to 140 weeks in adult participants with PsA who completed the feeder Phase 3 studies, PA0010 and PA0011.

The safety concerns, including serious infection, serious hypersensitivity reactions, MACE, malignancy, and IBD, are listed as safety topics of interest in the PA0012 study protocol.

Study design

For each study participant, the study lasts a maximum of up to 160 weeks including a treatment period of 140 weeks and a Safety Follow-Up Period of 20 weeks after the final dose. All study participants receive bimekizumab 160mg sc Q4W. Following the implementation of the country-specific Protocol Amendment 2.3 (addition of a 52-week open-label treatment period) in the US, France, Germany, and Japan, PA0012 is prolonged by an OLE 2 Period, during which participants are invited to continue or reinitiate bimekizumab treatment for an additional 52 weeks and are followed in a SFU Period of 20 weeks after the final dose of IMP (SFU Period), as appropriate.

Study population

Study participants with a diagnosis of adult-onset PsA.

Milestones

First protocol submission to EU national Health Authorities: 30 Jan 2019

Final reports submission: Estimated CSR data 18 Sep 2026.

2.7 AS0014

Study short name and title

AS0014 (EudraCT number: 2019-004163-47) is a multicenter, OLE study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of study participants with active axSpA (radiographic and non-radiographic).

Rationale and study objectives

The primary objective of this study is to assess the long-term safety and tolerability of bimekizumab over a period of up to 112 weeks in adult participants with axSpA who completed the feeder Phase 3 studies, AS0010 or AS0011.

The safety concerns, including serious infection, serious hypersensitivity reactions, MACE, malignancy, and IBD, are listed as safety topics of interest in the AS0014 study protocol.

Study design

For each study participant, the study lasts a maximum of up to 128 weeks including a treatment period of 112 weeks and a Safety Follow-Up Period of 20 weeks after the final dose. All study participants receive bimekizumab 160mg sc Q4W. Following the implementation of the country-specific Protocol Amendments 2.6 (Germany), 2.7 (US, France, China) and 2.5 (Japan) (addition of a 52-week open-label treatment period) AS0014 is prolonged by an OLE 2 Period, during which participants are invited to continue bimekizumab treatment for an additional 52 weeks and are followed in a SFU Period of 20 weeks after the final dose of IMP (SFU Period), as appropriate.

Study population

Study participants with a diagnosis of adult-onset axSpA (radiographic and non-radiographic).

Milestones

First protocol submission to EU national Health Authorities: 21 Oct 2019

Interim report submission: 30 Sep 2024

Final reports submission: 15 Dec 2026

2.8 HS0005

Study short name and title

HS0005 (Eudra CT Number 2020-004179-42) is an open-label, parallel group, multicenter, extension study evaluating the long-term treatment of bimekizumab in study participants with moderate to severe hidradenitis suppurativa.

Rationale and study objectives

The primary objective of this study is to evaluate the safety of long-term therapy of bimekizumab in study participants with moderate to severe HS who complete 1 of the Phase 3 feeder studies (HS0003 [EudraCT#2019-002550-23] or HS0004 [EudraCT#2019-002551-42]).

The safety concerns, including serious infection, serious hypersensitivity reactions, MACE, malignancy, and IBD, are listed as safety topics of interest in the HS0005 study protocol.

Study design

HS0005 includes 2 periods, a Treatment period (100 weeks) and a SFU period (20 weeks after the final dose of IMP). At the Week 48 Visit in the feeder studies, eligible study participants continuing into HS0005 will complete the final study visit assessments from the feeder study, sign an informed consent, complete Week 0 assessments for HS0005, and will then receive their first dose of bimekizumab in HS0005. Study participants receive the IMP (bimekizumab 320mg

Q2W or bimekizumab 320mg Q4W) based on their hidradenitis suppurativa clinical response ($HiSCR_{90}$) responder status using the average lesion counts from Week 36, Week 40, and Week 44 in the feeder study compared with the Baseline lesion count of the feeder study.

The HS0005 protocol has been amended globally with a substantial change being study participants receiving bimekizumab 320mg Q2W will be switched to bimekizumab 320mg Q4W. This is based on data from both the individual Phase 3 studies, as well as the pooled data from the 2 completed pivotal Phase 3 studies HS0003 and HS0004, which demonstrated similar efficacy for bimekizumab 320mg Q4W and bimekizumab 320mg Q2W during the Maintenance Treatment Periods (Weeks 16 to 48 of the HS0003 and HS0004 studies). In addition, local amendments in France and Germany will extend the treatment period for an additional 48 weeks. Local amendments for the United States and Japan will extend the treatment period for an additional 80 weeks.

Study population

The study population consists of adult study participants with moderate to severe HS (>=18 years of age at time of entry to the Phase 3 feeder studies) who have completed 1 of the feeder studies.

Milestones

First protocol submission to EU national Health Authorities: 05 Feb 2021

Final reports submission: 08 Dec 2026

3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The summary of ongoing and planned additional pharmacovigilance activities is provided in Table 3–1.

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PS0038: Bimekizumab real-world outcomes study Planned	The goal of this study is to evaluate any potential increase in the risk of safety outcomes of interest in bimekizumab exposed PSO, PsA, axSpA, and HS patients compared to PSO, PsA, axSpA, and HS patients exposed to other biologics (eg, anti-TNF, anti-IL-23, but not anti-IL-17).	Serious infections Serious hypersensitivity reactions MACE Malignancy IBD	Final protocol	Draft protocol for PSO submitted on 16 Dec 2022, final CHMP opinion received on 30 Mar 2023. Protocol amendment 1 submitted 01 Sep 2023 is under review at time of this RMP internal approval. Revised protocol to be submitted within 3 months after approval of HS indication in the EU.
			Interim reports	2 standalone interim reports will be submitted in Q3 2027 and in Q3 2030 respectively.
			Study progress updates	Will be included in PSUR submissions according to EURD list.
			Final study report	31 Dec 2034
PS0036: Bimekizumab pregnancy exposure and outcome registry Planned	To monitor the safety of bimekizumab use in pregnancy.	Missing information: Use during pregnancy and lactation	Final protocol	Approved 30 Mar 2023
			Annual recruitment report	01 Jun 2024 and annually thereafter until recruitment close
			Interim feasibility assessment	End of third year from start of recruitment
			Final study report	31 Dec 2034

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PS0037: An observational cohort study to evaluate bimekizumab exposure during pregnancy Planned	To monitor the safety of bimekizumab use in pregnancy.	Missing information: Use during pregnancy and lactation	Final protocol	Draft protocol submitted on 25 Nov 2021, endorsed 10 Nov 2022; protocol amendment 1 submitted 31 Aug 2023 is under review at time of this RMP internal approval.
			Progress report (Phase 1- monitoring of bimekizumab use during pregnancy)	31 Dec 2024 (annually until 50 bimekizumab-exposed pregnant women are identified).
			Interim report (Phase 2 – causal inference analysis)	Annually after end of Phase 1
			Final study report	31 Jun 2035
PS0014 (EudraCT Number: 2016-003427-30) A multicenter, open-label	Assess the safety and efficacy of long-term use of bimekizumab	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and	Submission of interim clinical study report	15 Aug 2023

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO Ongoing		IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of final clinical study report	31 Dec 2024
PS0015 (EudraCT Number: 2017-003784-35) A multicenter, randomized, double-blind, secukinumab-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate to severe chronic plaque PSO Ongoing	Assess the safety and efficacy of long-term use of bimekizumab	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of interim clinical study report	31 Jan 2023
			Submission of final clinical study report	31 Jul 2024

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PA0012 (EudraCT Number: 2018-004725-86) A multicenter, open label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of study participants with active PsA. Ongoing	Assess the safety and efficacy of long-term use of bimekizumab in PsA	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of clinical study report	Estimated clinical study report date 18 Sep 2026
AS0014 (EudraCT Number: 2019-004163-47) A multicenter, open-label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of study participants with active axSpA (radiographic and non-radiographic) Ongoing	Assess the safety and efficacy of long-term use of bimekizumab in axSpA (radiographic and non-radiographic)	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of interim clinical study report	30 Sep 2024
			Submission of clinical study report	15 Dec 2026

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
HS0005 (EudraCT Number: 2020-004179-42) An open-label, parallel group, multicenter, extension study evaluating the long-term treatment of bimekizumab in study participants with moderate to severe HS Ongoing	Assess the safety and efficacy of long-term use of bimekizumab	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of final clinical study report	08 Dec 2026

axSpa=axial spondyloarthritis; CHMP= Committee for Medicinal Products for Human Use; EudraCT=European Union Drug Regulating Authorities Clinical Trials Database; EURD=European Union reference date; HS= hidradenitis suppurativa; IBD=inflammatory bowel disease; IL=interleukin; MACE=major adverse cardiovascular events; PsA=psoriatic arthritis; PSO=psoriasis; PSUR=periodic safety update report; Q3=third quarter; TNF=tumor necrosis factor

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed postauthorization efficacy studies that are conditions of the marketing authorisation or that are specific obligations for bimekizumab.

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

Risk Minimization Plan

1 ROUTINE RISK MINIMIZATION MEASURES

Description of routine risk minimization measures by safety concern is presented in Table 1–1.

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Serious infections	**Routine risk communication**: Use of bimekizumab is contraindicated in patients with clinically important active infections (eg, active tuberculosis) (SmPC Section 4.3). Risk of infections is discussed in SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) PL Section 2 (What you need to know before you use Bimzelx) PL Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring of infections are included in SmPC Section 4.4 (Special warnings and precautions for use) Instructions to look out for signs of serious infections are included in PL Section 2 (What you need to know before you use Bimzelx) Do not use Bimzelx if you have an infection, including tuberculosis (TB), which your doctor thinks is important (PL Section 2 What you need to know before you use Bimzelx) Recommendation to talk to the doctor, pharmacist or nurse for patients who have infections are included in PL Section 2 (What you need to know before you use Bimzelx) Serious infections are included in PL Section 4 (Possible side effects) **Other routine risk minimization measure beyond the Product Information:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2).

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	**Routine risk communication**: SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) PL Section 2 (What you need to know before you use Bimzelx) PL Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for monitoring of inflammatory bowel disease are included in SmPC Section 4.4 (Special warnings and precautions for use) PL Section 2 (What you need to know before you use Bimzelx) **Other routine risk minimization measure beyond the Product Information:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2).
Important potential risks	
Serious hypersensitivity reactions	**Routine risk communication**: SmPC Section 4.3 (Contraindication) SmPC Section 4.4 (Warnings and Precautions) PL Section 2 (What you need to know before you use Bimzelx) PL Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Serious hypersensitivity reactions are included in PL Section 4 (Possible side effects) Instructions to look out for allergic reactions are included in PL Section 2 (What you need to know before you use Bimzelx) Patients who are allergic to bimekizumab or any of the other ingredients of this medicine must not use Bimzelx (PL Section 2 What you need to know before you use Bimzelx) **Other routine risk minimization measure beyond the Product Information:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2)

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Major adverse cardiovascular events	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measure beyond the Product Information:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2)
Malignancies	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measure beyond the Product Information:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2)
Missing information	
Use during pregnancy and lactation	**Routine risk communication**: SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) PL Section 2 (What you need to know before you use Bimzelx) **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) PL Section 2 (What you need to know before you use Bimzelx) **Other routine risk minimization measure beyond the Product Information:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2)

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Long-term safety	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measure beyond the Product Information:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2)

PL=patient information leaflet; SmPC=summary of product characteristics

2 ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Part V. 1 are sufficient to manage the safety concerns of the medicinal product. Additional risk minimization measures are not considered necessary.

3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 3–1 provides a summary table of pharmacovigilance activities and risk minimization activities by safety concern.

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Serious infections	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.3 (Contraindication) Risk of infections is discussed under SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005
Important potential risks		
Serious hypersensitivity reactions	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.3 (Contraindication) SmPC Section 4.4 (Special warnings and Precautions) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005
Major adverse cardiovascular events	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Malignancy	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005
Missing Information		
Use during pregnancy and lactation	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0036: Bimekizumab pregnancy exposure and outcomes registry PS0037: An observational cohort study to evaluate bimekizumab exposure during pregnancy
Long-term safety	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0014; PS0015; PA0012; AS0014; HS0005

PhV=pharmacovigilance; PL=patient information leaflet; SmPC=summary of product characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Bimzelx

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

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

This summary of the RMP for Bimzelx should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Bimzelx's RMP.

1 THE MEDICINE AND WHAT IT IS USED FOR

Bimzelx is authorised for:

Plaque psoriasis: Bimzelx is indicated for the treatment of adults with moderate to severe plaque psoriasis (PSO) who are candidates for systemic therapy (see SmPC for the full indication).

Psoriatic arthritis: Bimzelx, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis (PsA) in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs) (see SmPC for the full indication).

Axial spondyloarthritis:

- Non-radiographic axial spondyloarthritis (nr-axSpA): Bimzelx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).
- Ankylosing spondylitis (AS, radiographic axial spondyloarthritis): Bimzelx is indicated for the treatment of adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy (see SmPC for the full indication).

Hidradenitis suppurativa (HS): Bimzelx is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy (see SmPC for the full indication).

It contains bimekizumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Bimzelx’s benefits can be found in Bimzelx’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/bimzelx

2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERISE THE RISKS

Important risks of Bimzelx, together with measures to minimize such risks and the proposed studies for learning more about Bimzelx'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 authorised 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 patient (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 analysed, including periodic safety update report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Bimzelx is not yet available, it is listed under 'missing information' below.

2.1 List of important risks and missing information

Important risks of Bimzelx are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. 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 Bimzelx. 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).

Table 2–1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Serious infections
	Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
Important potential risks	Serious hypersensitivity reactions
	Major adverse cardiovascular events
	Malignancy

Table 2–1: List of important risks and missing information

List of important risks and missing information	
Missing information	Use during pregnancy and lactation
	Long-term safety data

2.2 Summary of important risks

Table 2–2: Summary of important identified risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Serious infections are considered as an important identified risk as a class effect for IL-17 inhibitors.
Risk factors and risk groups	**PSO:** Increasing age, diabetes mellitus, smoking, significant infection history, and PSO treatment were each associated with an increased risk (Kalb et al, 2015). Treatment with biologics or small molecules may increase risk of serious infection in PSO patients, with variability in the mechanism of action (Siegel and Winthrop, 2019). **PsA**: Increasing age, prednisone use, PGA scores of 4 or 5 at the time closest to the reported event, history of infection, diabetes, chronic pulmonary comorbidity and total duration of bDMARD use can potentially contribute to the risk of development of serious infections (Celkys et al, 2020, Ritchlin et al, 2019). **axSpA**: Annual average number of csDMARD prescriptions and time to first biological drug prescription are significantly associated with increased risk of hospitalization for infections in patients with AS (Quartuccio et al, 2019). The use of biologics among patients with AS and nr-axSpA are not significantly associated with an increased risk of serious infection (Wang et al, 2018b). **HS**: Patients with HS have multiple potential risk factors for serious and antibiotic-resistant infections, including epidermal disruption from suppurating lesions and erosions; treatment with immunosuppressants, topical agents and/or oral antibiotics; and comorbidities such as diabetes that are independently associated with infections (Lee et al, 2020; Bettoli et al, 2019).
Risk minimization measures	Routine risk minimization measures: Product labeling
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, AS0014, and HS0005 See Section 2.3 of this summary for an overview of the post-authorisation development plan.

Table 2–2: Summary of important identified risks

Important identified risk: Serious infections	
Important identified risk: Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	
Evidence for linking the risk to the medicine	This risk is based on safety evaluation performed including pharmacoepidemiological background incidence and prevalence rates of IBD, comparison of data from other IL-17 inhibitors, and review of bimekizumab clinical data.
Risk factors and risk groups	PSO: Risk of IBD in PSO patients increases with severity of disease and systemic medication usage. Cancer, obesity, and cardiovascular disease may also be risk factors of IBD in PSO patients (Lee et al, 2019; Radtke et al, 2017; Takeshita et al, 2017; Vlachos et al, 2016; Molodecky et al, 2012; Loftus Jr 2004). PsA: Risk of IBD in PsA increases with environmental risk factors such as smoking, infections, high doses of NSAIDs and genetic predisposition (Schreiber et al, 2019, Charlton et al, 2018). Previous failure of a TNF antagonist has also been associated with exacerbations and less disease control (Schreiber et al, 2019). axSpA: Risk of IBD in axSpA increases with environmental risk factors such as smoking, infections, genetic predisposition, previous failure of a TNF antagonist and high doses of NSAIDs (Schreiber et al, 2019; Fragoulis 2019). People in the older age group (≥65 years) and those with comorbidity of cancer also have a higher risk for IBD (Wang et al, 2020). HS: A study in the USA reported adjusted odds ratios for HS (vs non-HS) for CD (Garg et al., 2018) in subgroups, by testing effect modification. Sex significantly altered the odds ratios of CD, with men having a higher risk than women. They also found higher risk in older patients, higher risk in non-obese patients than in obese patients, and higher risk in non-smokers than in smokers.
Risk minimization measures	Routine risk minimization measures: Product labeling
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, AS0014 and HS0005 See Section 2.3 of this summary for an overview of the post-authorisation development plan.

AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; bDMARD=biologic disease-modifying antirheumatic drug; CD=Crohn's disease; csDMARD=conventional synthetic disease-modifying antirheumatic drug; HS: hidradenitis suppurativa; IBD=inflammatory bowel disease; IL=interleukin; NSAID=non-steroidal anti-inflammatory drug; nr-axSpA=non-radiographic axial spondyloarthritis; PGA=physician global assessment; PSO=psoriasis; TNF=tumor necrosis factor

Table 2–3: Summary of important potential risks

Important potential risk: Serious hypersensitivity reactions	
Evidence for linking the risk to the medicine	All monoclonal antibodies could potentially be associated with hypersensitivity reactions, including anaphylactic/anaphylactoid events. Data to evaluate safety concerns derive from clinical studies.
Risk factors and risk groups	Risk groups include patients who have hypersensitivity to the active substance or to any of the excipients.
Risk minimization measures	Routine risk minimization measures: Product labeling
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, AS0014, and HS0005 See Section 2.3 of this summary for an overview of the post-authorisation development plan.
Important potential risk: MACE	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies, comparison of data from other IL-17 inhibitors, and pharmacoepidemiological background incidence and prevalence rates.
Risk factors and risk groups	**PSO**: The increased cardiovascular risk in PSO patients is partly due to the association with factors that are known predictors of cardiovascular risk including hyperlipidemia, obesity, hypertension, and diabetes. In addition, PSO patients have an increased risk of vascular inflammation and MACE (defined as myocardial infarction, stroke and cardiovascular related death) beyond that attributable to known cardiovascular risk factors (Egeberg et al, 2017; Gelfand et al 2006). Observational studies have shown that if systemic inflammation is driving CVD risk then systemic treatment with methotrexate and biologic drugs may reduce elevated risk of MACE (Jindal and Jindal, 2018). Some clinical trials of IL-12/23 inhibitors have reported elevated risk of MACE; however, a recent review across 38 RCTs found no statistically elevated risk (Rungapiromnan et al, 2017; Parisi et al, 2015). **PsA**: In PsA patients, the risk of developing CV events is driven by traditional CV risk factors; however, the level of disease activity and the extent of systemic inflammatory factors and chronic recurring inflammation are predictors of CV events (Zheng et al, 2022, Eder et al, 2016). Alongside traditional CV risk factors, such as diabetes, dyslipidemia, and smoking, markers of PsA disease activity, including polyarthritis, dactylitis, extensive skin PSO, and elevated inflammatory markers, have been associated with clinical CV events (Karmacharya et al, 2021c, Ogdie et al, 2015). **axSpA**: Inflammation, disease activity or its severity measurements are well-recognized factors for accelerated atherosclerosis in axSpA, along with traditional CV risk factors such as smoking, hypertension, obesity, diabetes, and dyslipidemia (Toussirot et al, 2021).

Table 2–3: Summary of important potential risks

	HS: Mediation analyses in an EMR-based study in the USA revealed that age, sex, and race all significantly modified the association between HS and risk of the combined outcome of *MI or CVA*, while adjusting for cardiovascular risk factors (Reddy et al., 2020). Women had a higher risk than men. Patients <50 years of age had an increased risk, compared to non-HS patients, but in older patients, this was not the case anymore. African-Americans had the lowest risk of the different ethnic groups.
Risk minimization measures	Routine risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, AS0014, and HS0005 See Section 2.3 of this summary for an overview of the post-authorisation development plan.
Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical studies, comparison of data from other IL-17 inhibitors, and pharmacoepidemiological background incidence and prevalence rates.
Risk factors and risk groups	**PSO**: Several mechanisms may contribute to the increased risk of cancer among patients with PSO including chronic inflammation, impaired immunosurveillance associated with the disease itself. Other factors, such as treatment with certain pharmacologic agents or behavioral factors including smoking and alcohol consumption also may contribute to risk independently. A large meta-analysis showed that risk factors of cancer in PSO patients included alcohol and cigarette use, phototherapy, and disease severity (Pouplard et al, 2013). Two retrospective cohort studies examined severity of PSO disease and/or treatment in relation to cancer incidence (Kimball et al, 2015; Lee et al, 2012). These studies found a trend in the incidence of all cancers, lymphoma, melanoma, and NMSC associated with increased PSO disease severity defined by treatment. **PsA**: The increased risk of cancers in PsA could be driven by the chronic inflammatory nature of the disease itself and the requirement for long-term therapy with immunosuppressive agents and/or phototherapy. An increased risk of cancer can also be attributed to more severe form of PsA which requires more long-term use and high-cumulative dose of immunosuppressants. Although data on the risk of cancer for the different therapeutic domains in PsA are variable, patients treated with conventional synthetic disease modifying antirheumatic drugs are reported to present with increased cancer risk, but not those treated with biological therapies (Vaengebjerg et al, 2020; Woo et al, 2020; Fagerli et al, 2019; Luo et al 2019; Costa et al, 2016; Hagberg et al, 2016). **axSpA**: Chronic inflammatory activity in patients with AS can drive the risk of developing malignancies in axSpA. Evidence suggests that Asian

Table 2–3: Summary of important potential risks

	populations, but not American or European populations, have a higher risk of malignancy (Deng et al, 2016). A meta-analysis has indicated no overall elevated risk of malignancy among SpA patients (including axSpA and peripheral SpA) treated with biologics (Kwan et al, 2020). **HS**: The survey study in The Netherlands reported a higher prevalence of self-reported malignancies in men (7.8%) than in women (6.1%) (Prens et al., 2022). A study in the USA found that men with HS had 1.4 times higher odds to have squamous cell carcinoma, while this was 1.1 times in women (Hua et al., 2021). Whites had significantly increased risk, but this was not the case for other ethnic groups.
Risk minimization measures	Routine risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0038 (Bimekizumab real-world outcomes study) Review of safety data from studies PS0014, PS0015, PA0012, AS0014, and HS0005 See Section 2.3 of this summary for an overview of the post-authorisation development plan.

AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; COPD=chronic obstructive pulmonary disease; COX=cyclooxygenase; CV=cardiovascular; CVA=cerebrovascular accident; CVD=cardiovascular disease; HS=hidradenitis suppurativa; IL=interleukin; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=nonmelanoma skin cancer; PsA=psoriatic arthritis; PSO=psoriasis; RCT=randomized clinical trial; SpA=spondyloarthritis

Table 2–4: Summary of missing information

Missing information: Use during pregnancy and lactation	
Risk minimization measures	Routine risk minimization measures: Product labeling
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PS0036 (Bimekizumab pregnancy exposure and outcomes registry) PS0037 (An observational cohort study to evaluate bimekizumab exposure during pregnancy) See Section 2.3 of this summary for an overview of the post-authorisation development plan.
Missing information: Long-term safety	
Risk minimization measures	Routine risk minimization measures: None

Table 2–4: Summary of missing information

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Review of safety data from studies PS0014, PS0015, PA0012, AS0014, and HS0005 See Section 2.3 of this summary for an overview of the post-authorisation development plan.

2.3 Postauthorization development plan

2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Bimzelx.

2.3.2 Other studies in post-authorisation development plan

Additional pharmacovigilance activities include the following studies:

2.3.2.1 PS0038: Bimekizumab real-world outcomes study

- **Study short name:** Bimekizumab real-world outcomes study

  Purpose of the study: The primary objective of this observational cohort study will be to evaluate any potential increase in the risk of safety outcomes of interest in bimekizumab exposed PSO, PsA, axSpA, and HS patients compared to PSO, PsA, axSpA, and HS patients exposed to other biologics indicated for moderate-to-severe PSO, PsA, axSpA, and HS except for any other anti-interleukin(IL)-17 biologics (eg, anti-tumor necrosis factor[TNF], anti-IL-23) in the real-world setting.

  The safety outcomes of interest will include but are not limited to major adverse cardiovascular events, malignancy, serious infections, inflammatory bowel disease, and serious hypersensitivity reactions.

2.3.2.2 PS0036: Bimekizumab pregnancy exposure and outcomes registry

- **Study short name:** Bimekizumab pregnancy exposure and outcomes registry

  Purpose of the study: The objective of this study is to assess maternal, fetal, and infant outcomes among women who become pregnant while exposed to bimekizumab relative to the outcomes in 2 frequency matched comparator populations. The primary analysis will be a comparison of the birth prevalence of major structural defects in live born infants between the bimekizumab-exposed cohort and the disease comparison cohort. Additional outcome variables will be to evaluate the potential effect of bimekizumab exposure on other adverse pregnancy outcomes including, but not limited, to spontaneous abortion, elective termination, stillbirth, preterm delivery, and infant outcomes including small for gestational age, pattern of 3 or more minor structural defects, postnatal growth (to 1 year of age), developmental concerns (at approximately 1 year of age), and serious infections (up to 1 year of age).

2.3.2.3 PS0037: Observational cohort study to evaluate bimekizumab exposure during pregnancy

- **Study short name:** Observational cohort study to evaluate bimekizumab exposure during pregnancy

  Purpose of the study: The primary objective is to assess adverse pregnancy and infant outcomes, more specifically major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, preterm birth and infant infections, in women exposed to bimekizumab during pregnancy compared to women exposed to other biologics indicated for moderate-to-severe PSO, PsA, axSpA, and any other condition for which bimekizumab has an approved indication except for any other anti-IL-17 biologics (eg, anti-TNF, and-IL-23) during pregnancy using a cohort study design with data from a large electronic health database.

2.3.2.4 PS0014

- **Study short name:** A multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO (PS0014).

  Purpose of the study: To assess the long-term safety and tolerability of bimekizumab administered sc in adult study participants with moderate to severe chronic plaque PSO. This study will include 2 periods, a Treatment Period (144 weeks) and a SFU period (20 weeks after the final dose). A second open-label extension (OLE) Period was added, during which eligible study participants in Canada and the US are invited to continue or reinitiate bimekizumab treatment for an additional 40 weeks and are followed in a second SFU Period of 20 weeks after the final dose of investigational medicinal product (IMP), as appropriate. This will allow continuous access to bimekizumab for study participants in Canada and the US.

2.3.2.5 PS0015

- **Study short name:** A multicenter, randomized, double-blind, active comparator-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO (PS0015).

  Purpose of the study: The open label extension period will allow collection of long-term efficacy and safety data from eligible study participants on open-label bimekizumab for an additional 96 weeks (after 48 weeks of initial treatment). An OLE2 Period was added, during which eligible study participants in Canada and the US are invited to continue or reinitiate bimekizumab treatment for an additional 40 weeks and are followed in a second SFU Period of 20 weeks after the final dose of IMP, as appropriate. It will allow continuous access to bimekizumab for study participants in Canada and the US.

2.3.2.6 PA0012

- **Study short name**: A multicenter, open label extension study to evaluate the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with active PsA.

  Purpose of the study: The open label extension period will allow collection of long-term safety and tolerability data of bimekizumab over a period of up to 140 weeks in adult

participants with PsA who completed the feeder Phase 3 studies. An OLE 2 Period was added, during which eligible participants in the US, France, Germany, and Japan are invited to continue or reinitiate bimekizumab treatment for an additional 52 weeks and are followed in a SFU Period of 20 weeks after the final dose of IMP (SFU Period), as appropriate.

2.3.2.7 AS0014

- **Study short name:** A multicenter, open label extension study to evaluate the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with axSpA (radiographic and non-radiographic).

  Purpose of the study: The open label extension period will allow collection of long-term safety and tolerability data of bimekizumab over a period of up to 112 weeks in adult participants with axSpA who completed the feeder Phase 3 studies. An OLE 2 Period was added, during which eligible study participants in Japan, France, Germany, and US are invited to continue bimekizumab treatment for an additional 52 weeks and are followed in a SFU Period of 20 weeks after the final dose of IMP (SFU Period), as appropriate.

2.3.2.8 HS0005

- **Study short name:** An open-label, parallel group, multicenter, extension study evaluating the long-term treatment of bimekizumab in study participants with moderate to severe hidradenitis suppurativa

  Purpose of the study: To assess the long-term safety (primary) and efficacy (secondary) of bimekizumab administered sc in adult study participants with moderate to severe HS. This study will include 2 periods, a Treatment Period (100 weeks) and a SFU period (20 weeks after the final dose).

  The HS0005 protocol has been amended globally with a substantial change being study participants receiving bimekizumab 320mg Q2W will be switched to bimekizumab 320mg Q4W. This is based on data from both the individual Phase 3 studies, as well as the pooled data from the 2 completed pivotal Phase 3 studies HS0003 and HS0004, which demonstrated similar efficacy for bimekizumab 320mg Q4W and bimekizumab 320mg Q2W during the Maintenance Treatment Periods (Weeks 16 to 48 of the HS0003 and HS0004 studies). In addition, local amendments in France and Germany will extend the treatment period for an additional 48 weeks. Local amendments for the United States and Japan will extend the treatment period for an additional 80 weeks.

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable