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EU Risk Management Plan (Version 9.1)

Global Patient Safety
EU Risk Management Plan electronically approved by Lilly on date provided below.

Document ID: VV-PVG-130610

EU Risk Management Plan for Ixekizumab

RMP version to be assessed as part of the application: 9.1

Data lock point for this RMP: 02 April 2024

Date of final sign off: See cover page

Rationale for submitting an updated RMP: This updated European Union (EU) Risk Management Plan (RMP) is being submitted to request a revision to the timeline for the Study I1F-MC-B015 final study report, from Q2 2026 to Q2 2027. The proposed postponement will allow for the inclusion of an additional database and revised sample size targets, which are necessary to conduct the planned comparative analyses.

Summary of significant changes in this RMP:

The following milestones for Study I1F-MC-B015 have been revised:

- End of data collection: Updated to 30 November 2025
- Final study report submission due date: Updated to 30 June 2027

Additionally, the actual start of data collection (07 October 2021) for Study I1F-MC-B015 has been added.

Routine pharmacovigilance activities updated to remove all follow-up forms to align with the recent good pharmacovigilance practice guideline on specific adverse reaction follow-up questionnaires.

The summary of changes can be found in Annex 8.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP

Version number: 8.2

Approved with procedure: EMEA/H/C/003943/II/0053

Date of approval (opinion date): 22 August 2025

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Qualified Person for Pharmacovigilance (QPPV) of the marketing authorisation holder, Eli Lilly Nederland B.V. The electronic signature is available on file.

Table of Contents

List of Tables

Table **Page**

Part I: Product Overview

Table Part I.1. Product Overview

Active substance (INN or common name)	Ixekizumab
Pharmacotherapeutic groups (ATC code)	Interleukin-17A antagonist ATC code: L04AC13
Marketing authorisation	Eli Lilly Nederland B.V.
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Taltz™
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Humanised monoclonal antibody
	Summary of mode of action: Ixekizumab is an immunoglobulin G subclass 4 (IgG4) monoclonal antibody that binds with high affinity and specificity to interleukin-17A (IL-17A), a proinflammatory cytokine. In psoriasis, the IL-17A ligand plays a major role in driving excess keratinocyte proliferation and activation. In PsA and axial spondyloarthritis, IL-17A plays a major role in the pathogenesis of the disease process by driving inflammation leading to erosive bone damage and pathologic new bone formation. Neutralisation of IL-17A by ixekizumab inhibits these actions. Enthesitis related arthritis (ERA) and juvenile PsA (JPsA) bear resemblance to adult axSpA and PsA, respectively; therefore, therapeutic benefit of ixekizumab is expected in these 2 subtypes of juvenile idiopathic arthritis (JIA).
	Important information about its composition: The ixekizumab active drug substance is a humanised IgG4 monoclonal antibody against the proinflammatory cytokine IL-17A, which is produced in Chinese hamster ovary cells by recombinant DNA technology.
Hyperlink to the product information	The proposed PI is included in Module 1.3.1 of this submission.

Indications in the EEA	**Current:** Adult Plaque Psoriasis Taltz is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy. Psoriatic Arthritis Taltz, alone or in combination with methotrexate, is indicated for the treatment of active PsA in adult patients who have responded inadequately to, or who are intolerant to, one or more disease modifying anti-rheumatic drug (DMARD) therapies. Axial Spondyloarthritis *Ankylosing Spondylitis (Radiographic Axial Spondyloarthritis)* Taltz is indicated for the treatment of adult patients with active radiographic axial spondyloarthritis who have responded inadequately to conventional therapy. *Non-radiographic Axial Spondyloarthritis* Taltz is indicated for the treatment of adult patients 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 to nonsteroidal anti-inflammatory drugs (NSAIDs). Paediatric Plaque Psoriasis Taltz is indicated for the treatment of moderate-to-severe plaque psoriasis in children from the age of 6 years and adolescents who are candidates for systemic therapy. Juvenile Idiopathic Arthritis *Juvenile Psoriatic Arthritis (JPsA)* Taltz, alone or in combination with methotrexate, is indicated for the treatment of active JPsA in patients 6 years of age and older and with a body weight of at least 25 kg, who have had an inadequate response to, or who are intolerant of, conventional therapy. *Enthesitis-Related Arthritis (ERA)* Taltz, alone or in combination with methotrexate, is indicated for the treatment of active ERA in patients 6 years of age and older and with a body weight of at least 25 kg, who have had an inadequate response to, or who are intolerant of, conventional therapy.
	Proposed: Not applicable.
Dosage in the EEA	**Current:** Plaque Psoriasis The recommended dosage is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (1 injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (1 injection) every 4 weeks. Psoriatic Arthritis The recommended dosage is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (1 injection) every 4 weeks thereafter. For PsA patients with concomitant moderate-to-severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis. Radiographic Axial Spondyloarthritis The recommended dosage is 80 mg by subcutaneous injection every 4 weeks. For patients who have had an inadequate response or are intolerant to at least 1 TNF inhibitor, a dose of 160 mg (two 80-mg injections) by subcutaneous injection at

<table>
<tr><td></td><td>Week 0, followed by 80 mg every 4 weeks may be considered.
Non-radiographic Axial Spondyloarthritis
The recommended dosage is 80 mg by subcutaneous injection every 4 weeks. In radiographic and non-radiographic axial spondyloarthritis, conventional DMARD (for example, sulfasalazine), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be used during treatment with Taltz.
Paediatric Plaque Psoriasis (age 6 years to less than 18 years)
The recommended dose given by subcutaneous injection in children from 6 to less than 18 years of age, and at least 25 kg body weight, is based on the following weight categories:
<table>
<tr><th>Children’s Body Weight</th><th>Recommended Starting Dose (Week 0)</th><th>Recommended Dose every 4 weeks (Q4W) Thereafter</th></tr>
<tr><td>Greater than 50 kg</td><td>160 mg (two 80 mg injections)</td><td>80 mg</td></tr>
<tr><td>25 to 50 kg</td><td>80 mg</td><td>40 mg</td></tr>
</table>
Taltz can be used directly from the prefilled syringe. For instructions on preparation of Taltz 40 mg, see Section 6.6 of the SmPC.
JIA (ERA and JPsA):
The recommended dose given by subcutaneous injection in paediatric patients from 6 to less than 18 years of age is based on the following weight categories:
<table>
<tr><th>Paediatric Patient’s Weight</th><th>Recommended Starting Dose (Week 0)</th><th>Recommended Dose every 4 weeks (Q4W) Thereafter</th></tr>
<tr><td>Greater than 50 kg</td><td>160 mg (two 80 mg injections)</td><td>80 mg</td></tr>
<tr><td>25 to 50 kg</td><td>80 mg</td><td>40 mg</td></tr>
</table></td></tr>
<tr><td></td><td>Proposed:
Not Applicable.</td></tr>
<tr><td>Pharmaceutical forms and strengths</td><td>Current:
80-mg solution for injection in a prefilled syringe
80-mg solution for injection in a prefilled pen
40-mg solution for injection in a prefilled syringe
The revised, citrate-free formulation has been authorised for the already approved indications on 16 December 2021.</td></tr>
<tr><td></td><td>Proposed: Not applicable.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

Abbreviations: ATC = anatomical therapeutic chemical; CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; DNA = deoxyribonucleic acid; ERA= enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; EU = European Union; INN = international nonproprietary name; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PI = package insert; PsA = psoriatic arthritis; RMP = risk management plan; Q4W = every 4 weeks; SmPC = summary of product characteristics; TNF = tumour necrosis factor.

Part II: Safety Specification

Module SI - Epidemiology of the Indications and Target Populations

SI.1. Plaque Psoriasis in Adult Patients

SI.1.1. Incidence

The incidence of plaque psoriasis (hereafter referred to as psoriasis) reported in Europe varies within the region and has increased over time. In the Netherlands, United Kingdom (UK), and Italy, the incidences ranged between 140 and 230 per 100,000 patient-years (PYs) (Huerta et al. 2007; Vena et al. 2010; Parisi et al. 2013).

SI.1.2. Prevalence

The worldwide prevalence of psoriasis is estimated to be 2% to 3% (Radtke and Augustin 2008). In the UK, the prevalence of psoriasis estimated from the Clinical Practice Research Datalink (CPRD [formerly known as the General Practice Research Database]) between 1987 and 2002 was reported at 1.5% (Gelfand et al. 2005). In Germany, the 1-year prevalence of psoriasis was reported as 2.53% (study time period not specified; Augustin et al. 2010b), and in Spain, the prevalence in 1998 was estimated between 1.17% and 1.43% (Ferrándiz et al. 2001). In the United States (US), the overall prevalence of self-reported psoriasis among adults older than 20 years of age reported from the 2009 to 2010 National Health and Nutrition Examination Survey was 3.2% and was highest among Caucasians (3.6%) (Rachakonda et al. 2014).

SI.1.3. Demographics of the Population in the Indication – (Age, Gender, Racial, and/or Ethnic Origin) and Risk Factors for the Disease

Psoriasis is a common disorder that often begins in childhood, with up to one-third of adult patients with psoriasis reporting onset of disease during the first 2 decades of life and 10% reporting onset prior to age 10 years (Farber and Nall 1974). Psoriasis is a bimodally distributed disease with 1 major age of onset between 20 and 30 years and a later, smaller peak of onset between 50 and 60 years (Ayala-Fontánez et al. 2016). A recent systematic review suggested that countries further from the equator tend to have a higher prevalence of psoriasis among their populations (Parisi et al. 2013).

Paediatric psoriasis is discussed in Section SI.2.

Psoriasis is equally common in males and females (Gudjonsson and Elder 2007). It can occur in all age groups (Seminara et al. 2011) and ethnicities and is most prevalent in non-Hispanic whites (Helmick et al. 2014). In 2011, the annual database extract (N=9495) from the 12country Psoriasis Longitudinal Assessment and Registry (PSOLAR; 67.3% of US sites), race/ethnicity frequencies were as follows: White/Caucasian, 82.4%; Hispanic/Latino, 6.8%; Asian, 4.4%; Black/African American, 3.9%; and Other, 2.5% (Papp et al. 2012).

Estimates of psoriasis prevalence in the elderly population are not widely available. Seminara et al. (2011) reported the prevalence of psoriasis among people in the UK as 2.5% for ages 50 to

59 years, 3% for ages 60 to 69 years, 2.9% for ages 70 to 79 years, 2.6% for ages 80 to 89 years, and 1.4% for ages 90 years and older.

The pathogenesis of psoriasis is multifactorial (Chandran and Raychaudhuri 2010) and includes both intrinsic and extrinsic risk factors. Epidemiological studies have demonstrated a higher incidence of psoriasis among relatives of patients with the disease when compared to the general population, particularly among children born to parents with psoriasis (Basko-Plluska and Petronic-Rosic 2012), suggesting a genetic link. Race/ethnicity is also a commonly cited risk factor, as the burden of psoriasis varies by racial/ethnic group. In the US, psoriasis is significantly more prevalent among non-Hispanic whites than other groups (Helmick et al. 2014). Psoriasis is rare in Asians and Native Americans (Bowcock and Barker 2003).

Epidemiological studies have demonstrated a positive association between smoking and the development of psoriasis, adjusting for alcohol consumption (Behnam et al. 2005; Huerta et al. 2007). This association was replicated in a study that found a significant trend towards increased risk of psoriasis with increasing pack-years of smoking, and a reduction of risk with an increase in time since smoking cessation (Li et al. 2012). A prospective cohort study that controlled for smoking found an increased risk of psoriasis among women who consumed alcoholic beverages, suggesting that alcohol consumption may also increase the risk of psoriasis (Qureshi et al. 2010).

Obesity is also an identified risk factor for psoriasis. In the Nurses Health Study II, a dose-response relationship between obesity and the risk of developing psoriasis was identified, and it was estimated that 30% of incident psoriasis cases were due to obesity (Basko-Plluska and Petronic-Rosic 2012). In a population-based case-control study, a body mass index ≥30 was associated with a 2-fold increased risk of psoriasis when compared with normal body weight (Wolk et al. 2009).

Certain medications, including beta-blockers, lithium, antimalarials, tetracycline antibiotics, NSAIDs, as well as steroid withdrawal have been associated with the onset and exacerbation of psoriasis (Basko-Plluska and Petronic-Rosic 2012).

Psoriasis may be more severe in patients who are immunocompromised, as well as in those who have an active infection. Specifically, acute bacterial and viral infections have been associated with the onset or aggravation of psoriasis. Additionally, human immunodeficiency virus (HIV) has been associated with the onset of severe psoriasis that is not responsive to treatment (Basko-Plluska and Petronic-Rosic 2012).

SI.1.4. Main Existing Treatment Options

In commonly accepted treatment guidelines, moderate-to-severe psoriasis is a disease that cannot be controlled by routine skin care measures (for example, moisturisers, bath solutions) or by the use of topical psoriasis therapies alone. Treatment guidelines recommend systemic treatments to reduce disease severity as well as to improve quality of life and functioning (Pathirana et al. 2009; Smith et al. 2009; AAD Work Group 2011).

Systemic therapies include nonbiologic as well as biologic treatments. Traditional nonbiologics such as cyclosporine, methotrexate, acitretin, and phototherapy are widely used, but with these

treatments, significant numbers of patients fail to achieve a clinically meaningful reduction in disease severity as measured by 75% improvement in the Psoriasis Area and Severity Index (PASI 75; Pang et al. 2008; Dogra and Mahajan 2013). Oral systemic therapies, such as methotrexate and cyclosporine, are associated with considerable risk for hepatic and renal toxicities, respectively, and are considered inappropriate for use in many of the common medical comorbid conditions associated with psoriasis, such as diabetes, hypertension, and metabolic syndrome (Nast et al. 2012). Currently, there are several approved and investigational biological therapies for moderate-to-severe psoriasis. These agents attain greater efficacy compared with the traditional systemic nonbiologic therapies, as indicated by proportion of patients achieving clinically meaningful response.

Use of systemic treatments among the elderly warrants special consideration as these patients typically have a high prevalence of comorbid conditions and concomitant medications, diminished renal function, age-related changes in immune function, and altered pharmacokinetics and pharmacodynamics (Ryan et al. 2014). The medical board of the National Psoriasis Foundation recommends topical medications as first-line treatment for limited disease in elderly patients and narrowband ultraviolet B, psoralen and ultraviolet light A (PUVA), acitretin, methotrexate, alefacept, etanercept, adalimumab, infliximab, and ustekinumab as first-line treatment for extensive disease. Cyclosporine should be used rarely (Grozdev et al. 2011). A more recent review of available therapies suggests that apremilast may be considered when traditional therapies are ineffective or when patients have comorbidities that preclude the use of methotrexate or acitretin. Biologics such as ixekizumab are suggested after ineffective treatment with apremilast (Di Lernia and Goldust 2018). Although there is little available data about how often systemic medications are used in elderly patients with psoriasis, Wong and Koo (2012) report that dermatologists are often uncomfortable prescribing systemic medications to these patients.

Treatment for paediatric psoriasis is discussed in Section SI.2.4.

SI.1.5. Natural History of Psoriasis in the Population, Including Mortality and Morbidity

In 2011, the annual database extract (N=9495) from PSOLAR (67.3% US sites) reported the all-cause mortality rate for psoriasis at 0.37 per 100 PYs (Papp et al. 2012).

Observational studies conducted within UK administrative claims databases demonstrated that patients with severe psoriasis are at an increased risk of death from all causes. In the CPRD, the mortality rate among patients with severe psoriasis (any patient with a diagnostic code of psoriasis and a history of systemic therapy consistent with severe psoriasis) was reported as 21.3 per 1000 PYs compared to 12.0 per 1000 PYs in the control group (Gelfand et al. 2007). In the Health Improvement Network (THIN) database, patients with psoriasis requiring a DMARD, (marker of severe disease) had a significantly higher mortality rate (22.19 per 1000 PYs) than patients not requiring DMARDs (11.92 per 1000 PYs) (Ogdie et al. 2014).

A Danish cohort study using the entire Danish population from 1997 to 2006 also found that people with psoriasis had an increased risk of death relative to the general population

(all-cause mortality rate ratio: 1.16 for mild psoriasis and 1.73 for severe psoriasis; severe psoriasis identified by hospital-based treatment). Mortality peaked between ages 18 and 50 years and then decreased. The relative risk (RR) of mortality was highest in younger patients (18 to 50 years) with severe disease (Ahlehoff et al. 2011).

With respect to cardiovascular disease, the rate of cardiovascular mortality in the CPRD (after controlling for age, sex, smoking, hyperlipidaemia, hypertension, and diabetes) was 1.57 times higher in patients with severe psoriasis than in patients without psoriasis (severe psoriasis defined as a diagnostic code of psoriasis and a history of systemic therapy consistent with severe psoriasis). The authors observed an interaction with age such that the greatest differential risk was observed among the younger individuals with severe disease (Mehta et al. 2010).

SI.1.6. Important Comorbidities

The following comorbidities are not listed in any particular order of importance or incidence.

Cardiovascular Disease

People with psoriasis have an increased risk of cardiovascular disease, over and above an age- and sex-matched population. This trend appears across geographic regions. A retrospective cohort study in the UK reported that patients with psoriasis had a higher risk of myocardial infarction (hazard ratio [HR]=1.21), angina (HR=1.20), atherosclerosis (HR=1.28), peripheral vascular disease (HR=1.29), and stroke (HR=1.12) (Kaye et al. 2008). Similarly, after controlling for risk factors, a US veteran's hospital observational study demonstrated a significantly elevated burden of ischaemic heart disease (odds ratio [OR]=1.78), cerebrovascular disease (OR=1.70), and peripheral vascular disease (OR=1.98) in patients with psoriasis compared to controls. This study also demonstrated increased mortality among patients with psoriasis compared with controls (OR=1.86) (Prodanovich et al. 2009). The incidence rate per 100 PYs for myocardial infarction is reported as 0.16 among patients with newly diagnosed psoriasis and 0.15 among the general population (Brauchli et al. 2009). By comparison, incidence rates among patients with moderate-to-severe psoriasis and treated with systemic medications are higher and vary between 0.19 per 100 PYs and 0.61 per 100 PYs (Gelfand et al. 2006a, 2009; Wakkee et al. 2010; Abuabara et al. 2011; Wu et al. 2012; Ahlehoff et al. 2013; Gottlieb et al. 2013).

Psychiatric Diseases

Psychiatric and psychological morbidity related to psoriasis is significant, though it appears more often as an indicator of the disability experienced by the patient rather than the skin condition itself (Gupta and Gupta 2003). A population-based cohort study using data collected as part of patient electronic medical records from 1987 to 2002 reported that patients with psoriasis had a 39%, 31%, and 44% increased risk of depression, anxiety, and suicidality, respectively (Kurd et al. 2010).

Metabolic Syndrome

Psoriasis is associated with a number of metabolic abnormalities including diabetes, dyslipidaemia, and obesity (Miller et al. 2013). Two recent meta-analyses of observational studies evaluating metabolic syndrome in conjunction with psoriasis found that individuals with psoriasis were more likely to have metabolic syndrome compared to the general population, and that the prevalence was highest among individuals with severe psoriasis (pooled OR=1.8 [Miller et al. 2013]; pooled OR=2.26 [Armstrong et al. 2013a]).

Autoimmune Diseases

There is greater recognition of autoimmune comorbidities in psoriasis following recent genetic studies that found genetic links between psoriasis and certain autoimmune diseases (Armstrong et al. 2013b). In a German health insurance database, the prevalence ratios (PRs) of rheumatoid arthritis (RA), Crohn's disease (CD), and ulcerative colitis (UC) among patients with psoriasis were 3.8, 2.1, and 2.0, respectively (Augustin et al. 2010b).

Cancer and Lymphoma

The risk of developing cancer or lymphoma appears to be increased in patients with psoriasis without regard to geography. In a UK retrospective cohort study, there was nearly a 3-fold increase in the RR of developing lymphoma. The incidence rate of lymphoma per 10 000 PYs was 18.3 with psoriasis and 6.1 without psoriasis (Gelfand et al. 2003). In a subsequent large population-based study, lymphomas were substantially increased in both mild and severe forms of psoriasis (Gelfand et al. 2006b). For all cancers, US claims database reported that the psoriasis group had a 20% greater incidence rate than the general population (Kimball et al. 2014).

SI.2 Psoriasis in Paediatric Patients

SI.2.1 Incidence

Literature regarding the incidence of psoriasis in paediatric patients is limited. In Europe, the incidence rate of juvenile psoriasis was reported as 57 per 100,000 PYs for Italian children aged 0 to 14 years (Cantarutti et al. 2015) and 116 per 100,000 PYs for children in the UK aged 0 to 19 years (Huerta et al. 2007).

SI.2.2 Prevalence

The prevalence of psoriasis in children varies by geography. Population-based studies report a range from 0% to 2.1% (BurdenTeh et al. 2016). The highest values were from European studies, namely Italy, 2.1% (Naldi et al. 2009); Germany, 1.3% (Augustin et al. 2012); and the UK, 1.3% (Gelfand et al. 2005). By comparison, the prevalence of psoriasis among children in the US was below 1% (Tollefson et al. 2010; Wu et al. 2011). Studies that stratified prevalence according to age reported psoriasis to be more common after puberty (0.6 to 1.3%) than before puberty (0.1% to 0.5%) (BurdenTeh et al. 2016).

SI.2.3 Demographics of the Population in the Indication – (Age, Gender, Racial, and/or Ethnic Origin) and Risk Factors for the Disease

Global reviews of psoriasis note that approximately 30% to 50% of patients develop psoriasis prior to the age of 20 years (Bronckers et al. 2015). Among juveniles aged 0 to 18 years, the median age at onset of psoriasis was between 7 and 10 years (Radtke et al. 2011). The male to female ratio varies from 1.14:1 to 1:2.33. This female predominance seen in the prevalence of childhood psoriasis is the opposite of that commonly observed in adults (Burden-Teh et al. 2016).

Childhood prevalence of psoriasis increases with increasing age. Gelfand et al. (2005) found that the prevalence of psoriasis in childhood in the UK was about 0.55% in children aged 0 to 9 years and 1.37% in children aged 10 to 19 years. Comparable prevalence results have been reported within the German (age 0 to 9, 0.37%; age 10 to 19, 1.01%) (Augustin et al. 2010a) and Dutch populations (age 0 to 10, 0.4%; age 11 to 19, 1.0%) (De Jager et al. 2009).

The most common psoriasis type in children, reported from a study of 357 patients, was chronic plaque psoriasis (73.7%), and the most commonly involved sites were the extremities (59.9%) and the scalp (46.8%) (Tollefson et al. 2010).

Similar to adults, the prevalence of psoriasis is highest among children of European descent compared to other racial ethnic groups; however, it is important to note that Non-white individuals are more likely to have undiagnosed psoriasis than white individuals (in part owing to barriers to care and decreased health care utilisation in these groups), which suggests that the prevalence of psoriasis in black and Hispanic individuals may be underestimated (Kaufman and Alexis 2018).

The pathogenesis of psoriasis is complex and is assumed to result from an interaction between environmental and genetic factors. Family history of psoriasis appears to play an important role in the development of disease in paediatric patients, with up to 48.8% of paediatric patients reporting 1 or more family members also having psoriasis (Burden-Teh et al. 2016).

The most common predisposing genetic risk factor for early-onset psoriasis (onset under the age of 40 years) is the human leukocyte antigen (HLA) type Cw6 (*PSOR1*) (Nair et al. 2009). Less common is a pathogenic mutation in *CARD14* (caspase recruitment domain family 14; *PSOR2*), which is transmitted in an autosomal dominant fashion and may manifest as pityriasis rubra pilaris, erythrodermic psoriasis, pustular psoriasis, or plaque psoriasis (Jordan et al. 2012; Eytan et al. 2014; Berki et al. 2015). Environmental factors thought to contribute to the development of psoriasis include physical trauma to the skin, psychological stress, exposure to medications, and infections (Eichenfield et al. 2018).

SI.2.4 Main Existing Treatment Options

There are currently no international standardised guidelines for medical treatment of paediatric psoriasis. Although earlier publications point to the primary goal in the treatment of childhood psoriasis as effective control of disease and not complete clearance (Thomas and Parimalam

2016), a more recent publication suggests that the paradigm is shifting and that extracutaneous comorbidities and the potential for lifelong chronicity support a more aggressive approach (Eichenfield et al. 2018). The choice of the most appropriate treatment should be influenced by several factors such as patient age, clinical disease severity, impact on quality of life, psychological burden of the condition, presence of comorbidities (for example, PsA, obesity), and the patient's previous treatments and preferences (Napolitano et al. 2016).

Clinical consensus identifies topical therapy as appropriate for children who present with mild, localised psoriasis, although the Food and Drug Administration (FDA) has not approved any topical therapy for children younger than 12 years (Eichenfield et al. 2018). Phototherapy is typically recommended for patients with extensive or refractory disease; however, long-term side effects, including premature photoaging and carcinogenesis, should be considered (Napolitano et al. 2016). Additionally, the increased propensity of darker skin to tan during phototherapy may be deemed unacceptable by some patients depending on their cultural beliefs regarding beauty and ideal complexion (Kaufman and Alexis 2018).

Nonbiologic systemic therapy is an option for paediatric patients with severe psoriasis. Methotrexate, cyclosporine, and acitretin are the most commonly used agents. None of them is approved for psoriasis in children because of the lack of randomised controlled trials (RCTs) in this age group. Data on benefits and risks of these therapies come from long-term use in paediatric patients affected by other diseases such as ichthyoses, juvenile RA, and organ transplantation (Napolitano et al. 2016).

Concerns about the long-term use of oral retinoids, including acitretin, include skeletal side effects such as premature closure of epiphysis, calcification of tendons, and hyperostotic changes. Methotrexate and acitretin should be used with caution in paediatric patients of childbearing age due to the risk of teratogenicity (Kaushik and Lebwohl 2019).

Limited biologic therapies are currently approved for paediatric psoriasis in Europe and the United States. Where approved, these medications are indicated in patients with moderate-to-severe disease who have had intolerance or inadequate response to phototherapy or other nonbiologic systemic therapies. Because biologics directly target cytokines in the psoriasis inflammatory cascade, they are generally associated with less treatment-related toxicity than traditional systemic agents. Shifting perspectives on treatment, including the recognition that severe untreated inflammation in childhood may be associated with cardiovascular morbidity and mortality in adulthood, suggest that biologics may begin to play a larger role in the treatment of paediatric psoriasis (Eichenfield et al. 2018).

SI.2.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

A review of the literature on paediatric psoriasis found data to suggest that patients with child-onset psoriasis experience more significant disease and flares compared to patients who experience psoriasis onset in adulthood (Burden-Teh et al. 2016).

Psoriasis in children is associated with significant comorbidities (Osier et al. 2017) and there is growing recognition of a “psoriatic march” where severe untreated inflammation in childhood may be associated with cardiovascular morbidity and mortality in adulthood (Eichenfield et al. 2018).

SI.2.6 Important Comorbidities

Comorbidity Incidence and Prevalence in Paediatric Patients with Psoriasis		
Category		
Obesity	Incidence	8.05/1000 PYs (US MarketScan; 4-17yrs; Paller et al. 2019)
	Prevalence	8.4% (Germany; 0-20 yrs.; Augustin et al. 2010b) 20.2% overall from 9 countries (International; 5-17 yrs.; Paller et al. 2013) • 27.6% United States • 15.5% Europe
Elevated lipids	Incidence	6.9/1000 PYs (US claims data; age <19 yrs; Tollefson et al. 2018) 5.82/1000 PYs (Age not given; DataMart; Manos et al. 2017) 1.92/1000 PYs (US MarketScan; 4-17 yrs; Paller et al. 2019)
	Prevalence	2.12% (Germany; 0-20 yrs; Augustin et al. 2010b) 0.10% (US MarketScan; 4-17 yrs; Paller et al. 2019)
Diabetes mellitus	Incidence	1.16/1000 PYs (Age not given; DataMart; Manos et al. 2017) 2.6/1000 PYs (US claims data; <19 yrs; Tollefson et al. 2018) 1.58/1000 PYs (US MarketScan; 4-17 yrs; Paller et al. 2019)
	Prevalence	0.86% (Germany; 0-20 yrs; Augustin et al. 2010b)
Metabolic syndrome	Incidence	1.1/1000 PYs (US claims data; <19 yrs; Tollefson et al. 2018)
	Prevalence	Information not identified in the literature
Liver enzymes elevated	Incidence	6.0/1000 PYs (US claims data; <19 yrs; Tollefson et al. 2018)
	Prevalence	Information not identified in the literature
Any Cardiovascular Disease		
Hypertension	Incidence	4.19/1000 PYs (Age not given; DataMart; Manos et al. 2017) 4.9/1000 PYs (US claims data; <19 yrs; Tollefson et al. 2018) 1.71/1000 PYs (US MarketScan; 4-17 yrs; Paller et al. 2019)
	Prevalence	4.2% (United States; 0-17 yrs; hospitalised; Kwa et al. 2017) 0.26% (US MarketScan; 4-17 yrs; Paller et al. 2019)
Cardiovascular disease	Incidence	0.37/1000 PYs (Age not given; DataMart; Manos et al. 2017)
	Prevalence	Information not identified in the literature

Important Comorbidities

Comorbidity Incidence and Prevalence in Paediatric Patients with Psoriasis		
Category		
Any Cardiovascular Disease		
Valvular heart disease	Incidence	Information not identified in the literature
	Prevalence	1.5% (United States; 0-17 yrs; hospitalised; Kwa et al. 2017)
Arrhythmia	Incidence	Information not identified in the literature
	Prevalence	3.3% (US; 0-17 yrs; hospitalised; Kwa et al. 2017)
Category		
Autoimmune Diseases		
Crohn's disease	Incidence	0.97/1000 PYs (US MarketScan; 4-17 yrs; Paller et al. 2019)
	Prevalence	0.51% (Germany; 0-20 yrs; Augustin et al. 2010b) 0.21% (Denmark; <18 yrs; Blegvad et al. 2017)
Juvenile idiopathic arthropathy (includes RA, PsA, and AS)	Incidence	7.25/1000 PYs: PsA (US MarketScan; 4-17 yrs; Paller et al. 2019) 0.82/1000 PYs: RA (US MarketScan; 4-17 yrs; Paller et al. 2019) 0.07/1000 PYs: AS (US MarketScan; 4-17 yrs; Paller et al. 2019)
	Prevalence	0.63%: JIA (US MarketScan; 4-17 yrs; Paller et al. 2019) 4.2%: PsA (Denmark; <18 yrs; Blegvad et al. 2017) 5.6%: PsA (International; 5-17 yrs; Paller et al. 2013) 8.40%: RA (Germany; 0-20 yrs; Augustin et al. 2010b) 0.31%: RA (Denmark; <18 yrs; Blegvad et al. 2017) 0.04%; AS (US MarketScan; 4-17 yrs; Paller et al. 2019)
Ulcerative colitis	Incidence	0.62/1000 PYs (US MarketScan; 4-17 yrs; Paller et al. 2019)
	Prevalence	0.12% (Germany; 0-20 yrs; Augustin et al. 2010b) 0.16% (Denmark; <18 yrs; Blegvad et al. 2017)
Serious infection	Incidence	7.86/1000 PYs (US MarketScan; 4-17 yrs; Paller et al. 2019)
	Prevalence	0.82% (US MarketScan; 4-17 yrs; Paller et al. 2019)
Any Psychiatric Comorbidity		
Depression	Incidence	16.60/1000 PYs (US MarketScan; 4-17 yrs; Paller et al. 2019) 3.01% (US MarketScan; <18 yrs; Kimball et al. 2012) 3.06% (US; 4-17 yrs; Paller et al. 2019)
	Prevalence	1.69% (US MarketScan; 4-17 yrs; Paller et al. 2019)

Important Comorbidities

Comorbidity Incidence and Prevalence in Paediatric Patients with Psoriasis		
Category		
Any Psychiatric Comorbidity		
Anxiety	Incidence	4.74/1000 PYs (US MarketScan; 4-17 yrs; Paller et al. 2019) 1.81% (US MarketScan; <18 yrs; Kimball et al. 2012) 0.90% (US MarketScan; 4-17 yrs; Paller et al. 2019)
	Prevalence	0.46% (US MarketScan; 4-17 yrs; Paller et al. 2019)
Suicidal ideation	Incidence	5.16/1000 PYs (US MarketScan; 4-17 yrs; Paller et al. 2019) 0.45% (US MarketScan; <18 yrs; Kimball et al. 2012) 0.98% (US MarketScan; 4-17 yrs; Paller et al. 2019)
	Prevalence	0.23% (US MarketScan; 4-17 yrs; Paller et al. 2019)

Abbreviations: AS = ankylosing spondylitis; JIA = juvenile idiopathic arthritis; PsA = psoriatic arthritis; PY = patient-year; RA = rheumatoid arthritis; US = United States; yrs = years.

SI.3. Psoriatic Arthritis

SI.3.1. Incidence

Annual incidence of PsA among the general European population ranges from 3.02 per 100 000 persons in Greece to 23.1 per 100 000 persons in Finland (Catanoso et al. 2012). Estimates pooled across country and presented by region in a systematic review and meta-analysis showed a higher prevalence of PsA in Europe (0.19% compared to other regions: 0.13% in North America; 0.05% in Southeast Asia) (Stolwijk et al. 2016).

A higher incidence of PsA is observed among patients with psoriasis compared to the general population. A cross-sectional study of dermatologists from the UK, Italy, France, Spain, and Germany used information on patient medical history to estimate the incidence of PsA among patients with psoriasis. The percentage of patients with psoriasis developing PsA was largely below 1% per year during the 30 years studied, and the rate was constant over time (7400 per 100 000 PYs) (Christophers et al. 2010).

SI.3.2. Prevalence

A targeted literature review by Ogdie and Weiss (2015) reported a large variability in PsA prevalence in patients with psoriasis, with estimates ranging from 6% in China (Yang et al. 2011) to 41% in Canada (Khraishi et al. 2012). The prevalence of PsA among European patients with psoriasis diagnosed by a rheumatologist ranged from 18% in Belgium to 38% in Hungary (Mease et al. 2013). Variability of the estimates may be due to differences in PsA diagnostic criteria, patient populations, and study settings (Catanoso et al. 2012).

SI.3.3. Demographics of the Population in the Authorised Indication of Psoriatic Arthritis – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease

Psoriatic arthritis affects men and women equally, and generally occurs between 40 and 50 years of age, although it can also occur in young children and the elderly (Liu et al. 2014; Butt et al. 2015).

While the literature indicates that Whites are frequently affected with psoriatic disease, data in non-Whites are sparse (Kerr et al. 2015). A 2013 publication from the Consortium of Rheumatology Researchers of North America (CORRONA) RA Registry, a data registry capturing data on patients with RA and PsA, reported disparities in disease activity and clinical outcomes for Hispanic and African American patients versus White patients (Greenberg et al. 2013). A review of PsA in Asia found that the prevalence of PsA in China was similar to that in other areas of the world, while the incidence and prevalence was much lower in Japan. Furthermore, the prevalence of patients with psoriasis who reported PsA was also lower in Japan relative to other countries (Tam et al. 2009).

The aetiology of PsA is unknown; however, there are genetic, immunologic, environmental, and other factors that are believed to influence the onset of disease (Dewing 2015). Family studies of PsA have shown that PsA is 50 times more likely to occur in individuals with a first-degree relative with PsA, and increased frequency of psoriasis and PsA can be observed in monozygotic

and dizygotic twins (Farhey 2012). The major histocompatibility alleles, human leukocyte antigen B18, C07, B27, B38, and B8, have also shown a strong association with the disease. Human leukocyte antigen B27 is present in up to 50% of patients with PsA and is associated with radiographic sacroiliitis and axial involvement (Dewing 2015).

Obesity, uveitis, use of retinoid medication, and characteristics of psoriasis are risk factors for PsA (Eder et al. 2016). In particular, severe psoriasis, psoriasis involving intergluteal and/or perianal areas, and psoriasis in 3 or more areas are associated with a higher risk of developing PsA (Wilson et al. 2009).

Trauma to a joint and infection have also been indicated as etiologic agents in PsA development (Farhey 2012). Gram-positive infection and PsA have been linked, as sera from patients with PsA show higher streptococcal infection than does sera of patients without PsA. Human immunodeficiency virus has also been reported to have an association with PsA and psoriasis, as patients with HIV often have more severe PsA, skin disease, and psoriasis (Farhey 2012). A study by Thumboo et al. (2002) found that corticosteroid use (increased risk) and pregnancy (decreased risk) were associated with PsA, suggesting that changes in the immune system may contribute to this condition.

SI.3.4. Main Existing Treatment Options

Many patients with PsA are not receiving appropriate treatment. The MAPP survey, the largest multinational survey of patients with PsA and psoriasis, found that almost 60% of patients with PsA were receiving no treatment or topical treatment only (Lebwohl et al. 2014). Treating joint disease in chronic PsA is important to avoid developing permanent joint damage. Mild cases of PsA may be treated with NSAIDs, intra-articular corticosteroid injections, and physical therapy. In case of lack of response, or in case of moderate-to-severe peripheral disease, treatment relies traditionally on conventional DMARDs (cDMARDs) such as methotrexate, sulfasalazine, or leflunomide (cyclosporine is now used less frequently due to toxicity). In case of cDMARD failure (or in patients with prominent axial symptoms) a biologic is recommended, generally a tumour necrosis factor (TNF) antagonist (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab). Apremilast, a targeted synthetic DMARD, may be prescribed in patients who failed cDMARDs and for whom biologics are not appropriate. For patients who fail the first TNF antagonist, treatment may be switched to another TNF antagonist or to a drug with a different mechanism of action (IL-12/23 inhibitor [ustekinumab] and IL-17 inhibitor [secukinumab]) (Gossec et al. 2016). Because existing biologics fail in some patients and lose efficacy over time in others, an unmet need remains for additional treatment options.

SI.3.5. Natural History of Psoriatic Arthritis in the Population, Including Mortality and Morbidity

Psoriatic arthritis is a multisystem, chronic inflammatory condition, and there is strong evidence that patients with PsA experience significant morbidity that is often unrecognised and undertreated such as major systemic comorbidities, including cardiovascular risk factors and diseases, obesity, depression, uveitis, and cancer (Haroon and FitzGerald 2016). Husted et al.

(2013) reported that a high proportion of patients with PsA (42%) developed 3 or more comorbidities, often accompanied by poorer health and a greater risk of mortality.

In a 2012 review of the literature, Arumugam and McHugh collated published mortality rates and causes of death in patients with PsA. Death and causes of deaths were identified from the clinical databases and confirmed by death certificates and mortality databases. Mortality findings, including age- and sex-adjusted standardised mortality ratios (SMRs), were calculated and the SMR ranged from 0.82 to 1.62. In all countries apart from Hong Kong, the highest proportion of deaths among patients with PsA was of cardiovascular aetiology, ranging from 25% in Canada to 50% in Greece. In Hong Kong, the highest mortality rates were from infections, accounting for 33% of deaths among patients with PsA. Cardiovascular events and cancer each accounted for 20% of deaths. The high proportion of deaths from infection may be due to incorrect classification of respiratory deaths (Arumugam and McHugh 2012). In a published longitudinal cohort study using the UK THIN database, patients with PsA (N=8706) did not have a significant increased risk of mortality when compared with population controls after adjusting for age and sex (Ogdie et al. 2013b).

SI.3.6. Important Comorbidities

The following comorbidities are not listed in any particular order of importance or incidence.

Cardiovascular Disease

Cardiovascular diseases are a large source of morbidity and mortality for patients with PsA (Eder et al. 2013; Lin et al. 2014). A Canadian, clinic-based study reported that patients with PsA had a significantly greater burden of hypertension (standard prevalence ratio [SPR]=1.90), myocardial infarction (SPR=2.57), and angina (SPR=1.97), than people of a similar age and sex in the general population (Gladman et al. 2009). The risk of cardiovascular death and a composite of cardiovascular outcomes (myocardial infarction, stroke, and death) among patients with PsA were significantly higher than age- and sex-matched general population controls in a study of the Danish population (rate ratio for cardiovascular death=1.84 and composite cardiovascular outcome=1.79) and were comparable to patients with diabetes mellitus (Ahlehoff et al. 2011).

The aetiology of increased risk of cardiovascular disease among patients with PsA is thought to be due to a higher prevalence of traditional cardiovascular risk factors, PsA-related inflammation, and the use of some PsA treatments (for example, NSAIDS, cyclooxygenase-2 inhibitors, prednisone) (Zhu et al. 2012; Horreau et al. 2013; Jamnitski et al. 2013). Treatment with DMARDs is thought to decrease the risk of cardiovascular disease (Husni 2015); however, a population-based study found similar rates of myocardial infarction among patients with PsA with and without DMARD treatment (HR=1.36 for each group with overlapping confidence intervals [CIs]) (Ogdie et al. 2015). The role of DMARD treatment in the development of cardiovascular disease in PsA is difficult to elucidate, as treatment is often confounded by disease severity and duration.

Psychiatric Diseases

Anxiety and depression are important comorbidities among patients with PsA. In a study of 631 patients with PsA (2006 to 2012), the prevalence of depression/anxiety during the study period was 20.6% (Husted et al. 2013). In a large UK retrospective cohort study using CPRD data, the baseline prevalence of ever having depression and having depression in the last 12 months was 27.2% and 3.4%, respectively (Edson-Heredia et al. 2015). In a retrospective US study using data representing 15.5 million privately insured adults with moderate-to-severe psoriasis+PsA (n=1230), the prevalence of comorbid anxiety and depression during the 12-month study period was 5.9% and 9.1%, respectively (Feldman et al. 2015). Among patients with PsA in Toronto, Canada (n=306), the prevalence (probable + possible clinical disorder) of anxiety, depression, and anxiety with depression was 36.6%, 22.3%, and 17.7%, respectively (McDonough et al. 2014).

Depression is a major risk factor for suicidality (Miret et al. 2013). Given the high prevalence of depression in PsA, suicidal thoughts and behaviours are a concern. The literature regarding suicidal ideation in patients with PsA is limited. In a RCT of ustekinumab (PSUMMIT 1) among 615 patients with PsA, suicidal ideation and depression were reported in 1 patient after early placebo escape to 45-mg ustekinumab dosing (McInnes et al. 2013). In the PSUMMIT 2 trial, a placebo patient had suicidal ideation after early escape to ustekinumab 45-mg dosing. Later in the trial, there was 1 suicide attempt in the ustekinumab 90-mg dosing group (Ritchlin et al. 2014). In another RCT of secukinumab among 397 patients with PsA, there were no cases of suicide or suicidal ideation reported among treated patients (McInnes et al. 2015).

Metabolic Syndrome

The definition of metabolic syndrome is evolving. Current paradigms suggest that nonalcoholic fatty liver disease, including nonalcoholic steatohepatitis (NASH), is a strong determinant for the development of metabolic syndrome rather than a hepatic manifestation (Lonardo et al. 2015). Nonalcoholic fatty liver disease and NASH are highly prevalent among patients with psoriasis and PsA (Roberts et al. 2015). Analysis of patients with PsA from the US CORRONA RA Registry showed that 27% of patients with PsA also had metabolic syndrome (Labitigan et al. 2014). Similar results were reported from a cross-sectional study of patients with psoriasis and PsA in Belgium where the prevalence of metabolic syndrome was 25.5% (Bostoen et al. 2014). The presence of metabolic syndrome is associated with more severe PsA (OR=4.47; Haroon et al. 2014) and increased risk of cardiovascular disease (Lin et al. 2014).

Autoimmune Disease

Identifying autoimmune conditions associated with PsA is an active area of research (Armstrong et al. 2013b). Approximately 9% of patients with PsA from a university PsA clinic in Canada had concomitant autoimmune disease (thyroid disease, celiac disease, type 1 diabetes mellitus, Sjögren syndrome, lupus erythematosus) (Husted et al. 2013). Results from the Nurses' Health Study I/II found an increased risk of CD among patients with psoriasis and PsA relative to patients without psoriatic disease (RR=6.54; 95% CI: 2.07, 20.65) (Li et al. 2013). A US health care claims database including both men and women found that the prevalence of

inflammatory bowel disease (IBD), CD, and UC were significantly higher among patients with PsA than the prevalence observed in an age- and sex-matched controls (IBD overall PR=1.8; CDe PR=2.1; UC PR=2.0) (Makredes et al. 2009).

Cancer and Lymphoma

Published data on the risk of cancer and lymphoma among patients with PsA are minimal. A population-based study linking data from the Swedish National Patient Register to the National Cancer Register did not find an increased risk of lymphoma among patients with PsA relative to the general population (HR=1.2 [95% CI: 0.9, -1.7]); however, the risk was elevated for patients with PsA treated with methotrexate and/or sulfasalazine (Hellgren et al. 2014). Another cohort study of patients with PsA in Toronto also found no discernible difference in incidence of malignancies between the PsA population and the general population (Rohekar et al. 2008). No difference in cancer-specific mortality (HR=1.06 [95% CI: 0.86, -1.32]) among patients with PsA (n=8709) versus controls (n=82 170) was observed in a study from the UK THIN database (Ogdie et al. 2013a). The incidence rate (per 100 PYs) of cancers reported for patients with PsA in the CORRONA RA registry are as follows: overall malignancy, 0.56; nonmelanoma skin cancer (NMSC), 0.21; non-NMSC, 0.35; breast cancer, 0.20; prostate cancer, 0.09; colorectal cancer, 0.04; melanoma, 0.04; lymphoma, 0.04; multiple myeloma, 0.01; and leukaemia, 0.01 (Gross et al. 2014). The authors caution that the rates of NMSC may be lower in this group of patients with PsA because skin-directed therapy, including both PUVA and psoralen ultraviolet B (broadband and narrow-band), is indicated for cutaneous but not rheumatic disease activity. Therefore, patients with cutaneous predominant psoriasis may be more likely to experience the procarcinogenic effects of light therapy compared with patients with more active joint disease in the RA registry (Gross et al. 2014).

SI.4 Axial Spondyloarthritis

Axial spondyloarthritis (axSpA) is a term that includes ankylosing spondylitis (AS), also known as radiographic axSpA (r-axSpA), and nonradiographic axSpA (nr-axSpA) (Robinson et al. 2019).

In 2009, the Ankylosing Spondyloarthritis International Society introduced the concept of axSpA as a disease spectrum encompassing patients with established radiographic sacroiliitis, or r-axSpA (referred to as AS), and patients who have not developed radiographic sacroiliitis, referred to as nr-axSpA (Rudwaleit et al. 2009). The literature cited in the following sections represents the spectrum of axSpA. For some of the references cited, the term AS was used while others used the term r-axSpA. Therefore, r-axSpA/AS or AS is used in those situations.

SI.4.1 Incidence

There is a paucity of epidemiological data on nr-axSpA, as most available literature focuses on patients with AS. In Europe, the incidence rates for AS range from 0.44 per 100 000 PYs in Iceland to 7.26 per 100 000 PYs in Norway (Bohn et al. 2018).

SI.4.2 Prevalence

Prevalence of axSpA is not well characterised in the general population. Prevalence of Assessment of Spondyloarthritis International Society (ASAS)-defined axSpA within the chronic low back pain population ranged from 8.4% in Norway (Bakland et al. 2013) to 24% in the Netherlands (van Hoeven et al. 2014).

Prevalence of AS ranged from 70 per 100 000 persons in Poland to 180 per 100 000 persons in Sweden and 260 per 100 000 persons in Norway (Bohn et al. 2018). Throughout Europe, the mean AS prevalence was calculated at 238 per 100 000 persons (Dean et al. 2014).

The prevalence of nr-axSpA, available from a single US study and based on ASAS criteria, was 350 per 100 000 persons (Strand et al. 2013). Similar European data are not well represented in the literature.

SI.4.3 Demographics of the Population in the Proposed Indication of Axial Spondyloarthritis – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease

Current data suggest a strong genetic risk for the development of axSpA. A study using the Icelandic genealogy database and a population-wide survey reported that first-degree, second-degree, and third-degree relatives had significantly higher risk of developing axSpA compared with the risk in the general population (Geirsson et al. 2010).

Human leukocyte antigen B27 is thought to increase susceptibility to AS; however, the pathogenic role of this gene is not fully understood (Akassou and Bakri 2018). In Germany, 82.2% of the participants in the German Spondyloarthritis Inception cohort were HLA-B27 positive (Rudwaleit et al. 2009).

Axial spondyloarthritis typically manifests in the third decade of life, with a male:female ratio of 2:1 for r-axSpA and 1:1 for nr-axSpA (Sieper and Poddubnyy 2017). In Europe, the mean male:female ratio for AS was 3.8:1 (Dean et al. 2014).

SI.4.4 Main Existing Treatment Options

Current treatment recommendations for the management of AS are nonpharmacological management along with NSAIDs as the first line of treatment. Treatment with TNF inhibitors is recommended for patients who have persistent disease activity despite conventional treatment. Although most of the evidence for treatment efficacy of NSAIDs and TNF inhibitors was originally established in clinical trials of patients with AS (Poddubnyy 2013), recent evidence from a clinical trial of certolizumab pegol demonstrated efficacy among patients with nr-axSpA (Deodhar et al. 2019).

Treatment with cDMARDs such as methotrexate and sulfasalazine are recommended for peripheral joint involvement. Local steroids are also effective for peripheral manifestations and are used in the treatment of active sacroiliitis in pure axial disease. Systemic steroids are generally not recommended in axSpA, but short-term treatment may be beneficial if rapid reduction of disease activity is required (Poddubnyy 2013).

SI.4.5 Natural History of Axial Spondyloarthritis in the Population, Including Mortality and Morbidity

Axial spondyloarthritis is a chronic inflammatory condition with no predictable pattern of progression; thus, the disease does not follow a single defined course (Sieper et al. 2002). Many patients with nr-axSpA will progress to AS after years of disease. This radiographic progression can be seen in approximately 10% of patients over 2 years of follow-up on average, and up to 20% over 2 years among those with elevated C-reactive protein or active inflammation on magnetic resonance imaging. Some patients with nr-axSpA may never develop evidence of radiographic damage. There is no clear explanation for this phenomenon (Slobodin and Eshed 2015). Drug-induced, as well as subsequent drug-free, remission in patients with nr-axSpA has been reported repeatedly (Slobodin and Eshed 2015).

In Europe, the prevalence by country of common clinical manifestations of AS include:

Category	Prevalence	Country
Uveitis	20.1%[3] to 23.5%[2]	Sweden
Inflammatory bowel disease	2.6%[4] to 8.3%[2]	Germany/Sweden
Psoriasis	2.2%[1] to 10.2%[4]	Sweden/Germany
Peripheral arthritis	17.6%[2] to 37.4%[4]	Sweden/Germany

1 Bengtsson K et al, 2018

2 Exarchou S et al, 2015

3 Exarchou S et al, 2016

4 Rudwaleit M et al, 2009

Excess mortality has been documented in patients with AS. The overall mortality rate in patients with AS is 1.6- to 1.9-fold of that in the general population, and the excess cardiovascular mortality has been estimated at 20% to 40% (Mathieu et al. 2010).

SI.4.6 Important Comorbidities

Table SI.4.1. Comorbidity Incidence and Prevalence in Patients with Axial Spondyloarthritis

Category		
Heart		
ACS	Incidence	3.4 per 1000 PYs in Sweden (Eriksson et al. 2017)
	Prevalence	3.0% in Sweden (Eriksson et al. 2017)
AMI	Incidence	1.55 per 1000 PYs in the UK to 2.56 per 1000 PYs in Wales (Brophy et al. 2012; Essers et al. 2016)
	Prevalence	1.8% in the UK (Essers et al. 2016)
CVD	Incidence	Not well represented in the literature
	Prevalence	20% to 34.4% in Sweden (Exarchou et al. 2016; Eriksson et al. 2017)
Heart failure	Incidence	Not well represented in the literature
	Prevalence	0.6% in the UK to 3.1% in Sweden (Essers et al. 2016; Bengtsson et al. 2018)
IHD	Incidence	4.30 per 1000 PYs in the UK (Essers et al. 2016)
	Prevalence	2.4% in the EU to 7.3% in Sweden (López-Medina et al. 2018; Bengtsson et al. 2018)
Brain		
CBVD	Incidence	Not well represented in the literature
	Prevalence	2.5% to 3.1% in Sweden (Exarchou et al. 2016; Bengtsson et al. 2018)
Stroke	Incidence	2.36 per 1000 PYs in Wales to 3.0 per 1000 PYs in Sweden (Brophy et al. 2012, Eriksson et al. 2017)
	Prevalence	1.0% in Sweden to 1.5% in the EU (Eriksson et al. 2017; López-Medina et al. 2018)
VTE (DVT/PE)	Incidence	3.2 per 1000 PYs in Sweden (Eriksson et al. 2017)
	Prevalence	1.0% to 1.3% in Sweden (Exarchou et al. 2016; Eriksson et al. 2017)
Diabetes	Incidence	Not well represented in the literature
	Prevalence	4.0% Sweden to 4.9% Sweden (Exarchou et al. 2016; Eriksson et al. 2017)
Metabolic syndrome	Incidence	Not well represented in the literature
	Prevalence	Italian study of patients with AS (n=24): 45.8% according to the NCEP/ATPIII criteria (Malesci et al. 2007) Mediterranean patients with AS receiving anti-TNF therapy (n=63): 34.9% versus using NCEP/ATPIII criteria (Sidiropoulos et al. 2008).
Hypertension	Incidence	Not well represented in the literature
	Prevalence	8.3% in the UK to 19.2% in the EU (Essers et al. 2016; López-Medina et al. 2018)
Infection	Incidence	Not well represented in the literature

Category		
	Prevalence	32.9% in Sweden (Exarchou et al. 2016)
Malignancy	Incidence	Secukinumab trials of patients with AS Calculated incidence: 52 weeks: 0.70% in secukinumab arms and 0.51% in placebo arms (Baeten et al. 2015; Braun et al. 2017)
	Prevalence	2.0% to 5.0% in Sweden (Exarchou et al. 2016; Eriksson et al. 2017)
Psychiatric		
Depression	Incidence	AS: 6.94 per 100 PYs in the US (Wu et al. 2017) to 10 per 100 PYs in Sweden (Meesters et al. 2014)
	Prevalence	AS: 12.3% in France (Kreis et al. 2015) to 44% in Turkey (Kilic et al. 2014)
Suicidal ideation	Incidence	AS: 0.22 per 100 PYs for suicidal ideation, 1.48 per 100 PYs for suicide attempt, and 3.71 per 100 PYs for any suicidality in the US (Wu et al. 2017)
	Prevalence	Not well represented in the literature
Gastrointestinal		
Inflammatory bowel disease	Incidence	During postmarketing safety surveillance for secukinumab, the cumulative rate of reported inflammatory bowel disease events remained stable at approximately 0.20, varying between 0.16 to 0.22 per 100 PYs (Schreiber et al. 2019) • Pooled incidence of 794 patients with AS from 21 secukinumab trials was 0.1 per 100 PYs for inflammatory bowel disease unclassified (Schreiber et al. 2019)
	Prevalence	Clinically overt inflammatory bowel disease: 5% to 10% of patients with AS; asymptomatic subclinical gut inflammation revealed by ileocolonoscopy: 25% to 49% of patients with AS (Rudwaleit and Baeten 2006) Meta-analyses of 8 studies comprising 2236 patients with AS and 1242 patients with nr-axSpA were included. • AS: 4.1%; nr-axSpA: 6.4% (de Winter et al. 2016)
Crohn's disease	Incidence	Secukinumab trials of patients with AS • 52 weeks pooled incidence: 0.7 per 100 PYs in secukinumab-treated patients compared to 0% in the placebo arm (Baeten et al. 2015) • Long-term extension: 0.5 per 100 PYs in secukinumab-treated patients (Baraliakos et al. 2018) • Pooled incidence of 794 patients with AS from 21 secukinumab trials was 0.4 per 100 PYs (Schreiber et al. 2019)
	Prevalence	Patients with AS: 8.0% in males and 6.3% in females (Szabo et al. 2011)

Category		
Ulcerative colitis	Incidence	Secukinumab trial of patients with AS • 52 weeks: 0.1 per 100 PYs in secukinumab-treated patients • Long-term extension: 0.1 per 100 PYs in secukinumab-treated patients (Baraliakos et al. 2018) • Pooled incidence of 794 patients with AS from 21 secukinumab trials was 0.2 per 100 PYs (Schreiber et al. 2019)
	Prevalence	Patients with AS: 4.4% in males and 3.5% in females (Szabo et al. 2011)

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; AS = ankylosing spondyloarthritis; ATPIII = Adult Treatment Panel III; CBVD = cerebrovascular disease; CVD = cardiovascular disease; DVT = deep vein thrombosis; EU = European Union; IHD = ischaemic heart disease; NCEP = National Cholesterol Education Program; nr-axSpA = nonradiographic axial spondyloarthritis; PE= pulmonary embolism; PY = patient-year; TNF = tumour necrosis factor; UK = United Kingdom; US = United States; VTE = venous thromboembolism.

SI.5 *Juvenile Idiopathic Arthritis*

Nomenclature has evolved over the years, from the American Rheumatism Association's juvenile rheumatoid arthritis (JRA) to the European League Against Rheumatism's (EULAR) juvenile chronic arthritis (JCA) to, most recently, the International League Against Rheumatism's (ILAR) juvenile idiopathic arthritis (JIA) (Al-Mayouf et al. 2021; Nigrovic et al. 2021). Juvenile idiopathic arthritis (JIA) is an umbrella term for arthritis of unknown origin, lasting for greater than 6 weeks with onset before 16 years of age (Martini et al. 2022). JIA is the most common chronic inflammatory rheumatic condition of childhood. It represents a heterogeneous family of distinct paediatric rheumatological disorders caused by a variety of genetic and pathophysiological mechanisms (La Bella et al. 2023). According to ILAR, there are 7 different, mutually exclusive categories of JIA based on the number of joints affected, the presence of systemic symptoms, and detection of rheumatoid factor (Zaripova et al. 2021):

- oligoarticular JIA (persistent or extended)
- seropositive polyarticular JIA
- seronegative polyarticular JIA
- systemic-onset JIA (sJIA)
- juvenile psoriatic arthritis (JPsA)
- enthesitis-related arthritis (ERA) and
- undifferentiated JIA (any arthritis that does not fit into the previous categories or corresponds to more than1 subtype is considered undifferentiated).

SI.5.1 Incidence

Estimates of incidence and prevalence for JPsA and ERA have been difficult to ascertain because of differences in diagnostic criteria over time, case ascertainment, study designs (for example, population-based, hospital-based, questionnaires and registry data), geographic region (for example, limited information in the sub-Saharan Africa region, Eastern and Western differences), genetic or environmental risk factors between populations, access to a

rheumatologist in rural versus urban centre, as well as low disease frequency and small study numbers (Hahn 2018; Al-Mayouf et al. 2021; Martini et al. 2022), and confusion in the literature between incidence and prevalence. The incidence of JPsA is unclear which has presented challenges in gathering systematic data on treatment outcomes (Saad and Onel 2020; Correll et al. 2023). The incidence of ERA is similarly unclear from the literature (Li et al. 2022). Broadly speaking, in a worldwide systematic literature review of 43 articles on JIA, 33 papers reported annual incidence rates varying from 1.6 to 23 per 100,000 person-years. Pooled incidence was higher for girls (10.0 per 100,000 person-years) than for boys (5.7 per 100,000 person-years) (Thierry et al. 2014).

SI.5.2 Prevalence

Compared to incidence, more information is available in the literature on the prevalence of ERA and JPsA. Specifically, JPsA accounts for less than 10% of all JIA cases (Beukelman et al. 2017; Glerup et al. 2017; Naddei et al. 2023). ERA accounts for 5 to 30% of all JIA cases (Beukelman et al. 2017; Consolaro et al. 2019; Di Gennaro et al. 2023; Naddei et al. 2023).

SI.5.3 Demographics of the Population in the Proposed Indication of Juvenile Idiopathic Arthritis subtypes enthesitis-related arthritis and juvenile psoriatic arthritis and Risk Factors for the Disease

In terms of ERA, ethnicity is a risk factor as ERA is more commonly observed in Asian countries (Consolaro et al. 2019; Shih et al. 2019; Li et al. 2022) which may, at least in part, be related to a high frequency of the human leukocyte antigen (HLA)-B27 in these populations (Chan et al. 2023; Giancane et al. 2016). A number of studies have identified a male preponderance in ERA patients (for example, Hahn 2018; Shih et al. 2019; Lanças et al. 2024) whereas others have failed to support this finding (see Li et al. 2022). The average age at diagnosis is 10 to 15 years old, which is an older age of set compared to other JIA subtypes (Hahn 2018; Shih et al. 2019; Lanças et al. 2024). Patients with ERA tend to have higher pain intensity, more chronic disease, are human leukocyte antigen-B27 (HLA-B27)-positive, with 20% having a family history of HLA-B27-associated disease, a history of clinical or radiologic sacroiliitis, and poorer health status compared to their counterparts with other categories of JIA (Weiss 2013; Li et al. 2022; Chan et al. 2023).

The literature is inconsistent regarding features of JPsA (Zisman et al. 2018). A biphasic age of onset distribution has been noted with early-onset disease characterised by female predominance, small joint involvement, dactylitis, and positive antinuclear antibodies. Late-onset JPsA resembles adult-onset psoriatic arthritis, with male predominance, psoriasis, enthesitis, and axial disease (Zisman et al. 2018; Gavra et al 2022). Children with JPsA have a greater risk of disease flare after attaining inactive disease and stopping treatment (Gavra et al. 2022). Relatively little is known about the epidemiology and risk factors for development of JPsA among children with psoriasis (Gavra et al 2022).

SI.5.4 Main Existing Treatment Options

The American College of Rheumatology (ACR) recommends that ERA be managed using pharmacological and non-pharmacological measures depending on several factors, such as the number of active joints, the presence of enthesitis, and the occurrence of axial disease. According to the international treat-to-target recommendations for JIA published in 2018, therapeutic interventions are aimed to control the disease activity; to prevent joint damage; to avoid comorbidities and medication toxicities; and to optimise functional status, growth and development, quality of life, and social participation (Di Gennaro et al. 2023).

The pharmacological options for ERA treatment include (Di Gennaro et al. 2023; Naveen et al. 2023)

- non-steroidal anti-inflammatory drugs (NSAIDs) (first line of treatment)
- glucocorticoids
- conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including sulfasalazine (SSZ) and methotrexate (MTX) (MTX and SSZ are useful for treating peripheral arthritis/enthesitis, but has a limited role in axial disease), and
- biologic DMARDs (bDMARDs: etanercept, adalimumab, infliximab, golimumab, secukinumab, ustekinumab) and targeted synthetic DMARDs (tsDMARDs: tofacitinib and baricitinib).

The therapeutic recommendations for ERA do not differ from those used in other non-systemic JIA subtypes, unless sacroiliitis and/or enthesitis are present. In such cases, early use of tumour necrosis factor alpha inhibitors (TNFIs) should be promptly considered, which have been found to yield good improvement in active joints and other disease parameters in ERA patients (Di Gennaro et al. 2023; Naveen et al. 2023). Novel therapeutic agents are emerging, and hold promise for the treatment of ERA, including IL-17/IL-23 or Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways blockers. Tofacitinib is indicated to treat patients with JPsA while baricitinib is indicated to treat patients with ERA and JPsA (Di Gennaro et al. 2023).

Similar treatment strategies apply to JPsA following recommendations of the ACR (Brunello et al. 2022). Etanercept has demonstrated effectiveness for JPsA treatment in a real-world clinical setting involving 191 patients (median age at the start of follow-up = 12.0 years, median disease duration = 2.4 years) (Correll et al. 2023).

SI.5.5 Natural History of JIA subtypes enthesitis-related arthritis and juvenile psoriatic arthritis in the Population, Including Mortality and Morbidity

Very little is known about the natural history of ERA (Vendhan et al. 2014) or JPsA, with the literature instead focusing on JIA in general as summarised below.

Children and teenagers affected by JIA may experience persistent or recurring pain and impairment, which can greatly hinder their ability to carry out daily activities, impede their growth, and undermine their overall well-being. Relatedly, treatment requires frequent visits to the doctor, which reduces free time. Patients may choose to forgo education and withdraw from

social engagements due to the limitations imposed by their condition and the accompanying pain (Garner et al. 2021; Rongo et al. 2023). The pain can lead these children to feel misunderstood and stigmatised, in comparison to healthy children and lead to unfavourable mental health outcomes that may continue into adulthood (Rongo et al. 2023).

A substantial portion of youth transitioning into adult care have a high disease burden reflected by disease activity, joint damage, or ongoing medication use (Semalulu et al. 2024). Previous studies have shown that only 40 to 60% of patients achieve clinical remission or inactive disease at follow up and the duration of remission is highly variable (Garner et al. 2021). The damage caused by JIA can affect patients into adulthood and cause chronic disability. Up to half of the young adults will continue to have active disease, and up to one third will have chronic disability into adulthood. Despite the low rate of clinical remission achieved in JIA, there has been an improvement in functional disease outcomes over the past decade. The proportion of patients that develop profound functional disability ranges between 2.5 and 10% (Garner et al. 2021). Increasing evidence has demonstrated that early and aggressive treatment of JIA is associated with better long-term disease outcomes, which underscores the importance of achieving a prompt and accurate diagnosis of JIA so that early treatment can commence and disease outcomes can be optimised (Garner et al. 2021).

The knee is typically the most commonly involved joint at the time of diagnosis, affected as the initial joint in 69% of patients, with the ankle being the next most common (21%), and the elbow and wrist involved in 14% of patients at the time of diagnosis. Hip or shoulder involvement at initial diagnosis was uncommon (6% and 3%, respectively) (Krause et al. 2016). Uveitis is the most common extra-articular manifestation of JIA. Point prevalence is commonly reported between 10% and 15% of patients. Studies have shown that the majority of patients who develop uveitis do so in the first 4 years after disease onset (Rypdal et al. 2021). Those with JIA are also at increased risk of developing obstructive sleep apnoea, and the risk is particularly high among those with JIA associated deformity (Ma et al. 2022), as well as generally poor and fragmented sleep (Saidi et al. 2022).

In a population-based study in Finland following 4180 patients with JIA for an average of 6.6 years, mortality was not significantly increased among those with JIA compared with the general population (Kyllonen et al. 2019). In another study of 1556 patients with JIA in the UK, although death was a rare outcome, mortality rates were higher for patients with JIA based on a mortality ratio standardised to the population of England and Wales, particularly for patients with systemic JIA (Davies et al. 2017).

SI.5.6. Important Comorbidities

Important comorbidities observed in patients with JIA subtypes ERA or JPsA are summarised below. Since literature is limited for JIA subtypes of ERA and JPsA, the available data on JIA overall are summarised.

Depression and anxiety

Few studies have examined psychopathology in different JIA subtypes (McHugh et al. 2022). One of the limited studies in this field found that within a cohort of 111 children and young

people with JPsA, those with psoriasis had more depressive symptoms (coefficient = 9.8; 95% CI: 0.5, 19.0) than those without psoriasis at diagnosis (Low et al. 2024). In general, depression and anxiety are prevalent in children with JIA; however, prevalence rates are conflicting. A systematic literature review based on 28 papers from 2009 to 2019 found that most of the studies reviewed that used validated screens for depressive symptoms reported prevalences of clinically significant symptoms in the range of 7 to 36% in children with JIA (Fair et al. 2019). Patients who experience these symptoms have worse quality of life, with some evidence pointing to depression and anxiety symptoms having a greater impact on quality of life than other disease features, such as active joint count. Family members of JIA patients experience high rates of anxiety and depression symptoms which may impact their child's mental health and pain symptoms related to JIA. Conflicting reports of associations between depression/anxiety symptoms and disease features/disease outcomes and a paucity of longitudinal studies investigating the impact of treatment on mental health symptoms indicate areas in need of further research to effectively identify patients at greatest risk of depression and anxiety and to better understand how to treat and prevent these symptoms in youth with JIA (Fair et al. 2019).

Chronic anterior uveitis

Paediatric chronic anterior uveitis is a cause of significant visual morbidity. It is the most common extraarticular manifestation of JIA but can occur in isolation (Foeldvari et al. 2023). Literature on the clinical course and risk factors for the development of uveitis in childhood and adolescence among ERA (Walscheid et al. 2021) and JPsA patients (Baquet-Walscheid et al. 2022) are particularly scarce. Based on data from the German nationwide registry spanning 2002-2014 – the National Pediatric Rheumatological Database – Walscheid et al. (2021) identified 3778 (15.2%) of a total of 24 841 JIA patients who had ERA and, for these, 280 (7.4%) had developed uveitis. The authors found that uveitis onset was acutely symptomatic in 63% of patients. They also found that ERA patients with uveitis were more frequently male, HLA-B27–positive, younger at ERA onset, and they had higher erythrocyte sedimentation rate values at first uveitis documentation than those without uveitis. Uveitis was diagnosed at a mean age of 11.5 (± 3.9) years (50% within 2 years after ERA onset) (Walscheid et al. 2021). Using the same database, Baquet-Walscheid et al. (2021) found that uveitis developed in 6.6% of 1862 patients with JPsA. These patients were more frequently female (73.0 versus 62.9%, $p = 0.03$), antinuclear antibody (ANA) positive (60.3 versus 37.0%, $p < 0.001$), younger at JPsA onset (5.3 ± 4.1 versus 9.3 ± 4.4 yrs, $p < 0.001$), and treated with disease-modifying antirheumatic drugs (DMARDs) significantly more frequently compared with JPsA patients without uveitis.

Macrophage activation syndrome (MAS)

Macrophage activation syndrome (MAS) is a rare but life-threatening complication in children that can occur with any JIA subtype but the literature mainly focuses on the occurrence of MAS among systemic JIA patients (prevalence range 4 to 25%; Minoia et al. 2014; Hoeg et al. 2022; Kearsley-Fleet et al. 2022).

Secondary amyloidosis

Amyloid A amyloidosis, also referred to as secondary amyloidosis, is a rare systemic complication that can develop in any chronic inflammatory disorder. Amyloidosis is rarely seen in the paediatric age group (prevalence: 1 to 2% of JIA patients, specific data is not available for ERA or JPsA) (Gupta et al. 2020; Horneff et al. 2022). Patients who have a poor therapeutic response to the first-line agents should be routinely screened for the development of this complication. In comparison to the adult patients with secondary amyloidosis, the experience with tocilizumab in the treatment of this condition in the paediatric age group is very limited (Gupta et al. 2020).

Cardiac disease

Children with JIA remain at higher risk for developing cardiovascular disorders than their healthy peers. For example, pericardial disease is reported in 30% of JIA patients. Subclinical cardiovascular involvement begins shortly after the onset of the disease and worsens with disease duration. All cardiac structures may be affected, and the cardiac complications include a variety of clinical manifestations. Since cardiovascular involvement is associated with poor prognosis, the early detection of subclinical cardiac involvement in asymptomatic JIA patients is essential for timely treatment and better prognosis (Koca et al. 2017).

Osteopenia or osteoporosis

Osteopenia or osteoporosis occurs in all of the JIA forms, most typically in systemic and polyarticular forms of disease. The low bone mass is associated with the high activity of the disease and with the number of involved joints in JIA patients, also with the reduction of bone formation (Brabnikova Maresova 2011; Soliman et al. 2023). Reduced bone mineral density is observed at all sites of the skeleton in children and adolescents with JIA. Patients who suffered from JIA during childhood and adolescence may attain decreased bone mass and have an increased risk of fragility fractures. It is important to identify the subjects with an increased risk of fracture as early as possible (Brabnikova Maresova 2011).

Inflammatory bowel disease

Among all JIA patients, more than one-third report chronic gastrointestinal symptoms without associated bleeding. This relatively common extraarticular complaint has prompted deeper investigation into the significance of such symptoms. Findings thus far indicate that patients with JIA have an increased risk of immune-related gastrointestinal involvement, including Crohn's disease and ulcerative colitis. Indeed, inflammatory bowel disease (IBD) incidence in JIA patients, analysed as a whole, ranges from 20 to greater than 40 times the IBD rates in the general paediatric population (Maller et al. 2021). There is currently limited knowledge about the characteristics of JIA patients who develop IBD and risk factors for its development (van Straalen 2022).

Serious infections

The risk of infections in children with JIA is related to the JIA itself, to concurrent illnesses and to the immunosuppressive treatment. JIA patients without medication have a 2-fold incidence of bacterial infections requiring hospitalisation when compared with a control population of similar age. The use of glucocorticoids increases the risk of serious infections, while the effects of MTX and the most common group of bDMARDs used to treat paediatric patients, TNFIs, have yielded contradictory results on the occurrence of infections (Salonen et al. 2020).

In a prospective multicentre study with more than 300 children Udaondo et al. (2022) found no significant differences in the infection rate or infection severity between patients with and without JIA over a period of 9 months or more. Importantly, most infections were mild and there were no differences in the rate of severe infections or the type of infections between the groups. The findings suggested that children diagnosed with JIA might not have a significantly higher infection risk than children without JIA. Younger age and higher disease activity were associated with a higher rate of infection in patients with JIA (Udaondo et al. 2022). Furthermore, the first detailed, nationwide real-world study on JIA and pneumonia found that despite the increasing incidence of pneumonia and use of immunosuppressive treatment among children with JIA, the proportion of serious pneumonias in these patients has decreased over time (Salonen et al. 2020).

Metabolic syndrome

Metabolic syndrome is characterised by the presence of a cluster of metabolic abnormalities, especially overweight, abdominal obesity, insulin resistance, dyslipidemia, and hypertension, and it has become increasingly more important due to the association with the development of cardiovascular diseases and type 2 diabetes mellitus in adults (Zanette et al. 2010). The prevalence of metabolic syndrome, as well as obesity, is increasing rapidly in all age groups, including children (Zanette et al. 2010). JIA patients are at risk for metabolic syndrome in adulthood, but very limited data are available on metabolic risk in childhood and adolescence (Zanette et al. 2010; Gicchino et al. 2023).

Module SII – Nonclinical Part of the Safety Specification

SII.1 Toxicity

Repeat-Dose Toxicity

Nonclinical toxicity findings of potential clinical significance were limited to subcutaneous injection site reactions. These were typically sporadic, transient occurrences of mild swelling, with or without redness; 1 monkey had a pronounced and persistent reaction that was likely an immunogenic response. Injection site reactions have been reported in clinical studies.

Carcinogenicity

Carcinogenicity studies of ixekizumab have not been conducted. Animal and other studies that have investigated the role of IL-17 in tumourigenesis have been reported in the literature; the findings are equivocal. No tumours or precancerous lesions were observed in monkeys that received ixekizumab for 9 months.

Interleukin-17 is reported to have high expression in a variety of tumour types, and to promote angiogenesis, attract proinflammatory cells, and provide pro-survival signals to tumour cells. Depletion of IL-17A with a neutralising antibody inhibited tumour development in mice. Studies in mice genetically manipulated to be deficient in IL-17 or the IL-17 receptor have provided equivocal results, with either increased or reduced tumour growth compared to wild type mice.

While malignancies have been reported in clinical studies with ixekizumab, no clusters of malignancies or predominance of cell types were noted and no safety signal has been identified. The information provided in the nonclinical literature on the effects of IL-17 on malignancies, the nonclinical data available for ixekizumab, and the findings from the clinical development programme are consistent and do not suggest carcinogenicity or a promoting effect on malignant growth patterns for ixekizumab.

Developmental and Reproductive Toxicity

Fertility studies conducted in male and female monkeys demonstrated no impact to fertility endpoints evaluated, including no effects on sperm parameters or menstrual cycling, and no microscopic changes in reproductive organs.

Developmental toxicity studies with ixekizumab in pregnant monkeys revealed no evidence of harm to the foetus or infant.

SII.2 Safety Pharmacology

Not applicable, as there were no nonclinical safety pharmacology findings.

SII.3 Other Toxicity-Related Information or Data

Not applicable, as there were no other clinically-relevant findings in nonclinical studies.

Module SIII - Clinical Trial Exposure

Ixekizumab has been administered to adult patients with psoriasis as multiple subcutaneous injections from 5 mg to 150 mg with dosing frequencies of every 2 weeks (Q2W), every 4 weeks (Q4W), and every 12 weeks (Q12W) and as multiple intravenous infusions Q2W at 15 mg. In the Phase 3 studies, a starting dose of 160 mg ixekizumab (two 80-mg injections) at Week 0 was used.

Ixekizumab has been administered to paediatric patients with psoriasis as multiple subcutaneous injections with a dosing frequency of Q4W. Weight-based dosing for paediatric patients was as follows: 80 mg for patients >50 kg (with a starting dose of 160 mg); 40 mg for patients 25 to 50 kg (with a starting dose of 80 mg); and 20 mg for patients <25 kg (with a starting dose of 40 mg).

Ixekizumab has been administered to adult patients with PsA as multiple subcutaneous injections of 80 mg with dosing frequencies of Q2W and Q4W. A starting dose of 160 mg ixekizumab (two 80-mg injections) at Week 0 was used.

Ixekizumab has been administered to adult patients with axSpA as multiple subcutaneous injections of 80 mg with dosing frequencies of Q2W and Q4W. A starting dose of 80 mg or 160 mg ixekizumab (two 80-mg injections) at Week 0 was used.

Ixekizumab has been administered to paediatric patients with juvenile idiopathic arthritis (ERA and JPsA) as multiple subcutaneous injections with a dosing frequency of Q4W. Weight-based dosing for paediatric patients was as follows: 80 mg for patients more than 50 kg (with a starting dose of 160 mg); 40 mg for patients 25 and 50 kg (with a starting dose of 80 mg); and 20 mg for patients less than 25 kg (with a starting dose of 40 mg).

Study I1F-MC-RHCG (RHCG) is an open-label, non-controlled trial and is ongoing. This study is conducted in a group of patients with heterogenous underlying conditions of JIA subtypes of ERA (including JoAS) and JPsA. Thus, the exposure data for Study RHCG was not pooled with integrated CT exposure data for psoriasis (adult and paediatric), PsA, and axSpA.

Cumulatively, 9807 patients have been exposed to ixekizumab in the psoriasis (adults and paediatrics), PsA, and axSpA clinical trial programmes.

Another, 91 patients were exposed to ixekizumab in the JIA clinical trial programme.

Table SIII.1. Duration of Ixekizumab Exposure

Cumulative for Indications: Psoriasis (Adult and Paediatric), Psoriasis (paediatric), Psoriatic arthritis and Axial Spondyloarthritis		
Duration of Exposure	**Persons**	**Patient-Years**
>0 to <30 days	132	6.5
≥30 to <90 days	389	74.2
≥90 to <183 days	960	403.8
≥183 to <365 days	1470	1195.1
≥365 to <548 days	1945	2085
≥548 to <730 days	454	828.2
≥730 to <1095 days	1209	3161.6
≥1095 to <1460 days	492	1609.4
≥1460 to <1825 days	1405	6637.3
≥1825 days	1351	6902
Total	9807	22903
Psoriasis (Cumulative Adult and Paediatric)[a]		
Duration of Exposure	**Persons**	**Patient-Years**
>0 to <30 days	80	3.9
≥30 to <90 days	258	50.4
≥90 to <183 days	790	339
≥183 to <365 days	1030	859.5
≥365 to <548 days	1550	1654.7
≥548 to <730 days	228	397.4
≥730 to <1095 days	287	678.9
≥1095 to <1460 days	256	894.5
≥1460 to <1825 days	1405	6637.3
≥1825 days	1351	6902
Total	7235	18417.6
Psoriasis (Paediatric)[b]		
Duration of Exposure	**Persons**	**Patient-Years**
>0 to <30 days	0	0
≥30 to <90 days	3	0.6
≥90 to <183 days	4	1.7
≥183 to <365 days	8	6.2
≥365 to <548 days	22	26.7
≥548 to <730 days	78	139.4
≥730 to <1095 days	81	169.4
Total	196	344.0

Psoriatic Arthritis[c]		
Duration of Exposure	**Persons**	**Patient-Years**
>0 to <30 days	47	2.3
≥30 to <90 days	99	18.4
≥90 to <183 days	123	47.1
≥183 to <365 days	283	218.8
≥365 to <548 days	257	271.3
≥548 to <730 days	177	341.3
≥730 to <1095 days	423	1105
≥1095 to <1460 days	87	263.5
Total	1496	2267.8
Axial Spondyloarthritis[d]		
Duration of Exposure	**Persons**	**Patient-Years**
>0 to <30 days	5	0.4
≥30 to <90 days	32	5.4
≥90 to <183 days	47	17.7
≥183 to <365 days	157	116.9
≥365 to <548 days	138	159
≥548 to <730 days	49	89.4
≥730 to <1095 days	499	1377.6
≥1095 days to <1460 days	149	451.4
Total	1076	2217.7

[a] This includes all patients (adult and paediatric) who had ixekizumab exposure in psoriasis Studies I1F-MC-RHAG, I1F-MC-RHAJ, I1F-JE-RHAT, I1F-MC-RHAZ, I1F-MC-RHBA, I1F-MC-RHBC, I1F-MC-RHBL, I1F-US-RHBO, I1F-MC-RHBP, I1F-MC-RHBQ, I1F-MC-RHBS, I1F-MC-RHBU, I1F-EW-RHBZ, I1F-MC-RHCD, I1F-IN-RHCZ, I1F-JE-RHCV, I1F-MC-RHBH, I1F-MC-RHBN, and I1F-MC-RHCR.

[b] This includes all paediatric patients who had ixekizumab exposure in psoriasis Study I1F-MC-RHCD.

[c] This includes all adult patients who had ixekizumab exposure in psoriatic arthritis Studies I1F-MC-RHAP, I1F-MC-RHBE, I1F-MC-RHBF, I1F-MC-RHCF and I1F-IN-RHCZ.

[d] This includes all adult patients who had ixekizumab exposure in axial spondyloarthritis. Studies I1F-MC-RHBV, I1F-MC-RHBW, I1F-MC-RHBX, and I1F-MC-RHCH.

Source:

/lillyce/prd/ly2439821/regulatory_mar2024/output/shared/psa/original/ps/t_rmp_exp_cat_ps_psa_ax.rtf
/lillyce/prd/ly2439821/regulatory_mar2024/output/shared/psa/original/ps/t_rmp_exp_cat_ps.rtf
/lillyce/prd/ly2439821/regulatory_mar2024/output/shared/psa/original/ps/t_rmp_exp_cat_ps_RHCD
lillyce/prd/ly2439821/regulatory_mar2024/output/shared/psa/original/psa/t_rmp_exp_cat_psa.rtf
/lillyce/prd/ly2439821/regulatory_mar2024/output/shared/axspa/original/t_rmp_exp_cat_ax.rtf
Note: Patient-year is calculated as sum of the total person exposure days divided by 365.25.

Table SIII.2. Duration of Total Ixekizumab Exposure in Juvenile Idiopathic Arthritis Clinical Trial

Duration of Exposure	Persons	Patient-Years
>0 to <30 days	0	0
≥30 to <90 days	2	0.3
≥90 to <183 days	13	5.3
≥183 to <365 days	29	22.6
≥365 to <548 days	17	21.2
≥548 to <730 days	16	27.6
≥730 to <1095 days	14	31
Total	**91**	**107.9**

Note: This table includes all patients who have ixekizumab exposure in juvenile idiopathic arthritis study: Study I1F-MC RHCG.

Source: /lillyce/prd/ly2439821/regulatory_mar2024/output/shared/jia/original/t_rmp_exp_cat_jia.rtf

Table SIII.3. Age Group and Gender

Cumulative for Indications: Psoriasis (Adult and Paediatric), Psoriasis (paediatric), Psoriatic arthritis and Axial Spondyloarthritis						
Age Group	**Persons**			**Patient-Years**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<65 years	**5945**	**3090**	**9035**	**14397.5**	**6931.4**	**21328.9**
<30 years	874	516	1390	2064.3	1118	3182.3
≥30 to <50 years	3134	1422	4556	7561.1	3219.2	10780.3
≥50 to <65 years	1937	1152	3089	4772.1	2594.2	7366.3
≥65 years	**470**	**302**	**772**	**962.9**	**611.2**	**1574.1**
≥65 to <75 years	413	269	682	854.1	548.1	1402.2
≥75 to <85 years	55	32	87	101.9	60.2	162.1
≥85 years	2	1	3	6.8	3.0	9.8
Total	**6415**	**3392**	**9807**	**15360.4**	**7542.6**	**22903**
Psoriasis (Cumulative Adult and Paediatric)[a]						
Age Group	**Persons**			**Patient-Years**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<65 years	**4527**	**2132**	**6659**	**11822.3**	**5347.6**	**17169.9**
≥6 to <12 years	19	28	47	33.4	49.3	82.7
≥12 to <18 years	63	88	151	116.1	149.2	265.3
≥18 to <30 years	581	319	900	1527.7	773.5	2301.2
≥30 to <50 years	2349	966	3315	6105.7	2478.5	8584.2
≥50 to <65 years	1515	731	2246	4039.2	1897.1	5936.5
≥65 years	**370**	**206**	**576**	**808.5**	**439.1**	**1247.7**
≥65 to <75 years	322	179	501	708.4	388.9	1097.3
≥75 to <85 years	46	27	73	93.3	50.2	143.6
≥85 years	2	0	2	6.8	0	6.8
Total	**4897**	**2338**	**7235**	**12630.9**	**5786.7**	**18417.6**

Psoriasis (Paediatric)[b]						
Age Group	**Persons**			**Patient-Years**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<6 years	0	0	0	0	0	0
<12 years	**19**	**28**	**47**	**33.4**	**49.3**	**82.7**
6 years	2	2	4	3.4	2.8	6.2
7 years	2	3	5	2.5	5.6	8.1
8 years	2	4	6	4.1	7.5	11.7
9 years	5	8	13	7.9	12.4	20.3
10 years	3	3	6	6	5.9	11.9
11 years	5	8	13	9.4	15.1	24.5
≥12 years to <18 years	**62**	**87**	**149**	**112.6**	**148.7**	**261.3**
12 years	8	8	16	12.3	14.8	27.1
13 years	6	13	19	12.2	21.7	33.9
14 years	11	11	22	18.9	18.7	37.6
15 years	10	17	27	19.9	30.2	50.1
16 years	8	18	26	14.1	27.4	41.5
17 years	19	20	39	35.2	35.9	71.2
Total	**81**	**115**	**196**	**146**	**198**	**344**

Psoriatic Arthritis[c]						
Age Group	**Persons**			**Patient-Years**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<65 years	**669**	**677**	**1346**	**1012.3**	**1008.7**	**2021**
<18 years	0	0	0	0	0	0
≥18 to <30 years	53	38	91	85.5	53	138.5
≥30 to <50 years	338	321	659	518.7	461.5	980.3
≥50 to <65 years	278	318	596	408.1	494.1	902.2
≥65 years	**73**	**77**	**150**	**107.1**	**139.6**	**246.8**
≥65 to <75 years	68	71	139	103.9	126.7	230.6
≥75 to <85 years	5	5	10	3.2	10	13.2
≥85 years	0	1	1	0	3.0	3.0
Total	**742**	**754**	**1496**	**1119.4**	**1148.3**	**2267.8**
Axial Spondyloarthritis[d]						
Age Group	**Persons**			**Patient-Years**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<65 years	**749**	**281**	**1030**	**1562.9**	**575.1**	**2138**
<18 years	0	0	0	0	0	0
≥18 to <30 years	158	43	201	301.6	93	394.6
≥30 to <50 years	447	135	582	936.6	279.1	1215.8
≥50 to <65 years	144	103	247	324.7	203	527.7
≥65 years	**27**	**19**	**46**	**47.2**	**32.4**	**79.6**
≥65 to <75 years	23	19	42	41.9	32.4	74.3
≥75 to <85 years	4	0	4	5.3	0	5.3
≥85 years	0	0	0	0	0	0
Total	**776**	**300**	**1076**	**1610.1**	**607.6**	**2217.7**

[a] This includes all patients (adult and paediatric) who had ixekizumab exposure in psoriasis Studies I1F-MC-RHAG, I1F-MC-RHAJ, I1F-JE-RHAT, I1F-MC-RHAZ, I1F-MC-RHBA, I1F-MC-RHBC, I1F-MC-RHBL, I1F-US-RHBO, I1F-MC-RHBP, I1F-MC-RHBQ, I1F-MC-RHBS, I1F-MC-RHBU, I1F-EW-RHBZ, I1F-MC-RHCD, I1F-IN-RHCZ, I1F-JE-RHCV, I1F-MC-RHBH, I1F-MC-RHBN, and I1F-MC-RHCR.[b] This includes all paediatric patients who had ixekizumab exposure in psoriasis Study I1F-MC-RHCD.

[c] This includes all adult patients who had ixekizumab exposure in psoriatic arthritis Studies I1F-MC-RHAP, I1F-MC-RHBE, I1F-MC-RHBF, I1F-MC-RHCF and I1F-IN-RHCZ.

[d] This table includes all patients who have ixekizumab exposure in axial spondyloarthritis studies. Studies I1F-MC-RHBV, I1F-MC-RHBW, I1F-MC-RHBX, and I1F-MC-RHCH.

Note: Patient-year is calculated as sum of the total person exposure days divided by 365.25.

Table SIII.4. Age Group and Gender in Juvenile Idiopathic Arthritis Clinical Trial

Age Group	Persons			Patient-years		
	Male	Female	Total	Male	Female	Total
<12 years	**13**	**8**	**21**	**16.5**	**8.3**	**24.8**
5 years	1	0	1	1.5	0	1.5
6 years	1	1	2	0.9	0.9	1.8
7 years	4	1	5	6.2	2	8.2
8 years	0	1	1	0	0.8	0.8
9 years	4	1	5	5.8	0.6	6.4
10 years	2	1	3	1.3	0.7	2
11 years	1	3	4	0.8	3.3	4.1
≥12 to ≤18 years	**38**	**32**	**70**	**39.2**	**43.9**	**83.1**
12 years	4	4	8	4.4	5.9	10.4
13 years	8	5	13	8.3	7.3	15.6
14 years	12	1	13	12.7	1.5	14.2
15 years	6	5	11	6.8	7.7	14.5
16 years	6	11	17	5.2	12.7	17.9
17 years	2	4	6	1.7	4.7	6.4
18 years	0	2	2	0	4.1	4.1
Total	**51**	**40**	**91**	**55.7**	**52.2**	**107.9**

Note: This table includes all patients who have ixekizumab exposure in juvenile idiopathic arthritis Study I1F-MC-RHCG.

Table SIII.5. Dose

Psoriasis (Induction Dosing Period Only) (Adult)[a]		
Dose of Exposure	**Persons**	**Patient-Years**
IXE 80 mg Q2W	1167	268.6
IXE 80 mg Q4W	1161	265.9
Total	2328	534.5
Psoriasis (Maintenance Dosing Period Only) (Adult)[b]		
Dose of Exposure	**Persons**	**Patient-Years**
IXE 80 mg Q2W responder who re-randomised to IXE 80 mg Q12W	212	149.0
IXE 80 mg Q2W responder who re-randomised to IXE 80 mg Q4W	221	188.0
IXE 80 mg Q4W responder who re-randomised to IXE 80 mg Q12W	196	133.5
IXE 80 mg Q4W responder who re-randomised to IXE 80 mg Q4W	195	157.2
Total IXE responder who re-randomised to IXE 80 mg Q12W	408	282.4
Total IXE responder who re-randomised to IXE 80 mg Q4W	416	345.2

Total	824	627.6
Psoriasis (Paediatric)[c]		
Dose of Exposure	**Persons**	**Patient-Years**
IXE Q4W	196	344
Psoriatic Arthritis[d]		
Dose of Exposure	**Persons**	**Patient-Years**
IXE 80 mg Q2W	752	1234.7
IXE 80 mg Q4W	365	747.8
Total	1117	1982.5
Axial Spondyloarthritis[e]		
Dose of Exposure	**Persons**	**Patient-Years**
IXE 80 mg Q2W	518	731.5
IXE 80 mg Q4W	451	604.7
Total	969	1336.2

Abbreviations: IXE = ixekizumab; PsA = psoriatic arthritis; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks.

a This includes all adult patients who had ixekizumab exposure in the Induction Dosing Period of the placebo-controlled psoriasis Studies I1F-MC-RHAZ, I1F-MC-RHBA, and I1F-MC-RHBC. The studies were not fixed-dose studies across the study periods, but the dose groups were fixed dose during the Induction Dosing Period. Patients received a starting dose of 160 mg at Week 0.

b This includes all adult patients who responded to ixekizumab during the Induction Dosing Period and were re-randomised in the Maintenance Dosing Period of the placebo-controlled psoriasis Studies I1F-MC-RHAZ and I1F-MC-RHBA. The studies were not fixed-dose studies across the study periods, but the dose groups were fixed dose during the Maintenance Dosing Period until patient relapse. Data cutoff was 09 April 2015.

c This includes all paediatric patients who had ixekizumab exposure in the psoriasis Study I1F-MC-RHCD. For this paediatric study, weight-based dosing was applied as follows: 80 mg for patients >50 kg (with a starting dose of 160 mg); 40 mg for patients 25 to 50 kg (with a starting dose of 80 mg); and 20 mg for patients <25 kg (with a starting dose of 40 mg). Dosing was Q4W.

d This includes all adult patients who had ixekizumab exposure in the PsA Studies I1F-MC-RHAP, I1F-MC-RHBE, and I1F-MC-RHBF.

e This includes all adult patients who had ixekizumab exposure in axial spondyloarthritis Studies I1F-MC-RHBV, I1F-MC-RHBW, and I1F-MC-RHBX, and patients who completed Studies I1F-MC-RHBV, I1F-MC-RHBW, or I1F-MC-RHBX and subsequently enrolled in the open-label period of I1F-MC-RHBY.

Note: Patient-year is calculated as sum of the total person exposure days divided by 365.25.

Table SIII.6. Dose (Juvenile Idiopathic Arthritis Clinical Trial)

Dose of Exposure	Persons	Patient-Years
IXE Q4W	91	107.9

Abbreviations: IXE = ixekizumab; Q4W = every 4 weeks.

Note: This includes all paediatric patients who have ixekizumab exposure in the juvenile idiopathic arthritis Study I1F-MC-RHCG. For this paediatric study, weight-based dosing was applied as follows: 80 mg for patients more than 50 kg (with a starting dose of 160 mg); 40 mg for patients between 25 and 50 kg (with a starting dose of 80 mg); and 20 mg for patients less than 25 kg (with a starting dose of 40 mg). Dosing was Q4W.

Table SIII.7. Ethnic Origin

Cumulative for Indications: Psoriasis (Adult and Paediatric), Psoriasis (paediatric), Psoriatic arthritis and Axial Spondyloarthritis		
Ethnic Origin	**Persons**	**Patient-Years**
White	7739	19779.1
Black or African American	220	438
Asian	1555	2147.9
American Indian or Alaska Native	152	279.9
Native Hawaiian or Other Pacific Islander	16	45.0
Multiple	110	198.7
Unknown	15	14.6
Total	9807	22903
Psoriasis (Cumulative Adult and Paediatric)[a]		
Ethnic Origin	**Persons**	**Patient-Years**
White	5772	16185.7
Black or African American	212	424.4
Asian	1067	1477.5
American Indian or Alaska Native	79	136.7
Native Hawaiian or Other Pacific Islander	15	44.4
Multiple	78	138.9
Unknown	12	10.1
Total	7235	18417.6
Psoriasis (Paediatric)[b]		
Ethnic Origin	**Persons**	**Patient-Years**
White	160	280.8
Black or African American	6	11
Asian	6	12
American Indian or Alaska Native	3	5.4
Multiple	16	27.6
Unknown	5	7.2
Total	196	344
Psoriatic Arthritis[c]		
Ethnic Origin	**Persons**	**Patient-Years**
White	1278	2064.3
Black or African American	4	7.0
Asian	163	130
American Indian or Alaska Native	36	45.6
Native Hawaiian or Other Pacific Islander	1	0.6
Multiple	13	19.7
Unknown	1	0.6
Total	1496	2267.8

Axial Spondyloarthritis[d]		
Ethnic Origin	**Persons**	**Patient-Years**
White	689	1529.1
Black or African American	4	6.6
Asian	325	540.3
American Indian or Alaska Native	37	97.7
Native Hawaiian or Other Pacific Islander	0	0
Multiple	19	40.1
Unknown	2	3.9
Total	1076	2217.7

[a] This includes all patients (adult and paediatric) who had ixekizumab exposure in psoriasis Studies I1F-MC-RHAG, I1F-MC-RHAJ, I1F-JE-RHAT, I1F-MC-RHAZ, I1F-MC-RHBA, I1F-MC-RHBC, I1F-MC-RHBL, I1F US-RHBO, I1F-MC-RHBP, I1F-MC-RHBQ, I1F-MC-RHBS, I1F-MC-RHBU, I1F-EW-RHBZ, I1F-MC-RHCD, I1F-IN-RHCZ, I1F-JE-RHCV, I1F-MC-RHBH, I1F-MC-RHBN, and I1F-MC-RHCR.

[b] This includes all paediatric patients who had ixekizumab exposure in psoriasis Study I1F-MC-RHCD.

[c] This includes all adult patients who had ixekizumab exposure in psoriatic arthritis Studies I1F-MC-RHAP, I1F-MC-RHBE, I1F-MC-RHBF, I1F-MC-RHCF, and I1F-IN-RHCZ.

[d] This includes all patients who have ixekizumab exposure in axial spondyloarthritis Studies I1F-MC-RHBV, I1F-MC-RHBW, I1F-MC-RHBX, and I1F-MC-RHCH.

Note: Patient-year is calculated as sum of the total person exposure days divided by 365.25.

Table SIII.8. Ethnic Origin (Juvenile Idiopathic Arthritis Clinical Trial)

Ethnic Origin	Persons	Patient-Years
White	75	87.1
Black or African American	1	1.3
Asian	1	2
American Indian or Alaska Native	14	17.5
Total	**91**	**107.9**

Note: This table includes all patients who have ixekizumab exposure in juvenile idiopathic arthritis Study I1F-MC-RHCG.

Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criterion: The following patient age groups were excluded in the ixekizumab clinical development programme:

- Patients less than 6 years of age for paediatric psoriasis
- Patients less than 6 years of age for JIA (subtype ERA), and
- Patients less than 2 years of age for JIA (subtype JPsA).

Reason for exclusion: A waiver in the European Union paediatric investigation plan (EU-PIP) (EMEA-001050-PIP01-10-M05) was granted on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. The waiver applies to the paediatric population from birth to less than 6 years of age. Also, JIA subtype JPsA is rare and difficult to diagnose in paediatric patients less than 2 years of age.

Is it considered to be included as missing information?: No

Rationale: Biologic use among this group of patients is expected to be limited and there is no relevant use of ixekizumab below the age of 6 years in the treatment of moderate to severe plaque psoriasis. Therefore, use among patients less than 6 years of age will not be included as missing information.

Criterion: Women who are pregnant or lactating

Reason for exclusion: Insufficient clinical data on the effects of ixekizumab on maternal health and foetus prohibited the inclusion of this population.

Is it considered to be included as missing information?: Yes

Rationale: Not applicable

Criterion: Current history of lymphoproliferative disease or patients with active or a history of malignant disease

Reason for exclusion: To minimise confounding factors in safety data interpretation

Is it considered to be included as missing information?: No

Rationale: Malignancy is an important potential risk and will be further characterised via an observational postmarketing safety registry.

Criterion: Positive HIV serology, positive test for acute or chronic active hepatitis B virus (HBV) or acute or chronic hepatitis C virus (HCV) infection, any varicella zoster virus infection within 12 weeks of treatment, and evidence of active or latent tuberculosis (TB).

Reason for exclusion: To ensure safety of patients, including patients who could be at increased risk of infective complications in the context of treatment with immunosuppressive/ immunomodulatory agents, and to minimise confounding factors in safety data interpretation.

Is it considered to be included as missing information?: Yes

Rationale: Not applicable

Criterion: Had recently received live vaccines or plan to receive live vaccines during treatment.

Reason for exclusion: To ensure safety of patients, including patients who could be at increased risk of infective complications in the context of treatment with immunosuppressive/immunomodulatory agents, and to minimise confounding factors in safety data interpretation.

Is it considered to be included as missing information?: Yes

Rationale: Not applicable

SIV.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 exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table SIV.1. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities:	
Patients with severe hepatic impairment	Not included in the clinical development programme
Patients with severe renal impairment	Not included in the clinical development programme
Patients with cardiovascular impairment	Patients with significant uncontrolled cerebro-cardiovascular disease and uncontrolled hypertension were not included in the clinical development programme.
Immunocompromised patients	Patients were not formally assessed for their immunocompetence prior to enrolment.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme

Type of Special Population	Exposure
Population with relevant different ethnic origin	Per data presented in Module SIII, the distribution of patients of different ethnic origins is generally reflective of the anticipated target population.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme

Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Worldwide sales of ixekizumab have been collected for the cumulative time period ending on 29 February 2024.

Patient exposure for ixekizumab was estimated by collecting data from specialty pharmacy dispensing of ixekizumab in the US. The majority of dispensing of ixekizumab in the US occurs via specialty pharmacy, and the marketing authorisation holder has agreements with the specialty pharmacies that allow them to collect and analyse the distribution data. Patient exposure estimates of ixekizumab in the US were taken directly from this information. Patient exposure estimates outside of the US were estimated by comparing the percentage of sales of ixekizumab in the US versus other countries and then extrapolating the estimated number of patients in those countries on the basis of the US patient exposure estimate.

It is important to note that the worldwide sales data and the US patient exposure numbers are considered as known quantities. Also, the US sales data and the US exposure number are independent of one another, meaning both were obtained from separate data sources and one was not calculated based on the other. The US sales data expressed in milligrams of ixekizumab are obtained from the Lilly manufacturing site and the US patient exposure number is obtained from the specialty pharmacies. These data form the basis for the patient exposure estimate for all other regions. Given that the worldwide sales data are precisely known, and the US patient exposure number utilised represents almost the entire patient population in the US (the largest market for Taltz), the method described is more precise than other methods currently available for estimating patient exposure.

SV.1.2 Exposure

Cumulatively as of 29 February 2024, there have been 754 608 520 milligrams of ixekizumab sold worldwide.

Table SV.1. Cumulative Geographical Summary of Sales and Estimated Patient Exposure for Ixekizumab

Region	Sales (milligrams)	Estimated Patient Exposure (Number of Patients)
Europe	226 769 250	118 300
United States	341 841 250	178 300
Japan	26 450 960	13 700
Other Countries	159 547 060	83 200
Global Totals[a]	**754 608 520**	**393 600**

[a] Totals may not sum due to independent rounding.

Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 - Potential for Misuse for Illegal Purposes

The potential for misuse of ixekizumab for illegal purposes is not considered to be a risk.

Humanised IgG4 monoclonal antibodies such as ixekizumab have not been reported to be associated with cases of abuse or dependence, leading to the disorder of addiction. There have been no such reports in the scientific literature or in the ixekizumab clinical development programme, and no significant reports or trends associated with abuse or misuse have been reported in the post-marketing setting.

Module SVII - Identified and Potential Risks

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

Not applicable as the initial RMP was written prior to good pharmacovigilance practices Module V Revision 2 EU RMP format.

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

Not applicable.

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

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

The integrated safety database for psoriasis (adult and paediatric), PsA, and axSpA was updated for EU RMP (Version 8.1). The data for the safety concerns have been updated as a result. Overall integrated database has grown substantially since the last RMP Version 7.2 and therefore overall frequencies of risks were updated accordingly. However, no clinically meaningful differences in overall frequencies of risks were observed.

Study RHCG is an open-label trial and is ongoing. This is a small study conducted in a group of patients with heterogenous underlying conditions of JIA subtypes of ERA (including JoAS) and JPsA. Thus, the safety data for Study RHCG was not pooled with integrated safety data for psoriasis (adult and paediatric), adult PsA and axSpA. The safety data from this paediatric study are overall consistent with the known safety profile for ixekizumab and are not considered to have a clinically meaningful impact on the characterisation of the known risks for ixekizumab as based on the integrated dataset across the approved indications.

SVII.3.1.1 Adult and Paediatric Populations

Important Identified Risk: Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis)

Potential mechanisms:

Patients with psoriasis (adult and paediatric), PsA, and axSpA experience a higher burden of IBD than the general population (Augustin et al. 2010a; Eppinga et al. 2017; Walsh et al. 2018; Paller et al. 2019) and are at higher risk of developing CD and UC than matched reference populations (Li et al. 2013; Walsh et al. 2018; Egeberg et al. 2019; Paller et al. 2019).

Elevated concentrations of IL-17A have been implicated in the pathogenesis of a variety of autoimmune diseases, including IBD. In psoriasis, the IL-17A ligand plays a major role in driving excess keratinocyte proliferation and activation. Neutralisation of IL-17A by ixekizumab inhibits these actions. The mechanism by which the neutralisation of IL-17A might increase the risk of IBD is currently unknown. The specific role of the IL-17 pathway in UC and CD is unclear; Th17-produced cytokines can have both tissue-protective and inflammatory effects in the gut (Monteleone et al. 2011).

Axial spondyloarthritis is clinically associated with IBD, psoriasis, or reactive arthritis in approximately 15% to 20% of cases. This association may be due to shared inflammatory pathways. Barrier damage of dermal (psoriasis) and mucosal (IBD) surfaces and the subsequent exposure of the immune system to microorganisms seem to be relevant to axSpA pathogenesis. Considerable overlap between AS susceptibility loci and IBD susceptibility loci has been found (Sieper and Poddubnyy 2017).

Evidence source(s) and strength of evidence:

Crohn's disease and UC are long-term conditions that can flare up periodically.

Some patients receiving ixekizumab may experience a flare-up of CD or UC during treatment. Inflammatory bowel disease (CD and UC) is an ADR and an identified risk. A causal relationship between IBD and ixekizumab is at least a reasonable possibility based on the higher frequency observed in ixekizumab-treated patients compared to placebo patients in the adult and paediatric studies, the receipt of well-documented case reports from spontaneous/postmarketing sources and published literature, and the mechanistic and pathologic role of IL-17 in IBD.

Characterisation of the risk:

Frequency

In the adult and paediatric psoriasis, adult PsA, and adult axSpA integrated database (N = 9807; total PYs=22903), 15 patients (0.1 per 100 PYs) were confirmed after adjudication to have CD and 28 patients (0.1 per 100 PYs) were confirmed to have UC.

Risk factors and risk groups

No risk factors have been identified.

Preventability:

The occurrence of IBD in the adult and paediatric psoriasis, adult PsA, and adult axSpA clinical development programmes was unpredictable. Warnings and Precautions Section 4.4 of the SmPC advises that caution should be exercised when prescribing ixekizumab to patients with IBD, and patients should be monitored closely.

Impact on the risk-benefit balance of the product:

The current impact of IBD on the risk-benefit balance of ixekizumab is low. This assessment is based on the clinical profile from the adult and paediatric psoriasis, adult PsA, and adult axSpA integrated database, with cumulative exposure from 9807 patients (22 903 PYs). While the

incidence of IBD in the overall ixekizumab clinical programme is low, data from the paediatric psoriasis study (Study I1F-MC-RHCD) show the incidence rate of CD (1.9 per 100 PYs to be greater than that in the psoriasis integrated database (0.1 per 100 PYs [includes adult and paediatric patients]) and the general paediatric plaque psoriasis population (0.1 per 100 PYs) (Paller et al. 2019). Based on this observed incidence rate and the higher frequency of IBD in the ixekizumab-treated arm versus the placebo arm in the adult and paediatric studies and a mechanistic plausibility between IL-17 and IBD, a causal relationship between IBD and ixekizumab is at least a reasonable possibility.

Lilly will continue to closely monitor reported events of IBD associated with exposure to ixekizumab through ongoing routine pharmacovigilance activities, including continued assessment of long-term safety in clinical trials/long-term extension studies, post-marketing surveillance, and observational post-marketing safety studies.

The inclusion of IBD as an important identified risk for ixekizumab acknowledges the addition of IBD as an ADR to Section C.8 (Undesirable Effects) of the CDS. The SmPC will provide further guidance regarding ixekizumab therapy for patients with a history of IBD. With additional long-term information, it is expected that the impact on the risk-benefit balance will remain low. However, should the incidence, severity, or rate of serious outcomes change significantly with additional post-marketing data, any impact on the risk-benefit balance will be assessed.

Public health impact:

The higher incidence rate of CD observed in ixekizumab-treated patients in the paediatric psoriasis study and the higher incidence rate than that reported in the paediatric psoriasis literature suggest that the public health impact needs to be considered. The overall impact on public health is considered low because of the small proportion of ixekizumab-treated patients with confirmed CD (0.2%) and UC (0.3%) and incidence rates that are consistent with background rates in the adult psoriasis, PsA, and axSpA populations.

Important Identified Risk: Serious Infections

Potential mechanisms:

Interleukin-17 plays an important role in granulopoiesis by driving granulocyte-colony stimulating factor, which is directly responsible for the differentiation and proliferation of neutrophil precursors in the bone marrow (Forlow et al. 2001; Stark et al. 2005). Blocking this mechanism may lead to neutropenia, which could increase the risk of bacterial infections (Garber 2012). In addition, IL-17 has a protective role against fungi, such as *Candida albicans* (Garber 2012). Patients with genetic deficiencies of IL-17RA and IL-17F exhibit chronic mucocutaneous candidiasis in the skin, nails, and oral/genital mucosa, and are also prone to *Staphylococcus aureus* infection (Garber 2012).

Evidence source(s) and strength of evidence:

Ixekizumab works by modulating the immune system for the treatment of psoriasis, PsA, and axSpA. This may also reduce the body's ability to fight certain infections.

In clinical trials, more patients receiving ixekizumab than placebo reported nonserious infections such as upper airway infection, thrush, conjunctivitis ("pink eye"), and fungal skin infections. Neutropenia has been commonly observed in patients receiving ixekizumab, raising the concern for possible increased risk of serious infection. For the majority of clinical trial cases, neutropenia was transient in nature and did not result in treatment discontinuation or hospitalisation. Most infections were mild or moderate, with only a small proportion of patients (3%) reporting a severe infection in clinical trials.

Characterisation of the risk:

Frequency

Serious infections were those that met the criteria of a SAE. In the psoriasis (adult and paediatric), PsA, and axSpA integrated database (N = 9807, total PYs = 22903), 289 patients (1.3 per 100 PYs) reported a serious infection. The 95% CI is [1.1, 1.4] per 100 PYs.

Risk factors and risk groups:

No risk groups or specific risk factors have been identified from the psoriasis, PsA, or axSpA clinical development programmes.

Due to the mechanism of action and potential effect on decreasing immune response by anti-TNF or anti-IL 17 classes of medicines, patients with evidence of untreated latent (inactive) TB or certain viral infections such as chronic HBV may be at greater risk of reactivation or exacerbation of their underlying disease. It is reasonable to assume that this additional risk in patients with evidence of untreated latent TB or certain viral infections such as chronic HBV would apply to ixekizumab as well, even though this has not been observed in the clinical development programme.

Preventability:

Careful monitoring of patients for early detection of signs of infection and application of appropriate intervention may help to prevent milder infections from becoming serious. The EU SmPC has the following wording relating to prevention of infections in the Warnings and Precautions section, 'Taltz should be used with caution in patients with clinically important 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. If an infection develops, patients should be carefully monitored and Taltz discontinued if the patient is not responding to standard therapy or if the infection becomes serious. Taltz should not be resumed until the infection resolves. Taltz must not be given to patients with active tuberculosis (TB). Anti-TB therapy prior to initiation of Taltz in patients with latent TB should be considered.'

Impact on the risk-benefit balance of the product:

The current impact of infections on the risk-benefit balance of ixekizumab is very low. This assessment is based on the clinical profile from the psoriasis, PsA, and axSpA integrated database, with cumulative exposure from 9807 patients (22903 PYs).

Overall, nasopharyngitis (20.6%) and upper respiratory tract infection (15.3%) were the most commonly reported types of treatment-emergent infection. The majority of infections reported were mild to moderate, with a low frequency (2.9%) and a low incidence rate (1.3 per 100 PYs) of serious infections observed. Opportunistic infections occurred in 383 patients (3.9%) and *Candida* infections (high-level term) occurred in 339 patients (3.5%). The majority of patients recovered from infection, and in only 1% to 2% of patients did the infection led to discontinuation of ixekizumab therapy.

In addition, of the 9807 patients exposed to ixekizumab in the psoriasis (adult and paediatric), and adult PsA and axSpA integrated safety dataset, a total of 1351 patients (6902 PYs of exposure) have been exposed to ixekizumab for longer than 5 years. The safety data from these patients do not demonstrate an increase in infection risk, either in infection rate or in infection type.

It is estimated that approximately 393 600 patients have received ixekizumab worldwide in the post-marketing setting. The pattern of infections seen post marketing has been consistent with findings in the ixekizumab clinical programme. Patients with psoriasis, PsA, and axSpA are thought to be at an increased risk of infections due to the underlying disease; however, this may also be confounded by the prevalent use of immunosuppressive therapy in this population. Given that the association between immunosuppressive therapy and infection is well known to the treating physician, it can be expected that such infections may be anticipated and could be readily managed in the clinical practice setting. Therefore, the impact on risk-benefit balance will remain low, particularly if the incidence remains low. However, should the incidence, severity, or rate of serious outcomes change significantly with additional post-marketing data, any impact on the risk-benefit balance would be assessed.

Public health impact:

Ixekizumab is indicated for a clearly defined subset of the adult population with moderate-to-severe plaque psoriasis, active PsA, active r-axSpA, and nr-axSpA as well as in a paediatric population 6 years to less than 18 years of age with moderate-to-severe plaque psoriasis In the clinical development programme, including the psoriasis (adult and paediatric), and adult PsA and axSpA integrated safety dataset, the overall frequency (2.9%) and incidence rate (1.3 per 100 PYs) of serious infections remains low. Most patients (87.4%) recovered without sequelae. Additionally, the profile of infections in ixekizumab-treated patients in the post-marketing setting is consistent with the clinical trial data. The impact of serious infections on public health is considered low.

SVII.3.1.2 Adult Population Only

Important Potential Risk: Major Adverse Cardiovascular Events

Potential mechanisms:

The role of IL-17 in vascular inflammation and atherosclerosis is uncertain. Several animal studies have produced contradictory results, with some studies suggesting that IL-17 contributes to vascular inflammation (Dart et al. 2010; Kotla et al. 2013; Lim et al. 2014), while other studies report an anti-atherosclerosis effect (Taleb et al. 2009; Gisterå et al. 2013). Sustained IL-17 levels are present in the target population and may be linked to the pathology of atherosclerosis; however, the implications of this finding are uncertain.

Evidence source(s) and strength of evidence:

Cerebro-cardiovascular disease is a significant comorbidity in patients with psoriasis that may increase the disease burden and complicate disease management (Kim et al. 2010; Patel et al. 2011); however, the relationship between psoriasis, cardiovascular risk factors, and adverse cardiovascular events is not well defined. A report from the PSOLAR registry did not find an increased risk of major adverse cerebro-cardiovascular events (MACE) for biologic medications used to treat psoriasis relative to nonbiologic medications (Papp et al. 2015). The incidence of adjudicated MACE among ixekizumab-treated patients in the 12-Week Induction Dosing Period was low (0.1% to 0.2%) and did not differ significantly between treatment groups.

Characterisation of the risk:

Frequency

In the ixekizumab psoriasis, PsA, and axSpA integrated clinical trial database (N = 9807; total PYs = 22 903), 108 patients (0.5 per 100 PYs) were confirmed after adjudication to have experienced a MACE TEAE. The 95% CI is [0.4, 0.6] per 100 PYs.

Risk factors and risk groups:

Established cardiovascular risk factors include diabetes, hypertension, obesity, dyslipidaemia, smoking, and family history of cardiovascular disease (Kaye et al. 2008; Qureshi et al. 2009; Tsai et al. 2011). No specific risk factors for MACE in relation to treatment with ixekizumab have been identified.

Preventability:

The target population includes a high proportion of patients with cardiovascular risk factors such as diabetes, hypertension, and obesity. Although chronic inflammation increases the risk for MACE (Hansson 2005), controlling inflammation through the use of ixekizumab may help decrease the risk of MACE.

Impact on the risk-benefit balance of the product:

The current impact of MACE on the risk-benefit balance of ixekizumab is very low. This assessment is based on the clinical profile from the psoriasis, PsA, and axSpA integrated database, with cumulative exposure from 9807 patients (22903 PYs).

Cardiovascular disease is a comorbidity of psoriasis, PsA, and axSpA and is more common in patients with these autoimmune conditions than in the general population (Mathieu et al. 2011; Ahlehoff et al. 2013; Ogdie et al. 2015). In the psoriasis trials, patients with treatment-emergent MACE had a higher prevalence of established risk factors for acute atherothrombotic events than patients without MACE. Ixekizumab treatment was not associated with clinically meaningful adverse changes in established cardiovascular risk factors (blood pressure, body weight, glucose control, or proatherogenic components of the lipid panel).

In the ixekizumab clinical development programme, 108 patients were confirmed after independent adjudication to have experienced a MACE, with an incidence rate of 0.5 per 100 PYs. With substantial increase in exposure in the post-marketing setting, 662 MACE have been reported (0.17% of patient exposure), however the overall frequency remains to be uncommonly reported. Based on the available data, there is no evidence that treatment with ixekizumab modifies the underlying risk of cerebro-cardiovascular events such as stroke in patients with psoriasis, active PsA, or axSpA.

Lilly will continue to closely monitor reports of MACE associated with exposure to ixekizumab through ongoing routine pharmacovigilance activities, including continued assessment of long-term safety in clinical trials/long-term extension studies, post-marketing surveillance, and an observational additional post-marketing safety study. With additional long-term information, it is expected that the impact on the risk-benefit balance will remain low, particularly if the incidence of MACE remains low.

Public health impact:

The potential impact of the risk of MACE on public health is considered very low. The potential risk of MACE will only affect a small fraction of the adult population and is not anticipated to be a concern in the paediatric population.

Important Potential Risk: Malignancies

Potential mechanisms:

IL-17 is reported to have high expression in a variety of tumour types, promote angiogenesis, attract proinflammatory cells, and provide pro-survival signals to tumour cells. Mechanistically, the neutralisation of IL-17 could theoretically reduce the incidence and growth rate of malignancies. However, studies in mice genetically manipulated to be deficient in IL-17 or the IL-17 receptor have provided ambiguous results, with either increased or reduced tumour growth compared to wild-type mice. The current clinical and nonclinical data do not suggest that ixekizumab causes malignant tumours or promotes tumour growth.

Evidence source(s) and strength of evidence:

The pathogenesis of psoriasis includes immune dysregulation and chronic inflammation, which may be associated with an increased risk of malignancy. This association, however, is often confounded by the prevalence of behavioural risk factors and the use of immunomodulatory therapies to treat the disease (Kimball et al. 2008). Large observational cohort studies conducted prior to the use of biologic therapy (but with the use of traditional immunosuppressive agents such as methotrexate) suggest that psoriasis increases the risk of cancer relative to the general population (Hannuksela-Svahn et al. 2000; Boffetta et al. 2001; Margolis et al. 2001). More contemporary literature that includes patients treated with biologic medications also reports an increased risk of malignancy among patients with psoriasis; no increased risk was found for biologic treatment relative to traditional systemic medication (Kimball et al. 2015; Papp et al. 2015). The incidence rate of malignancies in ixekizumab studies (0.7 per 100 PYs) was consistent with the incidence rates reported in patients with psoriasis in observational studies. The incidence rate of malignancy reported in clinical trials of ixekizumab was consistent with the background rate in the general psoriasis population and did not suggest an increased risk associated with ixekizumab use.

Characterisation of the risk:

Frequency

In the psoriasis, PsA, and axSpA integrated database (N = 9807; total PYs = 22 903),166 patients (0.7 per 100 PYs) had reported a malignancy TEAE (95% CI: 0.6, 0.8 per 100 PYs). No malignancy related TEAEs have been reported in the paediatric psoriasis clinical trial (Study I1F-MC-RHCD)

Risk factors and risk groups:

None identified.

Preventability:

Early detection has a significant impact on progression of malignant disease, treatment success, or even prevention if precancerous lesions are identified and addressed appropriately.

Impact on the risk-benefit balance of the product:

The current impact of malignancy on the risk-benefit balance of ixekizumab is very low. This assessment is based on the clinical profile from the psoriasis, PsA, and axSpA integrated database, with cumulative exposure from 9807 patients (22903 PYs).

In the ixekizumab clinical development programme, malignancy has been reported in 166 patients, with an IR of 0.7 per 100 PYs. No cases have been reported in the paediatric clinical trial population. With substantial increase in exposure in the post-marketing setting, 1538 cases of malignancy have been reported (0.39% of patient exposure) but the overall frequency remains to be uncommonly reported. No clusters or predominance of malignancy types were noted, and no safety signal has been identified. The incidence rates of malignancies reported in ixekizumab psoriasis and PsA studies are consistent with the incidence rates reported

in the literature for these patient populations (Kavanaugh et al. 2015; McInnes et al. 2017; Geller et al. 2018). Literature for the axSpA population is limited; however, exposure-adjusted incidence rates of malignancies across the ixekizumab clinical development programme for axSpA are consistent with the incidence rates reported for secukinumab, another IL-17A antagonist (Braun et al. 2017).

Additionally, autoimmune diseases such as psoriasis, PsA, and axSpA are associated with an increased risk of cancer relative to the general population (Margolis et al. 2001; Deng et al. 2016; Wilton et al. 2016). As such, the observed rate of malignancies seen in the ixekizumab-treated population in the clinical development programme is considered to reflect the presence of this comorbidity in the target population rather than a potential effect of the drug.

Lilly will continue to closely monitor reported events of malignancy associated with exposure to ixekizumab through ongoing routine pharmacovigilance activities, including continued assessment of long-term safety in clinical trials/long-term extension studies, post-marketing surveillance, and an additional pharmacovigilance activity via an observational post-marketing safety registry.

Public health impact:

The potential impact on public health is very low. The potential risk of malignancy will only affect a small fraction of the adult population and is not anticipated to be a concern in the paediatric population.

SVII.3.2 Presentation of the Missing Information

Missing Information: Long-term safety in adults (such as events with a low frequency and/or long latency)

Evidence source:

Limited data are available to evaluate safety with respect to AEs that may develop following long-term exposure of ixekizumab, taking into account the chronic nature of psoriasis, PsA, and axSpA.

Population in need of further characterisation:

Of the 9807 patients exposed to ixekizumab in the psoriasis, PsA, and axSpA clinical development programmes, a total of 1351 (6902 PYs of exposure) have been exposed to ixekizumab for longer than 5 years. It could be anticipated that, with long-term use, adverse effects that are infrequent and/or have a longer latency period and/or are infrequent among patients with psoriasis (including genital psoriasis), PsA, and/or axSpA could occur. In these circumstances, use of ixekizumab in the target population in clinical practice warrants further characterisation.

Missing Information: Use in pregnancy and lactation

Evidence source:

Ixekizumab clinical studies excluded women who were pregnant, and pregnancy was a criterion for permanent discontinuation in all studies. Although there were cases of pregnancy exposures in the clinical development programme, there are insufficient data to establish the safety of ixekizumab during pregnancy in humans. Developmental toxicity studies in pregnant monkeys revealed no evidence of harm to the foetus or infant.

Population in need of further characterization

Psoriasis and PsA are equally common in males and females. Ankylosing spondylitis typically manifests in the third decade of life, with a male:female ratio of 2:1 for radiographic axSpA and of 1:1 for nr-axSpA. Women of childbearing potential are likely to be a target subpopulation in usual clinical practice. It is therefore assumed that women may become pregnant while taking ixekizumab.

Therefore, given the limitations of the existing evidence, further understanding of the use of ixekizumab in female patients during pregnancy and the subsequent pregnancy/infant outcomes is warranted.

Missing Information: Use in very elderly (≥75 years)

Evidence source:

Of the 9807 patients exposed to ixekizumab in the psoriasis, PsA, and axSpA clinical development programmes, a total of 682 patients were between 65 and 74 years of age and an additional 90 patients were ≥75 years of age. Exposure in the clinical development programme is therefore considered proportionate to anticipated use in clinical practice. The safety profile has thus far not revealed any specific safety concerns specific to this subpopulation warranting special instructions for use. No dose adjustment is required in this population.

Population in need of further characterisation:

The very elderly (≥75 years) with psoriasis, PsA, and axSpA are likely to be exposed to ixekizumab in usual clinical practice. Use of systemic treatments among the elderly warrants special consideration as these patients typically have a high prevalence of comorbid conditions and concomitant medications, diminished renal function, age-related changes in immune function, and altered pharmacokinetics and pharmacodynamics (Ryan et al. 2014).

Due to the low exposure in the very elderly, further understanding of the use of ixekizumab in this population is warranted.

Missing information: Long-term safety in paediatrics

Evidence source:

A systematic study of ixekizumab for moderate-to-severe plaque psoriasis in children and adolescents aged 6 to less than18 years (Study I1F-MC-RHCD), conducted per the respective PIP that Lilly agreed to implement at the request of the Paediatric Committee (PDCO) at the European Medicines Agency (EMEA-001050-PIP01-10-M05) and the US Food and FDA, is

complete. The safety profile of ixekizumab in the paediatric population was consistent with that observed in the overall safety population for ixekizumab, except for CD, which was reported at a higher frequency in paediatric patients with psoriasis than in adult patients with psoriasis. In Study I1F-MC-RHCD, 196 paediatric patients with moderate-to-severe plaque psoriasis were studied for up to 2 years (206.75 PYs of exposure). Only a small portion of patients were studied for longer than 1.5 years (14.3%). Long term safety in paediatric population is not yet established based on the available data from clinical trials and post-marketing sources.

Another pivotal study I1F-MC-RHCG is currently ongoing as a part of the European PIP, EMEA-001050-PIP02-18- M01, with the aim to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of ixekizumab when administered to paediatric patients with JIA categories of ERA (including JoAS) and JPsA. This study includes a long-term safety period of up to 5 years with a rationale to evaluate the long-term safety, tolerability, and efficacy of ixekizumab when administered to paediatric patients with JIA categories of ERA (including JoAS) and JPsA.

Population in need of further characterisation:

The population of paediatric psoriasis patients is relatively small, with global prevalence of psoriasis of approximately 1% (Gelfand et al. 2005; Napolitano et al. 2016). Even fewer of these patients are treated with a biologic therapy. Although this population is small, there is an unmet medical need for effective and safe biologic therapies for children and adolescents with moderate-to-severe psoriasis. It is therefore expected that a paediatric patient will be exposed to ixekizumab in routine clinical practice.

Given the limited number of patients and follow-up time accumulated in Study I1F-MC-RHCD and the chronic nature of psoriasis, further study of the long-term safety of ixekizumab in paediatric patients with plaque psoriasis, particularly relating to events most likely to impact the benefit-risk profile is warranted.

Treatment options for JIA subtypes ERA and JPsA are currently limited and there is a high unmet medical need for therapies for these two subtypes (Brunner et al. 2023).

Study I1F-MC-RHCG has a long-term extension period up to 5 years that intends to provide long-term safety and tolerability of ixekizumab when administered to paediatric patients with JIA categories of ERA (including JoAS) and JPsA.

Missing Information: Use in patients with active infections

Evidence source:

Although patients with active HIV, HBV, and HCV were excluded from study participation, no events indicative of clinically overt reactivation during treatment with ixekizumab have been detected to date. The SmPC lists clinically important active infections as a contraindication to treatment with ixekizumab.

Population in need of further characterisation:

Ixekizumab has not been studied specifically in patients with serious active infections such as HIV or in patients with active HBV or HCV. The risk in this patient population is therefore unknown.

Missing Information: Immune response to live vaccinations

Evidence source:

There are no data available on the response to live vaccines. Use of live vaccines during study participation was not permitted in studies conducted as part of the ixekizumab clinical development programme. The SmPC contains a warning and precaution instructing prescribers to avoid administering live vaccines during treatment with ixekizumab.

There are insufficient data on response to inactive vaccines. Use of inactive vaccines was permitted in all Phase 3 studies of ixekizumab in patients with moderate-to-severe psoriasis. A study of 2 inactive vaccines in healthy subjects receiving ixekizumab demonstrated no safety concerns, although the data were too limited to draw conclusions regarding the immune response to these vaccines following administration of ixekizumab.

Population in need of further characterisation:

Vaccination prevents infection by inducing and/or enhancing protective immunity. There may be circumstances whereby live-attenuated vaccines are necessary for patients receiving immunosuppressive therapy, per current treatment guidelines from the EU (European League against Rheumatism guidelines) recommending vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD) (Furer et al. 2020). However, the risks to patients receiving live-attenuated vaccines are uncertain beyond the theoretical risk of ixekizumab-treated patients becoming seriously infected by a live vaccine. Inactivated vaccines such as tetanus and pneumonia (pneumococcal) vaccines appear to be safe, but there is insufficient evidence to determine whether receipt of inactivated vaccines will result in appropriate protection in adults receiving ixekizumab.

Module SVIII - Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Inflammatory bowel disease (Crohn's disease and ulcerative colitis) Serious infections
Important potential risks	MACE[a] Malignancies[a]
Missing information	Long-term safety in adults (such as events with a low frequency and/or long latency) Use in pregnancy and lactation Use in very elderly (≥75 years of age) Long-term safety in paediatrics Use in patients with active infections Immune response to live vaccinations

Abbreviation: MACE = major adverse cerebro-cardiovascular events.

[a] In adult population.

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None

III.2 Additional Pharmacovigilance Activities

III.2.1 Paediatric Population

Study Short Name and Title: [I1F-MC-B015] Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Paediatric Psoriasis

Rationale and Study Objectives: Ixekizumab, a humanised IgG subclass 4 monoclonal antibody that neutralises IL-17A, is currently approved for the treatment of moderate-to-severe plaque psoriasis in children aged 6 years to less than 18 years of age. Data from clinical trials demonstrate that ixekizumab is effective and generally well tolerated; however, long-term safety pertaining to the important risks of inflammatory bowel disease and serious infections among paediatric patients treated in clinical practice is not fully characterised.

The objectives of this study are to monitor the uptake of ixekizumab in a real-world paediatric population with psoriasis, to characterise the demographic and clinical characteristics of paediatric patients receiving ixekizumab and appropriate comparator medications, and to obtain information about the long-term safety pertaining to serious infections and inflammatory bowel disease.

Study Design: This cohort study is being conducted using US administrative health care data.

Study Population: The study population consists of children (6 to less than 18 years of age) within large, US administrative insurance claims databases diagnosed with plaque psoriasis and exposed to ixekizumab or comparator medications: biologic medication (etanercept), non-biologic systemic medication (acitretin, cyclosporine, and methotrexate), and non-systemic topical treatment (corticosteroids and calcipotriene).

Milestones:

I1F-MC-B015 Milestones	Anticipated Due Date
Protocol submission	Submitted Dec 2020, Endorsed March 2021
Start of data collection	31 Aug 2021 (Estimated) 07 Oct 2021 (Actual)
End of data collection	30 Nov 2025
Final study report submission	30 Jun 2027

Study Short Name and Title: [Study I1F-MC-RHCG] An Open-Label Study of Ixekizumab (LY2439821) in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-Related Arthritis (Including Juvenile Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis.

Study design:

Study RHCG is a multicenter, randomised, open-label study of subcutaneous (SC) ixekizumab, with adalimumab as a reference arm (open-label treatment [OLT] period - 16 weeks), followed by an open-label extension (OLE) period of 88 weeks with ixekizumab and adalimumab in children from 2 to less than 18 years of age with JIA subtypes of ERA (including JoAS) and JPsA. The LTE period of 160 weeks will evaluate the safety, tolerability, and efficacy of ixekizumab in these children. As of the data lock point of 02 April 2024, all participants have completed the OLT period of this study. The OLE and LTE periods are ongoing.

Rationale and Objectives of the Long-term Extension (LTE) period:

This study has an LTE period with the objective of evaluating the long-term safety, tolerability, and efficacy of ixekizumab when administered to paediatric patients with JIA categories of ERA (including JoAS) and JPsA. In addition to the known safety profile of ixekizumab in the treatment of psoriasis, psoriatic arthritis, and axial spondyloarthritis, further assessments of safety, tolerability, and efficacy data from this study are intended to establish a better understanding of the long-term safety of ixekizumab in the treatment of paediatric patients with ERA and JPsA.

Study population:

The study will include participants aged 2 to less than 18 years at baseline, diagnosed with JIA and fulfilling the ILAR classification criteria for ERA (including JoAS) or JPsA but no other JIA category (Petty et al. 2004).

Milestones:

Milestones	Anticipated Due Date
Protocol approval	06 February 2020
FPV and study initiation date	13 April 2021
DBL for 16-week CSR	02 April 2024
End of data collection	22 January 2029
Final study report submission	22 July 2029

III.2.2 Adult Population

Study Short Name and Title: I1F-MC-RHBT– A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care

Rationale and Study Objectives:

Ixekizumab, a humanised IgG subclass 4 monoclonal antibody that neutralises IL-17A, is currently intended for systemic treatment of individuals with moderate-to-severe chronic plaque psoriasis and PsA. Data from clinical trials demonstrate that ixekizumab is effective and generally well tolerated; however, the long-term safety profile among patients treated in routine clinical practice is not fully characterised.

The objectives of this study are:

- To monitor the frequency and nature of infections, hypersensitivity (allergic) reactions, inflammatory bowel disease, "heart attack" (myocardial infarction) and stroke, and cancers in clinical practice
- To provide additional information on the long-term safety (effects which are infrequent, and/or take a long time to develop) in routine clinical practice
- To watch the frequency and nature of side effects in the very elderly in routine clinical practice
- To look for any new side effects
- To determine if the use of ixekizumab is associated with any new adverse effects, and to confirm the safety profile in a real-world setting

Study Design:

This study will use data from the CorEvitas Psoriasis Registry, an existing prospective, multicentre, observational, disease registry for patients with psoriasis. A cohort study design will be used to investigate the long-term safety of ixekizumab.

Study Population:

To be eligible for enrolment into the CorEvitas Psoriasis Registry, a subject must satisfy all of the registry inclusion criteria and none of the exclusion criteria.

Inclusion Criteria

- Has psoriasis diagnosed by a dermatologist
- At least 18 years of age
- Started on or switched to a systemic psoriasis treatment within the previous 12 months. FDA-approved biologic treatments for psoriasis and/or nonbiologic treatments (methotrexate, cyclosporine, or apremilast only) are allowed

Exclusion Criterion

- Unable or unwilling to provide informed consent to participate in the registry

Milestones:

A study protocol is included in Annex 3, Part C; the proposed milestones and anticipated due dates are as follows:

Study I1F-MC-RHBT Milestones	Anticipated Due Date
Start of data collection	20 April 2016[a]
Interim study report	To be initiated once the registry accrues 4000 ixekizumab exposures
Final study report submission	31 May 2030

[a] The study is being conducted within an independent registry, the CorEvitas Psoriasis Registry. CorEvitas enrolled the first ixekizumab-exposed patient on 20 April 2016.

Study Short Name and Title: I1F-MC-B005 – Observational Study to Assess Maternal and Foetal Outcomes Following Exposure to Ixekizumab

Rationale and Study Objectives:

Ixekizumab is an IL-17 antagonist approved in the US and other countries/regions for the treatment of moderate-to-severe plaque PS in adults and children, PsA, and axSpA (both radiographic and nonradiographic axSpA). Pregnant women were not included in the clinical development programme, and women who became pregnant during clinical development discontinued the medication. Therefore, information about a possible association between exposure during pregnancy and maternal and foetal outcomes is limited.

The objectives of this study are to monitor

- the uptake of ixekizumab among women of childbearing age
- the incidence of maternal and foetal/infant outcomes among pregnant women with a diagnosis of PS, PsA, or axSpA exposed to ixekizumab.

If sufficient exposures are identified, an additional objective is to compare maternal and foetal/infant outcomes among these pregnancies with 2 separate groups:

- pregnancies treated with TNF inhibitor biologics (“TNF inhibitor cohort”), and
- pregnancies with prior history of biologic treatment, but unexposed to medications indicated for PS, PsA, or axSpA in the 3 months prior to pregnancy until end of pregnancy (“unexposed cohort”).

The primary outcome of the cohort study is major congenital malformations of the infant. Secondary outcomes include the following:

- Pregnancy outcomes: Recognised spontaneous abortions, stillbirths, elective terminations, preterm delivery, and small for gestational age infants.
- Infant outcomes: Major and minor congenital anomalies and serious infections of the infant (up to 3 months of age).
- Maternal outcomes: Serious infections during pregnancy and serious peri-partum infections.

Study Design:

A retrospective, observational cohort study using US administrative claims and medical record data.

Study Population:

The study population will consist of women diagnosed with psoriasis or PsA and exposed to ixekizumab during pregnancy. If a sufficient number of exposures is identified to warrant comparative analyses, the population will expand to include 2 comparator groups:

(1) women with psoriasis or PsA exposed to a TNF inhibitor during pregnancy, and
(2) women who discontinued biologics and were unexposed to biologics and other systemic medications during pregnancy.

If ixekizumab is approved for additional indications during the study period, the study population will be expanded to include the new indications.

Milestones:

A study protocol is included in Annex 3, Part C; the proposed milestones and anticipated due dates are as follows:

Study I1F-MC-B005 Milestones	Anticipated Due Date
Protocol submission	30 September 2016
Start of data collection	01 October 2017
Interim study report	30 June 2021[a]
End of data collection	Ongoing[b]
Final study report submission	Not yet confirmed[c]

Abbreviations: PMR = post-marketing requirement; PSUR = periodic safety update report; RMP = risk management plan.

[a] An interim analysis was not performed as sufficient pregnancy exposures had not accrued by January 2020. As per the protocol, a summary of available data was provided in PSUR 8 with reporting interval 23 March 2020 through 22 March 2021. The commitment to EMA with respect to Study B005 was deemed fulfilled

[b] A sufficient number of exposures had not accrued by 31 March 2022 (end of data collection as per the protocol), and the FDA requested that Lilly continue the study. Hence the data collection is still ongoing.

[c] In May 2024, Lilly requested FDA release from Study B005 due to challenges in reaching sample size. In a response letter from the FDA dated 04 April 2025, the FDA agreed with Lilly that it is no longer feasible to meet the target sample size due to the limited number and low rate of accrual of exposed pregnancies. FDA requested a chart review of all identified pregnancies and analyses based on confirmed cases. Upon chart review, FDA will determine if the PMR is deemed fulfilled and is expected to confirm a final study report submission date. The final study report will also be provided to EMA upon fulfilment of this commitment with the FDA.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – Required additional pharmacovigilance activities				
[I1F-MC-B015] Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Pediatric Psoriasis Ongoing	• To monitor the uptake of ixekizumab in a real-world paediatric psoriasis population. • To characterise the demographic and clinical characteristics of paediatric psoriasis patients receiving ixekizumab. • To obtain information about the long-term safety pertaining to serious infections and inflammatory bowel disease.	Important identified risks: inflammatory bowel disease and serious infections Missing information: long-term safety in paediatrics (psoriasis population)	Final study report	30 June 2027

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – Required additional pharmacovigilance activities				
I1F-MC-RHBT[a] A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care Ongoing	• To monitor the incidence rate and nature of infections, hypersensitivity reactions, inflammatory bowel disease, MACE, and malignancies in clinical practice. • To provide additional information on the long-term safety (effects which are infrequent, and/or have a longer latency period) in routine clinical practice. • To monitor the incidence and nature of AEs in the very elderly in routine clinical practice. • Signal detection • To determine if the use of ixekizumab is associated with any new adverse effects, and to confirm the safety profile in a real-world setting	Important identified risks: inflammatory bowel disease and serious infections Important potential risks: MACE and malignancy Missing information: long-term safety in adults (such as events with a low frequency and/or long latency) and use in very elderly (≥75 years of age)	Interim study report Final study report	To be initiated once the registry accrues 4000 ixekizumab exposures 31 May 2030[b]

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – Required additional pharmacovigilance activities				
I1F-MC-B005 Observational Study to Assess Maternal and Foetal Outcomes Following Exposure to Ixekizumab Ongoing[c,d]	The objectives of this study are to monitor: • the uptake of ixekizumab among women of childbearing age • the incidence of maternal and foetal/infant outcomes among pregnant women with a diagnosis of PS, PsA, or axSpA exposed to ixekizumab. If sufficient exposures are identified, an additional objective is to compare maternal and foetal/infant outcomes among these pregnancies with 2 separate groups: • pregnancies treated with TNF inhibitor biologics ("TNF inhibitor cohort"), and • pregnancies with prior history of biologic treatment, but unexposed to medications indicated for PS, PsA, or axSpA in the 3 months prior to pregnancy until end of pregnancy ("unexposed cohort").	Missing information: Use in pregnancy	Interim study report Final study report	30 June 2021[c] Not yet confirmed[d]

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – Required additional pharmacovigilance activities				
Study I1F-MC-RHCG An Open-Label Study of Ixekizumab (LY2439821) in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-Related Arthritis (Including Juvenile Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis Ongoing	The objective of the LTE period of this study is to evaluate the long-term safety, tolerability, and efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JPsA.	Missing information: Long-term safety in paediatrics	Final study report	22 July 2029

Abbreviations: AE = adverse event; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; JoAS = juvenile onset ankylosing spondylitis; JPsA = juvenile psoriatic arthritis; MACE = major adverse cardiovascular events; PMR = post-marketing requirement; PSUR = periodic safety update report; RMP = risk management plan.

[a] The study is being conducted within an independent registry, the CorEvitas Psoriasis Registry. CorEvitas enrolled the first ixekizumab-exposed patient in April 2016.

[b] The final study report will be submitted with the PSUR/RMP and within 12 months of study completion.

[c] An interim analysis was not performed as sufficient pregnancy exposures had not accrued by January 2020. As per the protocol, a summary of available data was provided in PSUR 8 with reporting interval 23 March 2020 through 22 March 2021. The commitment to EMA with respect to Study B005 was deemed fulfilled.

[d] In May 2024, Lilly requested FDA release from Study B005 due to challenges in reaching sample size. In a response letter from the FDA dated 04 April 2025, the FDA agreed with Lilly that it is no longer feasible to meet the target sample size due to the limited number and low rate of accrual of exposed pregnancies. FDA requested a chart review of all identified pregnancies and analyses based on confirmed cases. Upon chart review, FDA will determine if the PMR is deemed fulfilled and is expected to confirm a final study report submission date. The final study report will also be provided to EMA upon fulfilment of this commitment with the FDA.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 advises caution and monitoring for patients with pre-existing inflammatory bowel disease. Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable
Serious infections	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 advises caution and careful monitoring in patients with clinically important chronic infection. If a patient does not respond to standard therapy for an infection or the infection becomes serious, ixekizumab is to be discontinued and not resumed until the infection resolves. Ixekizumab should not be given to patients with active TB. Prior to initiation of ixekizumab in patients with latent TB, anti-TB therapy is to be considered. Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable
MACE[a]	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable
Malignancy[a]	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None

Safety Concern	Routine Risk Minimisation Activities
	Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable
Long-term safety in adults (such as events with a low frequency and/or long latency)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable
Use in pregnancy and lactation	Routine risk communication: • SmPC Section 4.6 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.6 advises that ixekizumab is to be avoided during pregnancy or while breastfeeding. Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable
Use in very elderly (≥75 years)	Routine risk communication: • SmPC Section 5.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable
Long-term safety in paediatrics	Routine risk communication: • SmPC Section 4.2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable
Use in patients with active infections	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.3 contraindicates the use of ixekizumab in patients with clinically important active infections (e.g. active tuberculosis). • SmPC Section 4.4 advises not to give to patients with active tuberculosis. Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable
Immune response to live vaccinations	Routine risk communication: • SmPC Section 4.4 • SmPC Section 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety Concern	Routine Risk Minimisation Activities
	1. SmPC Section 4.4 advises that Taltz should not be used with live vaccines, that no data are available on the response to live vaccines and that insufficient data are available on the response to inactive vaccines. 2. SmPC Section 5.1 provides information on a study with 2 inactive vaccines in healthy subjects who demonstrated no safety concerns, but immunisation data were considered insufficient to conclude that there was an adequate immune response to these inactive vaccines. Other routine risk minimisation measures beyond the Product Information: None Pack size: Not applicable Legal status: Not applicable

Abbreviations: MACE = major adverse cerebro-cardiovascular events; SmPC = summary of product characteristics; TB = tuberculosis.

[a] For adult population.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) Study I1F-MC-B015: Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Paediatric Psoriasis (final study report due 30 Jun 2027)
Serious infections	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	SmPC Section 4.8 Additional risk minimisation measures: None proposed	Additional pharmacovigilance activities: Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) Study I1F-MC-B015: Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Pediatric Psoriasis (final study report due 30 Jun 2027)
MACE[a]	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study I1F-MC-RHBT A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030).
Malignancy[a]	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030).
Long-term safety in adults (such as events with a low frequency and/or long latency)	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030)
Use in pregnancy and lactation	Routine risk minimisation measures: SmPC Section 4.6 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study I1F-MC-B005 – Observational Study to Assess Maternal and Foetal Outcomes Following Exposure to Ixekizumab (Final report due date is not yet confirmed[b])
Use in very elderly (≥75 years)	Routine risk minimisation measures: SmPC Section 5.2 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030).
Long-term safety in paediatrics	Routine risk minimisation measures: SmPC Section 4.2 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study I1F-MC-B015: Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Pediatric Psoriasis (final study report due 30 Jun 2027) Study I1F-MC-RHCG is ongoing and has a long term extension (LTE) period of up to 5 years with a purpose of evaluating the long-term safety, tolerability, and efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JpsA (final study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		report due 22 Jul 2029).
Use in patients with active infections	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Immune response to live vaccinations	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 5.1 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Abbreviations: MACE = major adverse cerebro-cardiovascular events; PMR = post-marketing requirement; SmPC = summary of product characteristics.

[a] For adult population.

[b] In May 2024, Lilly requested FDA release from Study B005 due to challenges in reaching sample size. In a response letter from the FDA dated 04 April 2025, the FDA agreed with Lilly that it is no longer feasible to meet the target sample size due to the limited number and low rate of accrual of exposed pregnancies. FDA requested a chart review of all identified pregnancies and analyses based on confirmed cases. Upon chart review, FDA will determine if the PMR is deemed fulfilled and is expected to confirm a final study report submission date. The final study report will also be provided to EMA upon fulfilment of this commitment with the FDA.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Taltz (Ixekizumab)

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

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

I - The Medicine and What It is Used for

Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Taltz, alone or in combination with methotrexate, is indicated for the treatment of active PsA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARD therapies.

Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.

Taltz is indicated for the treatment of adult patients with active non-radiographic axSpA with objective signs of inflammation as indicated by elevated-C reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to NSAIDs.

Taltz is indicated for the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy.

Further information about the evaluation of Taltz's benefits can be found in Taltz'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/taltz

II - Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

Measures to minimise 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 providers
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly

- The medicine's legal status — the way a medicine is supplied to the patient (for example, with or without prescription) can help to minimise its risks

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

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

II.A List of Important Risks and Missing Information

Important risks of Taltz are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be taken safely. 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 Taltz. 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 (for example, on the long-term use of the medicine.

List of Important Risks and Missing Information	
Important identified risks	Inflammatory bowel disease (Crohn's disease and ulcerative colitis) Serious infections
Important potential risks	MACE[a] Malignancies[a]
Missing information	Long-term safety in adults (such as events with a low frequency and/or long latency) Use in pregnancy and lactation Use in very elderly (≥75 years) Long-term safety in paediatrics Use in patients with active infections Immune response to live vaccinations

Abbreviation: MACE = major adverse cerebro-cardiovascular events.

[a] In adult population.

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risk: Inflammatory Bowel Disease (Crohn's disease and ulcerative colitis)	
Evidence for linking the risk to the medicine	Crohn's disease and ulcerative colitis are long-term conditions that can flare up periodically. Some patients receiving ixekizumab may develop or experience a flare-up of Crohn's disease or ulcerative colitis during treatment.
Risk factors and risk groups	No risk factors have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) I1F-MC-B015: Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Pediatric Psoriasis (final study report due 30 Jun 2027) See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Ixekizumab works by modulating the immune system for the treatment of psoriasis, PsA, and axSpA. This may also reduce the body's ability to fight certain infections. In clinical trials, more patients on ixekizumab than on placebo experienced nonserious infections such as upper airway infection, thrush, conjunctivitis ("pink eye"), and fungal skin infections. Neutropaenia has been commonly observed in patients receiving ixekizumab, raising the concern for possible increased risk of serious infection. For the majority of cases, neutropaenia was transient in nature and did not result in treatment discontinuation or hospitalisation. The majority of infection events were mild to moderate, with only a small proportion of patients (3%) experiencing a severe infection in clinical trials.

Important Identified Risk: Serious Infections	
Risk factors and risk groups	No risk groups or specific risk factors have been identified from the psoriasis, PsA, or axSpA clinical development programmes. Due to the mechanism of action and potential effect on decreasing immune response by anti-TNF or anti-IL 17 classes of medicines, patients with evidence of untreated latent (inactive) TB or certain viral infections such as chronic HBV may be at greater risk of reactivation or exacerbation of their underlying disease. It is reasonable to assume that this additional risk in patients with evidence of untreated latent TB or certain viral infections such as chronic HBV would apply to ixekizumab as well, even though this has not been observed in the clinical development programme.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) I1F-MC-B015: Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Pediatric Psoriasis (final study report due 30 Jun 2027) See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Potential Risk: MACE[a]	
Evidence for linking the risk to the medicine	Current evidence is mixed regarding contributions of IL-17A to the atherosclerotic plaque instability. Sustained IL-17 levels are present in the target population and may be linked to the pathology of atherosclerosis; however, the role played by IL-17 and T helper-17 cells in atherosclerosis is still controversial. Several studies in mice suggest a contribution of the IL-17 pathway to vascular inflammation (Dart et al. 2010; Kotla et al. 2013; Lim et al. 2014), yet other studies in animal models suggest a stabilising effect on the atherosclerotic plaque related to an inhibitory effect on endothelial vascular cells adhesion molecules (VCAM-1) (Taleb et al. 2009) and to a stimulatory effect on fibrillar collagen synthesis by smooth muscle cells (Gisterå et al. 2013).
Risk factors and risk groups	No specific risk factors for MACE in relation to treatment with ixekizumab have been identified.
Risk Minimisation measures	Routine risk minimisation measures:

	None proposed Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) See Section II.C of this summary for an overview of the post-authorisation development plan.
Important Potential Risk: Malignancies[a]	
Evidence for linking the risk to the medicine	There are theoretical considerations which could link the pharmacologic mode of action of ixekizumab to the development of tumours; however, the current clinical and nonclinical data do not suggest that ixekizumab causes malignant tumours or promotes tumour growth.
Risk factors and risk groups	No specific risk factors for malignancy in relation to treatment with ixekizumab have been identified.
Risk Minimisation measures	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Long-term Safety in Adults (Such as Events with a Low Frequency and/or Long Latency)	
Risk minimisation measures	Routine risk minimisation measures: None proposed Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Use in Pregnancy and Lactation	
Risk minimisation measures	Routine risk minimisation measures:

	SmPC Section 4.6 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Study I1F-MC-B005 – Observational Study to Assess Maternal and Foetal Outcomes Following Exposure to Ixekizumab (Final report due date is not yet confirmed[b]) See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Use in Very Elderly (≥75 Years)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.2 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	Study I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care (final study report due 31 May 2030) See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Long-term Safety in Paediatrics	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	I1F-MC-B015 Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Pediatric Psoriasis (final study report due 30 Jun 2027) Study I1F-MC-RHCG is ongoing and has a long-term extension (LTE) period of up to 5 years with a purpose of evaluating the long-term safety, tolerability, and efficacy of ixekizumab in children with JIA subtypes of ERA (including JoAS) and JpsA (final study report due 22 Jul 2029). See Section II.C of this summary for an overview of the post-authorisation development plan.
Missing Information: Use in Patients with Active Infections	
Risk minimisation measures	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk:

	• SmPC Section 4.3 states that ixekizumab should not be used in patients with clinically important active infections (e.g. active tuberculosis). • SmPC Section 4.4 advises not to give to patients with active tuberculosis. Other routine risk minimisation measures beyond the Product Information: None
Additional Pharmacovigilance Activities	None
Missing Information: Immune Response to Live Vaccines	
	Routine risk communication: • SmPC Section 4.4 • SmPC Section 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 advises that Taltz should not be used with live vaccines, that no data are available on the response to live vaccines and that insufficient data are available on the response to inactive vaccines. • SmPC Section 5.1 provides information on a study with 2 inactive vaccines in healthy subjects who demonstrated no safety concerns, but immunisation data were considered too limited to conclude that there was an adequate immune response to these inactive vaccines. Other routine risk minimisation measures beyond the Product Information: None
Additional Pharmacovigilance Activities	None

Abbreviations: axSpA = axial spondyloarthritis; HBV = hepatitis B virus; IL = interleukin; MACE = major adverse cerebro-cardiovascular events; PsA = psoriatic arthritis; SmPC = summary of product characteristics; TB = tuberculosis; TNF = tumour necrosis factor.

[a] In adult population.

[b] In May 2024, Lilly requested FDA release from Study B005 due to challenges in reaching sample size. In a response letter from the FDA dated 04 April 2025, the FDA agreed with Lilly that it is no longer feasible to meet the target sample size due to the limited number and low rate of accrual of exposed pregnancies. FDA requested a chart review of all identified pregnancies and analyses based on confirmed cases. Upon chart review, FDA will determine if the PMR is deemed fulfilled and is expected to confirm a final study report submission date. The final study report will also be provided to EMA upon fulfilment of this commitment with the FDA.

II.C Post-Authorisation Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of Taltz.

II.C.2 Other Studies in Post-Authorisation Development Plan

II.C.2.1 Study Short Name and Title: [I1F-MC-B015]: Observational Post-Marketing Safety Study of Ixekizumab and Other Systemic and Non-Systemic Treatments for Paediatric Psoriasis.

Rationale and Study Objectives: Ixekizumab, a humanised IgG subclass 4 monoclonal antibody that neutralises IL-17A, is currently approved for the treatment of moderate-to-severe plaque psoriasis in children aged 6 years to less than 18 years of age. Data from clinical trials demonstrate that ixekizumab is effective and generally well-tolerated; however, long-term safety pertaining to the important risks of inflammatory bowel disease and serious infections among paediatric patients treated in clinical practice is not fully characterised.

The objectives of this study are:

- To monitor the uptake of ixekizumab in a real-world paediatric population
- To characterize the demographic and clinical characteristics of paediatric patients receiving ixekizumab and appropriate comparator medications, and
- To provide additional information about the long-term safety pertaining to serious infections and inflammatory bowel disease.

II.C.2.2 Study Short Name and Title: [I1F-MC-RHBT: A Prospective, Observational Study to Assess the Long-Term Safety of Ixekizumab Compared with Other Therapies Used in the Treatment of Adults with Moderate-to-Severe Psoriasis (May Include Psoriatic Arthritis) in the Course of Routine Clinical Care

Purpose of the study: Ixekizumab is an IL-17A antagonist approved for the treatment of moderate-to-severe plaque psoriasis and active psoriatic arthritis. Data from clinical trials demonstrate that ixekizumab is effective and generally well tolerated; however, the long-term safety profile among patients treated in routine clinical practice is not fully characterised.

The objectives of this study are:

- To monitor the frequency and nature of infections, hypersensitivity (allergic) reactions, inflammatory bowel disease, “heart attack” (myocardial infarction) and stroke, and cancers in clinical practice
- To provide additional information on the long-term safety (effects which are infrequent, and/or take a long time to develop) in routine clinical practice
- To watch the frequency and nature of side effects in the very elderly in routine clinical practice
- To look for any new side effects

- To determine if the use of ixekizumab is associated with any new adverse effects, and to confirm the safety profile in a real-world setting

II.C.2.3 Study Short Name and Title: [I1F-MC-B005]-Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Ixekizumab

Purpose of the study: Ixekizumab is an IL-17 antagonist approved in the US and other countries/regions for the treatment of moderate-to-severe plaque PS in adults and children, PsA, and axSpA (both radiographic and nonradiographic axSpA). Pregnant women were not included in the clinical development programme, and women who became pregnant during clinical development discontinued the medication. Therefore, information about a possible association between exposure during pregnancy and maternal and foetal outcomes is limited.

The objectives of this study are to monitor

- the uptake of ixekizumab among women of childbearing age, and
- the incidence of maternal and fetal/infant outcomes among pregnant women with a diagnosis of PS, PsA, or axSpA exposed to ixekizumab.

If sufficient exposures are identified, an additional objective is to compare maternal and fetal/infant outcomes among these pregnancies with 2 separate groups:

- pregnancies treated with TNF inhibitor biologics ("TNF inhibitor cohort"), and
- pregnancies with prior history of biologic treatment, but unexposed to medications indicated for PS, PsA, or axSpA in the 3 months prior to pregnancy until end of pregnancy ("unexposed cohort").

The primary outcome of the cohort study is major congenital malformations of the infant. Secondary outcomes include the following:

- Pregnancy outcomes: Recognised spontaneous abortions, stillbirths, elective terminations, preterm delivery, and small for gestational age infants.
- Infant outcomes: Major and minor congenital anomalies and serious infections of the infant (up to 3 months of age).
- Maternal outcomes: Serious infections during pregnancy and serious peri-partum infections.

II.C.2.4 Study Short Name and Title: [Study I1F-MC-RHCG] An Open-Label Study of Ixekizumab (LY2439821) in Children with Juvenile Idiopathic Arthritis Subtypes of Enthesitis-Related Arthritis (Including Juvenile Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis.

Rationale and Objectives of the Long-term Extension (LTE) period:

This study has an LTE period with an objective to evaluate the long-term safety, tolerability, and efficacy of ixekizumab when administered to paediatric patients with JIA categories of ERA (including JoAS) and JPsA. In addition to the known safety profile of ixekizumab in the treatment of psoriasis, psoriatic arthritis, and axial spondyloarthritis, further assessments of safety, tolerability, and efficacy data from this study are intended to establish a better

understanding of the long-term safety of ixekizumab in treatment of paediatric patients with ERA and JPsA.

Part VII: Annexes

Annex **Page**

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable.