EU Risk Management Plan (Version 22.2)

Global Patient Safety
Signatory information is available on request.

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EU Risk Management Plan for Baricitinib

RMP version to be assessed as part of the application: 22.2

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Date of final sign off: See cover page

Rationale for submitting an updated RMP: Proposed removal of an additional pharmacovigilance activity: Studies I4V-MC-JAJA (JAJA)/I4V-MC-JAJD (JAJD) from the currently approved EU risk management plan (RMP) version 21.2 (under procedure EMEA/H/C/004085/II/0037) (extension application of AD indication in paediatric patients).

Summary of significant changes in this RMP:

Removed Studies JAJA and JAJD from the pharmacovigilance plan in Part III and subsequent places in the RMP.

Minor administrative changes: Indication of paediatric patients with atopic dermatitis (AD) was moved from "proposed" to "current" indication in Part I and in Module SVII.3 (shown in yellow highlights in the WORD track change version); and the format of follow-up forms in Annex 4 has been updated.

Other RMP versions under evaluation

None

Details of the currently approved RMP

Version number: 21.2

Approved with procedure: EMEA/H/C/004085/II/0037

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

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Part I: Product(s) Overview

Table Part I.1. Product Overview

Active substance(s) (INN or common name)	Baricitinib
Pharmacotherapeutic group(s) (ATC Code)	Selective immunosuppressant: L04AA37
Marketing Authorisation	Eli Lilly and Company
Medicinal products to which this RMP refers	Baricitinib
Invented name(s) in the European Economic Area (EEA)	Olumiant
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Selective JAK inhibitor
	Summary of mode of action: Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, TYK2, and JAK3 with IC50 values of 5.9, 5.7, 53 and >400 nM, respectively
	Important information about its composition: Baricitinib is a synthetic chemical entity. The excipients (microcrystalline cellulose, croscarmellose sodium, magnesium stearate, mannitol) and colour mixture ingredients (ferric oxide, soy lecithin, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide) in the tablet formulation are all pharmacologically inactive at the quantities provided.
Hyperlink to the Product Information	The current PI is included in the respective eCTD sequence
Indication(s) in the EEA	**Current:** <u>Rheumatoid arthritis</u> Olumiant is indicated for the treatment of moderate-to-severe active rheumatoid arthritis in adult patients who have responded inadequately to or who are intolerant to one or more disease-modifying antirheumatic drugs. Olumiant may be used as monotherapy or in combination with methotrexate. <u>Atopic dermatitis</u> Olumiant is indicated for the treatment of moderate-to-severe atopic dermatitis in adult and paediatric patients 2 years of age and older who are candidates for systemic therapy. <u>Alopecia areata</u> Olumiant is indicated for the treatment of severe alopecia areata in adult patients <u>JIA</u> Olumiant is indicated for the treatment of active JIA in patients 2 years of age and older who have had an inadequate response or intolerance to 1 or more prior conventional synthetic or biologic DMARDs: • Polyarticular JIA (polyarticular RF+ or RF-, extended oligoarticular), • ERA, and

	• JPsA. Baricitinib may be used as monotherapy or in combination with methotrexate.
	Proposed: Not applicable
Dosage in the EEA	**Current:** <u>Rheumatoid Arthritis</u> The recommended dose of Olumiant is 4 mg once daily. A dose of 2 mg once daily is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2-mg once daily dose. A dose of 2 mg once daily should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering. <u>Atopic Dermatitis</u> <u>*Adults:*</u> The recommended dose of Olumiant is 4 mg once daily. A dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE, and malignancy, for patients aged ≥65 years, and for patients with a history of chronic or recurrent infections. A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2-mg once daily dose. A dose of 2 mg once daily should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering. *Children and adolescents (2 years of age and older)* The recommended dose of baricitinib is 4 mg once daily for patients weighing 30 kg or more. For patients weighing 10 kg to less than 30 kg, the recommended dose is 2 mg once daily. A reduction to half the dose should be considered for patients who have achieved sustained control of disease activity with the recommended dose and are eligible for dose tapering. <u>Alopecia areata</u> The recommended dose of baricitinib is 4 mg once daily. A dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2-mg once daily dose. A dose of 2 mg once daily should be considered for patients who have achieved sustained control of the disease activity with 4 mg once daily and are eligible for dose tapering. <u>JIA</u> The recommended dose of baricitinib is 4 mg once daily for patients weighing 30 kg or more. For patients weighing 10 kg to less than 30 kg, the recommended dose is 2 mg once daily.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Film-coated tablets: 1, 2 or 4 mg
	Proposed: Not applicable

Is/will the product be subject to additional monitoring in the EU?	No

Abbreviations: ATC = Anatomical Therapeutic Chemical; DMARD = disease-modifying antirheumatic drugs; eCTD = electronic common technical document; EEA = European economic area; ERA = enthesitis-related arthritis; IC50 = concentration of drug required for 50% inhibition; INN = International Non-proprietary Names; JAK = Janus kinase; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; MACE = major adverse cardiovascular event; PI = package insert; RMP = risk management plan; RF+ = rheumatoid factor-positive; RF- = rheumatoid factor-negative TYK = tyrosine kinase; VTE = venous thromboembolism.

Part II: Safety Specification

Module SI – Epidemiology of the Indication(s) and Target Population(s)

SI.1 Rheumatoid Arthritis

SI.1.1 Incidence

The worldwide incidence of rheumatoid arthritis (RA) varies greatly by geographic location (Global Burden of Disease 2016). The annual RA incidence in both North American and Northern European regions ranges from 20 to 50 per 100,000 persons per year (Scublinsky and Gonzalez 2016).

In Europe alone, the annual incidence of RA varies widely with reports of 8.3/100,000 per year in Spain to 50/100,000 in Sweden. Across studies, females exhibit 2.1- to 2.7-fold higher incidence compared to men, and incidence increases with increasing age (Guillemin et al. 1994; Aho et al. 1998; Doran et al. 2002a; Carbonell et al. 2008; Rodríguez et al. 2009; Englund et al. 2010; Myasoedova et al. 2010; Kuo et al. 2013; Sung et al. 2013; Rossini et al. 2014).

SI.1.2 Prevalence

The global prevalence of RA (all ages) is 0.24% and is approximately 2 times higher in females (mean 0.35%) than males (mean 0.13%). As with incidence, the prevalence of RA varies greatly among different geographic locations (Cross et al. 2014).

In European adults, prevalence ranges from 0.3% in France to 0.9% in England (Salaffi et al. 2005; Guillemin et al. 2005; Arthritis Research UK 2018). Prevalence by gender in Europe (male vs. female) was 0.15% vs. 0.41% for Central Europe, 0.14% vs. 0.38% for Eastern Europe, and 0.24% vs. 0.63% for Western Europe. In North America, similar prevalence is reported, with 0.24% for males to 0.63% for females. As with incidence, prevalence increases with increasing age (Cross et al. 2014).

SI.1.3 Demographics of the Population in the authorised Indication – and Risk Factors for the Disease

Age and Gender

RA affects adults of any age, yet prevalence and incidence increase with increasing age until the 70- to 79-year age group for both women and men, and thereafter decreases in the oldest age group (Symmons et al. 2006). RA is 2 to 3 times more common among women when compared to men (Riise et al. 2000; Cross et al. 2014). From a Pan European sample of patients with RA, the mean age was 55 years and consisted of 68% females and 32% males (O'Hara et al. 2017).

Risk Factors

The pathogenesis of RA is multifactorial and includes both intrinsic and extrinsic risk factors (Alamanos and Drosos 2005). Epidemiological studies have demonstrated a higher incidence of RA among relatives of patients with the disease, when compared to the general population, suggesting a genetic contribution (Aho et al. 1986; Silman and Pearson 2002; Sparks et al. 2014).

Nearly 60 genetic loci associated with susceptibility to RA have been identified across multiple populations, including multiple risk alleles within the human leukocyte antigen (HLA) region and in HLA-DRB1 in particular (Viatte et al. 2013).

Genetic factors account for approximately 50% of the risk of developing RA (Ruiz-Esquide et al. 2012), but the contribution of environmental factors to RA aetiology is likely substantial. Smoking is a recognised risk factor for the disease (Harel-Meir et al. 2007), and is also implicated as a determinant of disease severity (Alamanos and Drosos 2005).

SI.1.4 Main Existing Treatment Options

Pharmaceutical treatment options in RA include nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biologic DMARDs (bDMARDs) (that is, tumour necrosis factor [TNF] inhibitors, interleukin [IL]-6-inhibitors, T-cell co-stimulation modulators, and B-cell depletion therapies).

Recent guidelines recommend that DMARD therapy be started as soon as the diagnosis of RA is made with treatment aimed at reaching a target of remission or low disease activity in every patient (Aletaha et al. 2010; Singh et al. 2012; Smolen et al. 2020; Singh et al. 2016). In DMARD-naïve patients, the initial choice of DMARD is commonly methotrexate (MTX), used as monotherapy or in combination with other csDMARDs. Low doses of corticosteroids (for example, up to 10 mg per day of prednisone or prednisone equivalent) are frequently added, although the long-term beneficial effects have been poorly described (Rau 2014). The long-term risk of daily low-dose glucocorticoid use is also uncertain with some evidence for increasing toxicity and early mortality as the cumulative dose increases (del Rincón et al. 2014; Listing et al. 2015). Patients responding insufficiently to MTX and/or other csDMARDs commonly begin treatment with a bDMARD (usually a TNFα inhibitor) along with MTX; patients failing one bDMARD are switched to other bDMARDs.

Despite the availability of a number of agents for the treatment of RA with various methods of action, many patients fail to respond to initial treatment, do not tolerate treatment, or lose response over time. Even with some of the most effective treatments available, many patients still do not attain the therapeutic targets, despite all of our modern therapies and therapeutic strategies. Furthermore, any of the bDMARDs, if applied after at least one csDMARD and a bDMARD has failed, leads to only about 10% good treatment responses in terms of American College of Rheumatology (ACR) 70 rates (Smolen et al. 2017). In addition, some patients who initially respond to these treatments lose efficacy during therapy (secondary failures). Loss of efficacy may result from multiple reasons, including the development of anti-drug antibodies or activation of the pro-inflammatory Th17/IL-17 pathway (Alzabin et al. 2012). Furthermore, biologics are frequently prescribed concomitantly with MTX. This poses tolerability issues, as approximately 40% of patients receiving MTX experience gastrointestinal (GI) symptoms; nausea, vomiting, and abdominal pain (Ćalasan et al. 2013). Depending on the biologic agent, the risk profile may Include injection or infusion site reactions, anaphylaxis or serious allergic reactions, increased frequency of infections, reactivation of tuberculosis (TB) or viral infections,

GI perforations, other autoimmune conditions, and increased incidence of malignancy (Chatzidionysiou and van Vollenhoven 2011).

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

Information on the natural history of untreated RA is limited and comes from earlier periods with diagnostic criteria for RA that differ from modern standards (reviewed in Gabriel and Luthra 1988). Although some patients may truly reflect the absence of treatment, it is more likely that patients received some treatment with csDMARDs. In general, these studies suggest that most patients with RA experience remissions and exacerbations. Although the remissions may be prolonged, lasting several months or, in some cases, several years, they are more typically brief and the trend is toward continuing progression, disability, and a substantial decrease in survivorship. In modern RA, inadequate treatment and the associated irreversible joint damage, clinical symptomatology, and comorbid conditions lead to a decreased quality of life, disability, and unemployment. Almost 80% of all diagnosed patients report some disability, 35% require permanent work disability, and all are at risk for an overall reduction in life expectancy (Choy and Panayi 2001; Allaire et al. 2009; Wasserman 2011).

Increased mortality among patients with RA relative to the general population has been reported in multiple studies, primarily due to an increased risk of comorbidities such as cardiovascular disease (CVD) (Mutru et al. 1985; Sihvonen et al. 2004; Aviña-Zubieta et al. 2008), infections (Mutru et al. 1985; Doran et al. 2002b; Sihvonen et al. 2004), and lymphoma (Baecklund et al. 2006). There is also a link between disease severity and mortality, with higher disease severity increasing the risk of mortality, independent of comorbidity (Navarro-Cano et al. 2003; Mackey et al. 2015). A systematic review and meta-analysis of longitudinal studies of RA mortality (1955-2007) reported an average mortality of 2.7/100 patient-years (PY) (Dadoun et al. 2013). A large study conducted in the UK's Clinical Practice Research Datalink reports the age-adjusted mortality rate for patients with RA ≥40 years of age as 3.21/100 PY among females and 2.77/100 PY among males (Watson et al. 2003).

Particular attention has been given to cardiovascular (CV) morbidity and mortality within the RA population. Meta-analyses of observational studies suggest that patients with RA have a 48% increased risk of myocardial infarction (MI), compared to the general population, as well as a 50% increased risk of death due to MI and stroke (Aviña-Zubieta et al. 2008; Aviña-Zubieta et al. 2012). More details are provided in SI.1.6.

SI.1.6 Important Co-morbidities

Rheumatoid arthritis is a complex disorder that frequently occurs with other comorbid conditions. In the table below, where there is overlap between the CV morbidity and mortality covered in Section SI.1.5 and expected risk of co-morbidity in this section, prevalence/incidence data have been added.

Table SI.1.6.1. Common Comorbidities Observed in Patients with Rheumatoid Arthritis

Comorbidity	Expected Risks of Comorbidity	Expected Co-Medications of Comorbidity
Depression	Suicidality	SSRIs, SNRIs
Cardiovascular Disease	**Stroke (any type)** • Incidence rates: 0.43 to 11.8 per 1000 PY meta-analysis (Wiseman et al. 2016) • Prevalence: 0.0% to 5% UK and EU (Dougados et al. 2014; Ogdie et al. 2015; Dregan et al. 2017; Choi et al. 2013) **Hypertension** • Incidence: 12% The Netherlands (Ursum et al. 2013) • Prevalence: 17.7% to 57% EU countries (Rodríguez et al. 2009; Dougados et al. 2014; Choi et al. 2013; Ogdie et al. 2017) **Myocardial Infarction** • Incidence: 1% Germany (Meissner et al. 2016) Incidence rates: 4.6 to 4.8/1000 PY in England and the UK (Pujades-Rodriguez et al. 2016; Ogdie et al. 2015) • Prevalence: 2% to 7% EU countries (Dougados et al. 2014, Rodríguez et al. 2009; Ogdie et al. 2015) **Cardiovascular Death** • Incidence rates: 2.0 to 5.6/1000 PY England and UK (Pujades-Rodriguez et al. 2016; Ogdie et al. 2015) • Prevalence: Not well represented in the literature	Anticoagulants Antihypertensives Statins Aspirin
Venous thromboembolism Incidence: • Global meta-analysis reported 2.18% (Lee and Pope 2014). • Incidence rates: By country, 3.3 to 7.7/1000 PY in the UK and 6.1/1000 PY US (Choi et al. 2013, Ogdie et al. 2017, Kim et al. 2013 • Prevalence: 5% in the UK (Dregan et al. 2017)	**Deep Vein Thrombosis** • Incidence rate: 2.1 to 6.1/1000 PY UK and 4.5/1000 PY US (Choi et al. 2013, Ogdie et al. 2017, Kim et al. 2013) • Prevalence: Not well characterised in the literature **Pulmonary Embolism** • Incidence rates: 1.5/1000 PY in the UK and 2.6/1000 PY US (Choi et al. 2013, Kim et al. 2013). • Prevalence: Not well characterised in the literature • Thrombophlebitis	Anticoagulants
Anaemia	Fatigue	Iron supplements
Renal Disease	Anaemia Hypercholesterolaemia Increased infection risk Osteopathy (bone loss)	ACEI, ARB Antihypertensives Antibiotics Calcium, Vitamin D Statins/Ezetimibe Iron supplements Erythropoietin

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; EU = European; PY = patient-years; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitors; UK = United Kingdom; US = United States.

SI.2 Atopic Dermatitis

SI.2.1 Incidence

Worldwide, the incidence of atopic dermatitis (AD) is not well documented. The only identified study reported an incidence of 6.1 per 1000 PY during 2002 to 2006 in the Netherlands (6.5 vs. 5.7 for males vs. females, respectively) (Verhoeven et al. 2008).

Among people aged less than 18 years, the incidence rates for AD in Danish and Swedish children were 21.5 and 30.6 per 1000 PY, respectively (Henriksen et al. 2015). Among children in Norway of less than 6 years of age the incidence rate of AD was 34 per 1000 PY (Mohn et al. 2018). When given as incidence proportions for 2009-2014, the cumulative incidence, by age, was as follows: 6.30% (age 0 years), 11.06% (age 1 year), 13.79% (age 2 years), 15.37% (age 3 years), 16.54% (age 4 years), and 17.44% (age 5 years) (Mohn et al. 2018). Another prospective cohort of Danish children under the age of 3 years reported an AD cumulative incidence of 31% at age 1 years, 41% at age 2 years, and 44% at age 3 years (Halkjaer et al. 2006).

SI.2.2 Prevalence

The 1-year prevalence of AD among adults is estimated between 2% to 7% in Europe (Harrop et al. 2007; Diepgen et al. 2016). Approximately 30% of adult AD patients have moderate-to-severe disease (Bieber and Straeter 2015). The prevalence of AD among adults in various European countries is presented below (as shown in Harrop et al. 2007):

European Country	12-month prevalence (%) of atopic dermatitis (with 95% CI) (Harrop et al. 2007)
Switzerland	0.3 (0.0-0.7)
Spain	0.8 (0.2-1.3)
Germany	2.1 (0.77-33.4)
Belgium	2.4 (0.9-3.9)
France	3.4 (2.1-4.7)
Italy	1.4 (0.3-2.6)
UK	4.9 (2.7-7.2)
Iceland	1.4 (0.3-2.6)
Norway	3.0 (1.5-4.6)
Sweden	3.3 (2.2-4.5)
Estonia	6.2 (2.2-10.2)

Abbreviations: CI = confidence interval; UK = United Kingdom.

Global estimates of childhood AD prevalence have been generated using data from the International Study of Asthma and Allergies in Childhood (Odhiambo et al 2009).

- Among 385,853 participants aged 6 to 7 years, a wide variation in AD prevalence was reported with values ranging from 0.9% in India to 22.5% in Ecuador.
- Among 663,256 participants aged 13 to 14 years, the prevalence of AD ranged from
    - 0.2% (Tibet, China) to 24.6% (Barranquilla, Colombia) for current eczema symptoms, and
    - 0% to 5.8% (Marrakech, Morocco) for symptoms of severe eczema.

Among adolescents aged 12 to less than 18 years the estimated 1-year prevalence was 14.8% based on a multinational, cross-sectional survey study. Within this survey, less than 15% of patients with AD reported severe AD (Silverberg et al 2021). A review of Italian epidemiologic studies reported an estimated 1-year period prevalence of 8% to 10% in children aged 6 to 11 years and 8% to 11% in adolescents aged 12 to 17 years (El Hachem et al. 2021). Specific to children aged 2 years, a Norwegian study found a prevalence of 16.5% when defined as any eczema and itchy rash. However, more than two-thirds (70%) of children with AD in UK had mild disease (Smidesang et al. 2008). Lastly, a study of AD among children of the EpiChron Cohort aged 0 to 17 years in Spain reported the prevalence of AD by age group: 0-2 years (11.7%); 3-9 years (20.8%), 10-14 years (14.2%), and 15-17 years (7.79%) (Gilaberte et al. 2020).

SI.2.3 Demographics of the Population in the Authorised Indication and Risk Factors for the Disease

Age and Gender

Multiple EU studies have shown a higher prevalence of AD among females compared to males (Verhoeven et al. 2008; Vinding et al. 2014). Additionally, in a population-based study of nearly 8000 AD patients in Denmark, Egeberg et al. (2017a) reported a higher proportion of people with AD were female (61.8%) compared to male. Similarly, a recent study in Spain among children aged 0-17 years found a negligibly higher prevalence of AD among girls compared to boys (15.8% vs. 15.3%; odds ratio [OR] = 1.04, 95% confidence interval [CI]: 1.01, 1.06) (Gilaberte et al 2020). Furthermore, the International Study of Asthma and Allergies in Childhood, Phase 3 study that evaluated over 1 million children worldwide in 2 distinct age groups (aged 6 to 7 years and 13 to 14 years) also found that prevalence of “current eczema” was higher in girls than boys. This was more pronounced in the 13- to 14-year age group (8.3% in girls versus 6.2% in boys aged 13 to 14 years) (Odhiambo et al. 2009).

The prevalence of AD among adults is well-recognised to be lower than that of children (15% to 20% of children have AD [Nutten 2015]). Even within an adult population, the prevalence of AD decreases with increasing age (Wolkewitz et al. 2007; Vinding et al. 2014). For example, in a German study, the prevalence of AD was 5.3%, 3.9%, and 3.4% in adults aged 50 to 59, 60 to 69 years and 70 to 74 years, respectively (Wolkewitz et al. 2007). AD incidence and prevalence in paediatric populations increase with age, up to adolescence (Halkjaer et al. 2006; Mohn et al. 2018; Gilaberte et al. 2020).

Risk Factors

Risk factors for the development of AD include a family history of AD as well as family and personal history for other atopic diseases, including asthma, allergic rhinitis, food allergies, and hay fever. Genetic risk factors have been suggested, particularly mutations in the filaggrin gene (Weidinger and Novak 2016). Environmental risk factors for development of AD include western diets that are high in sugar and poly-unsaturated fatty acids, small family size, high education, and living in urban settings with low exposure to ultraviolet radiation and low humidity (Weidinger and Novak 2016).

SI.2.4 Main Existing Treatment Options

According to EU treatment guidelines (Wollenberg et al. 2018), topical corticosteroids (TCS) are the first-line treatment for moderate-to-severe AD and are effective as a short-term treatment or intermittent long-term treatment. However, continuous long-term use of TCS is not recommended because of the risk of local and systemic side effects (skin atrophy and dyspigmentation). Topical calcineurin inhibitors (TCIs) are considered as an alternative or adjunct treatment, especially where treatment with TCS is either inadvisable or not possible and for steroid-sparing in sensitive areas, such as face and skin folds. As with TCS, TCI are effective as continuous short-term treatments or intermittent long-term treatment. However, patients with moderate-to-severe AD often need additional therapies to control skin inflammation and alleviate their most bothersome symptoms.

Systemic immunosuppressive agents are often used when topical treatment does not achieve sufficient control of AD symptoms. Currently available systemic therapies include nonselective immunosuppressants, such as Ciclosporine A and systemic corticosteroids. Most guidelines recommend systemic corticosteroids only for short-term AD treatment due to severe toxicity and side effects. The safety profile of ciclosporine A limits its use to the short-term treatment of acute flares; for chronic severe AD, treatment duration should not exceed 1 year (Bieber and Straeter 2015). Ciclosporine A is approved for AD (only in some countries) for pediatric patients and is restricted to the treatment of patients aged 16 years and older with severe AD when systemic therapy is required.

Dupilumab is an injectable anti–IL-4/IL-13 antibody that was approved as the first biologic for moderate-to-severe AD in 2017. Dupilumab is an effective treatment for some patients, although there are some limitations to its use based on side effects such as injection site reactions and conjunctivitis (Simpson et al. 2016). Dupilumab is currently approved in EU for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy, and severe AD in children aged 6 to 11 years who are candidates for systemic therapy. Dupilumab is now approved in the US for patients with moderate to severe atopic dermatitis aged 6 months and older.

Upadacitinib, a Janus kinase inhibitor has received regulatory authorization in the EU for the treatment of moderate to severe atopic dermatitis in the patients aged 12 years and older.

Tralokinumab is an immunoglobulin G4 monoclonal antibody that has received regulatory authorization in the EU for the treatment of adolescent patients aged 12 years and older who are candidates for systemic therapy.

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

Atopic dermatitis is a disease more commonly associated with infancy and childhood; however, it is prevalent among adults as well. Among adult patients with AD, approximately 80% are relapsing-remitting disease from childhood, whereas an estimated 20% are new onset in adulthood (Akdis et al. 2006; Garmhausen et al. 2013). Approximately 30% of AD patients have moderate-to-severe disease (Bieber and Straeter 2015). The proportion of AD cases that are

severe increases with age (Silverberg and Simpson 2014), resulting in moderate-to-severe AD being more prevalent among adult patients than children. For example, an adult AD Danish study found that 58.2% of patients had severe disease (Egeberg et al. 2017a).

Depending on age of onset and disease course, atopy signs and concomitant atopic diseases may differ significantly (Garmhausen et al. 2013). Patients experience significant morbidity from moderate-to-severe AD including skin lesions, intractable pruritus, sleep disturbance and skin pain (Weidinger and Novak 2016; Vakharia et al. 2017). Furthermore, patients with AD have an increased risk of bacterial and viral infections, both cutaneous and non-cutaneous, due to defective skin barrier and immunologic dysregulation (Langan et al. 2017). Approximately 70% of patients with active AD have colonisation with Staphylococcus aureus (Clausen et al. 2017). The prevalence of methicillin-resistant S. aureus is significantly higher among patients with moderate-to-severe AD compared to those with mild AD (90% compared to 10%) (Ong and Leung 2016). There is a significant association between moderate-to-severe AD with occurrence of depression, anxiety, and suicidal ideation (Rønnstad et al. 2018; Thyssen et al. 2018a). A study of adults with moderate-to-severe AD found 21.8% of patients with clinically relevant anxiety or depression; in severe AD, 100% of patients had borderline and/or abnormal Hospital Anxiety and Depression Scale scores.

Atopic dermatitis is not a life-threatening condition and until recently there had been no published research on the impact, if any, on mortality. However, recent research suggests that while the absolute risk of death is very low, there may be a modestly increased risk of death among adult patients with AD compared with a general population (hazard ratio [HR]=1.71, 95% CI: 1.20-2.44 [Egeberg et al. 2017b] and HR=1.27, 95% CI: 1.11-1.45 [Thyssen et al. 2018b]). The mortality rate among the AD patients was 0.579 per 100 PY (95% CI: 0.511-0.656) (Thyssen et al. 2018b).

SI.2.6 Important Co-morbidities

Important Comorbidities Observed in Adult Patients with AD

Comorbidity	Prevalence	Expected Co-Medications of Comorbidity
Depression	3.0% to 10.1% [EU] (Egeberg et al. 2017a; Dalgard et al. 2015).	SSRIs SNRIs
Anxiety	1.2% to 17.6% [EU] (Egeberg et al. 2017a; Dalgard et al. 2015)	Anxiolytic medications (including SSRIs SNRIs, benzodiazepines)
Suicidal ideation/attempt/completion	Suicidal ideation: • 12.2% [Multinational, meta-analysis] (Patel et al. 2019) • 15.0% to 21.3% [EU] (Dalgard et al. 2015, Dieris-Hirche et al. 2017). Suicide attempt • 6.6% [EU] (Dieris-Hirche et al. 2017).	SSRIs SNRIs
Asthma/allergic rhinitis	Asthma • 4.0% (Poland; Sybilski et al. 2015) to 17.77% (Germany; Radtke et al. 2017). Allergic rhinitis • 21.0% (Poland; Sybilski et al. 2015) to 25.2% (Germany; Radtke et al. 2017).	Antihistamines Inhaled corticosteroids
Infections	*Staphylococcus aureus* colonisation • 73% to 77.5% (Germany, Thum et al. 2013; Ong and Leung 2016; Clausen et al. 2017). Eczema herpeticum • 2% to 3% (Blauvelt et al. 2017; Leung 2013)	Antibiotics Antiviral
Cardiovascular (CV) disease	Stroke • 0.27 per 100 PY (Denmark, Andersen et al. 2016; UK, Silverwood et al. 2018) • Myocardial infarction • 0.20 per 100 PY (Denmark, Andersen et al. 2016; UK, Silverwood et al. 2018) CV Death • 0.29 to 0.44 per 100 PY (Denmark, Andersen et al. 2016; UK, Silverwood et al. 2018)	Anticoagulants Antihypertensives Statins Aspirin

Abbreviations: AD = atopic dermatitis; CV = cardiovascular; EU = European; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitors.

Important Comorbidities Observed in Paediatric Patients with AD

Comorbidity	Prevalence	Expected Comedications of Comorbidity
Depression	• The prevalence of depression symptoms ranged from 6.0% to 21.6% among children aged 10 and 18 years, respectively (Kern et al. 2021). • the prevalence of internalizing behavior, ranged from 10.4% to 16.0% among children aged 4 to 16 years (Kern et al. 2021). • Among children with moderate AD in the UK THIN database (mean age 9 years, IQR: 4, 14 years), the prevalence of depression was 0.70% (Wan et al. 2022); • Among children with severe AD in the UK THIN database (mean age 5 years, IQR: 1, 10 years), the prevalence of depression was 0.28% (Wan et al. 2022).	SSRIs SNRIs
Anxiety	• Among children with moderate AD in the UK THIN database (mean age 9 years, IQR: 4, 14 years), the prevalence of anxiety was 1.01% (Wan et al. 2022); • Among children with severe AD in the UK THIN database (mean age 5 years, IQR: 1, 10 years), the prevalence of anxiety was 0.64% (Wan et al. 2022).	Anxiolytic medications (including SSRIs, SNRIs, benzodiazepines)
Suicidal ideation/attempt/ completion	Suicidal ideation/attempt: • Among children with moderate AD in the UK THIN database (mean age 9 years, IQR: 4, 14 years), the prevalence was 0.72% (Wan et al. 2022); • Among children with severe AD in the UK THIN database (median age 5 years, IQR: 1, 10 years), the prevalence was 0.39% (Wan et al. 2022).	SSRIs SNRIs
Asthma/allergic rhinitis	Asthma • 31.6% of children with AD (mean age 7.7 years) had asthma after 5 years of follow-up (Ćosićkić et al. 2017). • 43% of Swedish children with AD developed asthma after 7 years of follow-up (mean age at baseline was 18.3 months) (Gustafsson et al. 2000). Allergic rhinitis • 28.9% of children with AD developed allergic rhinitis after 5 years of follow-up (Ćosićkić et al. 2017). • 45% of Swedish children with AD developed allergic rhinitis after 7 years of follow-up (mean age at baseline was 18.3 months) (Gustafsson et al. 2000).	Antihistamines Inhaled corticosteroids
Infections	*Staphylococcus aureus* colonization • 6% to 19% of children with AD from the UK and Ireland were found to be colonized with MRSA (Arkwright et al. 2002). Eczema herpeticum • No epidemiological data were identified beyond case reports.	Antibiotics Antiviral

Abbreviations: AD = atopic dermatitis; IQR = interquartile range; MRSA = methicillin-resistant *Staphylococcus aureus*; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

S1.3 Alopecia Areata

SI.3.1 Incidence

Globally, the lifetime incidence of alopecia areata (AA) is approximately 2% (Fricke and Miteva 2015). In a systematic review and meta-analysis, the overall incidence proportion of AA was 1.72% (95% CI: 1.08-2.50) (Lee et al. 2020). According to data from the Rochester Epidemiology Project (1990-2009), the age-adjusted incidence rates (IRs) were 21.3 per 100,000 person-years for females and 20.2 per 100,000 person-years for males (Mirzoyev et al. 2014).

SI.3.2 Prevalence

In a recent systematic review and meta-analysis, the global prevalence of AA overall was 2.11% (95% CI: 1.82-2.42) (Lee et al. 2020). By subtype, the prevalence was 0.08% for alopecia totalis, 0.02% for alopecia ophiasis, and 0.03% for alopecia universalis (Lee et al. 2020). There were also variations in prevalence of overall AA when considering stratifications by age, region, setting of study, and time when the study was conducted. Population-based studies reported lower prevalence than clinic-based studies (0.75% [95% CI: 0.49-1.06] vs. 3.47% [95% CI: 3.01-3.96], respectively) (Lee et al. 2020). Regional differences reported in prevalence are as follows (Lee et al. 2020):

- 2.47% (95% CI: 2.05-2.94) in North America
- 0.58% (95% CI: 0.49-0.66) in Europe
- 1.46% (95% CI: 1.17-1.79) in Asia
- 8.66% (95% CI: 4.46-14.09) in South America, and
- 7.09% (95% CI: 2.27-14.30) in Africa.

SI.3.3. Demographics of the Population in the Authorised Indication and Risk Factors for the Disease

Age and Gender: A higher prevalence of AA is sometimes reported in females than in males (Lundin et al. 2014), yet reasons for this are unclear and hypothesised to relate to the increased incidence of autoimmune conditions among females or the increased likelihood of women to seek treatment due to societal pressures. Despite these reports of increased prevalence among females, a global systematic literature review of the epidemiology and the burden of AA found no sex predominance in the incidence of AA (Fricke and Miteva 2015).

The first onset of AA is most common in the third and fourth decades of life but may occur at any age. An earlier age of first onset corresponds with an increased lifetime risk of extensive disease. In 1 cross-sectional study of patients with AA from Greece, the median age was 30 years for men and 31 years for females (Kyriakis et al. 2009). More recently, a population-based study in UK primary care records indicated that AA onset peaked between age 25 and 29 years, and the median age at diagnosis was 31 years for males and 34 years for females (Harries et al. 2022).

Risk Factors

Many aetiologic factors have been suggested to contribute to the development of AA. These include

- stress
- infectious agents
- vaccinations
- hormonal factors, and
- genetics.

Most of the recent literature supports autoimmunity as a major pathogenic process in AA (Alkhalifah 2013). This is supported by common co-diagnosis of AA and other autoimmune conditions, including vitiligo, lupus erythematosus, ulcerative colitis, thyroiditis, celiac disease, and RA (Islam et al. 2015). Stress and environmental factors also seem to trigger AA. A specific stressful life event is reported as the trigger for AA in up to 77% of patients, and patients with AA seem to have experienced more stressful life events than healthy siblings and control patients (Mulinari-Brenner 2018).

SI.3.4. Main Existing Treatment Options

In the absence of approved treatment, a large range of therapeutic approaches have been proposed for the management of AA with inconsistent results. Treatments may vary based on patient's age, disease duration, and extent of hair loss (Meah et al. 2020).

Corticosteroids are often the first line of treatment. Potent topical steroids can be used on the scalp and eyebrows but should not be used on the eyelids and other areas of thin skin. They are the treatment of choice in the paediatric population and as first-line option in adults. However, in adolescents and adults, it is often preferred to use intralesional injections of triamcinolone acetonide, when the disease is limited to small surface such as eyebrows and limited patches on the scalp. Both treatment options can lead to local side effects such as skin atrophy and pigmentation changes (Meah et al. 2020).

Many other topical treatments have been proposed, usually in combination with oral or topical steroids, as their efficacy as monotherapy may be limited. These include

- minoxidil
- calcineurin inhibitors
- anthralin, and
- other irritants.

A separate mention should be made for topical prostaglandin analogues such as bimatoprost and latanoprost that can be prescribed as first-line topical treatment alone or in combination to treat eyelash AA (Meah et al. 2020).

For more extensive diseases, oral corticosteroids are often used with starting doses around 0.5 mg/kg. Doses are tapered progressively when remission is obtained. Other systemic agents have been used, after failure of oral corticosteroids or as cortico-sparing agents, including

ciclosporin with a starting dose of 3-5 mg/kg/day and MTX with a starting dose of 15-20 mg/week. The duration of use of systemic treatments is typically limited due to their toxicity. More recently, Janus kinase (JAK) inhibitors, primarily tofacitinib and ruxolitinib, have been described as alternative choice for systemic treatment of AA (Meah et al. 2020).

Alternative options for extensive disease include phototherapy and topical immunotherapies with diphenylcyclopropenone, squaric acid dibutyl ester, or dinitrochlorobenzene. Topical immunotherapy has been shown to be effective and is a treatment of choice for children with complete scalp hair loss. However, this modality of treatment is not widely available, and its use is also limited by the side effects due to induction of a strong allergic contact dermatitis (Meah et al. 2020).

SI.3.5. Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

Alopecia areata is a chronic inflammatory disease characterised by nonscarring immune-mediated hair loss on any part of the body. AA is unique in that its clinical manifestations including hair loss and nail effects are neither constant nor cyclic or expressed in all hair-bearing areas at any one time, but are expressed sporadically and can affect different areas of the scalp at different times during life, or cause hair loss in the entire scalp or the entire body at once (Olsen 2011). Consequently, AA may present as patchy AA, with partial hair loss in 1 or multiple well-circumscribed round patches on the scalp, or it can progress to hair loss involving the entire scalp (alopecia areata totalis [AT]), or extend to complete hair loss of head and body (alopecia areata universalis [AU]) (Olsen et al. 2004). Patchy alopecia, AT, and AU are considered part of the clinical spectrum of the same disease (Hordinsky and Junqueira 2015).

Persons with AA suffer considerable emotional and psychosocial distress (Hunt and McHale 2005). A 66% to 74% lifetime prevalence of psychiatric disorders has been reported in patients with AA, with a 38% to 39% lifetime prevalence of depression and a 39% to 62% prevalence of generalised anxiety disorder (Colon et al. 1991; Fricke and Miteva 2015). Quality of life is also consistently diminished in patients with AA (Jankovic et al. 2016). The Global Burden of Disease (GBD) study quantified the burden of AA through the “disability adjusted life year” (DALY), a measure where 1 is equivalent to 1 year of healthy life lost. The 2010 age-adjusted DALY for AA ranged from 18 to 24 years of healthy life lost in various worldwide geographies (Karimkhani et al. 2015). While the GBD study incorporated the sequelae of itch and disfigurement into the calculation, it did not account for other potential harms such as emotional distress and financial impact (Karimkhani et al. 2015).

Alopecia areata is not a life-threatening condition and thus mortality data are limited. In a nationwide, retrospective study in Korea, all-cause mortality was not increased in patients with AA but death due to intentional self-harm/psychiatric disease was increased (HR 1.20; 95% CI: 1.02-1.40) (Lee et al. 2019a).

SI.3.6 Important Comorbidities

Important Comorbidities Observed in Patients with AA

Comorbidity	Prevalence	Expected Comedications of Comorbidity
Depression	• 25% (depression or anxiety) reported in electronic records [US] (Huang et al. 2013) • 8.8% had signs of major depressive episode [US] (Koo et al. 1994) • 2.9% depression diagnosed by electronic records [Taiwan] (Chu et al. 2012) • 65.9% signs of depression or anxiety according to Hospital Anxiety and Depression Scale [Mexico, smaller study] (Velez-Muniz et al. 2019) • 18.9% depression reported in systematic review and meta-analysis (Lee et al. 2019b) • 40.9% had depression, 9.4% severe depression reported by Beck Depression Inventory [Korea] (Yoon et al. 2019) • 4% depression [Finland, smaller study] (Laitinen et al. 2020)	SSRIs SNRIs
Anxiety	• 27.1% anxiety reported in systematic review and meta-analysis (Lee et al. 2019b) • 10.1% had anxiety, 4.2% severe anxiety reported by Beck Anxiety Inventory [Korea] (Yoon et al. 2019) • 5.0% anxiety diagnosed by electronic records [Taiwan] (Chu et al. 2012)	Anxiolytic medications (including SSRIs, SNRIs, benzodiazepines)
Suicidal ideation/attempt/ completion	Suicidal ideation: • 0% [Canada, small study] (Gupta and Gupta 1998) • 12.8% at risk of committing suicide, Plutchik Suicide Risk Scale [Mexico] (Velez-Muniz et al. 2019)	SSRIs SNRIs
Atopic comorbidities	Atopy: • 38.2% atopy (allergic rhinitis, asthma, and/or eczema) [US] (Huang et al. 2013) Atopic dermatitis: • 9.6% reported in systematic review and meta-analysis (Lee et al. 2019b) • 5.0% [Taiwan] (Chu et al. 2011) • 3.9% [Israel] (Kridin et al. 2020) • 8.3% [Korea] (Lee and Lee 2019) • 3.3% [Korea] (Lee et al. 2014) Asthma: • 9.9% reported in systematic review and meta-analysis (Lee et al. 2019b) • 5.7% [Taiwan] (Chu et al. 2011) • 7.8% [Israel] (Kridin et al. 2020) • 3.5% [Korea] (Lee and Lee 2019)	Antihistamines Corticosteroids (topical, inhaled)

Comorbidity	Prevalence	Expected Comedications of Comorbidity
	Allergic rhinitis: • 17.7% reported in systematic review and meta-analysis (Lee et al. 2019b) • 14.3% [Taiwan] (Chu et al. 2011) • 16.0% [Israel] (Kridin et al. 2020) • 5.1% [Korea] (Lee and Lee 2019) • Allergic Conjunctivitis • 23.5% [Israel] (Kridin et al. 2020)	
Malignancy	Overall (excluding non-melanoma skin cancer): • 3.7/1,000 person-years [Korea] (Lee et al. 2018) • Cumulative incidence from 1997 to 2013 among patients with AA without prior cancer: 1.3% [Taiwan] (Chen et al. 2019). Lymphoma: • 0.078/1000 person-years [Korea] (Lee et al. 2018) • Cumulative incidence from 1997 to 2013 among patients with AA without prior cancer: 0.05% [Taiwan] (Chen et al. 2019) Thyroid cancer: • Systematic review and meta-analysis: OR of thyroid cancer 1.89 (95% CI: 1.53-2.34), prevalence 0.5% (Lee et al. 2019b)	
Thyroid disease	Hashimoto's thyroiditis: • 0.54% [Korea] (Han et al. 2018) • 2.9% reported in systematic review and meta-analysis (Lee et al. 2019b) Graves' disease: • 0.52% [Korea] (Han et al. 2018) • 1.4% reported in systematic review and meta-analysis (Lee et al. 2019b) Autoimmune thyroid diseases: • 13.9% reported in systematic review and meta-analysis (Lee et al. 2019b)	
Anaemia	• 11.8% reported in systematic review and meta-analysis (Lee et al. 2019b) • 19.6% [US] (Huang et al. 2013).	
Vitamin D deficiency	• 73.8% prevalence of vitamin D deficiency (below 20 or 30 ng/dL depending on the study; systematic review and meta-analysis (Lee et al. 2018)	

Abbreviations: AA = alopecia areata; CI = confidence interval; OR = odds ratio; SNRI =serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

SI.4 Juvenile Idiopathic Arthritis

SI.4.1 Incidence

JIA is an uncommon condition affecting children worldwide. Estimates of incidence and prevalence have been difficult to ascertain because of variations in diagnostic criteria, differences in data ascertainment or study design, low disease frequency, geographic region, and small study numbers. Epidemiologic studies report annual incidence rates between 0.8 and 22.6 per 100 000 children (Gowdie and Tse 2012).

Based on a systematic review and meta-analysis, the worldwide incidence rate of JIA was 7.8 per 100 000 per year (Thierry et al. 2014). However, there were differences by geography, and this pooled rate was based on studies using 3 different JIA classifications (International League Against Rheumatism [ILAR], ACR, and European League Against Rheumatism [EULAR]). In Europe, there is a general tendency toward decreasing incidence from North to South (Heiligenhaus et al. 2013). The incidence rates of juvenile arthritis in European countries have been reported as follows:

- 24.1 per 100 000 PY in Denmark (ILAR) (Cardoso et al. 2021),
- 15.0 per 100 000 PY in 5 Nordic countries (ILAR) (Berntson et al. 2003),
- 12.8 per 100 000 PY in Sweden (ILAR) (Berthold et al. 2019),
- 6.9 per 100 000 PY in Catalonia (Spain) (ILAR) (Modesto et al. 2010),
- 5.61 per 100 000 PY in the UK (ILAR) (Costello et al. 2021), and
- 3.2 per 100 000 PY in Alsace (France) (ILAR) (Danner et al. 2006).

SI.4.2 Prevalence

In a systematic review that included 29 publications, the overall pooled prevalence of JIA was 20.5 per 100 000 (95% CI: 19.8 to 21.3), with individual studies reporting a prevalence that ranged from 3.8 to 400 per 100 000 (Thierry et al 2014). Overall prevalence differed by classification methods are as follows:

- ACR classification method (11 studies); prevalence was 43.0 per 100 000
- ILAR classification method (7 studies); prevalence was 30.0 per 100 000, and
- EULAR classification method (13 studies); prevalence was 12.8 per 100 000.

SI.4.3 Demographics of the Population in the Authorised Indication and Risk Factors for the Disease

Age and gender

In a large cohort of German patients with JIA, the median age at first symptom onset was 8 years (Barth et al. 2016). Some studies have reported an earlier peak in the age of onset for girls compared to boys (Berntson et al. 2003; Yu et al. 2013). Prevalence of JIA was higher for males, overall and in all JIA subtypes in 1 study in Taiwan (Yu et al. 2013). Dissimilarly, in a German (Barth et al. 2016) registry study, JIA prevalence was higher in females versus males. This has also been observed in other geographies (Angeles-Han et al. 2013; Harrold et al. 2013; Ringold et al. 2013a). Overall, more females than males are affected by JIA (2:1) (Heiligenhaus et al. 2013); however, the gender distribution may vary by JIA subcategory. There is a female

predominance in oligoarticular and polyarticular onset, even distribution of genders in systemic onset, and male predominance in enthesitis-related arthritis (Heiligenhaus et al. 2013).

Risk factors

Many etiologic factors have been suggested to contribute to the development of JIA. These include European descent, genetics, environmental factors; including viral and bacterial infections; fish consumption; and heavy metals, vaccinations, stressful life events, psychosocial factors, foetal environment, maternal age, and tobacco exposure (Oen et al. 1995; Berkun and Padeh 2010; Kindgren et al. 2019). In a population-based nationwide study in Taiwan, kids with allergic diseases were at increased risk for developing JIA (Lin et al. 2016). In a Swedish population-based study, exposure to antibiotics during various ages of childhood was significantly associated with increased risk for JIA (Kindgren et al. 2021).

SI.4.4 Main Existing Treatment Options

First-line treatment for patients with non-systemic JIA includes NSAIDs, corticosteroids, and csDMARDs, but a substantial proportion of patients does not achieve an adequate response to these therapies (Ringold et al. 2013b; Hinze et al. 2015; Ravelli 2016). Biologic agents approved for RA have improved the treatment armamentarium available to children with JIA over the past 20 years (Lovell et al. 2000; Ruperto et al. 2010; Brunner et al. 2015), which include etanercept, adalimumab, abatacept, and tocilizumab. Of these, etanercept and adalimumab are TNF-blocking agents that have similar mechanisms of action. Abatacept inhibits T-cell production. Tocilizumab is an anti-IL-6 receptor monoclonal antibody. Although these biological treatments have led to clinical improvements, many patients do not respond and do not achieve long-lasting remission (Hinze et al. 2015; Onel et al. 2022). Tofacitinib, a JAK inhibitor, was the first oral-targeted synthetic DMARD approved in the EU in 2021 for the treatment of JIA.

Unmet medical need

The prognosis of JIA varies based on the individual patient as well as the distinct disease category. Between 25% and 70% of children with JIA will still have active arthritis 10 years after disease onset; more than 40% will enter adulthood with active arthritis (Lovell 2006; Selvaag et al. 2016). Children with JIA are at risk for significant morbidity in terms of joint damage, impairments in physical function, and reduced health-related quality of life (Prakken et al. 2011; Gidman et al. 2015; Ringold et al. 2019).

Although treatment of JIA has resulted in improved clinical outcomes, a considerable number of patients remain unresponsive to the treatment, emphasising the need for further understanding of disease progression and remission to support the stratification of patients to treatment pathways (Zaripova et al. 2021).

In terms of route of administration, patients with JIA as well as their caregivers prefer oral therapy compared with medications requiring subcutaneous or intravenous administration. Medications administered once daily report higher adherence rates as compared with medications requiring more frequent administration, regardless of therapeutic indication of the medications (Coleman et al. 2012; Batchelor and Marriott 2015).

SI.4.5 Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity

JIA is a term that collectively refers to a group of chronic childhood arthropathies of unknown origin. JIA imposes significant burden on various spheres of life. Symptoms associated with JIA, such as fatigue, pain, stiffness, physical disability, visual loss due to uveitis, and drug side effects may lead to reduced participation in regular activities (Heiligenhaus et al 2013). While children diagnosed in their pre-school years may be at risk for worse physical outcomes than children diagnosed later in life, it is not clear whether they have worse psychological outcomes and whether these outcomes have an impact on their everyday life (April et al. 2013).

The knee was the most commonly involved joint at the time of diagnosis, affected as the initial joint in 69% of patients, with 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 a majority of patients who develop uveitis do so in the first 4 years after disease onset (Rypdal et al. 2021).

While recent outcome studies document that 60% of patients reach adulthood without functional limitations, patients still face considerable morbidity (Heiligenhaus et al. 2013). The disease and its associated symptoms frequently continue into adulthood; between 25% and 70% of patients with JIA will have active disease 10 years after the disease onset (Lovell 2006). The probability of remission varies significantly with disease-onset type, being best in oligoarticular JIA, at approximately 50%, and worst in polyarticular JIA, at only 15% (Heiligenhaus et al. 2013).

Polyarticular JIA is not a life-threatening illness and thus mortality data are limited. In 1 population-based study in Finland following 4180 patients with JIA for an average of 6.6 years, mortality is 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.4.6 Important Comorbidities

Important Comorbidities Observed in Patients with JIA.

Comorbidity	Prevalence
Anxiety/depression	• 28.1% with JIA reported anxiety/depression (Germany) (Barth et al. 2016) • 24% experienced mild depression and 7% experienced moderate depression (Romania) (Sur et al. 2021) • 7 - 36% with depression based on systematic literature review (Fair et al. 2019).
MAS	• 53% (8/15) with systemic JIA had bone marrow aspirates suggestive of MAS, while 13% (2/15) were clinically diagnosed (Behrens et al. 2007) • 31.25% (5/16) with systemic JIA had serum levels comparable to those with acute MAS, 2/16 (12.5%) developed overt MAS (Bleesing et al. 2007) • 22% had MAS at onset of systemic JIA (Minoia et al. 2014).

Comorbidity	Prevalence
Chronic anterior uveitis	Uveitis (broadly defined) • 5.0 - 19.1% with JIA had history of uveitis (global) (Consolaro et al. 2019). • 18.4% cumulative incidence of chronic asymptomatic uveitis (Nordic countries) (Nordal et al. 2017) • 8.3% cumulative incidence of uveitis in JRA in systematic review (global) (Carvounis et al. 2006). Anterior uveitis • 15.7% had anterior uveitis (Nordic countries, cross-sectional assessment 18 years after onset) (Rypdal et al. 2018). • 10.3% had anterior uveitis (Germany) (Heiligenhaus et al. 2007)
Secondary amyloidosis	• 9% had renal amyloidosis at follow up (Sweden) (Svantesson et al. 1983a) • 1.4% developed amyloidosis (Germany) (Minden et al. 2002) • 1.4% developed amyloidosis (Turkey) (Yilmaz et al. 2008)
Growth disturbances	• 39% had severe growth retardation at follow up (Sweden) (Svantesson et al. 1983a) • 39% had growth restriction (22% moderate, 17% severe), 7% short stature after 3-year follow up (UK) (McErlane et al. 2018) • 8.5% and 3.0% with cumulative incidence of growth delay and short stature, respectively (similar to general population); 22.5% with cumulative incidence of growth delay, and 9.3% with short stature in systemic arthritis (Canada) (Guzman et al. 2017).1.4% had growth disturbance (height below third percentile) during follow up, approximately 25% had local growth disturbances. Overall; 9.5% had micrognathia (Germany) (Minden et al. 2002)
Cardiac disease (myocarditis, endocarditis)	• 3.7% with history of pericarditis; 1.9% with history of myocarditis (Germany) (Minden et al. 2002) • 3.1% with pericarditis, 0.6% with myocarditis, 0.6% with peri-myocarditis at follow up in JRA (Sweden) (Svantesson et al. 1983b) • 1.5% developed pericarditis, 0.5% developed myocarditis (Turkey) (Yilmaz et al. 2008)
Osteopenia, osteoporosis	Osteopenia • 45.6% hip and 35.4% spine of adults with a history of JCA (Denmark) (Zak et al. 1999) • 41% of adolescents with early onset JIA had low bone mass >11 years after onset (Norway) (Lien et al. 2003) • 36.5% (Romania) (Rusu et al. 2008) • 24% of children with early JIA evaluated in a 2-year prospective follow up had low or very low total body BMD and bone mineral content (Norway) (Lien et al. 2005) • <5% had low BMD (Spain) (Zavala et al. 2017) Osteoporosis • 7.0% hip and 7.7% spine of adults with a history of JCA (Denmark) (Zak et al. 1999) Bone Fracture • 22% of patients with treatment-resistant JIA had vertebral compression fractures mostly in thoracic spine (Finland) (Markula-Patjas et al. 2012) • 10% of patients with JIA taking glucocorticoids had compression fractures (Finland) (Valta et al. 2007)

Abbreviations: BMD = bone-mineral density; JCA = juvenile chronic arthritis; JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; MAS = macrophage activation syndrome.

Module SII – Nonclinical Part of the Safety Specification

SII.1 Toxicity

Key Issues Identified from Repeat-Dose Toxicity Studies

- Immunosuppressive effects in repeat-dose rat, mouse, and dog studies, including generalised decreased red cell mass, lymphoid depletion, and bone marrow hypocellularity (consistent with pharmacologic action), which were dose-dependent and reversible. While immunosuppression associated with species-specific infection (demodectic mange) was observed at high doses in dogs (approximately 7 times the human exposure), immunomodulation not associated with infection occurring in rats and dogs at exposures similar to the clinically efficacious dose (1- to 3.4-fold).
    - Based on these findings, infections would be anticipated to occur in human use, but an increased risk of serious infections or serious infections due to either lymphopenia or neutropenia are not expected at the proposed clinical doses of 2 mg and 4 mg once daily. No serious infections were observed in rat and mouse toxicology studies. The primary immunomodulatory effects (decreased eosinophils and lymphocytes) associated with mange in dogs are monitorable and reversible.
- Evidence of liver toxicity in the 39-week (but not 6-month) dog study included elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and/or gamma glutamyltransferase activity, moderate infiltrates/inflammation, and/or biliary hyperplasia.
    - The relationship of the liver findings to baricitinib is uncertain because of the confounding severe inflammation and demodectic mange that were aggressively treated with ivermectin and NSAIDs. The secondary effect of baricitinib on the liver was supported by the nonclinical study data collected through the live phase and end of study evaluation (including clinical chemistry and full histopathology evaluation). On the basis of these considerations, the dog findings were not considered relevant to human use in terms of identifying an important risk in clinical practice.

Reproductive/Developmental Toxicity

- Fertility: In the rat fertility study, decreased fertility (decreased mating performance, copulation indices, decreased numbers of corpora lutea and implantation sites, increased pre-implantation loss, and/or adverse effects on intrauterine survival of the embryos) occurred at the highest doses (50 mg/kg males, 100 mg/kg females) evaluated in the combined male and female rat fertility study. The margin of safety is 12-fold for males and 4-fold for females.
    - Fertility effects are not expected at the doses proposed for human use because the changes in male and female rats occurred at baricitinib exposure multiples 55- to 83-fold above the clinically efficacious exposure.

- Embryo-foetal development: In a rat embryo-foetal development study, skeletal malformations (bent limbs and rib anomalies) and an increased incidence of skeletal development variations occurred in foetuses at the mid and high doses. In rabbits, there was an increased incidence of skeletal malformations (rib and vertebral anomalies). The margin of safety is 2-fold for rats and 6-fold for rabbits.
    - The JAK/signal transducers and activators of transcription (STAT) pathway have been shown to be involved in early embryonic development. There is a potential for hazard to the foetus if the patient becomes pregnant while taking baricitinib. Baricitinib administration to date during pregnancy has not been associated with teratogenicity, but experience at the time of submission was limited. As the relevance to use in human pregnancy is uncertain, "foetal malformation following exposure in utero" has been classified as an important potential risk.

Genotoxicity

No significant effects were observed related to genotoxicity.

Carcinogenicity

No significant effects were observed related to carcinogenicity.

SII.2 Safety Pharmacology

No significant effects were observed related to Safety Pharmacology.

SII.3 Other Toxicity-Related Information or Data

Juvenile Rat Study

- A juvenile rat study was completed to support the dosing of baricitinib to patients 1 to <12 years old. Administration of baricitinib by once daily oral gavage at 1, 5, or 25 mg/kg/day from post-natal day 10 to 90 resulted in changes that were most notable with regard to overall growth, the immune system, and the bone.
- Reductions in overall growth were evidenced by lower body weights and body weight gains up to approximately 20% relative to controls at the 5- and 25-mg/kg doses. For the immune system, decreases in peripheral and tissue lymphocyte counts, reduced lymphoid organ weights, and decreased lymphoid cellularity in the thymus, spleen, and lymph node were associated with a decrease in the T-cell-dependent antibody response (a functional immune measurement), at doses ≥5 mg/kg. These findings, which were reversible after the 8-week recovery period, are indicative of a decreased immune response, which can be expected based on the pharmacological effects of baricitinib.
- Skeletal effects were observed in the juvenile rat study. A single male rat receiving 25 mg/kg was euthanised after 10 days of dosing because of a multicentric bacterial osteomyelitis with secondary pathologic fracture of the tibia. No other fractures or evidence of increased bone fragility were observed. Thus, the fracture was not considered a direct test-item effect, although a role of baricitinib cannot be ruled out because the pharmacologic effects on the immune system may have contributed to the susceptibility to, or severity of, infection in this rat. Degeneration/atrophy of the bone of the femoral

head and neck that was associated with structural collapse of the femoral head and degenerative joint disease of the affected coxofemoral joint was present in a low number of control rats, but was observed at increased incidence and severity in rats receiving 25 mg/kg. Spontaneous necrosis and collapse of the femoral head has been described in rats (Suehiro et al. 2000), but the exact pathogenesis of baricitinib-related exacerbation of this finding is unknown.

- Several additional skeletal effects occurred in rats receiving ≥1 mg/kg. There were marginal-to-slight decreases in femur and tibia width and/or length in males and females given ≥5 mg/kg, as well as decreases in femur and vertebrae bone size, geometry, and mass in males receiving ≥1 mg/kg and females receiving ≥5 mg/kg. There was also an apparent acceleration of normal maturation of secondary ossification centres of proximal femur in females receiving ≥1 mg/kg/day and males receiving ≥5 mg/kg/day and of proximal humerus of males receiving ≥5 mg/kg/day observed microscopically relative to the concurrent age-matched controls. These findings were not associated with premature closure of growth plates or other functional consequences. Microscopically, there was a focal increase in woven bone in the diaphysis of the tibia and/or humerus, a focal increase in cortical bone of the tibia, and a focal increase in trabecular bone in the distal humerus. The effects on secondary ossification centres, and on woven and cortical bone, were localised to specific anatomic sites, were primarily of minimal to slight severity, and were observed in concurrent control rats.
- Adverse effects on body weight and immune function were observed at doses ≥5 mg/kg and bone at doses ≥1 mg/kg. The exposure multiples to the doses associated with body weight and immune adverse effects (≥5 mg/kg) are 3.3- to 10-fold the exposure in humans at 4 mg/day. Effects on bone (≥1 mg/kg) occurred at exposure multiples of 0.6- to 1.9-fold the exposure in humans at 4 mg/day. An overall no-observed-adverse-effect level was not established based on bone effects observed at the low dose.
- Administration of baricitinib had no adverse effects on clinical signs, sexual maturation, ophthalmology, behavioural performance, reproductive performance, or male reproductive assessments. Relevant safety monitoring measures assessing immune, growth, and bone effects are implemented in paediatric clinical studies.
- Implications for use in patients
    - **Adults**: The bone findings seen in the juvenile toxicology study only occurred in young animals during a time of rapid growth, they were not seen in older rats, and occurred at juvenile rat exposures 1.1- to 3.8-fold greater than a 2-mg clinical dose and 0.6- to 1.9-fold greater than a 4-mg clinical dose in adult patients with RA. The exposure multiples for the adult AD indication are 1.3- to 4.5-fold greater than a 2-mg clinical dose and 0.7- to 2.2-fold greater than a 4-mg clinical dose Therefore, these juvenile rodent findings do not have any implications for use of baricitinib in adult patients, either in its licensed indications or in subjects participating in ongoing adult studies.
    - **Children and Adolescents:** Relevant safety monitoring measures have been implemented in paediatric clinical studies and include height and weight measures. Hand, including wrist and finger, and knee x-rays have been included

to monitor bone age and other growth and bone effects in the study population. The potential of off-label use in children is considered low in unapproved indications due to no reimbursement and existence of licensed alternatives in many countries. For paediatric patients with Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) and similar diseases who have been previously treated under compassionate use, the number of patients treated (n=71) in the context of a significant and debilitating condition for which no other treatment exists, the impact on benefit risk in this patient population is considered to be negligible.

Module SIII – Clinical Trial Exposure

Table SIII.1. Duration of Baricitinib Exposure

Duration of exposure	Number of Patients	Person time (Years)
Cumulative for all indications		
1 to 30 days	221	11.6
31 to 180 days	1108	354.5
181 days to 1 year	1104	856.3
> 1 year	5962	21 227.7
Total	**8395**	**22,450.1**
All BARI RA Analysis Set		
1 to 30 days	123	7.0
31 to 180 days	434	146.1
181 days to 1 year	285	222.0
1 to 2 years	413	567.9
2 to 3 years	256	636.9
> 3 years	2259	13 164.5
Total	**3770**	**14,744.4**
All BARI AD Analysis Set		
1 to 30 days	76	3.4
31 to 180 days	527	162.1
181 days to 1 year	397	292.0
>1 year	1636	4171.0
Total	**2636**	**4628.4**
All BARI AD Peds Analysis Set		
1 to 30 days	3	0.2
31 to 180 days	46	14.6
181 days to 1 year	146	108.4
>1 year	271	410.4
Total	**466**	**533.6**

All BARI AA Analysis Set		
1 to 30 days	17	0.9
31 to 180 days	76	24.3
181 days to 1 year	253	217.1
>1 year	957	1975.6
Total	**1303**	**2217.9**
All BARI JIA Analysis Set		
1 to 30 days	2	0.1
31 to 180 days	25	7.4
181 days to 1 year	23	16.8
1 year to 2 years	109	161.3
2 years to 3 years	61	140.1
>3 years	0	0
Total	**220**	**325.7**

Abbreviations: AA = alopecia areata; AD = atopic dermatitis; BARI = baricitinib; JIA = juvenile idiopathic arthritis; RA = rheumatoid arthritis.

All BARI RA Analysis Set (Studies JADA/JADY, JADB, JADC, JADN, JADV/JADY, JADW/JADY, JADX/JADY, JADZ/JADY and JAGS/JADY). final data.

All BARI AD Analysis Set (Studies JAHG, JAHL/JAHN, JAHM/JAHN, JAIN, JAIW/JAIX and JAIY/JAHN). Data cut as of 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX. All BARI AD includes BARI 1-mg, 2-mg, and 4-mg doses.

All BARI AD Peds Analysis Set (Study JAIP). Data cutoff as of 20 June 2022. Includes BARI dosage of 1, 2 and 4 mg exposure equivalents.

All BARI AA Analysis Set (Studies JAHO and JAIR). Data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO. All BARI AA Analysis Set includes BARI 1-mg, 2-mg, and 4-mg doses.

All BARI JIA Analysis Set (Studies JAHV and JAHX). Data cutoff 21 April 2022.

Total person-time (years) = Sum of duration of exposure in days (for all patients in treatment group)/365.25. Time spent within any temporary study drug interruption is included within exposure time. Time after permanent study drug discontinuation is not included within exposure time.

Note: Person-Time (years) may not sum due to independent rounding

Table SIII.2. Age Group and Gender

Age Group	Number of Patients		Person time (Years)	
	M	**F**	**M**	**F**
Cumulative for all indications				
<65 years	2987	4645	6679.4	13,363.6
<18 years	299	387	359.8	499.5
≥18 to <30 years	860	791	1597.4	1573.5
≥30 to <50 years	1127	1760	2577.5	5335.8
≥50 to <65 years	701	1707	2144.8	5954.8
≥65 years	196	567	598.0	1808.9
≥65 to <75 years	173	493	536.2	1577.7
≥75 to <85 years	22	73	59.9	229.7
≥85 years	1	1	1.9	1.5
Total	**3183**	**5212**	**7277.5**	**15,172.5**

All BARI RA Analysis Set				
<65 years	645	2493	2699.6	9879.0
18 to <30 years	27	145	115.7	513.2
≥30 to <50 years	215	989	949.7	4025.5
≥50 to <65 years	403	1359	1634.1	5340.3
≥65 years	142	490	495.4	1670.5
≥65 to <75 years	128	423	453.2	1448.4
≥75 to <85 years	14	66	42.1	220.6
≥85 years	0	1	0	1.5
Total	**787**	**2983**	**3194.9**	**11,549.4**
All BARI AD Analysis Set				
<65 years	1544	991	2791.0	1649.4
18 to <30 years	630	405	1135.4	642.5
≥30 to <50 years	683	405	1251.3	675.3
≥50 to <65 years	231	181	404.4	331.7
≥65 years	54	47	102.8	85.2
≥65 to <75 years	45	40	83.0	76.1
≥75 to <85 years	8	7	17.8	9.1
≥85 years	1	0	1.9	0
Total	**1598**	**1038**	**2893.8**	**1734.6**
All BARI AD Peds Analysis Set				
<65 years	231	235	261.8	271.8
≥2 to <6 years	19	22	11.5	13.2
≥6 to <9 years	33	43	29.9	40.7
≥9 to <12 years	54	44	68.6	59.2
≥12 to <18 years	125	126	151.7	158.7
Total	**231**	**235**	**261.8**	**271.8**
All BARI AA Analysis Set				
<65 years	499	774	829.1	1335.6
18 to <30 years	203	241	346.3	417.8
≥30 to <50 years	229	366	376.5	635.0
≥50 to <65 years	67	167	106.3	282.8
≥65 years	0	30	0	53.2
≥65 to <75 years	0	30	0	53.2
≥75 years	0	0	0	0
Total	**499**	**804**	**829.1**	**1388.8**
All BARI JIA Analysis Set				
<65 years	68	152	98.0	227.7
≥2 to <6 years	1	5	1.2	5.3
≥6 to <9 years	3	6	4.4	8.7
≥9 to <12 years	7	23	7.4	29.7
≥12 to <18 years	57	118	85.1	184.1
Total	**68**	**152**	**98.0**	**227.7**

Abbreviations: AA = alopecia areata; AD = atopic dermatitis; BARI = baricitinib; F = female; JIA = juvenile idiopathic arthritis; M = male; RA = rheumatoid arthritis.
Total person-time = Sum of duration of exposure in days (for all patients in treatment group)/365.25.
Note: Person-Time (years) may not sum due to independent rounding.
All BARI RA Analysis Set (Studies JADA/JADY, JADB, JADC, JADN, JADV/JADY, JADW/JADY, JADX/JADY, JADZ/JADY, and JAGS/JADY) final data.
All BARI AD Analysis Set (Studies JAHG, JAHL/JAHN, JAHM/JAHN, JAIN, JAIW/JAIX and JAIY/JAHN). Data cut as of 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX. All BARI AD includes BARI 1-mg, 2-mg, and 4-mg doses.
All BARI AD Peds Analysis Set (Study JAIP). Data cutoff as of 20 June 2022. Includes BARI dosage of 1, 2 and 4 mg exposure equivalents.
All BARI AA Analysis Set (Studies JAHO and JAIR). Data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO. All BARI AA Analysis Set includes BARI 1, 2, and 4-mg doses.
All BARI JIA Analysis Set (Studies JAHV and JAHX). Data cutoff 21 April 2022.
Time spent within any temporary study drug interruption is included within exposure time. Time after permanent study drug discontinuation is not included within exposure time.

Table SIII.3. Dose

Dose of exposure	Number of Patients
Cumulative for all indications	
1 mg	826
2 mg	3689
4 mg	5850
5 mg	17
7 mg	46
8 mg	182
10 mg	64
15 mg	18
Total	**8395**
All BARI RA Analysis Set	
1 mg	73
2 mg	1271
4 mg	3253
5 mg	17
7 mg	46
8 mg	182
10 mg	64
15 mg	18
Ever exposed to BARI 2 mg or 4 mg in RA	3575
Total	**3770**
All BARI AD Analysis Set	
1 mg	605
2 mg	1703

4 mg	1012
Total	**2636**
All BARI AD Peds Analysis Set	
1 mg exposure equivalents	120
2 mg exposure equivalents	120
4 mg exposure equivalents	369
Total	**466**
All BARI AA Analysis Set	
1 mg	28
2 mg	595
4 mg	996
Total	**1303**
All BARI JIA Analysis Set	
4 mg[a]	**220**
Total	**220**

Abbreviations: AA = alopecia areata; AD= atopic dermatitis; BARI = baricitinib; JIA = juvenile idiopathic arthritis; RA = rheumatoid arthritis.

[a] All patients were dosed at 4 mg equivalent in All BARI JIA Analysis Set.

All BARI RA Analysis Set (Studies JADA/JADY, JADB, JADC, JADN, JADV/JADY, JADW/JADY, JADX/JADY, JADZ/JADY, and JAGS/JADY); final data.

All BARI AD Analysis Set (Studies JAHG, JAHL/JAHN, JAHM/JAHN, JAIN, JAIW/JAIX and JAIY/JAHN). Data cut as of 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX. All BARI AD includes BARI 1-mg, 2-mg, and 4-mg doses.

All BARI AD Peds Analysis Set (Study JAIP). Data cutoff as of 20 June 2022. Includes BARI dosage of 1, 2 and 4 mg exposure equivalents.

All BARI AA Analysis Set (Studies JAHO and JAIR). Data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO. All BARI AA Analysis Set includes BARI 1-mg, 2-mg, and 4-mg doses.

All BARI JIA Analysis Set (Studies JAHV and JAHX). Data cutoff 21 April 2022

Person-time is not provided for individual doses due to the complexity of the study designs, in which patients changed doses (involving rescue, switching, or step-down in dose) and were exposed to more than one dose level during the study. Patients who switched dose are counted in multiple rows, once for each dose received.

Table SIII.4. Ethnic Origin

Ethnic origin	Number of Patients	Person time (Years)
Cumulative for all indications		
White	5190	14,167.9
Black or African American	325	536.5
Asian	2462	6537.7
American Indian or Alaska Native	250	890.4
Native Hawaiian or Other Pacific Islander	11	12.0
Multiple	122	258.4
Not provided	14	7.6
Unknown	21	39.6
Total	**8395**	**22,450.1**

All BARI RA Analysis Set		
White	2354	9601.5
Black or African American	97	285.1
Asian	1115	4000.6
American Indian or Alaska Native	168	732.7
Native Hawaiian or Other Pacific Islander	2	1.8
Multiple	26	103.2
Unknown	8	19.3
Total	**3770**	**14,744.4**
All BARI AD Analysis Set		
White	1673	2792.7
Black or African American	109	116.7
Asian	719	1477.4
American Indian or Alaska Native	49	109.0
Native Hawaiian or Other Pacific Islander	5	3.9
Multiple	77	126.2
Unknown	4	2.7
Total	**2636**	**4628.4**
All BARI AD Peds Analysis Set		
White	346	388.4
Black or African American	12	11.1
Asian	85	115.5
American Indian or Alaska Native	8	10.3
Multiple	1	0.7
Not provided	14	7.6
Total	**466**	**533.6**
All BARI AA Analysis Set		
White	665	1158.0
Black or African American	102	118.0
Asian	495	874.3
American Indian or Alaska Native	18	30.1
Native Hawaiian or Other Pacific Islander	4	6.3
Multiple	16	24.7
Unknown	3	6.6
Total	**1303**	**2217.9**
All BARI JIA Analysis Set		
White	152	227.3
Black or African American	5	5.6
Asian	48	69.9

American Indian or Alaska Native	7	8.3
Multiple	2	3.6
Unknown	6	11.0
Total	**220**	**325.7**

Abbreviations: AA = alopecia areata; AD = atopic dermatitis; BARI = baricitinib; JIA = juvenile idiopathic arthritis; RA = rheumatoid arthritis.

All BARI RA Analysis Set (Studies JADA/JADY, JADB, JADC, JADN, JADV/JADY, JADW/JADY, JADX/JADY, JADZ/JADY, and JAGS/JADY) final data.

All BARI AD Analysis Set (Studies JAHG, JAHL/JAHN, JAHM/JAHN, JAIN, JAIW/JAIX and JAIY/JAHN). Data cut as of 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX. All BARI AD includes BARI 1-mg, 2-mg, and 4-mg doses.

All BARI AD Peds Analysis Set (Study JAIP). Data cutoff as of 20 June 2022. Includes BARI dosage of 1, 2 and 4 mg exposure equivalents.

All BARI AA Analysis Set (Studies JAHO and JAIR). Data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO. All BARI AA Analysis Set includes BARI 1-mg, 2-mg, and 4-mg doses.

All BARI JIA Analysis Set (Studies JAHV and JAHX). Data cutoff 21 April 2022.

Time spent within any temporary study drug interruption is included within exposure time. Time after permanent study drug discontinuation is not included within exposure time.

Total patient-years = Sum of duration of exposure in days (for all patients in treatment group)/365.25.

Note: Person-Time (years) may not sum due to independent rounding.

Module SIV – Populations Not Studied in Clinical Trials

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

[Note: Exclusion criterion applies to RA, JIA, AD (including paediatric AD), and AA clinical trials, unless otherwise noted.]

History or presence of CV disorders, which in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfered with the interpretation of data

Myocardial infarction, unstable ischaemic heart disease, stroke, or New York Heart Association Stage IV heart failure within 12 weeks of study entry (RA, AD [including paediatrics AD], and AA clinical trials only)

Reason for exclusion: These criteria excluded individuals with previous or concomitant medical conditions that may have increased the risk for safety observations if allowed participation in the study based on theoretical concerns and to minimise confounding factors in data interpretation.

Is it considered to be included as missing information?: Yes (long-term safety) and MACE [important potential risk].

Rationale: Not applicable.

History and/or high risk of venous thromboembolic events (VTEs)

Reason for exclusion: These criteria excluded individuals in the RA and AD programmes with recent VTEs (any VTE within 12 weeks prior to screening) and recurrent VTEs (≥2 episodes) and with any VTE in the JIA and AA programme. These patients were excluded due to the increased risk for safety observations if allowed participation in the study, and to minimise confounding factors in data interpretation.

Is it considered to be included as missing information? No

Rationale: VTE is already a listed safety concern of baricitinib and is subject to systematic study in the Pharmacovigilance Plan for this product in both RA and AD indications.

History or symptoms of lymphoproliferative disease; active or recent primary or recurrent malignant disease

Reason for exclusion: These criteria excluded individuals with previous or concomitant medical conditions that may have increased their risk for safety observations if allowed participation in the study based on theoretical concerns, and to minimise confounding factors in data interpretation.

Is it considered to be included as missing information?: Yes (long-term safety, including malignancies).

Rationale: Not applicable.

Recent and/or concomitant treatment with a biologic for the treatment of RA or JIA; high-dose oral or parenteral corticosteroids; new or unstable dosing regimen of NSAIDs; concomitant use of any 3 csDMARDs (RA and JIA clinical trials only)

Reason for exclusion: These criteria excluded individuals with recent or concomitant use of specified RA or JIA medications to minimise confounding factors in safety and efficacy data interpretation.

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

Rationale: Removed following agreement with Pharmacovigilance Risk Assessment Committee (PRAC) (Procedure number: EMEA/H/C/004085/II/0006).

Recent and/or concomitant treatment with systemic or biologic therapies for the treatment of AD and AA, such as oral corticosteroids, ciclosporin or interleukin inhibitors; recent treatment with other systemic immunomodulators such as methotrexate, mycophenolate mofetil, and azathioprine (AD and AA clinical trials only)

Reason for exclusion: These criteria excluded individuals with recent or concomitant use of specified AD therapies or of most commonly used off-label therapies in AA to minimise confounding factors in safety and efficacy data interpretation.

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

Rationale: For AD and AA, Section 4.5 of the Summary of Product Characteristics (SmPC) states that combination with biologic immunomodulators, other JAK inhibitors, c1closporine, or other potent immunosuppressants has not been studied and is not recommended.

As a result of these warnings and precautions, it is unlikely that concomitant use of baricitinib and these medicinal products will occur in the target population of patients and hence this is not considered to constitute anticipated utilisation or a safety concern in usual clinical practice.

History of chronic liver disease with AST or ALT >1.5 x upper limit of normal (ULN) in RA clinical trials and ≥2 x ULN in JIA, AD, and AA clinical trials or total bilirubin ≥1.5 x ULN

Reason for exclusion: This criterion excluded individuals who may have had an increased risk for safety observations if allowed participation in the study and aimed to minimise confounding factors in data interpretation.

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

Rationale:

Removed following agreement with PRAC (Procedure number: EMEA/H/C/004085/II/0006).

Exposure to or receipt of a live vaccine

Reason for exclusion: This criterion excluded individuals exposed to a live vaccine who may have had an increased risk of infective complications or immunosuppression based on theoretical concerns and to minimise confounding factors in data interpretation.

Is it considered to be included as missing information?: Yes, at authorisation; subsequently removed.

Rationale: Vaccine study agreed in the initial EU – risk management plan (RMP) to address this safety concern has been completed and submitted. In addition, use with live vaccines has not been studied during clinical development and administration during, or immediately prior to, therapy is not recommended per the SmPC. International treatment guidelines on vaccination in patients with RA should be followed including when varicella zoster vaccination is considered prior to treatment. As use with live vaccines is not recommended and use with varicella vaccine only in conjunction with established treatment guidelines, this is not considered to constitute anticipated utilisation or a safety concern in usual clinical practice.

Serious infection, herpes zoster (HZ) infection (current or past), TB, positive test for hepatitis B virus (HBV) or hepatitis C virus (HCV)

Significant (2 or more lifetime episodes) and/or recent (within the past 12 months) history of eczema herpeticum (EH) (AD and AA clinical trials only)

Reason for exclusion: These criteria excluded individuals with previous or concomitant serious infections that may have increased the risk for safety observations if allowed participation in the study based on theoretical concerns and to minimise confounding factors in data interpretation.

Is it considered to be included as missing information?:

- Patients with evidence of HBV or HCV: Yes
- Patients with HZ, TB, and EH: Not applicable
    - HZ is classified as an important identified risk
    - TB is classified as an important potential risk [under serious and opportunistic infections]
    - Serious EH is also captured under the “serious and opportunistic infection” important potential risk.

As such, serious and opportunistic infections are subject to systematic study.

Rationale: The SmPC for baricitinib clearly states that it should not be given to patients with active TB and to consider anti-TB therapy prior to initiation of baricitinib in patients with previously untreated latent TB. Furthermore, the SmPC also clearly advises caution in patients with clinically important chronic or active infection such that if an infection develops, it should be monitored and baricitinib therapy interrupted if the patient is not responding to standard therapy. Furthermore, treatment should not be resumed until the infection resolves. These labelling recommendations are also included in prevailing EU treatment guidelines and established clinical practice by rheumatologists. As a result, initiating or continued use of

baricitinib in patients with any serious infection is unlikely to constitute anticipated utilisation and hence does not qualify as missing information.

Herpes zoster has been classified as an important identified risk, and serious/opportunistic infections as an important potential risk subject to systematic study.

Patients less than 18 years of age (AA clinical trials only)

Reason for exclusion: The safety and efficacy for patients less than 18 years of age has not been studied in AA. To establish the efficacy and safety of baricitinib, trials were conducted first in adults. Safety in patients 2 to less than 18 years of age in RA and AD has been evaluated through the JIA and paediatric AD trials.

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

Rationale: Not applicable.

Women who are pregnant

Reason for exclusion: Use in pregnant women is a standard exclusion criterion in clinical development. In addition, the JAK-STAT pathway has been shown to be involved in early embryonic development, and embryo-foetal skeletal malformations were observed in nonclinical studies.

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

Rationale: Removed following agreement with PRAC (Procedure number: EMEA/H/C/004085/II/0006).

Women who are lactating

Reason for exclusion: Available pharmacodynamic/toxicological data in animals have shown excretion of baricitinib in milk but it is unknown whether baricitinib is also excreted in human milk.

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

Rationale: Removed following agreement with PRAC (Procedure number: EMEA/H/C/004085/II/0006).

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

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

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	Pregnancy was an exclusion criterion in the clinical development programmes; however, 70 pregnancies in maternal exposure and 20 pregnancies from paternal exposure were reported during the clinical development programmes as of the database cutoff of 31 July 2022.
Breastfeeding women	Not included in the clinical development programmes.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Patients with a history of chronic liver disease and with AST or ALT >1.5 x ULN or total bilirubin ≥1.5 x ULN were not included in the RA clinical development programme. • In a clinical pharmacology study (I4V-MC-JAGC [JAGC], baricitinib was studied in 8 patients with mild to moderate hepatic impairment. • Not studied in patients with severe hepatic impairment. Patients with a history of chronic liver disease or AST or ALT ≥2.0 x ULN, alkaline phosphatase ≥2 x ULN, or total bilirubin ≥1.5 x ULN during study screening were not included in the JIA, AD (including the paediatric AD programme), and AA programmes. Therefore, there was no exposure to patients with ongoing mild to moderate hepatic impairment.
Patients with renal impairment	• Patients with a screening eGFR <40 mL/min/1.73m^2 (for RA, JIA, AD, and AA studies) and eGFR <60 mL/min/1.73m^2 (for the paediatric AD study) were excluded. • A total of 190 patients were included in the ALL BARI analysis set (177 in RA; none in JIA, 5 in adult AD [none in paediatric AD]; 8 in AA) with moderate renal impairment at baseline (eGFR <60 mL/min/1.73m^2).
Patients with cardiovascular impairment	Baricitinib has not been specifically studied in patients with cardiovascular impairment.
Immunocompromised patients	Baricitinib has not been specifically studied in immunocompromised patients.

Type of special population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials	The RA clinical development programme included a representative population of patients with moderately to severely active RA, including patients who were MTX-naïve, inadequate responders to MTX, and inadequate responders to csDMARDs. In addition, baricitinib was studied in patients with moderately to severely active RA who previously failed one or more TNF inhibitor, representing patients considered to be the least likely to respond to treatment. The JIA clinical trial (JAHV) included a representative population of patients who have had an inadequate response or intolerance to csDMARDs or bDMARDs. The AD clinical development programme (including the paediatric AD study) included a representative population of patients with moderate-to-severe AD, who are candidates for systemic therapy. The AA clinical development programme included a representative population of patients with severe AA.
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 and is not considered to be a limitation in terms of predicting safety in patients of different racial or ethnic origins.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.

Abbreviations: AA = alopecia areata; AD = atopic dermatitis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BARI = baricitinib; bDMARD = biological disease-modifying anti-rheumatic drug; csDMARD = conventional synthetic disease-modifying antirheumatic drug; CT = clinical trial; eGFR = estimated glomerular filtration rate; JIA = juvenile idiopathic arthritis; MTX = methotrexate; RA = rheumatoid arthritis; TNF = tumour necrosis factor; ULN = upper limit of normal.

Module SV – Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Patient exposure estimates for baricitinib were calculated by dividing the total number of milligrams sold by the estimated average daily dose (ADD) to obtain the total days of therapy. The total days of therapy were then divided by the estimated average length of treatment (ALOT) for an individual patient to obtain the estimated number of patients exposed or 365 to obtain the estimated number of patient-years of exposure (PYE) to baricitinib.

Estimates of ADD and ALOT for different indications were determined as follows:

- ADD = 1 mg, 2 mg, and 4 mg. Baricitinib is available in 1-, 2-, and 4-mg doses with recommended dosing of 1 mg, 2 mg, or 4 mg once daily. For the purposes of this estimate, the sum of all 1 mg, 2 mg, or 4 mg baricitinib sales were divided by an ADD of 1 mg, 2 mg, or 4 mg, respectively.
- ALOT = 217.6 days. This assumption is based upon baricitinib length of therapy data from US specialty pharmacy dispensing. The extent to which experience in the US is generalisable to use outside the US is unknown; however, this is the best model available at the time of this report.

Patient exposure estimates for baricitinib in the treatment of coronavirus disease 2019 (COVID-19) were based upon the
following assumptions:

- ADD = 4 mg.
- ALOT = 7.5 days in the US and 10 days in all other countries or regions.

SV.1.2 Exposure

Since the initial approval of baricitinib, as of 31 July 2022, there have been an estimated 849 000 and 473 000 patients exposed to baricitinib for COVID-19 and all other indications, respectively, and 21 500 PY of exposure for COVID-19 and 282 000 PY of exposure for all other indications.

Table SV.1. Exposure Table by Region and Indication

	Patient Exposure			Patient-Years Exposure		
Region	**COVID-19 Indication**	**All Other Indications (RA and AD)**	**Total**	**COVID-19 Indication**	**All Other Indications**	**Total**
Europe	54 000	274 700	328 800	1400	163 800	165 200
Japan	23 400	71 000	94 400	640	42 300	43 000
Other Countries	528 800	107 600	636 500	14 400	64 100	78 600
US	242 600	19 600	262 200	5000	11 600	16 600
Global Totals[a]	**849 000**	**473 000**	**1 322 100**	**21 500**	**282 000**	**303 600**

Abbreviations: AD = atopic dermatitis; COVID-19 = coronavirus disease 2019; RA = rheumatoid arthritis.

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

Note: There were updates to data sources used in previous RMP v12.3 that had an impact on non-COVID and overall patient exposure estimates
Source: Baricitinib Cumulative Patient Exposure Estimate through 31 July 2022

Module SVI – Additional EU Requirements for the Safety Specification

SVI.1 – Potential for Misuse for Illegal Purposes

The potential for misuse of baricitinib for illegal purposes is not considered to be a risk, particularly in the absence of any associated euphoric or other central nervous system effects associated with addictive behaviour. Similarly, other JAK inhibitors have not been reported to be associated with cases of abuse or dependence leading to addiction (tofacitinib [XELJANZ EU SmPC, 2021], upadacitinib [Rinvoq EU SmPC, 2021] ruxolitinib [JAKAVI EU SmPC, 2021]), nor have there been reports in the scientific literature.

There has been no finding in clinical studies of baricitinib, or in the post-marketing experience to date, indicating that baricitinib causes physical or mental dependency.

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 RMP format.

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

Missing information of "*Use in paediatric patients*" is changed to "*Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination*" based on PRAC comments.

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

Important Identified/Potential Risk:

Important Identified Risk: Herpes zoster

Potential mechanisms:

There is some biologic basis for JAK inhibition affecting zoster susceptibility specifically. Schub et al. (2015) found that multifunctional (IFN-γ+IL-2+TNF-α+) CD4+ cells are involved in immune surveillance against latent HZ, and their waning function is associated with reactivation into clinical episodes of HZ. Patients with rheumatic diseases have lower levels of VZV-specific CD4+ cells than healthy controls. While not specifically tested, inhibition of the signalling target for these CD4+ cells could augment the effect of the functional energy observed prior to an episode of zoster.

Evidence source(s) and strength of evidence:

In the clinical trial (CT) development programmes, observed cases of HZ have been predominantly classified as nonserious (88% in RA, 100% in JIA, greater than 99% in AD, 100% in paediatric AD, and 98% in AA). The majority (94% in RA, 100% in JIA, 95% in AD, 100% in paediatric AD, and 98% in AA) of the reported cases were classified by the investigator as mild to moderate in severity. A similar profile has also been reported from everyday clinical practice since baricitinib was first marketed in the EU for RA on 13 February 2017. As would be expected in a medical condition that is usually treated by specialists, a majority of HZ cases have been readily diagnosed, managed, and typically resolved without long-term sequelae.

More clinically important manifestations of HZ with cases in which the rash spreads beyond the primary or adjacent dermatomes (multidermatomal HZ) have been reported in

- 10% of patients that reported HZ in RA CTs

- no confirmed case in JIA
- 4.7% patients that reported HZ in AD CTs
- 0.2% patients that reported HZ in paediatric AD CTs, and
- 0.1% patients that reported HZ in AA CTs.

HZ was associated with motor nerve involvement in 0.1% of cases in RA and none in JIA, AD (including paediatric), and AA. A common complication of this infection, irrespective of the cause, is post-herpetic neuralgia. This has been reported in a low proportion of patients who developed HZ (8% in RA). In JIA, AD (including paediatrics), and AA, information on post-herpetic neuralgia was not solicited for.

In the JIA CT programme, 1.8% of the patients developed HZ infection. There was no serious case of HZ reported, and all events were reported as mild or moderate in severity. No patients discontinued the treatment due to HZ. A majority (75%) of events were resolved without sequelae.

In the AD CT development programme, 4.8% of the patients developed a HZ infection. There were 2 (0.1%) serious cases of HZ, and a majority of the events were mild or moderate in severity. A majority (93.7%) of events were readily diagnosed, managed, and resolved without sequelae.

In the paediatric AD CT development programme, 0.9% of the patients developed a HZ infection. There were no serious cases of HZ reported and all events that were reported were mild or moderate in severity. Only 0.4% of patients discontinued treatment due to HZ. The majority (75%) of events were readily diagnosed, managed, and resolved without sequelae.

In the AA CT development programme, 3.4% of the patients developed a HZ infection. There was 1 serious case of HZ that also was severe. All other cases were nonserious and mild or moderate in severity. Only 0.1% of patients discontinued treatment due to HZ. The majority (94%) of events were readily diagnosed, managed, and resolved without sequelae at the time of follow up.

Characterisation of the risk:

Frequency

RA

Incidence rate: 2.98 per 100 PY (95% CI: 2.70 to 3.28)

- Serious cases: 11.8%
- Severity:
  - Mild (39.8%)
  - Moderate (54.5%)
  - Severe (5.7%)
- Outcomes: Recovered or resolved: 91.0%
- Incidence of multidermatomal HZ: 0.28 per 100 PY
  - This rate has also remained relatively stable over time.

- Data Source: All BARI RA analysis set; final data

JIA

Incidence rate: 1.2 per 100 PY (95% CI: 0.3 to 3.1)

- Serious cases: none
- Severity:
  - Mild (50%)
  - Moderate (50%)
  - Severe (0%)
- Outcomes: recovered or resolved: 75%
- Incidence of multidermatomal HZ: none confirmed
- Data source: All BARI JIA analysis set; data cutoff 21 April 2022

AD

Incidence rate: 2.8 per 100 PY (95% CI: 2.3 to 3.3)

- Serious cases: 0.1%
- Severity:
  - Mild (36%)
  - Moderate (59%)
  - Severe (4.7%)
- Outcomes: recovered or resolved: 93.7%
- Incidence of multidermatomal HZ: 0.13 per 100 PY
- Data source: All BARI AD analysis set; data cutoff 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX

Paediatric AD

Incidence rate: 0.74 per 100 PY (95% CI: [0.2, 1.9])

- Serious cases: none
- Severity:
  - Mild (50%)
  - Moderate (50%)
  - Severe (0%)
- Outcomes: recovered or resolved: 75%
- Incidence of multidermatomal/disseminated HZ: 0.19 per 100 PY
- Data Source: All BARI AD Peds Analysis Set; data cutoff 20 June 2022

AA

Incidence rate: 2.0 per 100 PY (95% CI [1.4, 2.6])

- Serious cases: 1 (0.1%, IR <0.1) / (2% of all HZ cases)
- Severity of events:

  - Mild (50%)
  - Moderate (48%)
  - Severe (2%)
- Outcomes: recovered or resolved: 94%
- Incidence of multidermatomal HZ: <0.1 per 100 PY
- Data source: All BARI AA analysis set; data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO

Risk factors and risk groups:

A notable proportion of the cases of HZ (26.4%) reported in the baricitinib RA CTs were reported from Japan, where the reporting rate was higher than that from any other country. Whether this represents a true risk factor or is representative of other factors such as detection bias is unclear. Similar findings were seen with tofacitinib.

Heavily pretreated RA elderly patients appear to be at higher risk of HZ.

Preventability:

Other than the risk factors highlighted above, the occurrence of HZ is not usually predictable. The nature of the infection, however, is such that it is readily apparent to patients and hence early consultation with their physician is likely. In addition, the need to instruct patients to seek immediate medical attention if signs or symptoms suggesting infection appear, (to ensure rapid evaluation and appropriate treatment) is highlighted in the current risk minimisation materials for the product. Furthermore, prevailing treatment guidelines in RA in the EU (European League Against Rheumatism and ACR guidelines) recommend vaccination before initiation of treatment (van Assen et al. 2011; Singh et al. 2016). Overall management of herpes and other infections is integrated into everyday clinical practice in the target patient populations in the EU.

Impact on the risk-benefit balance of the product:

RA and JIA

Based on the profile, clinical presentation, and outcomes of the HZ cases reported to date, the current impact of HZ on the benefit-risk balance of baricitinib in RA or JIA is considered to be low. In particular for RA, the events are predominantly (88%) classified by the investigators as nonserious, and manifestations that would be of particular clinical significance, such as multidermatomal HZ or post-herpetic neuralgia, account for 10% and 8% of HZ reports, respectively. In JIA CT programme, there were no serious HZ events, none considered severe, and there were no confirmed multidermatomal cases. Moreover, during the placebo-controlled period, there were no HZ in baricitinib group in JIA.

As RA and JIA are chronic medical conditions, it is possible that HZ could be seen more frequently and with more clinically significant outcomes in a real-world setting, sufficient to warrant close monitoring and systematic study. This eventuality would be covered under “serious infections” as an important potential risk.

Overall, as the potential for infections such as HZ reports are well known in the RA and JIA field and are subject to standard treatment guidelines, it is expected that such reactions would continue to be readily managed in the usual clinical practice. Therefore, the impact on risk-benefit balance will remain low, particularly if the profile remains consistent in everyday clinical practice with that seen in the clinical trial development programme.

AD and AA

The impact on risk-benefit balance of baricitinib in AD and AA is small.

- In AD, there were 2 serious events, 6 considered severe, and 6 were multidermatomal with 5 disseminated disease.
- In paediatric AD, there were no serious events, none considered severe, and only 1 was multidermatomal with disseminated disease.
- In AA, there was 1 serious event that was also considered severe and 1 multidermatomal event.

Moreover, during the placebo-controlled period, the frequency was similar between baricitinib and placebo at 0.5% in AD, no cases in paediatric AD with the baricitinib 4 mg exposure equivalent dose and was 0.9% with baricitinib 4 mg in AA. As the potential for infections is well known by dermatologists, especially skin-related infections, it is expected that such reactions would be readily managed in clinical practice. Therefore, the impact on the risk-benefit balance is low, especially if the profile remains consistent in everyday clinical practice with that seen in the clinical trial development programme.

Public health impact:

Baricitinib is indicated for a clearly defined subset of the adult population with moderately to severely active RA and paediatric patients with JIA. The incidence rate of HZ in the RA CTs was 2.98 per 100 PY. Serious cases of HZ were 11.8%; none had fatal outcomes. The incidence rate of HZ in All BARI JIA was 1.2 per 100 PY with no serious event. The overall impact of HZ on public health is considered to be low.

Baricitinib is indicated for adult patients with moderate-to-severe AD and severe AA, and paediatric patients with moderate-to-severe AD. The incidence rate of HZ in the CTs was 2.8 per 100 PY with 2 serious events in AD, 0.74 per 100 PY with no serious events in paediatric AD, and 2.0 per 100 PY with 1 serious event (resolved) in AA. The overall impact of HZ on public health is considered to be low.

Important Identified Risk: Venous thromboembolic events (VTE)

Potential Mechanisms: No putative mechanism has been identified. Although increases in platelet count have been observed during treatment with baricitinib, no association with these increases and the development of VTE has been established.

Evidence Source(s) and Strength of Evidence:

Venous thromboembolism is considered an ADR of baricitinib treatment. A numerical imbalance in reports of deep vein thrombosis (DVT) and pulmonary embolism (PE) during the 16-week placebo-controlled portion of the baricitinib CTs was noted in clinical development (5 cases vs. 0). This imbalance formed the basis for VTE being classified as an important potential risk. Further data, including the imbalances noted in the AD clinical programme led to VTE being classified by the company as an adverse drug reaction, supporting the re-classification to an important identified risk.

In the observational Study B023, meta-analysis of results from 14 data sources shows a significantly elevated incidence rate ratio (IRR) for VTE in baricitinib compared with tumour necrosis factor inhibitor (TNFi)-treated cohorts. The incidence rate of VTE was greater among patients treated with baricitinib than with TNFi, with a difference of 0.26 (95% CI: -0.04, 0.57) per 100 PY. Data analysed for this study was primarily from insurance claims records and also included the data from RA registries. Patients compared in these analyses were propensity score-matched based on risk factors for VTE, including age, sex, cancer history, cardiovascular disease, immune disorders, diabetes, prescription medication use, and health care resource utilisation.

Characterisation of the Risk

Frequency

RA

- Incidence rate of VTE: 0.49 per 100 PY.
    - The incidence rate is in line with background rates expected for an RA population, based on literature and real-world (claims) data (0.3 to 0.8 per 100 PY [Romero-Diaz et al. 2009; Ogdie et al. 2017]).
- The 95% CI is: 0.38 to 0.61 per 100 PY.
- Data Source: All BARI RA analysis set; final data.
- Study B023 meta-analysis of data from 14 sources with information on patients in routine clinical care shows
    - IRR for VTE was significantly elevated for baricitinib compared to TNFi: IRR = 1.51; 95% CI: 1.10, 2.08.
    - A greater incidence rate of VTE among patients treated with baricitinib than with TNFi, with a difference of 0.26 (95% CI: 0.04, 0.57) per 100 PY.

JIA

- Incidence of VTE: 0.5 % out of 220 patients, incidence rate: 0.3 per 100 PY (95% CI: 0.0 to 1.7).
- Data source: All BARI JIA analysis set; data cutoff 21 April 2022.

AD

- Incidence rate of VTE: 0.08 per 100 PY.
    - The incidence rate is not exceeding the background rates expected for the AD population based on real-world (claims) data (approximately 0.2 per 100 PY in a

population with AD, with variations in subgroups based on age, comorbidities, and comedications).

- The 95% CI is: 0.0 to 0.2 per 100 PY.
- Data Source: All BARI AD analysis set; data cutoff 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX.

Paediatric AD

- No cases of VTE were reported.
- Data Source: All BARI AD Peds Analysis Set; data cutoff 20 June 2022

AA:

- Incidence rate of VTE: 0.1 per 100 PY; 95% CI: 0.01 to 0.32
- Data Source: All BARI AA Analysis Set; data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO

Risk Factors and Risk Groups: All patients who developed VTE had recognised and well-established risk factors for thromboembolism, namely older age, obesity, NSAID use, immobilisation, and medical history of DVT and PE.

Preventability:

Venous thromboembolism is unlikely to be preventable, but the current SmPC advice in Section 4.4 for careful monitoring of patients with risk factors for DVT/PE is expected to mitigate the risk as management of VTE is well established in usual clinical practice. In addition, advice is provided in the SmPC to discontinue treatment, conduct prompt evaluation, and institute appropriate treatment if evidence of VTE occurs. These measures would be anticipated to prevent more severe outcomes, including, for instance, progression of DVT to PE. Furthermore, additional risk minimisation measures promote early detection and management of VTE. Moreover, SmPC Section 4.4 advises that in patients with cardiovascular or malignancy risk factors baricitinib should only be used if no suitable treatment alternatives are available.

Impact on the Risk-Benefit Balance of the Product:

Deep vein thrombosis and PE can be serious and life-threatening conditions, but the current impact on benefit-risk is low as the exposure-adjusted incidence rate (EAIR) over time demonstrates that the observed rate of VTE is within the expected rates for the target population and invariably involves patients with well-established risk factors for VTE. In addition, the outcomes of the reported VTE cases have remained consistent over time and have not changed since VTE was determined to be a safety concern.

Public Health Impact: The potential impact of VTE on public health is very low. Baricitinib is indicated for a clearly defined subset of the adult population with moderate-to-severe RA, AD and severe AA, paediatric patients with JIA, and paediatric patients with moderate-to-severe AD, and VTE will only affect a small fraction of this population.

Important Potential Risk: Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers)

Potential mechanisms: The use of immunosuppressant medications has been hypothesised to potentially increase risk of malignancies because of its effect on the immune system and the capacity for cancer immunosurveillance. Results of studies to evaluate this hypothesis in RA have been inconclusive (Michaud et al. 2014; Mercer et al. 2015).

Evidence source(s) and strength of evidence:

The association between immunomodulatory products like baricitinib and malignancy is largely theoretical and based on a putative effect on the immune system and the capacity for cancer immunosurveillance (a process by which the body's immune system recognises transformed cells to inhibit the growth of neoplastic tissue). In contrast, it is also suspected that the chronic inflammation present in RA and other autoimmune conditions, rather than its treatment, may underlie the increased incidence of lymphoma observed in these patients compared to the general population, through its continuous stimulation of B cells (Baecklund et al. 2006; Beyaert et al. 2013) or through induction of Epstein Barr virus replication (Hollander et al. 2015). Similarly in patients with AD, there is a slightly increased risk of lymphoma, with severity of AD as a significant risk factor (Legendre et al. 2015; Paller et al. 2018). The literature regarding risk of various other malignancies in patients with AD is inconclusive with some literature suggesting increased risks for skin cancers and others suggesting no increased risk (Andersen et al. 2017; Paller et al. 2018).

A systematic literature review (Lee et al. 2019b) found no increased risks for hematologic, cutaneous, or solid organ malignancies among patients with AA. The single exception was that thyroid cancer was found to be more prevalent among patients with AA (OR=1.89, 95% CI: 1.53 to 2.34; Lee et al. 2019b).

There are suggestions that patients with JIA may be at increased risk for malignancy, although the studies are small with wide CIs (Nordstrom et al. 2012; Kok et al. 2014). In 1 study from Sweden, patients with JIA were at increased risk for lymphoproliferative malignancies (HR = 3.6, 95% CI: 1.1 to 11.2), but not all cancers overall (HR = 1.4, 95% CI: 0.7 to 2.9) (Horne et al. 2019).

The most commonly reported malignancies (excluding non-melanoma skin cancer [NMSC]) in the baricitinib RA clinical development programme have been breast, lung, colorectal, prostate, and renal, which are malignancies more frequently observed in the general RA population (Raheel et al. 2016). Uncertainties therefore remain as to whether the malignancies observed are reflective of disease morbidity in the target population or a true effect of treatment. There was no malignancy in the JIA CT programme.

In the AD and AA programmes, few malignancies (except NMSC) were reported:

- 14 cases in AD, with

  - 5 lymphomas
  - 4 prostate cancer, and
  - 1 each of lung carcinoma, rectal cancer, small-cell lung cancer metastatic, testis cancer, and uterine cancer,
- 4 cases in AA, with
  - 1 B-Cell lymphoma
  - 1 chronic lymphocytic leukaemia
  - 1 malignant melanoma in situ, and
  - 1 breast cancer.

The number and type of malignancies reported were in line with the age range of this patient population.

There was no malignancy reported in the paediatric AD CT programme.

Characterisation of the risk:

Clinical Trial sources

Frequency

RA

- Incidence rate of malignancies (excluding NMSC): 0.92 (95% CI: 0.77 to 1.09) per 100 PY.
- Lymphomas: 0.06 per 100 PY (0.03 to 0.11).
- Data Source: All BARI RA dataset; final data.

JIA

- There was no malignancy in the JIA CT programme.
- Data source: All BARI JIA analysis set; data cutoff 21 April 2022.

AD

- Incidence rate of malignancies (excluding NMSC): 0.30 per 100 PY (95% CI: 0.2 to 0.5)
- EAIR of Lymphomas: 0.1 per 100 PY.
- Data Source: All BARI AD dataset; data cutoff 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX.

Paediatric AD

- No malignancy reported.
- Data Source: All BARI AD Peds Analysis Set; data cutoff 20 June 2022

AA

- Incidence: The EAIR for malignancies (excluding NMSC) was 0.2 per 100 PY (95% CI: 0.05-0.45)
- Lymphomas: <0.1 per 100 PY (95% CI: 0.001, 0.25)

- Data Source: All BARI AA dataset; data cutoff 10 May 2022 for JAIR and 24 May 2022 for JAHO

Risk factors and risk groups:

No specific risk groups or specific risk factors have been identified from the clinical development programme for baricitinib.

Preventability:

Malignancy is intrinsically neither preventable nor predictable. However, SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, or with other malignancy risk factors (for example, current malignancy or history of malignancy) baricitinib should only be used if no suitable treatment alternatives are available.

Impact on the risk-benefit balance of the product:

As an important potential risk of baricitinib for which causality has not been established, there is no ostensible direct impact on the benefit risk profile at this time. This position takes into account the theoretical basis of a possible association between immunomodulatory products in general and subsequent negative affect on patients' capacity for cancer immunosurveillance. On the other hand, there remains the possibility that chronic inflammation in the target RA population may also impose an increased risk for malignancy, notably lymphoma. These uncertainties, including whether or not this is a possible class effect, underpin the current PV plan to provide further characterisation over longer-term exposure in everyday clinical practice.

Current evidence is inconclusive but to date appears to show that the profile of malignancies reported are consistent with those expected for the general RA population. In addition, the IRs of malignancies reported for baricitinib in the clinical development programme remain within the rates expected for patients with RA.

Should further characterisation of malignancies reported with baricitinib in the proposed RA registries demonstrate that they are occurring at a higher rate than expected for the population, or other RA therapies, then this may have an impact on benefit-risk. In the face of treatment in a significant medical condition, the impact would depend on a number of different factors, including frequency and profile versus other therapies. Based on current evidence, the expected impact is still considered to be low and any further discussion on putative impact in the future is speculative at this point in time. There was no malignancy in the JIA CT programme.

The impact on benefit-risk in the AD and AA population does not differ significantly from that in the RA patient population. One difference is that data are very limited on the impact of AD and AA on the occurrence of malignancies. For AD, some literature suggests there is no impact while others suggest a risk with regard to skin cancers and a slightly increased risk of lymphoma, with severity of disease being a risk factor. The IRs of malignancies in the baricitinib AD and AA development programmes are low and no malignancy was reported in the paediatric AD CT programme. Further characterisation of the risk will be monitored through the current PV Plan.

Based on current evidence, the expected impact is considered low and supports use in AD and AA.

Public health impact:

Based on current data, the potential impact on public health is considered to be very low. Baricitinib is indicated for a clearly defined subset of the adult population with moderate-to-severe RA, AD and severe AA, paediatric patients with JIA, and paediatric patients with moderate-to-severe AD, and any putative causal association between treatment with baricitinib and malignancy has yet to be established.

Important Potential Risk: Serious and opportunistic infections (including tuberculosis, candida infections, progressive multifocal leukoencephalopathy)

Potential Mechanisms
Various pro-inflammatory cytokines, interferon, and the chemokine receptor, CXCR4, signal via the JAK-STAT pathway, as do the haematologic growth promoters, granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. Excessive inhibition of these signalling pathways could impair the body's ability to mount an effective response to invading microorganisms.

The IL-6 cytokine, which signals through the JAKs, plays an important role in fighting infection through its activity as a lymphocyte stimulating factor (Hunter and Jones 2015). Continuous inhibition of its pro-inflammatory signalling pathway could lead to impaired innate and adaptive immunity to viral, parasitic, and bacterial infection (Smolen et al. 2008; Kremer et al. 2011; Hunter and Jones 2015). Baricitinib administered once daily produces inhibition of IL-6 cytokine activity that is partial and transient.

Evidence Source(s) and Strength of Evidence

As would be expected from its mode of action, various infections were consistently observed throughout the clinical development programme for baricitinib and, overall, affected approximately one-half of the RA, JIA, and AD study populations (including paediatric) and one-third of the AA study population exposed to baricitinib, respectively. The evidence was considered sufficient to conclude that some infections (such as upper respiratory tract infections, HZ, herpes simplex, and urinary tract infection) were adverse effects of the product. The profiles of infections observed were mainly of a nonserious nature with rates consistent with those observed with other RA therapies. In the All BARI JIA Analysis Set, the IR of serious infections was 1.5 per 100 PY.

In AD randomised CTs, serious infections were uncommon and numerically less frequent with baricitinib treatment than with placebo. This was similar for serious herpes simplex infections where the only serious infections were reported in placebo. In baricitinib-treated patients in the paediatric AD programme, the IR of serious infections was 1.3 per 100 PY. In the All BARI AA analysis set, few patients reported serious infections with an IR of 0.7 events per 100 PY.

In RA, more clinically significant infections, including opportunistic infections, have been reported rarely and were generally well managed. Pneumonia has been added to the SmPC as an adverse effect of baricitinib at the request of the PRAC. The evidence source for the request to add progressive multifocal leukoencephalopathy (PML) to this safety concern was on the basis of a single case report with another JAK inhibitor. To date, no cases of PML have been reported with baricitinib.

In All BARI JIA Analysis Set, there have been no confirmed cases of opportunistic infections.

In the All BARI AD Analysis Set, the IR for opportunistic infections is 0.3 per 100 PY, with a majority of cases being multidermatomal HZ, and no TB infections have been reported.

In baricitinib-treated patients in the paediatric AD programme and the AA programme, there was one case each of opportunistic infection (IR: 0.19 per 100 PY in paediatric AD and <0.1 per 100 PY in AA), both due to a multidermatomal herpes zoster. There were no TB infections reported in paediatric AD or AA programme.

Results from the meta-analysis in the B023 observational study show a numerically greater IRR of incident serious infection in patients with RA treated with baricitinib compared with TNFi. The incidence rate of first serious infection was greater among patients treated with baricitinib than with TNFi, and the difference was 0.57 (95% CI: -0.07, 1.21) per 100 PY. Data analysed for this study came primarily from health insurance claims records and also included some data from RA registries. Patients compared in these analyses were propensity score-matched based on risk factors for serious infection, such as age, sex, immune disorders, diabetes, ischaemic heart disease, prescription medication use including glucocorticoids, count of previous bDMARDs, and health care resource utilisation.

Characterisation of the Risk

Frequency

RA

- Incidence rate of serious infections: 2.58 per 100 PY; 95% CI: 2.33 to 2.86.
- Incidence rate of pneumonia: 1.39 per 100 PY.
- Incidence rate of multidermatomal HZ: 0.28 per 100 PY; 95% CI: 0.20 to 0.38
- Incidence rate of TB: 0.13 per 100 PY; 95% CI: 0.08 to 0.20.
- Data Source: All BARI RA Analysis Set; final data.
- Study B023 meta-analysis of data from 14 sources with information on patients in routine clinical care shows
    - IRR for serious infection was numerically greater for baricitinib compared with TNFi but did not attain statistical significance (IRR = 1.36; 95% CI: 0.86, 2.13).
    - A greater incidence rate of serious infection was seen in patients treated with baricitinib than with TNFi, and the difference was 0.57 (95% CI: -0.07, 1.21) per 100 PY.

JIA

- Incidence rate of serious infection: 1.5 per 100 PY; 95% CI: 0.5 to 3.6.
- Incidence rate of pneumonia: 0.6 per 100 PY; 95% CI: 0.1 to 2.2.

- Incidence rate of multidermatomal HZ: none confirmed.
- Incidence rate of serious herpes simplex: none reported.
- Incidence rate of TB: none reported.
- Data source: All BARI JIA Analysis Set; data cutoff 21 April 2022.

AD

- Incidence rate of serious infections 1.8 per 100 PY, 95% CI: 1.4 to 2.2.
- Incidence rate of pneumonia: 0.4 per 100 PY.
- Incidence rate of multidermatomal HZ: 0.13 per 100 PY.
- Incidence rate of serious herpes simplex: 0.3 per 100 PY.
- Incidence rate of TB: none reported.
- Data Source: All BARI AD Analysis Set; data cutoff 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX.

Paediatric AD

- Incidence rate of serious infection: 1.3 per 100 PY, 95% CI (0.5 to 2.7).
- Incidence rate of pneumonia: 0.7 per 100 PY.
- Incidence rate of multidermatomal/disseminated HZ: 0.19 per 100 PY.
- Incidence rate of serious herpes simplex: 0.75 per 100 PY.
- Incidence rate of TB: none reported.
- Data Source: All BARI AD Peds Analysis Set; data cutoff 20 June 2022.

AA

- Incidence rate of serious infections: 0.7 per 100 PY, 95% CI (0.4 to 1.1).
- Incidence rate of pneumonia (PT): 0.3 per 100 PY, 95% CI (0.1, 0.6).
- Incidence rate of multidermatomal HZ: <0.1 per 100 PY.
- There have been no reports of serious herpes simplex, and TB.
- Data Source: All BARI AA analysis set; data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO.

Risk Factors and Risk Groups

Analysis of the CT data for baricitinib in RA shows that concomitant corticosteroids use, prior biological medicines use, being underweight, overweight, or obese, living in the Asian region, and advanced age (≥50 years old) are the key risk factors for serious infections.

No specific risk factors for serious infections have been identified for patients with JIA, AD (including paediatric patients), and AA. A serious form of herpes simplex (eczema herpeticum – EH) has been reported and is associated with poor skin condition that may occur in AD.

Preventability

Although there are no data to support the predictability of serious infections, specific risk factors have been determined in the target population of patients with RA and JIA. In AD and AA, the risk for serious infection is limited and readily amenable to early detection and mitigation, particularly in a specialist healthcare system in which management of serious infections is an integral part of everyday clinical practice. As advised in the SmPC, careful monitoring of

patients for early detection of signs of infection and application of appropriate intervention, including discontinuation of treatment, may help to mitigate against more clinically significant outcomes of serious infections. Additionally, as there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients over 65 years of age, baricitinib should only be used if no suitable treatment alternatives are available. Furthermore, additional risk minimisation measures are in place in the EU/ European Economic Area as described in Part V of this RMP.

Impact on the Risk-Benefit Balance of the Product

The current impact of serious infections on the benefit-risk balance of baricitinib is very low. This assessment is based on the clinical profile (upper respiratory tract infections and other infections, such as HZ, herpes simplex, and urinary tract infections, that are largely judged to be mild or moderate by investigators) and incidence rate of serious infections, including pneumonia observed to date (approximately 2.58, 1.5, 1.8, 1.3, and 0.7 per 100 PY in RA, JIA, AD, paediatric AD, and AA, respectively). As an inhibitor of IL-6 cytokine activity, more serious manifestations of infection could become apparent in everyday clinical practice and with higher frequency and more clinically significant outcomes than those observed in a CT setting. As serious infections are well known in the RA, JIA, and dermatologic field, and are subject to standard treatment guidelines, it is expected that such reactions would continue to be readily managed in the usual clinical practice and, therefore, the impact on risk-benefit balance will remain low, particularly if the incidence remains similar to that observed in clinical development. If the incidence rate of serious outcomes increases significantly in a real-world setting, then a more negative impact on benefit risk would be anticipated.

Public Health Impact

Although infections overall affected about half of the RA, JIA, and AD study populations (including paediatric) and one-third of the AA study population exposed to baricitinib, the incidence rate for serious infections was,

- 2.58 per 100 PY in the All BARI RA population
- 1.5 per 100 PY in the All BARI JIA population
- 1.8 per 100 PY in the All BARI AD population
- 1.3 per 100 PY in All BARI AD Peds population and
- 0.7 per 100 PY in the All BARI AA population.

Baricitinib is indicated for a clearly defined subset of the adult population with moderately to severely active RA, moderate-to-severe AD, and severe AA, paediatric patients with JIA, and paediatric patients with moderate-to-severe AD, and the impact of serious infections on public health is considered low.

Important Potential Risk: Myelosuppression (agranulocytosis)

Potential mechanisms: JAK inhibitors block multiple aspects of cytokine signalling including interference with cytokines such as colony stimulation factors (Borie et al. 2005; O'Shea et al. 2013) and could potentially result in leucopoenia.

Evidence source(s) and strength of evidence: Treatment with baricitinib was associated with decreased neutrophil counts in 21.3% of patients in RA, 27.4% in JIA, 15% in AD, 20.2% in paediatric AD, and 22.6% in AA, and this was consistent across CTs. The frequency with which the absolute neutrophil count (ANC) fell transiently to less than 500/mm^3 (Common Terminology Criteria for Adverse Events [CTCAE] Grade 4 neutropenia) was very low in RA (0.2%), JIA (0.5%), AA (0.4%), and none in AD (including paediatric). Importantly, the observed neutropenia, regardless of CTCAE Grade, was not associated with a higher risk of serious infections.

Although "neutropenia <1000 cells/mm^3" is an acknowledged adverse effect of baricitinib treatment and listed as such in the SmPC, there is no current evidence to support agranulocytosis (defined as <100 cells/mm^3) as an important potential risk independent of the "Serious Infections" already included as a safety concern in the EU-RMP, this takes into account that the well-known outcome of low white cell counts is infection.

Characterisation of the risk:

Frequency

RA

- 0.2% patients experienced a CTCAE Grade 4 neutropenia.
- No cases indicative of agranulocytosis (<100 cells/mm^3) have been reported.
- Data Source: All BARI RA Analysis Set; final data.

JIA:

- 0.5% patients experienced a CTCAE Grade 4 neutropenia.
- No cases indicative of agranulocytosis (<100 cells/mm^3) have been reported.
- Data source: All BARI JIA Analysis Set; data cutoff 21 April 2022.

AD

- No patients experienced a CTCAE Grade 4 neutropenia, and 0.5% had a Grade 3 neutropenia.
- No cases indicative of agranulocytosis (<100 cells/mm^3) have been reported.
- Data Source: All BARI AD Analysis Set; data cutoff 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX.

Paediatric AD

- No patients experienced a CTCAE Grade 4 neutropenia.
- No cases indicative of agranulocytosis (<100 cells/mm^3) have been reported.
- Data Source: All BARI AD Peds Analysis Set; data cutoff 20 June 2022.

AA

- 0.4% patients experienced a CTCAE Grade 4 neutropenia.
- No cases indicative of agranulocytosis (<100 cells/mm^3) have been reported.

- Data Source: All BARI AA Analysis Set; data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO.

Risk factors and risk groups: No risk factors for neutropenia or myelosuppression (agranulocytosis) have been identified. Agranulocytosis during baricitinib treatment either in clinical development or post-marketing has not been observed.

Preventability: Myelosuppression is intrinsically neither preventable nor predictable, but neutropenia and its associated risk of infections are readily amenable to early detection and mitigation, particularly in a specialist RA, JIA, and AD/AA healthcare system in which management of myelosuppression and associated infections is an integral part of everyday clinical practice and prevailing treatment guidelines. In the warnings and precautions section of the SmPC, clear advice is provided on not starting treatment or interrupting treatment should ANC or absolute lymphocyte count (ALC) fall below a certain value. In addition, the need for careful monitoring of patients for early detection of signs of infection and application of appropriate intervention are provided in both the SmPC and additional risk minimisation materials described in Part V of this RMP. Such actions are likely to help mitigate against more clinically significant outcomes of serious infections, and this has proved to be the case in the CT setting.

Impact on the risk-benefit balance of the product: The current impact of myelosuppression on the benefit-risk balance of baricitinib is very low. This assessment is based on the clinical profile that showed a low incidence of neutropenia Grade 4 in RA, JIA, and AA, and none in AD (including paediatric), and cases qualifying as agranulocytosis have not yet been observed or reported.

Myelosuppression (in terms of an impact on reducing ANC) is listed as an adverse effect of treatment with baricitinib, as would be expected with any product with immunomodulatory action. To date, evidence of Grade 4 neutropenia is very limited and there have been no cases indicative of agranulocytosis (<100 cells/mm^3). Importantly, the expected outcome (risk) of neutropenia would be infections and a demonstrated association with serious infections would be an important risk. To date, there is no evidence that the levels of neutropenia observed to date have been directly associated with serious infections and hence have no direct negative impact on the benefit risk profile of baricitinib. Serious infection as a putative outcome of agranulocytosis (which, to date, has not been observed) is already listed as an important potential risk.

Public health impact: There is no direct impact on public health and any that exists would be linked to any associated serious infections as an outcome of the effects on ANC and ALC. Baricitinib is indicated for a clearly defined subset of the adult population with moderate-to-severe RA, AD and severe AA, paediatric patients with JIA, and paediatric patients with moderate-to-severe AD, and the potential risk of agranulocytosis will only affect a small fraction of this population.

Important Potential Risk: Myopathy including rhabdomyolysis

Potential mechanisms: There are no strong mechanistic reasons for considering that the changes in creatine phosphokinase (CPK) observed during treatment with baricitinib are directly linked to adverse muscle-related outcomes, including rhabdomyolysis.

Early literature suggested that patients with RA have lower CPK values, which increase during remission (Sanmarti et al. 1994). Increases in CPK with treatment have also been reported for nonrheumatologic diseases, including a transient increase in mild asthmatics treated in a Phase 1 study with an anti-IL-5 receptor monoclonal antibody (Busse et al. 2010). While it is unclear whether the increase in CPK is related to an increase in muscle mass, relatively recent publications have suggested that STAT3 signalling is increased in adult muscle satellite cells, and that inhibition of STAT signalling increased muscle regeneration (Doles and Olwin 2014; Price et al. 2014; Tierney et al. 2014).

Evidence source(s) and strength of evidence:

Although increased CPK >5x ULN is a common adverse effect of baricitinib listed in the SmPC, the strength of evidence linking the muscle enzyme (CPK) elevations observed during treatment with clinically significant or concerning adverse outcomes such as myopathy or severe muscle damage (rhabdomyolysis) is weak. As described in the summary of product characteristics (SmPC), treatment with baricitinib was associated with a rapid (within 1 week) increase in CPK values. In RA, the mean CPK value plateaued after approximately 8 to 12 weeks of treatment, while in AD and AA it varied throughout therapy. Discontinuation of baricitinib due to an increased CPK or musculoskeletal adverse event (AE) symptoms was uncommon in RA (0.7%), AD (0.3%), and AA (0.2%), and no discontinuations were reported in paediatric AD and JIA. In addition, there have been no confirmed cases of rhabdomyolysis from CTs and limited information from post-marketing experience to date.

Characterisation of the risk:

Frequency

RA

- Incidence rate of myopathy: 0.05 per 100 PY.
- There have been no confirmed cases of rhabdomyolysis in the baricitinib clinical development programme.
- Data Source: All BARI RA Analysis Set; final data.

JIA

- There have been no reports of myopathy, myositis, or rhabdomyolysis with baricitinib in the JIA clinical development programme.
- Data source: All BARI JIA Analysis Set; data cutoff 21 April 2022.

AD

- Incidence rate of myositis: 0.02 per 100 PY.

- There have been no cases of myopathy or rhabdomyolysis in the AD baricitinib clinical development programme.
- Data Source: All BARI AD Analysis Set; data cutoff 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX.

Paediatric AD

- There have been no cases of myopathy, myositis, or rhabdomyolysis in the paediatric AD clinical trial.
- Data Source: All BARI AD Peds Analysis Set; data cutoff 20 June 2022.

AA

- There have been no reports of myopathy, myositis, or rhabdomyolysis with baricitinib in the AA clinical development programme.
- Data Source: All BARI AA Analysis Set; data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO.

Risk factors and risk groups: As the incidence rate of muscle symptoms in CT development has been so low and no confirmed cases of rhabdomyolysis have been reported, it is not possible to identify any specific patient risk factors for these conditions.

Preventability: Myopathy and rhabdomyolysis as putative adverse outcomes of the observed CPK increases are intrinsically neither preventable nor predictable. No risk factors have been identified, including concomitant use of statins, that impact the CPK elevations or possible outcomes

Impact on the risk-benefit balance of the product: As myopathy, including rhabdomyolysis, is an important potential risk of baricitinib for which causality has not been established, there is no ostensible direct impact on the benefit-risk profile at this time. The increases in CPK observed in the vast majority of patients treated have been largely asymptomatic; appear to have no clinical significance with no evidence of an increased risk of serious muscle-related AEs. In particular, there have been no confirmed cases of rhabdomyolysis either in the clinical development programme or from limited post-marketing experience to date.

With increased exposure and more prolonged treatment in everyday clinical practice, it is possible that this profile may change and hence is being closely monitored in the systematic setting of the studies included in the PV plan for this product. Any putative impact on the benefit-risk profile will be dependent on whether a causal association with these adverse outcomes is established, their frequency, severity, and the extent to which they are managed in the healthcare setting.

If the frequency of adverse muscular outcomes (including rhabdomyolysis) reported in everyday clinical practice, remains similar to the low rates seen in clinical development, then the likely impact on benefit-risk will remain very low, especially if no clear causal association can be established.

Public health impact:

The incidence rate for myopathy, including myositis, in the All BARI RA Analysis Set was 0.05 per 100 PY and 0.02 per 100 PY for AD (no cases reported in JIA, paediatric AD, or AA), and there is no confirmed evidence of rhabdomyolysis to date as a putative outcome of the CPK increases observed. The potential impact on public health is therefore considered to be very low.

Important Potential Risk: Potential for drug-induced liver injury

Potential Mechanisms: No biological mechanism to explain the observed increases in aminotransferase liver enzymes (AST and ALT) has been identified.

Evidence Source(s) and Strength of Evidence: Within the RA CT programme, ALT and AST ≥5 x ULN were reported by 1.5% and 0.5% patients, respectively, and ALT and AST ≥10 x ULN were reported in 0.3 and 0.1% of patients, respectively. ALT and AST ≥3 x ULN are considered to be adverse effects of baricitinib. In the All BARI JIA Analysis Set, 2.7 and 0.9% of patients had increased ALT ≥5 x ULN and AST ≥5 x ULN, respectively; and 0.5% had increased ALT ≥10 x ULN (no patient had AST elevation of ≥10 x ULN). Within the AD CT programme, ALT and AST ≥5× ULN were reported in 0.5% and 0.9% patients, respectively, and ALT and AST ≥10 x ULN were reported by 0.1% and 0.2% of patients, respectively. In the paediatric AD CT, no patient had ALT elevations of ≥5x ULN; AST ≥5x ULN were observed for 0.2% of patients; there were no patients with AST or ALT elevations of ≥10x ULN. In the AA CT programme, 0.8% and 0.9% of patients had increases of ALT and AST ≥5x ULN, respectively, and 0.15% and 0.23% had increases of ALT and AST ≥10× ULN, respectively. None of these enzyme changes were linked to clinically significant evidence of drug-induced liver injury (DILI). Of the total AEs, 0.3% of AEs for hepatic disorders were considered by the investigators to be serious in RA, 0.5% in JIA, 0.04% in AD, 0.1% in AA, and none in paediatric AD.

The available information on potential hepatotoxicity with baricitinib treatment derived from completed CTs, post-marketing safety studies, published scientific literature, and spontaneously reported AEs from post-marketing experience cumulatively was reviewed through 13 February 2022:

- The CT data in RA, AD (adults), and AA include 7635 patients and 19 415 PYE. Of these patients, 5183 (68%) were exposed to baricitinib 4 mg. Among these, there were no cases of severe DILI probably related to baricitinib. A total of 9 cases had transaminases ≥3 x ULN and total bilirubin ≥2 x ULN (7 in RA, 1 in AD, 1 in AA). Based on the medical review, it was concluded that none of them met the Hy's law definition due to the presence of alternative aetiology in these patients.
- The placebo-controlled data from RA, AD, and AA clinical trials do not show a consistent difference in frequency of treatment-emergent transaminases increase to ≥3x, 5 x, or 10 x ULN between baricitinib 2 mg, 4 mg, and placebo. The incidence of these elevations did not increase with longer exposure. In addition, there was no difference in the frequency of transaminases increase between baricitinib and placebo in the COVID-19 clinical trials.

- There were no cases that met Hy's law definition or severe DILI cases in about 390 000 patients treated for RA or AD and 850 000 patients treated for COVID-19 in the post-marketing setting.

The current evidence including significant baricitinib exposure in the clinical trial and post-marketing settings, indicates that the risk for hepatotoxicity with baricitinib is not manifesting as severe DILI.

Characterisation of the Risk

Frequency

RA

- Incidence of serious hepatic AEs: 0.3%; 0.08 per 100 PY.
- Incidence of permanent discontinuations due to hepatic AEs: 34 (0.9%); EAIR of 0.22 per 100 PY**.**
- Incidence of abnormal liver tests:

	Patients with Elevated Analyte [n/N-obs (%)]
ALT	
≥3 x ULN	188/3741 (5.0%)
≥5 x ULN	55/3741 (1.5%)
≥10 x ULN	10/3741 (0.3%)
Total bilirubin	
≥2 x ULN	3/3741 (0.1%)

Abbreviations: ALT = alanine aminotransferase; n = number of patients who have at least 1 measure falling into both the baseline and post-baseline categories; N-obs = number of patients in the baseline category and that have at least 1 post-baseline measurement; ULN = upper limit of normal.

- Confidence intervals: Not available.
- Data source: All BARI RA Analysis Set; final data.

JIA:

- Serious hepatic AEs: 0.5%, IR: 0.3 per 100 PY (95% CI: 0 to 1.7).
- Permanent discontinuations due to hepatobiliary disorders: n = 1 (0.5%), IR: 0.3 per 100 PY, 95% CI: 0.0 to 1.7).
- Incidence of abnormal liver tests:

	Patients with Elevated Analyte [n/N-obs (%)]
ALT	
≥ 3 × ULN	9/219 (4.1)
≥ 5 × ULN	6/219 (2.7)
≥ 10 × ULN	1/219 (0.5)
TBL	
≥2 × ULN	0

Abbreviations: ALT = alanine transaminase; n = number of patients who have at least 1 measure falling into both the baseline and post-baseline categories; N-obs = number of patients in the baseline category and that have at least 1 post-baseline measurement; TBL = total bilirubin, ULN = upper limit of normal.

- Data Source: All BARI JIA Analysis Set; data cutoff 21 April 2022.

AD

- Incidence of serious hepatic AEs: 0.04%; IR: less than 0.1 per 100 PY.
- Incidence of permanent discontinuations due to hepatic AEs: 1 (0.04%); IR= <0.1 per 100 PY.
- Incidence of abnormal liver tests:

	Patients with Elevated Analyte [n/N-obs (%)]
ALT	
≥3 × ULN	83/2605 (3.2%)
≥5 × ULN	13/2605 (0.5%)
≥10 × ULN	2/2605 (0.1%)
Total bilirubin	
≥2 × ULN	12/2605 (0.5%)

Abbreviations: ALT = alanine aminotransferase; n = number of patients who have at least 1 measure falling into both the baseline and post-baseline categories; N-obs = number of patients in the baseline category and that have at least 1 post-baseline measurement; ULN = upper limit of normal.

- Data source: All BARI AD Analysis Set; data cutoff 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX.

Paediatric AD

- Serious hepatic events: None.
- Incidence of permanent discontinuations due to hepatic AEs: None.
- Incidence of abnormal liver tests in the All BARI AD Peds Analysis Set:

	Patients with Elevated Analyte [n/N-obs (%)]
ALT	
≥3x ULN	1/462 (0.2%)
≥5x ULN	0
≥10x ULN	0
Total bilirubin	
≥2x ULN	7/462 (1.5%)*

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT= gamma glutamyl transferase; n = number of patients who have at least 1 measure falling into both the baseline and post-baseline categories; N-obs = number of patients in the baseline category and that have at least 1 post-baseline measurement; TBL= total bilirubin; ULN = upper limit of normal.

* No participants with TBL ≥2x ULN had elevated ALT, AST, GGT, or ALP levels at the time of the TBL elevation. Direct bilirubin was 30% or less of the TBL level at the time of the elevation. Cases of elevated TBL levels appear to be consistent with Gilbert's syndrome.

- Data source: All BARI AD Peds Analysis Set; data cutoff 20 June 2022

AA

- Serious hepatic events: 1 (0.1%); IR <0.1 per 100 PY
- Incidence of permanent discontinuations due to hepatic AEs: 7 (0.5%); IR 0.3 per 100 PY
- Incidence of abnormal liver tests in the All BARI AA Analysis Set:

	Patients with Elevated Analyte [n/N-obs (%)]
ALT	
≥3 × ULN	48/1296 (3.7%)
≥5 × ULN	11/1296 (0.8%)
≥10 × ULN	2/1296 (0.2%)
Total bilirubin	
≥2 × ULN	10/1296 (0.8%)

Abbreviations: ALT = alanine aminotransferase; n = number of patients who have at least 1 measure falling into both the baseline and post-baseline categories; N-obs = number of patients in the baseline category and that have at least 1 post-baseline measurement; ULN = upper limit of normal.

- Data Source: All BARI AA Analysis Set; data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO

Risk Factors and Risk Groups

No risk groups or specific risk factors have been identified from the clinical development programmes, although concurrent use of baricitinib with potentially hepatotoxic medicinal products, such as MTX, results in a higher frequency of liver enzyme elevations. In the AD and AA programmes, no specific risk factors have been identified.

Preventability

The changes observed in aminotransferases are unlikely to be preventable, particularly as no risk factors have been identified that could inform risk minimisation activities. The SmPC advises that if increases in ALT or AST are observed during routine patient management and DILI is suspected, baricitinib should be temporarily interrupted until this diagnosis is excluded. Routine monitoring of aminotransferases, defined as the testing of otherwise asymptomatic individuals, is not useful in the setting of random transient changes that typically need no intervention because the occurrences of such changes are a poor indicator of whether a patient will subsequently develop hepatotoxicity.

Impact on the Risk-Benefit Balance of the Product

The majority of hepatic disorders reported in the baricitinib CT programme have been mild-to-moderate in nature, with no evidence of DILI identified. Nevertheless, it is unknown what clinical impact there may be in everyday clinical practice and outside the confines of a controlled CT, particularly in higher patient exposure over longer periods of time. Should the future profile of outcomes remain consistent with current experience, the impact on benefit-risk will remain low and of a potential nature. This takes into account prevailing EU guidelines and standard

medical practice since hepatotoxicity associated with MTX as first-line treatment is well known to rheumatologists. If evidence of clinically significant hepatotoxicity becomes apparent with sufficient frequency and adverse clinical outcomes, then impact on benefit-risk profile is likely to be negative.

Public Health Impact

Given the rarity of any clinically significant adverse hepatic outcomes and lack of evidence of DILI to date, the impact of hepatotoxicity on public health is considered to be low. This takes into account that baricitinib is indicated for a clearly defined subset of the adult population with moderately to severely active RA, moderate-to-severe AD and severe AA, paediatric patients with JIA, and paediatric patients with moderate-to-severe AD.

Important Potential Risk: Gastrointestinal perforation

Potential mechanisms: There is evidence for a beneficial role of IL-6 in intestinal wound healing early after injury (Kuhn et al. 2014). Therefore, a pharmacologically plausible mechanism exists for an association with baricitinib related to the interruption and prolonged inhibition of IL-6 signalling. As once daily administration appears to allow for recovery of the IL-6 signalling pathway within the dosing interval of baricitinib, this, in theory could mitigate against a frequent adverse effect or significant impact on the product`s benefit risk profile.

Evidence source(s) and strength of evidence:

Although there is a pharmacologically plausible basis for an association between baricitinib and GI perforation, there are insufficient data to establish it as an adverse effect of treatment at this time. The frequency of cases indicative of GI perforation is very low in CTs (≤0.2% of patients with RA, AD, and AA, and no cases observed in patients with JIA and paediatric AD). In most cases, there have been significant confounding factors, such as use of steroids and GI surgery. The overall incidence rate of GI perforations was 0.06 per 100 PY in RA, and this is within the published rates reported in patients with RA (0.02-0.39 per 100 PY).

Patients with RA or JIA may be at an increased risk of GI perforation because of prescribed medication, and/or because of the consequences of the disease process itself (e.g., vasculitis). As a result, the determination of whether or not the limited observations reflect underlying disease morbidity as opposed to an adverse effect of baricitinib is challenging and will be systematically monitored in the proposed studies in the PV plan for the product. Similar risks are not seen with AD and AA, and systemic steroid use is limited to times of severe AD flares and to more extensive manifestation of AA, respectively.

Characterisation of the risk:

Frequency

RA

- Incidence rate: 0.06 per 100 PY.
- 95% CI: 0.03 to 0.11.
- Data Source: All BARI RA Analysis Set; final data .

JIA

- There have been no reports of GI perforation in the JIA CT programme.
- Data source: All BARI JIA Analysis Set; data cutoff 21 April 2022.

AD

- Incidence rate: 0.02 per 100 PY.
- Data Source: All BARI AD Analysis Set; data cutoff 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX.

Paediatric AD

- There have been no reports of GI perforation in the paediatric AD clinical trial.
- Data Source: All BARI AD Peds Analysis Set; data cutoff 20 June 2022.

AA

- Incidence rate: <0.1 per 100 PY.
- The 95% CI is: 0.001 to 0.25.
- Data Source: All BARI AA Analysis Set; data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO.

Risk factors and risk groups: No specific risk factors for GI perforation have been identified with baricitinib.

Preventability: There is insufficient experience with GI perforation to determine whether it is preventable or predictable.

Impact on the risk-benefit balance of the product: As there is insufficient evidence to establish GI perforation as an ADR or identified risk for baricitinib, it has no ostensible impact on the product`s benefit-risk profile at this time. There is an acknowledged pharmacological basis for hypothesising that baricitinib (which interrupts IL-6 signalling) may hence interfere with the beneficial role of IL-6 in intestinal wound healing early after injury. Nevertheless, current data have shown a very low rate of reporting that appears to be within the limits expected for the target RA population confounded by concomitant corticosteroid use. There was 1 case of perforated appendicitis in the AA population and 1 case of acute perforated appendix in the AD population, whereas GI perforation has not been seen in the JIA and paediatric AD populations during clinical development.

Over time and increasing exposure, should the profile of outcomes observed to date remain consistent with current experience, the impact on benefit-risk will remain low, and hence no longer considered to be an important potential risk. If evidence of GI perforation emerges with a frequency higher than expected for the target population and associated with clinically significant adverse clinical outcomes, then a more negative impact on benefit risk is likely to warrant further risk minimisation measures.

Public health impact:

Baricitinib is indicated for a clearly defined subset of the adult population with moderately to severely active RA, moderate-to-severe AD and severe AA, paediatric patients with JIA, and paediatric patients with moderate-to-severe AD. The incidence rate of GI perforations was 0.06 per 100 PY in RA, 0.02 per 100 PY in AD, less than 0.1 per 100 PY in AA, and no events have been reported in JIA and paediatric AD. Given the low number of case reports and low incidence rates, the overall impact of GI perforations on public health is considered to be very low.

Important Potential Risk: MACE as an outcome of hyperlipidaemia

Potential mechanisms: The putative mechanism for MACE as an important potential risk is based on uncertainties surrounding the clinical effect of elevated cholesterol in the target population over a prolonged period of chronic treatment. Such levels would likely lead to concern in the general population and patients with AD and AA, although the impact is less clear in patients with RA. There is growing evidence suggesting that the excessive inflammatory burden of RA is accountable, at least partially, for the 'lipid paradox' in which cholesterol, an important CV risk factor in the general population, is inversely related to CV risk in patients with untreated RA. Suppression of RA-associated inflammation leads to elevation of lipid values, which also coincides with a reduction of CV events. The mechanisms by which the inflammatory process in RA can lead to these lipid changes are still not fully understood.

Evidence source(s) and strength of evidence: Consistent with a pharmacologic effect of JAK inhibition, dose-dependent increases in blood lipid levels (including total cholesterol, triglycerides, low-density lipoprotein [LDL] cholesterol, and high–density lipoprotein [HDL] cholesterol) were observed throughout the RA clinical development programme for baricitinib. The increase in LDL-cholesterol (LDL-C) and all other parameters occurred within the first 12 weeks of treatment and remained stable thereafter.

In JIA, lipid changes were similar for patients treated with baricitinib or placebo.

In the AD and AA populations, increases in lipids were seen by 12 weeks for total cholesterol, LDL and HDL. Mean values for HDL remained fairly stable after Week 12. Mean total and LDL cholesterol increased through Week 52. Triglyceride changes were small and not different from placebo.
The overall evidence was considered sufficient to conclude that hypercholesterolaemia was an adverse effect of the product. Long-term exposure to increases in blood lipids in the general population would be expected to be associated with adverse CV outcomes (MACE), but literature sources indicate that they may not be harmful to patients with RA as the benefits of suppression of inflammation may outweigh the risk of the lipid changes. In this regard, few MACE were observed in RA clinical development and no relationship was observed between MACE and LDL-C increases. As noted in the original RA submission, the increases in LDL-C observed with baricitinib treatment are responsive to statin treatment, and no direct link to major adverse CV outcomes has been established to date. In the AD clinical programme, the incidence rate of MACE was lower than in RA. No cases of MACE were seen in the JIA and paediatric AD

clinical programmes. One case was reported in AA clinical development in a patient with multiple risk factors.

In a randomised post-authorisation safety study in patients with RA aged 50 years or above with at least 1 additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared with TNFi (Xeljanz SmPC).

Meta-analysis of B023 observational study results from 14 data sources showed a numerically greater IRR for MACE in baricitinib compared with TNFi-treated cohorts. The incidence rate of MACE was greater among patients with RA treated with baricitinib than with TNFi. Data analysed for this study were primarily from insurance claims records and included some data from RA registries. Patients compared in these analyses were propensity score-matched based on risk factors for MACE, such as age, sex, history of cardiovascular disease, diabetes, dyslipidaemia, hypertension, immune disorders, prescription medication use including aspirin, glucocorticoids, lipid-lowering or anti-platelet agents, count of prior bDMARDs, and health care resource utilisation.

RA, JIA, AD, and AA are, however, chronic conditions and, in the case of RA, one in which patients are already at higher risk of cardiovascular disease. As such, patients treated with baricitinib in usual clinical practice may be treated for several years and in higher numbers than exposed in CTs. As the long-term effects of these lipid changes on adverse CV outcomes in these circumstances are uncertain, MACE has been classified as an important potential risk warranting further systematic study in the PV Plan of this RMP.

Characterisation of the risk

Frequency

RA

- Incidence rate of MACE: 0.5 per 100 PY.
    - The incidence rate by 6-month time blocks showed no increase over time.
- The 95% CI for MACE: 0.40 to 0.64.
- Incidence of hyperlipidaemia (preferred term [PT]) is 1.60 per 100 PY (6.4%).
- Data Source: All BARI RA Analysis Set; final data.
- Study B023 meta-analysis of data from 14 sources with information on patients in routine clinical care shows
    - IRR for MACE was numerically greater for baricitinib compared to TNFi but did not attain statistical significance: IRR = 1.54; 95% CI: 0.93, 2.54.
- A greater incidence rate of MACE among patients treated with baricitinib than with TNFi, with a difference of 0.22 (95% CI: -0.07, 0.52) per 100 PY.

JIA

- Incidence rate of MACE: none reported.
- Incidence of hyperlipidaemia (PT): none reported.
- Data source: All BARI JIA Analysis Set; data cutoff 21 April 2022.

AD

- Incidence rate of MACE: 0.15 per 100 PY, 95% CI: 0.1 to 0.3.
- Incidence of hyperlipidaemia: 0.5 per 100 PY (0.6%).
- Data Source: All BARI AD Analysis Set; data cutoff 03 November 2021 for Study JAHN, 15 December 2021 for Study JAIN, and 21 December 2021 for Study JAIX.

Paediatric AD

- Incidence of MACE: none reported.
- Incidence rate of hyperlipidaemia: none reported.
- Data Source: All BARI AD Peds Analysis Set; data cutoff 20 June 2022.

AA

- Incidence rate of MACE: <0.1 per 100 PY, 95% CI (0.001, 0.25).
- Incidence rate of hyperlipidaemia (PT) is 1.2 per 100 PY (2%).
- Data Source: All BARI AA Analysis Set; data cutoff 10 May 2022 for Study JAIR and 24 May 2022 for Study JAHO.

Risk factors and risk groups: No specific risk factors for hyperlipidaemia have been identified with baricitinib. Similarly, the number of patients in whom MACE has been reported in CTs remains very low in RA, AD, and AA, and none were reported in JIA and paediatric AD. As a result, no specific risk factors for MACE have been identified with baricitinib.

Based on RA CT data, compared to the patients without MACE, patients with MACE were more likely to have the following CV risk factors at baseline: older age, longer disease duration, cigarette smoking, prior cardiac disorder, hypertension, obesity, and hypercholesterolaemia. However, the risk factors for MACE observed in this CT population are typical of risk factors for MACE in the general population. The extent to which prevalence of CVD in patients with RA is a contributory factor is unknown.

Preventability: The observed increases in lipids are unlikely to be preventable but do respond to standard treatment with statins, as noted in the SmPC. For MACE, the risk factors identified in the few patients with RA treated with baricitinib are typical of those that would be expected in the general population and would be managed as such in accordance with usual clinical practice. Section 4.4 of the SmPC advises that increases in lipid parameters, including total cholesterol, LDL, HDL-cholesterol (HDL-C), and triglycerides, were reported in patients treated with baricitinib, and that lipid parameters should be assessed approximately 12 weeks following initiation of therapy and according to international clinical guidelines thereafter. Moreover, SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other

cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available.

Impact on the risk-benefit balance of the product:

As an important potential risk and putative adverse outcome of the increases in lipids considered to be an adverse effect of baricitinib treatment, there is no ostensible impact on benefit-risk at this time. To date, a definitive link between the hypercholesterolaemia (notably LDL-C) has not been established, and further systematic study in the studies proposed in the PV Plan aim to provide further clarification and characterisation. Any impact on benefit-risk will also need to take into account that, compared to the general population, RA increases the risk of CV mortality by up to 50% (Aviña-Zubieta et al. 2008; Meune et al. 2009) and CVD is the leading cause of death in patients with RA (Nielen et al. 2012; Meune et al. 2010). As a result, it will require long-term study to establish whether the observed lipid changes are causally linked to MACE outcomes or if the risk is increased over and above what is expected for the population. Data on MACE with tofacitinib in an at-risk RA population present the possibility of a risk of MACE with the JAKi class. The findings from Study B023 are aligned with this possibility. However, these data are not aligned with data from the long-term baricitinib extension study, neither in the overall RA population nor in the at-risk sub-population, and from the Japan post-marketing study, as these studies show an incidence of MACE well within the range expected for the target population and similar to the reported incidence of MACE with TNFi. Given the limitations of the Study B023 data including few events in specific post-launch settings, the evidence for an increased risk of MACE with baricitinib remains insufficient.

There were no positively adjudicated MACE reported in the JIA CT programme.

When adjusted for risk factors, severe and predominantly active atopic eczema is associated with modestly increased risk of the individual cardiovascular events typically considered as MACE including myocardial infarction (MI), stroke, and cardiovascular death (~10% to 40% increased risk compared to general population; Silverwood et al. 2018; Yuan et al. 2018). The low incidence of MACE in the AD programme (0.15 per 100 PY) is not unexpected given the low background rate of MACE in patients with AD with average age in the mid-thirties. Epidemiological studies in patients with AD have reported IRs for the 3 individual outcomes commonly considered in the composite outcome of MACE: MI (0.20 per 100 PY), stroke (0.27 per 100 PY), and cardiovascular death (0.29 to 0.44 per 100 PY) (Andersen et al. 2016; Silverwood et al. 2018).

Patients with AA have not been shown to have increased prevalence of CV risk factors or outcomes (Lee et al. 2019b).

Any future assessment of impact on benefit-risk following the proposed study in the PV plan will depend on the extent to which:

- A causal association with MACE can be established
- MACE incidence rates and profile on treatment remain consistent within those expected for patients with RA, AD, and AA and those observed with other RA treatments of similar efficacy.

- The risk is well managed in everyday clinical practice.

Public health impact:

The aetiological relation between elevated lipid levels and MACE remains uncertain based on limited information on patients with RA, AD, and AA. The incidence rate of MACE observed to date following treatment with baricitinib in RA (0.5 per 100 PY) remains within that expected for the general RA population. The absence of MACE in those treated with baricitinib in the paediatric AD programme and the low incidence rate in the AD (0.15 per 100 PY) and AA programme (<0.1 per 100 PY) is not unexpected given the low background rate of MACE in the AD and AA populations with average age in the mid-thirties. Given these uncertainties and that baricitinib is indicated for a clearly defined subset of the adult population with moderately to severely active RA, moderate-to-severe AD, and severe AA, paediatric patients with JIA, and paediatric patients with moderate-to-severe AD, the impact of potential MACE on public health is considered to be low.

Important Potential Risk: Foetal malformation following exposure in utero

Potential Mechanism: The JAK-STAT pathway has been shown to be involved in cell adhesion and cell polarity, which can affect early embryonic development.

Evidence Source(s) and Strength of Evidence: Studies in rats and rabbits dosed in excess of the maximum human exposure have shown reproductive toxicity when baricitinib was dosed during the early stages of pregnancy. These animal studies indicate that baricitinib may have an adverse effect on bone development in utero at these higher dosages. There is no current evidence of similar findings in the babies of mothers who have been treated with baricitinib during pregnancy but experience at this time is very limited. As a result, the effects of baricitinib on the bone development of the baby prior to birth are unknown and, as advised in the prescribing information, women of childbearing potential should not become pregnant when treated with baricitinib.

Characterisation of the Risk: It is not possible to characterise the risk in terms of use in pregnant women, as, to date, the foetal malformations observed in the offspring of rats and rabbits have not been seen following in utero exposure of baricitinib in humans.

Risk Factors and Risk Groups: No risk factors have been identified as there are currently no data from CTs or post-marketing data sources in human pregnancy indicative of the bone effects observed in the nonclinical studies. The highest risk period is considered to be the first 12 weeks of pregnancy; however, pregnant or lactating women were excluded from CTs with baricitinib, and experience in human pregnancy is limited. Therefore, neither specific duration of treatment nor risk period have been identified.

Preventability: This potential risk has not been observed in human pregnancy so, to mitigate the risk, use in pregnancy is contraindicated in women of childbearing potential. Advice to take appropriate precautions to avoid becoming pregnant during treatment with baricitinib and for at

least 1 week after the final treatment is provided in both routine and additional risk minimisation measures for patients and prescribers (described in Part V of this RMP).

Impact on the Risk-Benefit Balance of the Product: There is no current impact on benefit-risk in human use during pregnancy, as no adverse effects indicative of the skeletal effects seen in nonclinical species have been observed. Experience in pregnant women and foetal outcomes is, however, very limited, and post-authorisation exposure is still too early to determine whether the risk minimisation measures implemented in the SmPC, Patient Information Leaflet, and additional risk minimisation tools are effective. Should further experience indicate consistent evidence of skeletal effects in human use, then this could have a negative impact on benefit risk, depending on the nature and frequency of the postnatal effects observed.

Public Health Impact: Baricitinib is indicated for a clearly defined subset of the adult population with moderate-to-severe RA, moderate-to-severe AD and severe AA; paediatric patients with JIA, and paediatric patients with moderate-to-severe AD. Because the effects of baricitinib on human foetal development are unknown, its use is contraindicated during pregnancy. The overall impact on public health in these circumstances is unknown.

SVII.3.2 Presentation of the Missing Information

Missing Information: Long-term safety

Anticipated risk/consequence of the missing information:

MACE

In the clinical development programme, initiation of treatment with baricitinib to patients with moderately to severely active RA, JIA, moderate-to-severe AD in adult and paediatric patients, and severe AA was not associated with an increased CV risk. Although patients with RA, and to a lesser extent patients with AD, have a higher prevalence of comorbid CV risk factors and an increased risk of adverse CV outcomes, the differences in study populations and control for confounding factors in studies, including patients treated in clinical practice, make the precise quantification of the risk challenging. Patients with AA have not been shown to have increased prevalence of CV risk factors or outcomes (Lee et al. 2019b), and patients with JIA are also at low risk for MACE given the relatively young age of affected patients. Patients with significant underlying CVD were excluded from CTs. The long-term effects of the lipid changes in a target population known to be at risk of CVD are unknown. This is worthy of further study to determine if the findings in clinical development remain consistent with experience over longer periods of time and with higher patient numbers in everyday clinical practice. MACE (as an outcome of hyperlipidaemia) has also been classified as an important potential risk.

Malignancies

The incidence rate for malignancies observed for baricitinib does not appear to exceed background rates in the target populations based on available data for baricitinib and across the class. There do remain uncertainties around long-term incidence of malignancies over time because of the immunosuppressive effect. The use of immunosuppressant medications has been

hypothesised to potentially increase the risk of malignancies because of its effect on the immune system and the capacity for cancer immunosurveillance (Vajdic and van Leeuwen 2009).

In contrast, it is also suspected that the chronic inflammation present in RA and other autoimmune conditions, rather than its treatment, may underlie the increased incidence of lymphoma observed in these patients, compared to the general population, through its continuous stimulation of B cells (Baecklund et al. 2006; Beyaert et al. 2013) or through induction of Epstein Barr virus replication (Hollander et al. 2015).

There are suggestions that patients with JIA may be at increased risk for malignancy, although the studies are small with wide CIs (Nordstrom et al 2012; Kok et al 2014). In 1 study from Sweden, patients with JIA were at increased risk for lymphoproliferative malignancies (HR = 3.6, 95% CI: 1.1 to 11.2), but not all cancers overall (HR = 1.4, 95% CI: 0.7 to 2.9) (Horne et al. 2019).

The literature regarding risk of various malignancies in patients with AD is inconclusive with some literature suggesting increased risks for skin cancers and others suggesting no risk (Andersen et al. 2017; Paller et al. 2018). There is a slightly increased risk of lymphoma in patients with AD, with severity of AD as a significant risk factor (Legendre et al. 2015; Paller et al. 2018).

A systematic literature review (Lee et al. 2019b) found no increased risks for hematologic, cutaneous, or solid organ malignancies among patients with AA. The single exception was that thyroid cancer was found to be more prevalent among patients with AA (OR=1.89, 95% CI 1.53 to 2.34; Lee et al. 2019b).

As the exposure to baricitinib is limited (up to 9 years in RA), the long-term effects in the target populations are unknown. This is worthy of further study to determine whether the findings in clinical development remain consistent with experience over longer periods of time and higher patient numbers in everyday clinical practice. Malignancy (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) has also been classified as an important potential risk.

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

Population in need of further characterisation:

Across the RA, AD, and AA development programmes, the clinical experience with baricitinib in patients 75 years of age or older is limited to less than 100 patients in RA and 16 patients in AD, and no patients in AA, although use in the very elderly is likely in everyday clinical practice for RA and less likely in AD and AA, as this disease becomes less prevalent as the population ages and AA is overlaid by androgenic alopecia, which is becoming more prevalent with age.

An interim analysis from the ongoing all-case post-marketing surveillance study (Study B005) in patients with RA treated with baricitinib in Japan included completed data up to 24 weeks of exposure and extension data up to 25 February 2021. Safety analyses included 4731 patients with

a mean age of 63.9 years. A total of 1064 patients (22%) were 75 years of age or older and had a total exposure of 692 PY.

The incidence of AEs in this post-marketing surveillance study was generally similar to that observed in clinical trials. As expected, a greater proportion of patients aged 75 years or older had SAEs (10%) compared with the younger age groups (age less than 75 years, 6%). In particular, patients aged 75 years or older appear to have a higher incidence of deaths (2.75 per 100 PY), serious infections (6.47 per 100 PY), HZ (8.44 per 100 PY), and malignancies (1.89 per 100 PY) compared with the younger age groups (0.35, 3.54, 6.18, 0.97 per 100 PY, respectively). There were few events of MACE (n = 3) and GI perforation (n = 3) occurring in patients aged 75 years or older. There were no other meaningful differences observed.

Generally, elderly patients have more comorbidity, including accidents and diseases likely to lead to hospitalisation, are treated with more pharmaceutical products and are at increased risk for AEs to any product. Although no specific safety signals were identified for very elderly patients during the CT development programme, exposure in this age group was limited to very few patients, although they are likely to comprise an appreciable component of the anticipated RA target population in everyday clinical practice. Knowledge of the safety profile overall in the very elderly is therefore a gap in current knowledge and worthy of further study.

Missing Information: Use in patients with evidence of hepatitis B or hepatitis C infection

Population in need of further characterisation:

Although patients with evidence of active hepatitis B or C infection were excluded from CTs, no events indicative of clinically overt reactivation have been detected to date during treatment with baricitinib in some 500 patients in RA, 19 in JIA, 72 in AD, 4 in paediatric AD, and 52 in AA with evidence of prior HBV infection. Among patients tested for HBV DNA based on their screening HBV antibody status, a small proportion exhibited detectable HBV DNA at any time postbaseline. These patients were predominantly positive for hepatitis B surface and core antibodies and were enrolled in countries in Asia. Among these patients, a large majority exhibited DNA levels which did not prompt action with regard to study drug or other treatment. Of the patients with a quantifiable elevation in DNA, none had clinical evidence of hepatitis based on liver chemistry (none had ALT or AST elevation ≥3 x ULN).

Given the epidemiology of HBV, transient detection of HBV DNA at unquantifiable levels in patients with evidence of prior exposure (core and surface Ab positive), in endemic regions, with no evidence of liver inflammation, is of doubtful clinical significance and unlikely to be reflective of the target patient population in the EU. Few patients were transiently positive for HBV DNA and were from endemic regions. None of the patients with detectable HBV DNA had evidence of liver injury based on clinical chemistry findings.

In addition, the SmPC is very specific in warning about viral reactivation, the need to screen for viral hepatitis before starting therapy with baricitinib, and the fact that patients with evidence of active hepatitis B or C infection were excluded from CTs. As a result, use in this population is not expected. The advice to contact a specialist is standard in DMARD SmPCs given the need to

manage liver safety in such patients. If HBV is detected, consultation with a hepatologist is recommended for a number of reasons, including the fact that withdrawal of immunomodulatory therapy during active viral hepatitis may increase the risk of unwanted flare in hepatitis in such a setting (Harigai et al. 2014).

Missing Information: Use in patients with a history of or current lymphoproliferative disease

Population in need of further characterisation:

Patients with a history or symptoms of lymphoproliferative disease or active or recent primary or recurrent malignant disease were excluded from the clinical development programme. It is anticipated that patients treated with baricitinib may have this history as there is an increased risk for lymphoproliferative disorders (including lymphoma and leukaemia) in RA and AD patients with long-standing, highly active inflammatory disease, irrespective of treatment.

While preclinical data and currently available CT data do not suggest an increased risk for lymphoproliferative disease or provide evidence that patients with lymphoproliferative disease would be at increased risk, long-term experience is limited and the safety profile in these patients is unknown. Lymphoma will be studied under malignancy as an important potential risk. Routine pharmacovigilance was deemed adequate to study use in patients with a history of or current lymphoproliferative disease.

Missing Information: Use in patients with active or recent primary or recurrent malignant disease

Population in need of further characterisation

Patients with active or recent primary or recurrent malignant disease were excluded from the CT development programme, so experience in this subpopulation is limited. The SmPC clearly warns of the increased risk of malignancies, including lymphoma, in patients with RA and that use of immunomodulatory medicinal products may increase this risk. It also advises that the clinical data are insufficient to assess the potential incidence of malignancies following exposure to baricitinib. Furthermore, current RA clinical guidelines caution against the use of anti-TNF drugs in individuals with a recent history of cancer (in the last 5-10 years). As such, it is established clinical practice in RA to avoid use of bDMARDs in patients with active or recent primary or recurrent malignant disease. Similar guidance is in place for drugs to treat severe AD, such as ciclosporine (SmPC for ciclosporine).

In these circumstances, it is unlikely that baricitinib will be used in patients with active or recent primary or recurrent malignant disease and hence not relevant to the anticipated target population. In addition, malignancy is already included as an important potential risk and will be systematically studied in the proposed registries. Information on whether or not there is evidence of active or recent malignant disease will be included in the data collection in these registries.

Missing Information: Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination

Anticipated risk in paediatric patients

Paediatric patients were excluded from the RA, AD, and AA development programmes, although systematic study in children and adolescents is being addressed by the CTs included in the paediatric investigation plan, with juvenile idiopathic arthritis (JIA) trials initiated in 2018 and a paediatric AD trial initiated in 2019. The total exposure globally in the CT programme is 686 paediatric patients. However, information on long-term safety in these patients is still limited. For paediatric patients with AD and polyarticular JIA patients that continue in the long-term extension period of Study JAIP and JAHX, respectively, safety parameters including vaccine response, growth and bone safety, maturation and pubertal development will continue to be carefully monitored and evaluated. Please see Part III.2 and Table Part III.1.

Exposure in the expanded access programme (JAGA) includes 71 patients globally, 10 of these patients are European children with CANDLE, of whom 6 were sent for management in the US and 4 were treated in a single centre in the UK.

The potential for off-label use of baricitinib in paediatric patients is anticipated to be low. Not all paediatric patients with AA require treatment because most episodes of AA are often mild and last less than 6 months (Tan et al. 2002; Guzmán Sánchez et al. 2007). In addition, there is a reluctance to treat younger children with systemic and biologic therapies (Stahle et al. 2010) and baricitinib would not be reimbursed when used in an unapproved paediatric patient population.

As there are acknowledged uncertainties regarding the juvenile rat findings and the possible impact on growth and bone development of children treated with baricitinib, the potential for off-label use was studied further in the clinical practice research database (CPRD) per the PV Plan. Specifically, in Study B016, it was found that 12 of 1527 (0.79%) patients in CPRD who were prescribed baricitinib were under 18 years of age, thus not representing a public health concern.

Module SVIII – Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Herpes zoster VTE
Important potential risks	Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) Myelosuppression (agranulocytosis) Myopathy including rhabdomyolysis Potential for drug-induced liver injury Gastrointestinal perforation MACE as an outcome of hyperlipidaemia Foetal malformation following exposure in utero
Missing information	Long-term safety Use in very elderly (≥75 years) Use in patients with evidence of hepatitis B or hepatitis C infection Use in patients with a history of or current lymphoproliferative disease Use in patients with active or recent primary or recurrent malignant disease Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination

Abbreviations: MACE = major adverse cardiovascular event; PML = progressive multifocal leukoencephalopathy; VTE = venous thromboembolic events.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Event Follow-Up Forms:

The following follow-up forms will be used as routine PV materials to obtain structured information on reported suspected adverse reactions of special interest for the safety concerns included in the RMP:

- Herpes Zoster
  - HZ follow-up form
- Venous Thromboembolism
  - Thromboembolic follow-up form
  - Clotting and/or coagulation disorders follow-up form
- Serious Infections
  - *Candida* infection follow-up form
  - Pneumonia follow-up form
  - Viral reactivation follow-up form
  - Unspecified infection follow-up form
  - Pulmonary TB follow-up form
  - Extrapulmonary TB follow-up form
- Hepatotoxicity
  - Hepatic disorders follow-up form
- Foetal malformation following exposure in utero
  - Pregnancy data collection – maternal follow-up form
  - Pregnancy data collection – paternal follow-up form
  - Pregnancy outcome – maternal follow-up form
  - Pregnancy outcome – paternal follow-up form
- Myopathy Including Rhabdomyolysis
  - Rhabdomyolysis follow-up form
- Long-term safety (MACE as an outcome of hyperlipidaemia)
  - Cardiac disorders follow-up form
  - Cerebrovascular accident follow-up form
  - Mortality follow-up form
- Pregnancy
  - Pregnancy data collection – maternal follow-up form
  - Pregnancy data collection – paternal follow-up form
  - Pregnancy outcome – maternal follow-up form
  - Pregnancy outcome – paternal follow-up form
  - Breastfeeding follow-up form
- Gastrointestinal perforation
  - Fistula and/or GI perforation follow-up form
- Myelosuppression

  - Blood and bone marrow disorders follow-up form
- Malignancies
  - Cancer/neoplasm follow-up form

III.2 Additional Pharmacovigilance Activities

Study I4V-MC-B011: A Retrospective Cohort Study to Assess the Safety of Baricitinib Compared with Other Therapies Used in the Treatment of Rheumatoid Arthritis and Atopic Dermatitis in Nordic Countries

Rationale and Study Objectives:

The rationale for conducting this study is to characterise the long-term safety of baricitinib among RA and AD patients treated in routine clinical care in Nordic countries using a retrospective study design.

Specifically, the objectives include 1) to compare the incidence rates and profiles of: serious and opportunistic infections, MACE, malignancies, and VTE in RA and AD patients (separately) with long-term exposure to baricitinib (this will be compared to similar patients with long-term exposure to other indicated medications) and 2) to describe the occurrence of lymphoma; HZ; opportunistic and fungal infections; GI perforations; serious disorders of the muscle, bone marrow, blood lipids, white blood cell count, and liver; and all-cause mortality.

A secondary objective is to monitor the incidence of the major outcomes among patients aged 75 years or older. Another secondary objective is to assess the effectiveness of risk minimisation activities by describing the pattern of use of baricitinib and the occurrence of pregnancy, active TB or active viral hepatitis, and the monitoring of lipid levels in relation to baricitinib use in routine clinical care. Of note, this objective has been completed for patients with RA and is ongoing in patients with AD.

Study Design:

This study will be based on retrospective national cohorts of RA and AD patients in 4 Nordic countries: Denmark, Finland, Norway, and Sweden. The basis for the study or analytic cohort will be patients included in the national rheumatology registries and, therefore, secondary use of data.

Study Population:

This study will be based on data from patients included in the public health care registries in the 4 Nordic countries over the calendar period of interest for the study. Two cohorts will be generated for separate analyses: 1 consisting of patients with RA and 1 cohort of patients with AD. With a total population of 26.6 million, the Nordic RA population consists of approximately 175,000 patients. Since approximately 10 per 100,000 adults initiate bDMARDs each year, this will correspond to approximately 2600 new patients with RA in treatment each year. The Nordic AD population consists of approximately 624,000 patients, of which 30% (n=187,200) have

moderate-to-severe disease (Bieber and Straeter 2015) and would therefore be a candidate for treatment with systemic medication.

Milestones

Milestone	Planned Date
Start of data collection/extraction[a]	Estimated 31 December 2019 for RA cohort Estimated 31 December 2021 for AD cohort
Study Progress Reports[b]	Included annually in baricitinib PBRER/PSUR
Final Report for Objective 4 (AD cohort)	To be determined based on at least 24 months of data in at least 50% of the discrete healthcare databases
End of data collection[c]	Estimated 31 December 2026 for RA Estimated 31 December 2027 for AD cohort
Final study report (Objectives 1, 2, 3)	Approximately 1 year after the end of data collection; Estimated 31 December 2027 for RA report Estimated 31 December 2028 for AD report

Abbreviations: AD = atopic dermatitis; PBRER = periodic benefit-risk evaluation report; PSUR = periodic safety update report; Q = quarter; RA = rheumatoid arthritis.

[a] For secondary data sources, the start of data collection corresponds to the date when data extraction is initiated.

[b] Progress reports will provide updates on enrolment until the study has enrolled 1000 patients exposed to baricitinib. Subsequent progress reports will include descriptive information on participants and outcomes.

[c] Date at which the complete analytic dataset is available.

Study I4V-MC-B012: Post-Marketing Safety Surveillance of Baricitinib in Three European Registries

Rationale and Study Objectives:

The rationale for this study is to provide prospective, long-term safety monitoring for baricitinib in routine clinical practice in the EU.

The study objectives are to monitor the incidence rate and profile of various serious and opportunistic infections, MACE, malignancies, and VTE in EU patients with RA with long-term exposure to baricitinib. This information will be compared to patients with long-term exposure to other medications used for moderate-to-severe RA. A second objective will aim to describe the occurrence of lymphoma; HZ; opportunistic infections; GI perforations; and serious disorders of the muscle, bone marrow, white blood cell count, and liver.

Study Design:

Observational post-marketing disease registries

Study Population:

Each registry will enrol patients treated with baricitinib and other medications used for RA per their usual operating procedures, and Lilly will have no influence on the available sample size. Information from the ARTIS registry will be supplemented by linkage to Nordic healthcare data and may include additional patients with RA not enrolled in the registry, if they are available.

Milestones

Milestone	Planned Date
Start of data collection	BSRBR: 31 January 2018 RABBIT: 31 May 2017 ARTIS: 31 May 2017
Study progress reports[a]	Included annually in baricitinib PBRER/PSUR after updates are received from the registries
End of data collection[b]	BSRBR: 30 September 2022 RABBIT: 31 December 2021 ARTIS: 30 June 2022[c]
Registry delivery of final reports	BSRBR: 31 March 2023 RABBIT: 30 June 2022 ARTIS: 30 September 2022
Lilly's final report	Anticipated 31 March 2024

Abbreviations: ARTIS = Antirheumatic Therapies in Sweden; BSRBR = the British Society for Rheumatology Biologics Register; PBRER/PSUR = Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report; Q = quarter; RABBIT = Rheumatoid Arthritis Observation of Biologic Therapy.

a Progress reports will provide updates on enrolment and will include descriptive information on participants and outcomes.

b Reflects the data lock point for the registry's final report.

C Data from the National Patient Registers used by ARTIS are currently only available on an annual basis with a lag of approximately 1 year (delivery at the end of each year). The dataset available in Q2 2022 will contain data through 2020 because of the National Patient Registers delivery schedule. More data will be included if the delivery schedule changes.

Study I4V-MC-B025: Survey to Assess the Effectiveness of the Baricitinib Additional Risk Minimisation Measures

Rationale and Study Objectives:

The rationale for conducting this study is 2-fold. The first objective is to assess the effectiveness of the updated baricitinib health care professional (HCP) Educational Materials and Patient Alert Card (PAC) among dermatologists treating patients with AD or AA and rheumatologists treating patients with RA.

The second objective of this study is to assess the effectiveness of a direct healthcare professional communication (DHPC) distributed to dermatologists and rheumatologists to communicate changes in the SmPC.

Study Design:

This observational study is a multinational, cross-sectional survey.

Study Population:

The survey will be conducted in at least 3 European countries and will target approximately 400 HCPs (approximately 200 dermatologists and approximately 200 rheumatologists).

Milestones

Milestone	Planned Date*
Submission of protocol	25 April 2023
Start of data collection	Within 3 months after both the DHPC and updated risk minimisation materials have been distributed in each participating country and the CHMP opinion of the protocol: estimated 31 October 2023
End of data collection	When at least 400 surveys have been completed, (~200 dermatologists and ~200 rheumatologists), estimated 31 October 2024
Registration in the EU PAS register	Prior to start of data collection
Final study report	6 months after the end of data collection; estimated 30 April 2025

Abbreviations: CHMP = Committee on Human Medicinal Products; DHPC = direct healthcare professional communication; EMA = European Medicines Agency; HCP = health care professional; PAC = Patient Alert Card; PAM= post-authorisation measure; PAS = post-authorisation safety; Q = quarter.

* The submission of protocol is the predicted date for within 3 months of completion of the Article 20 referral. The proposed start date for the survey depends up on the timing of CHMP opinion of the protocol (based on EMA timetable for PAM assessment) as well as the DHPC distribution and implementation of updated risk minimisation materials (that is, the PAC and HCP educational material) in each participating country.

Study short name and title: Drug Utilisation Study to Assess Prescribing Patterns of Baricitinib

Rationale and study objectives:

As an outcome of the Article 20 referral and review, prescribing of baricitinib is expected to change in the treated populations. This drug utilisation study aims to measure the effectiveness of newly implemented prescribing recommendations following completion of the Article 20 referral procedure. This will be accomplished by evaluating prescribing behaviours after implementation of the recommended changes in prescribing and addressed through the following objective:

- To describe characteristics of patients with a dispensing of baricitinib for RA, AA, or AD, specifically with respect to the characteristics of the treated populations per revised SmPC.

Study design:

A cross-sectional cohort of patients with a prescription for Olumiant, defined as ≥1 dispensing, in relevant European databases with information on demographics, clinical history, dose, and prior prescription medication use.

Study population:

Adult patients with RA, AD, or AA with ≥1 dispensing of Olumiant.

Milestones:

The study milestone dates rely on:

- completion of the Article 20 procedure and CHMP opinion (estimated December 2022), and
- distribution of the DHPC in the region of each of the included data sources.

We will assess the feasibility of the DUS.

Milestone	Planned Date
Submission of protocol	25 April 2023
Start of data collection[a]	When 12 months of prescription data are available after distribution of the DHPC + 6 months for prescribing behaviour to stabilise, and allowing for an average 1.5 year lag in the availability of data, **estimated 30 June 2026**
End of data collection[a]	6 months after start of data collection, **estimated 31 December 2026**
Registration in the EU PAS register	Prior to extraction of study data
Final report of study results	Within 12 months after the end of data collection, **estimated 30 December 2027**

Abbreviations: DHPC = direct healthcare professional communication; PAS = post-authorisation studies.

[a]For studies relying on use of secondary data, that is, data that is collected for other purposes independently of the study, the start and end of data collection refer to the date of first data extraction and the completion date of the analytic dataset, respectively.

Study I4V-MC-JAHX: A Phase 3 Multicentre Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients from 1 Year to less than 18 Years of Age with Juvenile Idiopathic Arthritis (JIA)

Rationale and Study Objectives:

Primary objective: To evaluate the long-term safety and tolerability of baricitinib in patients with JIA or systemic JIA.

Secondary Objectives:

- to evaluate the long-term efficacy of baricitinib in children with JIA or sJIA
- to assess the long-term efficacy of baricitinib in children with juvenile psoriatic arthritis (JPsA)
- to evaluate the long-term efficacy of baricitinib in children with enthesitis-related arthritis or JpsA, and
- to evaluate the potential effects of baricitinib on the cellular and humoral immune system.

Study Design:

Study JAHX is a multicentre, long-term extension study evaluating the safety and efficacy of baricitinib in patients with JIA. Patients who participated in an originating study (Study JAHV [for JIA] or JAHU [for systemic JIA]) are eligible for enrolment into Study JAHX.

Study JAHX will consist of a treatment period lasting up to 264 weeks (approximately 5 years) from enrolment into Study JAHX and a posttreatment follow-up period of 28 days. Screening should occur during the last visit of the originating study. However, in particular circumstances, time between the last visit of the originating study and the first visit of JAHX may be extended after consultation with the sponsor.

Patients may continue to receive the background, non-investigational, open-label MTX, NSAIDs, corticosteroids, and other analgesic therapies that they were receiving at completion of the originating study.

Study Population:

The study population consists of patients from 1 year to less than 18 years of age with JIA who have been treated with baricitinib and were participants in Study JAHV or JAHU.

Milestones:

Milestone	Planned Date
Start of data collection	**JAHX**: 05 April 2019
Database lock (JAHV cohort)	05 January 2028
Study report (JAHV cohort)	04 April 2028
Final study report[a]	31 March 2031

[a] Final study report will include both JAHV and JAHU cohorts.

Study I4V-MC-JAIP: A phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib in paediatric patients with moderate-to-severe atopic dermatitis.

Rationale and study objectives:

Primary objective:

- To demonstrate the superiority of each dose of baricitinib versus placebo in the treatment of patients with moderate-to-severe AD.

Select secondary objectives, relevant for the purposes of pharmacovigilance:

- To evaluate the potential effects of baricitinib on the cellular and humoral immune system.
- To assess growth and bone safety of baricitinib during longer-term treatment.

In addition to the stated objectives, Study JAIP collects all investigator-reported AEs and thus will allow characterisation of safety over longer-term treatment (up to 4 years).

Study design:

Study JAIP is a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib compared with placebo in paediatric patients with moderate-to-severe AD. The study is divided into 5 periods, a 5-week screening period, a 2-week open-label PK lead-in period, a 16-week double-blind treatment period, an up to 4-year long-term extension period, and a 4-week post-treatment follow-up period.

Study population:

The study population consists of paediatric patients (2 to less than 18 years old) with moderate-to-severe AD who have responded inadequately to or who are intolerant to topical treatments.

Milestones:

Milestone	Planned Date
Start of data collection	**JAIP**: 24 May 2019 (first patient, first visit)
Database lock	30 September 2026
Final study report	31 December 2026

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 1 – Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
I4V-MC-B011: Retrospective Cohort Study to Assess Safety of Baricitinib in Nordic countries (Ongoing)	Primary Objectives: 1) To compare the incidence rates and profiles of the following aggregate outcomes of serious infections overall (including herpes zoster) and opportunistic infections (including tuberculosis,	Important identified risks: • Herpes zoster • VTE Important potential risks: • Serious and opportunistic infections (including tuberculosis,	**For RA study**: Study progress reports Final study report	**For RA study:** Annually in PBRER/PSUR submitted in April of each year 31 December 2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	Candida infections, and PML), MACE, malignancies overall (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers), and VTE, among RA and AD patients treated with baricitinib versus similar patients treated with other medications indicated for respective condition. 2) To describe the incidence rates of the following individual outcomes: lymphoma; herpes zoster; opportunistic infections such as tuberculosis, *Candida*, and PML; rhabdomyolysis; agranulocytosis; hyperlipidaemia (hypercholesterolaemia, hypertriglyceridaemia); GI perforations; liver injury; and all-cause mortality. Secondary Objectives: 3) To monitor the incidence rates of the aggregate outcomes of serious infections overall, MACE, malignancies overall, and VTE in very elderly patients, that is, ≥75 years of age. 4) To assess the effectiveness of risk minimisation activities by describing the	*Candida* infections, PML) • Potential for DILI • MACE as an outcome of hyperlipidaemia • Malignancy (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Foetal malformation following exposure in utero • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • GI perforation Missing information: • Long-term safety • Use in very elderly (≥75 years)	(Objectives 1-3*)* **For AD Study:** Study progress reports Final report for Objective 4, AD cohort Final Report	**For AD Study**: Annually in PBRER/ PSUR submitted in April of each year To be determined based on at least 24 months of data in at least 50% of the discrete healthcare databases 31 December 2028

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	pattern of use of baricitinib among patients with AD and the occurrence of pregnancy, active tuberculosis or active viral hepatitis, and the monitoring of lipid levels in relation to baricitinib use in routine clinical care.			
I4V-MC-B012 Observational post marketing Surveillance in 3 European Registries (Ongoing)	Primary Objectives: 1) To monitor the incidence rate and profile of the following aggregate outcomes of serious infections (including herpes zoster) and opportunistic infections (including tuberculosis, *Candida* infections, and PML), MACE, malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers), and VTE among patients with long-term exposure to baricitinib compared to patients with long-term exposure to other medications used for moderate-to-severe RA, as possible given the data available in the BSRBR, RABBIT, and ARTIS registries. To describe the occurrence of the following individual outcomes: lymphoma,	Important identified Risks: • Herpes zoster • VTE Important potential risks: • Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Serious and opportunistic infections (including Tuberculosis, *Candida* infections, PML), • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • Potential for drug-induced liver injury • GI perforation • MACE as an outcome of hyperlipidaemia	Study progress reports Final study report	Annually in PBRER/ PSUR submitted in April of each year 31 March 2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	herpes zoster, opportunistic infections, rhabdomyolysis, agranulocytosis, PML, GI perforations, and evidence of DILI.			
I4V-MC-B025: Survey to Assess the Effectiveness of the Baricitinib Additional Risk Minimisation Measures (Planned)	1. To assess the understanding of and adherence to the key risk minimisation messages and required mitigating actions in the updated HCP educational material and PAC among a sample of dermatologists and rheumatologists. 2. To assess the effectiveness of a DHPC distributed to communicate changes in SmPC	Important Identified Risks • Herpes zoster • VTE Important Potential Risks: • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • MACE as an outcome of hyperlipidaemia • Foetal malformation following exposure in utero • Malignancy	Protocol submission Final study report	25 April 2023 Six months after the end of data collection; estimated 30 April 2025
Drug Utilisation Study to Assess Prescribing Patterns of Baricitinib (Planned)	This study aims to measure the effectiveness of newly updated prescribing recommendations by evaluating prescribing behaviours.	Important Identified Risks • VTE Important Potential Risks: • MACE • Opportunistic infection • Serious infection • Malignancy	Protocol submission Final study report	25 April 2023 Within 12 months of end of data collection, estimated 30 December 2027
I4V-MC- JAHX (Ongoing)	Primary objective: To evaluate the long-term safety and tolerability of baricitinib in patients with JIA or systemic JIA. Secondary objective: To evaluate the long-term efficacy of baricitinib in children with JIA or sJIA,	Missing information • Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and	Study report (JAHV cohort) Final study report (including both JAHV and JAHU)	04 April 2028 31 March 2031

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	ERA or JPsA, and the potential effects of baricitinib on the cellular and humoral immune system.	adverse response to vaccination		
I4V-MC-JAIP (ongoing)	Primary Objective: To demonstrate the superiority of each dose of baricitinib versus placebo in the treatment of patients with moderate-to-severe AD. Select secondary objectives: To evaluate potential effect of baricitinib on cellular and humoral immune system. To assess growth and bone safety during longer-term treatment.	Missing information • Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination	Final study report	31 December 2026

Abbreviations: AD = atopic dermatitis; ARTIS = Antirheumatic Therapies in Sweden; BSRBR = the British Society for Rheumatology Biologics Register; DHPC = direct healthcare professional communication; DILI = drug-induced liver injury; ERA = enthesitis-related arthritis; GI = gastrointestinal; HCP = Healthcare Professional; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; MACE = major adverse cardiovascular events; PAC = Patient Alert Card; PBRER = periodic benefit-risk evaluation report; PML = progressive multifocal leukoencephalopathy; PSUR = periodic safety update report; ; RA = rheumatoid arthritis; RABBIT = Rheumatoid Arthritis Observation of Biologic Therapy; sJIA = systemic juvenile idiopathic arthritis; SmPC = summary of product characteristics; TNF = tumour necrosis factor; VTE = venous thromboembolic event.

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
Herpes zoster	[Routine risk communication:] SmPC Sections 4.4 and 4.8 PL Sections 2 and 4 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.4 recommends that if an infection develops, the patient should be monitored carefully, and Olumiant should be temporarily interrupted and not be resumed until the infection resolves. There is a further recommendation that, prior to starting treatment, all patients including paediatric patients with JIA and AD be brought up to date with all immunisations in line with current immunisation guidelines. • SmPC Section 4.4 also advises that if a patient develops herpes zoster, treatment should be temporarily interrupted until the episode resolves. • PL Section 2 advises that the patient should tell their doctor if they get painful skin rash with blisters during treatment as these can be signs of shingles.

VTE	[Routine risk communication:]
	SmPC Sections 4.2, 4.4, and 4.8
	PL Section 2
	
	[Routine risk minimisation activities recommending specific clinical measures to address the risk:]
	SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections.
	
	• SmPC Section 4.4 advises that
	  ○ In patients with cardiovascular or malignancy risk factors baricitinib should only be used if no suitable treatment alternatives are available. In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, baricitinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder.
	  ○ If clinical features of DVT/PE occur, treatment should be discontinued and patients should be evaluated promptly followed by appropriate treatment.

	• PL Section 2 advises patients to ○ Talk to their doctor or pharmacist before and during treatment if they have previously had blood clots in the veins of their legs (DVT) or lungs (PE) Tell their doctor if they get a painful swollen leg, chest pain, or shortness of breath as these can be signs of blood clots in the veins.
Malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers)	[Routine risk communication:] SmPC Section 4.2 and 4.4 PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections. • SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, or with other malignancy risk factors (for example, current malignancy or history of malignancy) baricitinib should only be used if no suitable treatment alternatives are available. • PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer because their doctor will have to decide if they can still be given Olumiant.
Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML)	[Routine risk communication:] SmPC Sections 4.4 and 4.8 PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.4 advises that the risks and benefits of treatment should be considered prior to initiating therapy in patients with active, chronic, or recurrent infections. In patients over 65 years of age, baricitinib should only be used if no suitable treatment alternatives are available. It also recommends that if an infection develops, the patient should be monitored carefully and Olumiant should be temporarily interrupted for any infection that is not responding to standard therapy. Treatment should not be resumed until the infection resolves. • SmPC Section 4.4 advises that patients should be screened to rule out active TB and active viral hepatitis before starting Olumiant. • There is no reference to PML in the SmPC. • SmPC Section 4.4 advises that live, attenuated vaccines should not be used during or immediately prior to treatment. There is a further recommendation that, prior to starting treatment, all patients including paediatric patients with JIA and AD be brought up to date with all immunisations in line with current guidelines. • Section 2 of the PL advises patient that they need to talk to their doctor or pharmacist before and during treatment with Olumiant if they have an infection or if they often get infections. It also advises patents that they should tell their doctor if they get signs of TB, herpes zoster or have, or have previously had hepatitis B or C.
Myelosuppression (agranulocytosis)	[Routine risk communication:] SmPC Sections 4.2, 4.4, 4.8, and 5.3 PL Sections 2 and 4

	[Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Sections 4.2 and 4.4 recommend that treatment should not be initiated or should be temporarily interrupted in patients with an ANC < 1 x 10^9 cells/L, ALC < 0.5 x 10^9 cells/L, or haemoglobin <8 g/dL. • PL Section 2 advises patients that they may need blood tests prior to or during treatment to check if they have a low red blood cell count (anaemia) or low white blood cell count (neutropaenia or lymphopaenia) to ensure that treatment is not causing problems.
Myopathy including rhabdomyolysis	[Routine risk communication:] SmPC Section 4.8 (increases in CPK) PL Section 4 (increases in creatinine kinase) [Routine risk minimisation activities recommending specific clinical measures to address the risk:] None
Potential for drug-induced liver injury	[Routine risk communication:] SmPC Sections 4.2, 4.4, and 4.8 PIL Sections 2 and 4 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.2 recommends that Olumiant is not recommended for use in patients with severe hepatic impairment. • Section 4.4 recommends that if increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, Olumiant should be interrupted until this diagnosis is excluded. • Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C or if they have poor liver function.
MACE (as an outcome of hyperlipidaemia)	[Routine risk communication:] SmPC Sections 4.2, 4.4, and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PL Sections 2 and 4 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections. • SmPC Section 4.4 recommends that lipid parameters should be assessed approximately 12 weeks following initiation of Olumiant therapy and thereafter patients should be managed according to clinical guidelines for hyperlipidaemia. Moreover, SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available. • PL Section 2 advises patients that they may need blood tests before or while taking Olumiant to check if they have a high blood fat (cholesterol) to ensure that treatment with Olumiant is not causing problems.
Foetal malformation	[Routine risk communication:] SmPC Sections 4.3, 4.6, and 5.3

following exposure in utero	PIL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • SmPC Sections 4.3 and 4.6 state that pregnancy is a contraindication. • SmPC Section 4.6 advises that patients of childbearing potential should use effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last treatment. • PL Section 2 o States that patients should not take Olumiant if they are pregnant or think that they may be pregnant o Advises patients that if they are pregnant, think they may be pregnant, or are planning to have a baby, they should ask their doctor or pharmacist for advice before taking this medicine o States that patients should use an effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last Olumiant treatment o States that patients must tell their doctor if they become pregnant as Olumiant should not be used during pregnancy.
Gastrointestinal perforation	[Routine risk communication:] None [Routine risk minimisation activities recommending specific clinical measures to address the risk:] None
Long-Term Safety	[Routine risk communication:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PL Sections 2 and 4 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] No additional recommendations other than those already stated for malignancy and MACE
Use in Very Elderly (≥75 Years)	[Routine risk communication:] SmPC Sections 4.2, 4.4 (lymphocytosis), and 5.2 PL Section 3 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] SmPC Section 4.2 states that: • Clinical experience in patients aged ≥75 years is very limited • a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with history of chronic or recurrent infections.
Use in patients with evidence of hepatitis B or hepatitis C infection	[Routine risk communication:] SmPC Section 4.4 PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:]

	• SmPC Section 4.4 recommends that screening for viral hepatitis should be performed before starting treatment and that if HBV DNA is detected, a liver specialist should be consulted to determine if treatment interruption is warranted. • Section 2 of the PL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C.
Use in patients with a history of or current lymphoproliferative disease	[Routine risk communication:] SmPC Section 4.4 PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer because their doctor will have to decide if they can still be given Olumiant.
Use in patients with active or recent primary or recurrent malignant disease	[Routine risk communication:] PL Section 2 [Routine risk minimisation activities recommending specific clinical measures to address the risk:] • PL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer because their doctor will have to decide if they can still be given Olumiant.

Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination	[Routine risk communication:]
	SmPC Section 4.2
	PL Section 2
	
	[Routine risk minimisation activities recommending specific clinical measures to address the risk:]
	• SmPC Section 4.2 states:
	  • The safety and efficacy of baricitinib in children less than 2 years of age have not yet been established. No data are available.
	  • The safety and efficacy of baricitinib in children less than 18 years of age with AA have not yet been established. No data are available.
	• PL Section 2 advises that Olumiant is not for use in children younger than 2 years of age. It also advises that Olumiant is not for use in children and adolescents under 18 years old with AA because there is no information on use in this disease state.

Abbreviations: AA = alopecia areata; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; DVT = deep vein thrombosis; HBV = hepatitis B virus; JIA = juvenile idiopathic arthritis; MACE = major adverse cardiovascular event; PE = pulmonary embolism; PL = Patient Information Leaflet; PML = progressive multifocal leukoencephalopathy; SmPC = Summary of Product Characteristics; TB = tuberculosis; VTE = venous thromboembolic event.

V.2 Additional Risk Minimisation Measures

Activity 1: HCP Educational Material and PAC

Objectives:

The HCP educational material and PAC will inform prescribers and patients of the need to avoid using baricitinib during pregnancy. The materials will also provide advice on common signs and symptoms of infections, VTE, malignancy, MACE, and the need to inform the doctor if these occur, as well as the need to monitor blood lipids during treatment.

Risks addressed:

- HZ
- Serious infections (including tuberculosis, *Candida* infections, PML)
- MACE (as an outcome of increased lipid parameters)
- Malignancy
- Foetal malformation following exposure in utero
- VTE

Rationale for the additional risk minimisation activity:

- HCPs should be informed that there is a potentially increased risk of malignancy, MACE, and VTE in patients with certain risk factors using JAK inhibitor treatment. Prescribers should discuss with patients the risks associated with the use of JAK inhibitors. Baricitinib should only be used if no suitable treatment alternatives are available:
    - in patients with a history of atherosclerotic cardiovascular disease, malignancy, or venous thromboembolism
    - in patients 65 years of age and older, or
    - in patients who are current or past smokers
- HCPs should be informed that a dose of 2 mg daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2-mg once daily dose.
- Foetal malformation following exposure in utero: Nonclinical findings in 2 species (skeletal malformations) have not been refuted by limited pregnancy exposure in humans, and the significance remains unknown.
- Serious and opportunistic infections: Although infections overall affected about half of the study population exposed to baricitinib, the EAIR for serious infections in the All BARI RA population was 2.58 events per 100 PY. Since the number of patients treated in the CTs is relatively limited, the potential exists that more frequent and clinically significant outcomes of serious and opportunistic infections or different serious infections may be seen in everyday clinical practice. As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. Baricitinib should only be used in patients 65 years of age and older if no suitable treatment alternatives are available.
- Hyperlipidaemia and hypercholesterolaemia are acknowledged ADRs of baricitinib treatment; however, the potential for adverse CV outcomes as a result of the observed lipid changes has been neither confirmed nor refuted due to limited long-term exposure
- VTE, specifically DVT and PE, are acknowledged ADRs of baricitinib treatment. Patients may not recognise a possible VTE and hence, it may be useful to inform them on the symptoms to watch out for and to recommend seeking medical advice immediately if they occur. Baricitinib should be used with caution in patients with known risk factors.

For all the safety concerns highlighted above, it is considered advisable to provide specific advice to patients who may not be aware of this eventuality, particularly in relation to use in pregnancy. Specific reference in the HCP communication is intended to ensure that they are aware of the key information to be provided to patients at the time of the initial prescription (i.e., to enable an informed discussion).

Target audience and planned distribution path:

The HCP educational material will be provided as agreed, at an individual Member State level, with the Competent Authorities.
PACs will be provided to the patient via 2 methods:

1. From the prescribing physician or HCP
2. In the pack as part of the patient leaflet with every prescription.

Plans to evaluate the effectiveness of the interventions and criteria for success:

a) A cross-sectional survey of HCPs will assess understanding of, and adherence to, the key risk minimisation messages and required mitigating actions in the updated HCP educational material and PAC among a sample of dermatologists and rheumatologists (Study I4V-MC-B025 [B025]).
b) A cohort of patients with AD who receive treatment with baricitinib will be observed for the occurrence of events related to the safety messages included in the risk minimisation activities (e.g., use of baricitinib during pregnancy, monitoring of blood lipids, use in patients with active TB, or hepatitis) (Study I4V-MC-B011, AD cohort). The pattern of use of baricitinib (e.g., among pregnant women and patients with active TB or hepatitis) will also be evaluated in this cohort.
c) A drug utilisation study aims to measure the effectiveness of newly implemented prescribing recommendations following completion of the Article 20 referral procedure. As feasible, the objective of the study will be to describe characteristics of patients with a dispensing of baricitinib for RA, AA, or AD, specifically with respect to the characteristics of the treated populations in line with updated SmPC.

Activity 2: Direct Healthcare Professional Communication (DHPC)

Objectives:

The DHPC will inform prescribers of new safety information in the SmPC

Risks addressed:

- MACE
- Malignancy
- Serious infections
- VTE

Rationale for the additional risk minimisation activity:

New safety information became available from a clinical trial with another JAK inhibitor and from an observational Study B023, which lead the EMA to start an Article 20 review procedure for the class of JAKi. The safety recommendations resulting from this procedure will be communicated through a DHPC.

Target audience and planned distribution path:

The DHPC will be distributed to prescribers of baricitinib consistent with approved indications (that is, rheumatologists, dermatologists). Additional HCPs such as orthopaedists, specialised primary care physicians, and hospital pharmacists may also be notified in individual member states during national implementation depending on health care systems in which baricitinib is prescribed.

Plans to evaluate the effectiveness of the interventions and criteria for success:

A cross-sectional survey of HCPs will assess effectiveness of the DHPC (Study B025).

Removal of additional risk minimisation activities:

Not applicable.

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
Herpes zoster	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 • SmPC section 4.4 recommends that if an infection develops, the patient should be monitored carefully, and Olumiant should be temporarily interrupted and not be resumed until the infection resolves. There is a further recommendation that, prior to starting treatment, all patients including paediatric patients with JIA and AD, be brought up to date with all immunisations. PIL Sections 2 and 4 PIL Section 2 advises that the patient should tell their doctor if they develop signs of shingles. [Additional risk minimisation measures:]	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • Herpes zoster follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of herpes zoster in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study

	• Healthcare Professional Educational Material • Patient Alert Card	
VTE	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4, and 4.8 (DVT and PE) PIL Section 2 SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections. SmPC Section 4.4 advises that in patients with cardiovascular or malignancy risk factors baricitinib should only be used if no suitable treatment alternatives are available. In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, baricitinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder. If clinical features of VTE occur, treatment should be discontinued and patients should be evaluated promptly and appropriately treated. PIL Section 2 advises patients: • To talk to their doctor or pharmacist before and during treatment if they have previously had a VTE or if they develop symptoms of VTE • Olumiant should be used with caution in patients with risk factors for VTE • That treatment should be discontinued if clinical symptoms of VTE occur. [Additional risk minimisation measures:] • Healthcare Professional Educational Material	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Thromboembolic follow-up form • Clotting and/or coagulation disorders follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of VTE, including VTE validated based on clinical information, among patients exposed to baricitinib being treated for moderate-to-severe: RA: • EU registries • Nordic healthcare study AD: Nordic healthcare study

	• Patient Alert Card • DHPC	
Malignancies (including lymphoma and typically virus-induced malignancies, such as cervical and many oropharyngeal cancers)	[Routine risk minimisation measures:] SmPC Sections 4.2 and 4.4 PIL section 2 SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections. SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, or with other malignancy risk factors (e.g., current malignancy or history of malignancy) baricitinib should only be used if no suitable treatment alternatives are available. PIL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] • Health care professional educational material • DHPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cancer/neoplasm follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of malignancy in patients exposed to baricitinib with patients exposed to other medications used for: Moderate-to-severe RA: • EU registries • Nordic healthcare study Moderate-to-severe AD: • Nordic healthcare study
Serious and opportunistic infections (including TB *Candida* infections, PML)	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 PIL Section 2 SmPC Section 4.4 advises that the risks and benefits of treatment should be considered prior to initiating therapy in patients with active, chronic, or recurrent infections. In patients over 65 years of age, baricitinib should only be used if no suitable treatment alternatives are available. It also recommends that if an infection develops, the patient should be monitored carefully and Olumiant should be temporarily interrupted for any infection that is not responding to standard therapy. Treatment should not be resumed until the infection resolves.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Candida* infection follow-up form • Pneumonia follow-up form • Viral reactivation follow-up form • Unspecified infection follow-up form • Extrapulmonary TB follow-up form • Pulmonary TB follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of serious and opportunistic infections (including TB, *Candida*, and PML) in patients exposed to baricitinib with patients exposed to other medications used for moderate-to-severe: RA: • EU registries • Nordic healthcare study

	•SmPC Section 4.4 advises that patients should be screened to rule out active TB and active viral hepatitis before starting Olumiant. •SmPC Section 4.4 advises that live, attenuated vaccines should not be used during or immediately prior to treatment. It also recommends that, prior to starting treatment, all patients including paediatric patients with JIA and AD, be brought up to date with all immunisations. •Section 2 of the PIL advises patient that they need to talk to their doctor or pharmacist before and during treatment with Olumiant if they have an infection or if they often get infections. It also advises patents that they should tell their doctor if they get signs of TB, herpes zoster or have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card • DHPC	AD: • Nordic healthcare study
Myelosuppression (agranulocytosis)	[Routine risk minimisation measures:] SmPC Sections 4.2,4.4, 4.8, and 5.3 PIL Sections 2 and 4 SmPC Sections 4.2 and 4.4 recommend that treatment should not be initiated or should be temporarily interrupted in patients with white cell counts or a haemoglobin that is below a certain level. PIL Section 2 advises patients that they may need blood tests prior to or during treatment to check if they have a low red or white blood cell counts. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Blood and Bone Marrow Disorders follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of myelosuppression in patients exposed to baricitinib: RA: • EU registries • Nordic healthcare study AD • Nordic healthcare study

Myopathy including rhabdomyolysis	[Routine risk minimisation measures:] SmPC Section 4.8 (increases in CPK PIL Section 4 (increases in CPK) [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Rhabdomyolysis follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of myopathy including rhabdomyolysis in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study
Potential for drug-induced liver injury	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4, and 4.8 PIL Sections 2 and 4 SmPC Section 4.2 recommends that Olumiant should not be used in patients with severe hepatic impairment. Section 4.4 recommends that if increases in ALT or AST are observed and drug-induced liver injury is suspected, Olumiant should be interrupted. •Section 2 of the PIL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C or if they have poor liver function. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Hepatic disorders follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of potential drug-induced liver injury among patients exposed to baricitinib: RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study

GI Perforations	[Routine risk minimisation measures:] None [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Fistula and/or GI perforation follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of GI perforations in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study
MACE (as an outcome of hyperlipidaemia)	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4, and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PIL Section 2 and 4 SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for patients with a history of chronic or recurrent infections. SmPC Section 4.4 advises that lipid parameters should be assessed at 12 weeks following treatment initiation and thereafter according to international guidelines for hyperlipidaemia. Moreover, SmPC Section 4.4 advises that in patients over 65 years of age, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available. PIL Section 2 advises patients that they may need blood tests while taking Olumiant to check if they have a high cholesterol level.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cardiac disorders follow-up form • Cerebrovascular accident follow-up form • Mortality follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to compare the incidence of hyperlipidaemia and MACE among patients exposed to baricitinib: RA: • EU registries • Nordic healthcare study AD • Nordic healthcare study

	[Additional risk minimisation measures:] • Healthcare Professional Educational Material (lipid monitoring) • Patient Alert Card • DHPC	
Foetal malformation following exposure in utero	[Routine risk minimisation measures:] SmPC Sections 4.3, 4.6, and 5.3 PIL Section 2 SmPC Sections 4.3 and 4.6 state that pregnancy is a contraindication. SmPC Section 4.6 advises that patients of childbearing potential should use effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last treatment. Section 4.6 of the SmPC also advises that a decision must be made whether to discontinue breastfeeding or to discontinue Olumiant therapy. PIL Section 2 • States that patients should not take Olumiant if they are pregnant or think that they may be pregnant • Advises patients that if they are pregnant, think they may be pregnant, or are planning to have a baby, they should ask their doctor or pharmacist for advice before taking the medicine • States that patients should use an effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last Olumiant treatment • States that patients must tell their doctor if they become pregnant as Olumiant should not be used during pregnancy [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Pregnancy data collection – maternal follow-up form • Pregnancy data collection – paternal follow-up form • Pregnancy outcome – maternal follow-up form • Pregnancy outcome – paternal follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of foetal malformation following exposure in utero among patients exposed to baricitinib for both RA and AD: • Nordic healthcare study

Long-term safety	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PIL Sections 2 and 4 No additional recommendations are included in the SmPC or PIL other than those already stated for malignancy and MACE. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cardiac disorders follow-up form • Cerebrovascular accident follow-up form • Mortality follow-up form Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor long-term safety in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study
Use in very elderly (≥75 years)	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4 (lymphocytosis) and 5.2 PIL Section 3 • SmPC Section 4.2 states that • Clinical experience in patients, ≥75 years is very limited. • a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. [Additional risk minimisation measures:] None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Observational post-marketing safety studies to monitor the incidence of use in very elderly (≥75 years) in patients exposed to baricitinib: RA: • Nordic healthcare study AD: • Nordic healthcare study
Use in patients with evidence of hepatitis B or hepatitis C infection	[Routine risk minimisation measures:] SmPC Section 4.4 PIL Section 2 SmPC Section 4.4 recommends that screening for viral hepatitis should be performed before starting treatment and that if the test is positive, a liver specialist should be consulted	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: hepatic disorders follow-up Additional pharmacovigilance activities: None

	Section 2 of the PIL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] None.	
Use in patients with a history of or current lymphoproliferative disease	[Routine risk minimisation measures:] SmPC Section 4.4 PIL Section 2 PIL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with active or recent primary or recurrent malignant disease	[Routine risk minimisation measures:] PIL Section 2 PIL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination	[Routine risk minimisation measures:] SmPC Section 4.2 PIL Section 2 SmPC Section 4.2 states: • The safety and efficacy of baricitinib in children less than 2 years of age have not yet been established. No data are available. • The safety and efficacy of baricitinib in children less than 18 years of age with AA have not yet been established. No data are available. PIL Section 2 advises that Olumiant is not for use in children younger than 2 years of age. It also advises that Olumiant is not for use in children and adolescents under 18 years old with AA, because there is no information on use in this disease state.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Long-term extension in children with JIA (Study JAHX) • Long-term extension in children with AD (Study JAIP)

	[Additional risk minimisation measures:] None	

Abbreviations: AA = alopecia areata; AD = atopic dermatitis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; DHPC = Direct Healthcare Professional Communication; DVT = deep vein thrombosis; GI = gastrointestinal; JIA = juvenile idiopathic arthritis; MACE = major adverse cardiovascular event; PE = pulmonary embolism; PIL = Patient Information Leaflet; PML = progressive multifocal leukoencephalopathy; RA = rheumatoid arthritis; SmPC = Summary of Product Characteristics; TB = tuberculosis; VTE = venous thromboembolic event.

Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Olumiant (Baricitinib)

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

Olumiant's SmPC and its package leaflet give essential information to HCPs and patients on how Olumiant should be used.

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

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

I – The Medicine and What It is Used for

Olumiant is authorised for moderate-to-severe RA, JIA, moderate-to-severe AD in adult and paediatric patients, and severe AA in adult patients (see SmPC for the full indication). It contains baricitinib as the active substance and it is given by mouth.

Further information about the evaluation of Olumiant's benefits can be found in Olumiant's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004085/human_med_002074.jsp

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

Important risks of Olumiant, together with measures to minimise such risks and the proposed studies for learning more about Olumiant'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 professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

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

In the case of Olumiant, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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

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

II.A List of Important Risks and Missing Information

Important risks of Olumiant are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Olumiant. 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 (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Herpes zoster • VTE
Important potential risks	• Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers) • Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML) • Myelosuppression (agranulocytosis) • Myopathy including rhabdomyolysis • Potential for drug-induced liver injury • Gastrointestinal perforation • MACE as an outcome of hyperlipidaemia • Foetal malformation following exposure in utero

List of Important Risks and Missing Information	
Missing information	• Long-term safety • Use in very elderly (≥75 years) • Use in patients with evidence of hepatitis B or hepatitis C infection • Use in patients with a history of or current lymphoproliferative disease • Use in patients with active or recent primary or recurrent malignant disease • Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination

Abbreviations: MACE = major adverse cardiovascular event; PML = progressive multifocal leukoencephalopathy; VTE = venous thromboembolic event.

II.B Summary of Important Risks

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

Important identified risk: Herpes Zoster	
Evidence for linking the risk to the medicine	In the clinical trial (CT) development programmes, observed cases of herpes zoster (HZ) have been predominantly classified as nonserious (88% in RA, 100% in JIA, >99% in AD, 100% in paediatric AD, and 98% in AA). The majority (95% RA, 100% AD (including paediatrics), and 98% in AA) of the reported cases were classified by the investigator as mild to moderate in severity. A similar profile has also been reported from everyday clinical practice since baricitinib was first marketed in the European Union (EU) for RA on 13 February 2017. As would be expected in a medical condition that is usually treated by specialists, a majority of HZ cases have been readily diagnosed, managed, and typically resolved without long-term sequelae. More clinically important manifestations of HZ have been reported very rarely with cases in which the rash spreads beyond the primary or adjacent dermatomes (multidermatomal HZ). Multidermatomal HZ has been reported in • 10% of patients that reported HZ in RA CTs • no confirmed case in JIA • 4.7% patients that reported HZ in AD CTs • 0.2% of patients that reported HZ in paediatric AD CTs, and • 0.1% patients that reported HZ in AA CTs. HZ was associated with motor nerve involvement in 0.1% of cases in RA and none in AD (including paediatrics) and AA. A common complication of this infection, irrespective of the cause, is post-herpetic neuralgia. This has been reported in a low proportion of patients who developed herpes zoster (8% in RA). In JIA, AD (including paediatrics) and AA, information on post-herpetic neuralgia was not solicited for. In the JIA CT programme, 1.8% of the patients developed HZ infection. There was no serious case of HZ reported, and all events were reported as mild or moderate in severity. No patients discontinued the treatment due to HZ. A majority (75%) of events were resolved without sequelae. In the AD CT development programme, 4.8% of the patients had a HZ infection. There were 2 (0.1%) serious cases of HZ, and a majority of the

	events were mild or moderate in severity.. A majority (93.7%) of events were readily diagnosed, managed, and resolved without sequelae. In the paediatric AD CT development programme, 0.9% of the patients developed a HZ infection. There were no serious cases of HZ reported and all events that were reported were mild or moderate in severity. Only 0.4% patients discontinued treatment due to HZ. The majority (75%) of events were readily diagnosed, managed, and resolved without sequelae. In the AA CT development programme, 3.4% of the patients developed a HZ infection. There was 1 serious case of HZ that also was severe. All other cases were nonserious and mild or moderate in severity. Only 0.1% of patients discontinued treatment due to HZ. The majority (94%) of events were readily diagnosed, managed, and resolved without sequelae at the time of follow up.
Risk factors and risk groups	A notable proportion of the cases of HZ (26.4%) reported in the baricitinib RA CTs were reported from Japan, where the reporting rate was higher than that from any other country. Whether this represents a true risk factor or representative of other factors such as detection bias are unclear. Similar findings were seen with tofacitinib. Heavily pretreated RA elderly patients appear to be at higher risk of HZ.
Risk minimisation measures	[Routine risk minimisation measures:] Summary of Product Characteristics (SmPC) Section 4.8 • SmPC section 4.4 recommends that if an infection develops, the patient should be monitored carefully, and Olumiant should be temporarily interrupted and not be resumed until the infection resolves. There is a further recommendation that, prior to starting treatment, all patients including paediatric patients with JIA and AD be brought up to date with all immunisations. Patient information leaflet (abbreviated as PIL) Sections 2 and 4 • PL Section 2 advises that the patient should tell their doctor if they develop signs of shingles. [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card
Additional pharmacovigilance (PV) activities	Observational post-marketing safety studies to monitor the incidence of HZ in patients exposed to baricitinib. RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Venous thromboembolic events	
Evidence for linking risk to the medicine	Venous thromboembolism is considered an ADR of baricitinib treatment. A numerical imbalance in reports of DVT and PE during the 16-week placebo-controlled portion of the baricitinib CTs was noted in clinical development (5 cases vs. 0). This imbalance formed the basis for VTE being classified as an

	important potential risk. Further data, including the imbalances noted in the AD clinical programme led to VTE being classified by the company as an ADR, supporting the change to an important identified risk. In the observational Study B023, meta-analysis of results from 14 data sources shows a significantly elevated incidence rate ratio for VTE in baricitinib compared to TNFi-treated RA cohorts. The incidence rate of VTE was greater among patients with treated with baricitinib than with TNFi, with a difference of 0.26 (95% CI: -0.04, 0.57) per 100 PY. Data analysed for this study was primarily from insurance claims records and also included data from RA registries. Patients compared in these analyses were propensity score-matched based on risk factors for VTE, including age, sex, cancer history, cardiovascular disease, immune disorders, diabetes, prescription medication use including treatments for RA, and health care resource utilisation.
Risk factors and risk groups	All patients who developed VTE had recognised and well-established risk factors for thromboembolism, namely older age, obesity, NSAID use, immobilisation, and medical history of DVT and PE.

Risk minimisation measures	[Routine risk minimisation measures:]
	SmPC Sections 4.2, 4.4 and 4.8
	(DVT and PE)
	PIL Section 2
	
	• SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections.
	• SmPC Section 4.4 advises that
	  o Olumiant should be used with caution in patients with risk factors for VTE and that if clinical features of VTE occur, treatment should be discontinued and patients should be evaluated promptly and appropriately treated.
	• PIL Section 2 advises patients:
	  o To talk to their doctor or pharmacist before and during treatment if they have previously had a VTE or if they develop symptoms of VTE
	  o Olumiant should be used with caution in patients with risk factors for VTE
	  o That treatment should be discontinued if clinical symptoms of VTE occur.
	
	[Additional risk minimisation measures:]
	• Healthcare Professional Educational Material
	• Patient Alert Card
	• DHPC

Additional PV activities	Observational post-marketing safety studies to compare the incidence of VTE, including VTE validated based on clinical information, among patients exposed to baricitinib being treated for moderate-to-severe: RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Malignancies (including lymphoma and typically virus-induced malignancies such as cervical and many oropharyngeal cancers)	
Evidence for linking the risk to the medicine	The association between immunomodulatory products like baricitinib and malignancy is largely theoretical and based on a putative effect on the immune system and the capacity for cancer immunosurveillance (a process by which the body's immune system recognises transformed cells to inhibit the growth of neoplastic tissue). In contrast, it is also suspected that the chronic inflammation present in RA and other autoimmune conditions, rather than its treatment, may underlie the increased incidence of lymphoma observed in these patients compared to the general population, through its continuous stimulation of B cells (Baecklund et al. 2006; Beyaert et al. 2013) or through induction of Epstein Barr virus replication (Hollander et al. 2015). Similarly in patients with AD, there is a slightly increased risk of lymphoma, with severity of AD as a significant risk factor (Legendre et al. 2015; Paller et al. 2018). The literature regarding risk of various other malignancies in patients with AD is inconclusive with some literature suggesting increased risks for skin cancers and others suggesting no increased risk (Andersen et al. 2017; Paller et al. 2018). A systematic literature review (Lee et al. 2019b) found no increased risks for hematologic, cutaneous, or solid organ malignancies among patients with AA. The single exception was that thyroid cancer was found to be more prevalent among patients with AA (OR=1.89, 95% CI: 1.53-2.34) (Lee et al. 2019b). There are suggestions that patients with JIA may be at increased risk for malignancy, although the studies are small with wide CIs (Nordstrom et al. 2012; Kok et al. 2014). In 1 study from Sweden, patients with JIA were at increased risk for lymphoproliferative malignancies (HR = 3.6, 95% CI: 1.1 to 11.2), but not all cancers overall (HR = 1.4, 95% CI: 0.7 to 2.9; Horne et al. 2019). The most commonly reported malignancies (excluding NMSC) in the baricitinib RA clinical development programme have been breast, lung, colorectal, prostate, and renal, which are malignancies more frequently observed in the general RA population (Raheel et al. 2016). Uncertainties therefore remain as to whether the malignancies observed are reflective of disease morbidity in the target population or a true effect of treatment. There was no malignancy in the JIA CT programme. In the AD and AA programmes, few malignancies (except NMSC) were reported; 14 cases in AD, with 5 lymphomas, 4 prostate cancers, and 1 each of

	lung carcinoma, rectal cancer, small-cell lung cancer metastatic, testis cancer, and uterine cancer; and 4 cases in AA, with 1 B-cell lymphoma, 1 breast cancer, 1 chronic lymphocytic leukaemia, and 1 malignant melanoma in situ. The number and type of malignancies reported were in line with the age range of this patient population. There was no malignancy reported in the paediatric AD CT programme.
Risk factors and risk groups	No specific risk groups or specific risk factors have been identified from the clinical development programme for baricitinib.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.2 and 4.4 PIL Section 2 • SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. • PIL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] • Health care professional educational material • DHPC
Additional PV activities	Observational post-marketing safety studies to compare the incidence of malignancy in patients exposed to baricitinib with patients exposed to other medications used for: Moderate-to-severe RA: • EU registries • Nordic healthcare study Moderate-to-severe AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Serious and opportunistic infections (including tuberculosis, *Candida* infections, PML)	
Evidence for linking the risk to the medicine	As would be expected from its mode of action, various infections were consistently observed throughout the clinical development programme for baricitinib and, overall, affected approximately one-half of the RA, JIA and AD study populations (including paediatric) and one-third of the AA study population exposed to baricitinib, respectively. The evidence was considered sufficient to conclude that some infections (such as upper respiratory tract infections, HZ, herpes simplex, pneumonia and urinary tract infection) were adverse effects of the product. The profiles of infections observed were mainly of a nonserious nature with rates consistent with those observed with other RA therapies. In the All BARI JIA Analysis Set, the IR of serious infections was 1.5 per 100 PY.

	In AD randomised CTs, serious infections were uncommon and numerically less frequent with baricitinib treatment than with placebo. This was similar for serious herpes simplex infections where the only serious infections were reported in placebo. In baricitinib-treated patients in the paediatric AD programme, the IR of serious infections was 1.3 per 100 PY. In the All BARI AA analysis set, few patients reported serious infections with an IR of 0.7 events per 100 PY. In RA, more clinically significant infections, including opportunistic infections, have been reported rarely and were generally well managed. Pneumonia has been added to the SmPC as an adverse effect of baricitinib at the request of the PRAC. The evidence source for the request to add PML to this safety concern was on the basis of a single case report with another JAK inhibitor. To date, no cases of PML have been reported with baricitinib. In All BARI JIA Analysis Set, there have been no confirmed cases of opportunistic infections. In the All BARI AD Analysis Set, the IR for opportunistic infections is 0.3 per 100 PY, with a majority of cases being multidermatomal HZ, and no TB infections have been reported. In baricitinib-treated patients in the paediatric AD programme and all BARI AA analysis set, there was 1 case each of opportunistic infection (IR: 0.19 per 100 PY in paediatric AD and <0.1 per 100 PY in AA), both due to a multidermatomal herpes zoster. There was no TB infection reported in paediatric AD or AA programme. Results from the meta-analysis in the B023 observational study show a numerically greater incidence rate ratio of incident serious infection in patients with RA treated with baricitinib compared with TNFi. The incidence rate of first serious infection was greater among patients treated with baricitinib than with TNFi, and the difference was 0.57 (95% CI: -0.07, 1.21) per 100 PY. Data analysed for this study came primarily from health insurance claims records and also included some data from RA registries. Patients compared in these analyses were propensity score-matched based on risk factors for serious infection, such as age, sex, immune disorders, diabetes, ischaemic heart disease, prescription medication use including glucocorticoids, count of previous bDMARDs, and health care resource utilisation.
Risk factors and risk groups	Analysis of the CT data for baricitinib in RA shows that concomitant corticosteroids use, prior biological medicines use, being underweight, overweight, or obese, living in the Asian region, and advanced age (≥50 years old) are the key risk factors for serious infections. No specific risk factors for serious infections have been identified for patients with JIA, AD (including paediatric patients), and AA. A serious form of herpes simplex (eczema herpeticum) has been reported and is associated with poor skin condition that may occur in AD.

Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 PIL Section 2 • SmPC Section 4.4 advises that the risks and benefits of treatment should be considered prior to initiating therapy in patients with active, chronic, or recurrent infections. It also recommends that if an infection develops, the patient should be monitored carefully and Olumiant should be temporarily interrupted for any infection that is not responding to standard therapy. Treatment should not be resumed until the infection resolves. • SmPC Section 4.4 advises that patients should be screened to rule out active tuberculosis (TB) and active viral hepatitis before starting Olumiant. • SmPC Section 4.4 advises that live, attenuated vaccines should not be used during or immediately prior to treatment. It also recommends that, prior to starting treatment, all patients including paediatric patients with JIA and AD be brought up to date with all immunisations. • Section 2 of the PIL advises patient that they need to talk to their doctor or pharmacist before and during treatment with Olumiant if they have an infection or if they often get infections. It also advises patients that they should tell their doctor if they get signs of TB, HZ or have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card • DHPC
Additional PV activities	Observational post-marketing safety studies to compare the incidence of serious and opportunistic infections (including TB, *Candida*, and PML) in patients exposed to baricitinib with patients exposed to other medications used for moderate-to-severe: RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Myelosuppression (agranulocytosis)	
Evidence for linking the risk to the medicine	Treatment with baricitinib was associated with decreased neutrophil counts in 21.3% of patients in RA, 27.4% in JIA, 15% in AD, 20.2% in paediatric AD and 22.6% in AA, and this was consistent across CTs. The frequency with which the absolute neutrophil count (ANC) fell transiently to <500/mm^3 (Common Terminology Criteria for Adverse Events [CTCAE] Grade 4 neutropenia) was very low in RA (0.2%), JIA (0.5%) and AA (0.4%) and none

	in AD (including paediatric). Importantly, the observed neutropenia, regardless of CTCAE grade, was not associated with a higher risk of serious infections. Although "neutropenia <1000 cells/mm^3" is an acknowledged adverse effect of baricitinib treatment and listed as such in the SmPC, there is no current evidence to support agranulocytosis (defined as <100 cells/mm^3) as an important potential risk independent of the "Serious Infections" already included as a safety concern in the EU risk management plan (RMP), this takes into account that the well-known outcome of low white cell counts is infection.
Risk factors and risk groups	No risk factors for neutropenia or myelosuppression (agranulocytosis) have been identified. Agranulocytosis during baricitinib treatment either in clinical development or post-marketing has not been observed.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.2,4.4, 4.8, and 5.3 PIL Sections 2 and 4 • SmPC Sections 4.2 and 4.4 recommend that treatment should not be initiated or should be temporarily interrupted in patients with white cell counts or a haemoglobin that is below a certain level. • PIL Section 2 advises patients that they may need blood tests prior to or during treatment to check if they have a low red or white blood cell counts. [Additional risk minimisation measures:] None
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of myelosuppression in patients exposed to baricitinib: RA: • EU registries • Nordic healthcare study AD • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Myopathy including rhabdomyolysis	
Evidence for linking the risk to the medicine	Although increased CPK >5x upper limit of normal (ULN) is a common adverse effect of baricitinib listed in the SmPC, the strength of evidence linking the muscle enzyme (CPK) elevations observed during treatment with clinically significant or concerning adverse outcomes such as myopathy or severe muscle damage (rhabdomyolysis) is weak. As described in the SmPC, treatment with baricitinib was associated with a rapid (within 1 week) increase in CPK values. In RA, the mean CPK value plateaued after approximately 8 to 12 weeks of treatment, while in AD and AA it varied throughout therapy. Discontinuation of baricitinib due to an increased CPK or musculoskeletal adverse event (AE) symptoms was uncommon in RA (0.7%), AD (0.3%) and AA (0.2%) and no discontinuations were reported in paediatric AD and JIA. In

	addition, there have been no confirmed cases of rhabdomyolysis from CT and from limited information from post-marketing experience to date.
Risk factors and risk groups	As the incidence rate of muscle symptoms in CT development has been so low and no confirmed cases of rhabdomyolysis have been reported, it is not possible to identify any specific patient risk factors for these conditions.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Section 4.8 (increases in CPK) PIL Section 4 (increases in CPK) [Additional risk minimisation measures:] None.
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of myopathy including rhabdomyolysis in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Potential for drug-induced liver injury	
Evidence for linking the risk to the medicine	Within the RA CT programme, ALT and AST ≥5 × ULN were reported by 1.5% and 0.5% patients, respectively; and ALT and AST ≥10 x ULN were reported in 0.3 and 0.1% of patients, respectively. ALT and AST ≥3 x ULN are considered to be adverse effects of baricitinib. In the All BARI JIA Analysis Set, 2.7 and 0.9% of patients had increased ALT ≥5 x ULN and AST ≥5 x ULN, respectively; and 0.5% had increased ALT ≥10 x ULN (no patient had AST elevation of ≥10 x ULN. Within the AD CT programme, ALT and AST ≥5× ULN were reported in 0.5% and 0.9% patients, respectively; and ALT and AST ≥10 x ULN were reported by 0.1% and 0.2% of patients, respectively. In the paediatric AD clinical trial, no patient had ALT elevations of ≥5x ULN; AST ≥5x ULN was observed for 0.2% of patients; there were no patients with AST or ALT elevations of ≥10× ULN. In the AA CT programme, 0.8% and 0.9% of patients had increases of ALT and AST ≥5 ×ULN, respectively, and 0.15% and 0.2% had increases of ALT and AST ≥10 × ULN, respectively. None of these enzyme changes were linked to clinically significant evidence of drug-induced liver injury (DILI). Of the total AEs, 0.3% of AEs for hepatic disorders were considered by the investigators to be serious in RA, 0.5% in JIA, 0.04% in AD, 0.1% in AA, and none in paediatric AD. The available information on potential hepatotoxicity with baricitinib treatment derived from completed CTs, post-marketing safety studies, published scientific literature, and spontaneously reported adverse events from post-marketing experience cumulatively was reviewed through 13 February 2022: • The CT data in RA, AD (adults), and AA include 7635 patients and 19 415 PYE. Of these patients, 5183 (68%) were exposed to baricitinib 4

	mg. Among these, there were no cases of severe DILI probably related to baricitinib. A total of 9 cases had transaminases ≥3 x ULN and total bilirubin ≥2 x ULN (7 in RA, 1 in AD, 1 in AA). Based on the medical review, it was concluded that none of them met the Hy's law definition due to the presence of alternative aetiology in these patients. • The placebo-controlled data from RA, AD, and AA clinical trials do not show a consistent difference in frequency of treatment-emergent transaminases increase to ≥3x, 5x, or 10x ULN between baricitinib 2 mg, 4 mg, and placebo. The incidence of these elevations did not increase with longer exposure. In addition, there was no difference in the frequency of transaminases increase between baricitinib and placebo in the COVID-19 clinical trials. • There were no cases that met Hy's law definition or severe DILI cases in about 390 000 patients treated for RA or AD and 850 000 patients treated for COVID-19 in the post-marketing setting. The current evidence including significant baricitinib exposure in the clinical trial and post marketing settings, indicates that the risk for hepatotoxicity with baricitinib is not manifesting as severe DILI.
Risk factors and risk groups	No risk groups or specific risk factors have been identified from the clinical development programmes, although concurrent use of baricitinib with potentially hepatotoxic medicinal products, such as methotrexate (MTX), results in a higher frequency of liver enzyme elevations. In the AD and AA programmes, no specific risk factors have been identified.
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4, and 4.8 PIL Sections 2 and 4 • SmPC Section 4.2 recommends that Olumiant should not be used in patients with severe hepatic impairment. • Section 4.4 recommends that if increases in ALT or AST are observed and DILI is suspected, Olumiant should be interrupted. • Section 2 of the PIL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C or if they have poor liver function. [Additional risk minimisation measures:] None.
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of potential DILI among patients exposed to baricitinib: RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Gastrointestinal perforation	

Evidence for linking the risk to the medicine	Although there is a pharmacologically plausible basis for an association between baricitinib and gastrointestinal (GI) perforation, there are insufficient data to establish it as an adverse effect of treatment at this time. The frequency of cases indicative of GI perforation is very low in CTs (≤0.2% of patients with RA, AD and AA, and no cases observed in patients with JIA and paediatric AD). In most cases, there have been significant confounding factors, such as use of steroids and GI surgery. The overall incidence rate of GI perforations was 0.06 per 100 patient-years (PY) in RA, and this is within the published rates reported in patients with RA (0.02-0.39 per 100 PY). Patients with RA or JIA may be at an increased risk of GI perforation because of prescribed medication, and/or because of the consequences of the disease process itself (e.g., vasculitis). As a result, the determination of whether or not the limited observations reflect underlying disease morbidity as opposed to an adverse effect of baricitinib is challenging and will be systematically monitored in the proposed studies in the PV plan for the product. Similar risks are not seen with AD and AA, and systemic steroid use is limited to times of severe AD flares and to more extensive manifestation of AA, respectively.
Risk factors and risk groups	No specific risk factors for GI perforation have been identified with baricitinib.
Risk minimisation measures	[Routine risk minimisation measures:] None [Additional risk minimisation measures:] None.
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of GI perforations in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Major adverse cardiovascular events as an outcome of hyperlipidaemia	
Evidence for linking the risk to the medicine	Consistent with a pharmacologic effect of Janus kinase (JAK) inhibition, dose-dependent increases in blood lipid levels (including total cholesterol, triglycerides, low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]) were observed throughout the RA clinical development programme for baricitinib. The increase in LDL-C and all other parameters occurred within the first 12 weeks of treatment and remained stable thereafter. In JIA, lipid changes were similar for patients treated with baricitinib or placebo. In the AD and AA populations, increases in lipids were seen by 12 weeks for total cholesterol, LDL and HDL. Mean values for HDL remained fairly stable after Week 12. Mean total and LDL cholesterol increased through Week 52. Triglyceride changes were small and not different from placebo.

	The overall evidence was considered sufficient to conclude that hypercholesterolaemia was an adverse effect of the product. Long-term exposure to increases in blood lipids in the general population would be expected to be associated with adverse CV outcomes (MACE), but literature sources indicate that they may not be harmful to patients with RA as the benefits of suppression of inflammation may outweigh the risk of the lipid changes. In this regard, few MACE were observed in RA clinical development and no relationship was observed between MACE and LDL-C increases. As noted in the original RA submission, the increases in LDL-C observed with baricitinib treatment are responsive to statin treatment, and no direct link to major adverse CV outcomes has been established to date. In the AD clinical programme, the incidence rate of MACE was smaller than in RA. No cases of MACE were seen in the JIA and paediatric AD clinical programmes. One case was reported in AA clinical development in a patient with multiple risk factors. In a randomised post-authorisation safety study in patients with RA aged 50 years or above with at least 1 additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared with TNFi. Meta-analysis of B023 observational study results from 14 data sources showed a numerically greater IRR for MACE in baricitinib compared with TNFi-treated cohorts. The incidence rate of MACE was greater among patients with RA treated with baricitinib than with TNFi. Data analysed for this study were primarily from insurance claims records and included some data from RA registries. Patients compared in these analyses were propensity score-matched based on risk factors for MACE, such as age, sex, history of cardiovascular disease, diabetes, dyslipidaemia, hypertension, immune disorders, prescription medication use including aspirin, glucocorticoids, lipid-lowering or anti-platelet agents, count of prior bDMARDs, and health care resource utilisation. RA, JIA, AD, and AA are, however, chronic conditions and, in the case of RA, one in which patients are already at higher risk of CV disease. As such, patients treated with baricitinib in usual clinical practice may be treated for several years and in higher numbers than exposed in CTs. As the long-term effects of these lipid changes on adverse CV outcomes in these circumstances are uncertain, MACE has been classified as an important potential risk warranting further systematic study in the PV Plan of this RMP.
Risk factors and risk groups	No specific risk factors for hyperlipidaemia have been identified with baricitinib. Similarly, the number of patients in whom MACE has been reported in CTs remains very low in RA, AD, and AA and none were reported in JIA and paediatric AD. As a result, no specific risk factors for MACE have been identified with baricitinib. Based on RA CT data, compared to the patients without MACE, patients with MACE were more likely to have the following CV risk factors at baseline: older age, longer disease duration, cigarette smoking, prior cardiac disorder, hypertension, obesity, and hypercholesterolaemia. However, the risk factors for MACE observed in this CT population are typical of risk factors for MACE in the general population. The extent to which prevalence of cardiovascular disease (CVD) in patients with RA is a contributory factor is unknown.

Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4, and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PIL Section 2 and 4 • SmPC Section 4.2 states that a dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥65 years and for patients with a history of chronic or recurrent infections. • SmPC Section 4.4 advises that lipid parameters should be assessed at 12 weeks following treatment initiation and thereafter according to international guidelines for hyperlipidaemia. Olumiant should be used with caution in patients with risk factors for MACE. • PIL Section 2 advises patients that they may need blood tests while taking Olumiant to check if they have a high cholesterol level and to speak to their doctor if they have or have previously had heart problems. [Additional risk minimisation measures:] • Healthcare Professional Educational Material (lipid monitoring) • Patient Alert Card • DHPC
Additional PV activities	Observational post-marketing safety studies to compare the incidence of hyperlipidaemia and MACE among patients exposed to baricitinib: RA: • EU registries • Nordic healthcare study AD • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Foetal malformation following exposure in utero	
Evidence for linking the risk to the medicine	Studies in rats and rabbits dosed in excess of the maximum human exposure have shown reproductive toxicity when baricitinib was dosed during the early stages of pregnancy. These animal studies indicate that baricitinib may have an adverse effect on bone development in utero at these higher dosages. There is no current evidence of similar findings in the babies of mothers who have been treated with baricitinib during pregnancy but experience at this time is very limited. As a result, the effects of baricitinib on the bone development of the baby prior to birth are unknown and, as advised in the prescribing information, women of childbearing potential should not become pregnant when treated with baricitinib.
Risk factors and risk groups	No risk factors have been identified as there are currently no data from CTs or post-marketing data sources in human pregnancy indicative of the bone effects observed in the nonclinical studies. The highest risk period is considered to be the first 12 weeks of pregnancy; however, pregnant or lactating women were excluded from CTs with baricitinib, and experience in human pregnancy is limited. Therefore, neither specific duration of treatment nor risk period have been identified.

Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.3, 4.6, and 5.3 PIL Section 2 • SmPC Sections 4.3 and 4.6 state that pregnancy is a contraindication. • SmPC Section 4.6 advises that patients of childbearing potential should use effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last treatment. • Section 4.6 of the SmPC also advises that a decision must be made whether to discontinue breastfeeding or to discontinue Olumiant therapy. • PIL Section 2 o States that patients should not take Olumiant if they are pregnant or think that they may be pregnant o Advises patients that if they are pregnant, think they may be pregnant, or are planning to have a baby, they should ask their doctor or pharmacist for advice before taking the medicine o States that patients should use an effective method of contraception to avoid becoming pregnant during treatment and for at least 1 week after the last Olumiant treatment o States that patients must tell their doctor if they become pregnant as Olumiant should not be used during pregnancy [Additional risk minimisation measures:] • Healthcare Professional Educational Material • Patient Alert Card
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of foetal malformation following exposure in utero among patients exposed to baricitinib for both RA and AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important missing information: Long-term safety	
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.4 and 4.8 (hypercholesterolaemia and hypertriglyceridaemia) PIL Sections 2 and 4 No additional recommendations are included in the SmPC or PIL other than those already stated for malignancy and MACE. [Additional risk minimisation measures:] None.

Additional PV activities	Observational post-marketing safety studies to monitor long-term safety in patients exposed to baricitinib RA: • EU registries • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important missing information: Use in very elderly (≥75 years)	
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Sections 4.2, 4.4 (lymphocytosis) and 5.2 PIL Section 3 • SmPC Section 4.2 recommends that in patients, ≥65 years, a starting dose of 2 mg is appropriate. [Additional risk minimisation measures:] None.
Additional PV activities	Observational post-marketing safety studies to monitor the incidence of use in very elderly (≥75 years) in patients exposed to baricitinib: RA: • Nordic healthcare study AD: • Nordic healthcare study See Section II.C of this summary for an overview of the post-authorisation development plan.
Important missing information: Use in patients with evidence of hepatitis B or hepatitis C infection	
Risk minimisation measures	[Routine risk minimisation measures:] SmPC Section 4.4 PIL Section 2 • SmPC Section 4.4 recommends that screening for viral hepatitis should be performed before starting treatment and that if the test is positive, a liver specialist should be consulted • Section 2 of the PIL advises patients to speak to their doctor if they have, or have previously had, hepatitis B or C. [Additional risk minimisation measures:] None.
Important missing information: Use in patients with a history of or current lymphoproliferative disease	

Risk minimisation measures	[Routine risk minimisation measures:] SmPC Section 4.4 PIL Section 2 • PIL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer. [Additional risk minimisation measures:] None
Important missing information: Use in patients with active or recent primary or recurrent malignant disease	
Risk minimisation measures	[Routine risk minimisation measures:] PIL Section 2 • PIL Section 2 advises patients to tell their doctor or pharmacist before and during treatment if they have cancer [Additional risk minimisation measures:] None
Important missing information: Long-term safety in paediatric patients including growth and bone development, maturation and pubertal development, and adverse response to vaccination	

Risk minimisation measures	[Routine risk minimisation measures:]
	SmPC Section 4.2
	PIL Section 2
	
	• SmPC Section 4.2 states:
	  • The safety and efficacy of baricitinib in children less than 2 years of age have not yet been established. No data are available.
	  • The safety and efficacy of baricitinib in children less than 18 years of age with AA have not yet been established. No data are available.
	• PIL Section 2 advises that Olumiant is not for use in children younger than 2 years of age. It also advises that Olumiant is not for use in children and adolescents under 18 years old with AA because there is no information on use in this disease state.
	
	[Additional risk minimisation measures:]
	None

Additional PV activities	• Long-term extension in children with JIA (Study JAHX) • Long-term extension in children with AD (Study JAIP) See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: AA = alopecia areata; AD = atopic dermatitis; ADR = adverse drug reaction; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; BARI = baricitinib; COVID-19 = coronavirus disease 2019; CPK = creatinine phosphokinase; CT = clinical trial; CTCAE = Common Terminology Criteria for Adverse Events; CV = cardiovascular; CVD = cardiovascular disease; DHPC = direct healthcare professional communication; DILI = drug-induced liver injury; DVT = deep vein thrombosis; EU = European Union; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol;

IR = incidence rate; IRR = incidence rate ratio; JAK = Janus kinase; JIA = juvenile idiopathic arthritis; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; NMSC = non-melanoma skin cancer; NSAID = nonsteroidal anti-inflammatory drug; PE = pulmonary embolism; PIL = patient information leaflet; PML = progressive multifocal leukoencephalopathy; PV = pharmacovigilance; PY = patient years; RA = rheumatoid arthritis; RMP = risk management plan; SmPC = Summary of Product Characteristics; TB = tuberculosis; TNFi = tumour necrosis factor inhibitor; ULN = upper limit of normal; VTE = venous thromboembolism.

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 Olumiant.

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

Study short name: **Study I4V-MC-B011**; Retrospective Cohort Study to Assess Safety of Baricitinib in Nordic countries

Purpose of the study: The rationale for conducting this study is to characterise the long-term safety of baricitinib among RA and AD patients treated in routine clinical care in Nordic countries using a retrospective study design.
Specifically, the objectives include 1) to compare the incidence rates and profiles of: serious and opportunistic infections, MACE, malignancies, and VTE in RA and AD patients (separately) with long-term exposure to baricitinib, which will be compared to similar patients with long-term exposure to other indicated medications; and 2) to describe the occurrence of lymphoma; HZ; opportunistic and fungal infections; GI perforations; and serious disorders of the muscle, bone marrow, blood lipids, white blood cell count, and liver.

A secondary objective is to monitor the incidence of the major outcomes among patients aged 75 years or older. Another secondary objective is to assess the effectiveness of risk minimisation activities by describing the pattern of use of baricitinib and the occurrence of pregnancy, active TB, or active viral hepatitis and the monitoring of lipid levels in relation to baricitinib use in routine clinical care. Of note, this objective has been completed for patients with RA and is ongoing in patients with AD.

Study short name: **Study I4V-MC-B012**; Observational post marketing surveillance in 3 EU registries

Purpose of the study: The rationale for this study is to provide prospective, long-term safety monitoring for baricitinib in routine clinical practice in the EU.

The study objectives are to monitor the incidence rate and profile of various serious and opportunistic infections, MACE, malignancies, and VTE in EU patients with RA with long-term exposure to baricitinib. This information will be compared to patients with long-term exposure to other medications used for moderate-to-severe RA. A second objective will aim to describe the occurrence of lymphoma; HZ; opportunistic infections; GI perforations; and serious disorders of the muscle, bone marrow, white blood cell count, and liver.

Study short name: **Study I4V-MC-B025;** Observational, multinational, cross-sectional survey

Purpose of the study: To assess the effectiveness of the updated baricitinib additional risk minimisation activities in Europe in prescribers treating patients with RA, AD, or AA.

This survey will also assess the effectiveness of a DHPC distributed to dermatologists and rheumatologists to communicate changes in the SmPC.

Study short name: **Drug Utilisation Study** to Assess Prescribing Patterns of Baricitinib

Purpose of study: This drug utilisation study aims to measure the effectiveness of newly implemented prescribing recommendations. This will be accomplished by evaluating prescribing behaviours after implementation of the recommended changes. The feasibility of this assessment will be evaluated prior to the initiation of the study.

Study short name: **Study I4V-MC-JAHX** Long-term extension study evaluating safety and efficacy of baricitinib in patients from 1 year to less than 18 years of age with JIA.

Purpose of study: The rationale for this study is to evaluate the long-term efficacy and safety profile of oral baricitinib when administered once daily to paediatric patients with JIA and systemic JIA.

Study short name: **Study I4V-MC-JAIP**; Phase 3, randomised, double-blind, placebo-controlled, parallel-group, outpatient study in paediatric AD.

Purpose of study: To evaluate the pharmacokinetics, efficacy, and safety including long-term safety (vaccine response, growth, and bone safety) of baricitinib in paediatric patients 2 to less than 18 years old with moderate-to-severe AD. The long-term extension of the study will continue to monitor patients for up to 4 years and evaluate overall safety including vaccine response, sexual maturation based on menarche status and gonadal hormone levels, physical growth compared to age- and sex-matched peers, and bone safety via imaging of the hand, including wrist and fingers, and knee.

Part VII: Annexes

Annex **Page**

Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms

Specific Adverse Event Follow-up Form	Event(s) Associated with the form
Form #1 Spontaneous Follow-Up Form – Herpes Zoster	Herpes zoster
Form #2 Spontaneous Follow-Up Form – Cancer/Neoplasm	Cancer/Neoplasm
Form #3 Spontaneous Follow-Up Form – Cardiac Disorders	Cardiac, hyperlipidaemia
Form #4 Spontaneous Follow-Up Form – Cerebrovascular Accident	Cerebrovascular Accident
Form #5 Spontaneous Follow-Up Form – General	Hyperlipidaemia (without cardiac event)
Form #6 Spontaneous Follow-Up Form – Unspecified Infection	Infection
Form #7 Spontaneous Follow-Up Form – Extrapulmonary Tuberculosis	Extrapulmonary Tuberculosis
Form #8 Spontaneous Follow-Up Form – Pulmonary Tuberculosis	Pulmonary Tuberculosis
Form #9 Spontaneous Follow-Up Form – *Candida* Infection	*Candida* Infection
Form #10 Spontaneous Follow-Up Form – Pneumonia	Pneumonia
Form #11 Spontaneous Follow-Up Form – Viral Reactivation	Viral Reactivation
Form #12 Spontaneous Follow-Up Form – Hepatic Disorders	Hepatotoxicity
Form #13 Spontaneous Follow-Up Form – Pregnancy Data Collection – Maternal	Pregnancy
Form #14 Spontaneous Follow-Up Form – Pregnancy Data Collection – Paternal	Pregnancy
Form #15 Spontaneous Follow-Up Form – Pregnancy Outcome – Maternal	Pregnancy
Form #16 Spontaneous Follow-Up Form – Pregnancy Outcome – Paternal	Pregnancy
Form #17 Spontaneous Follow-Up Form – Breastfeeding	Pregnancy
Form #18 Spontaneous Follow-Up Form – Fistula and/or Gastrointestinal Perforation	Gastrointestinal Perforation
Form #19 Spontaneous Follow-Up Form – Mortality	Death
Form #20 Spontaneous Follow-Up Form – Blood and Bone Marrow Disorders	Myelosuppression
Form #21 Spontaneous Follow-Up Form – Clotting and/or Coagulation Disorders	Venous thromboembolic events
Form #22 Spontaneous Follow-up Form – Thromboembolism	Venous thromboembolic events
Form #23 Spontaneous Follow-Up Form – Rhabdomyolysis	Rhabdomyolysis

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

⊞

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Herpes Zoster			
Presenting Symptoms			
☐ Vesicular rash	☐ Ophthalmic involvement	☐ Headache	☐ Otic (Ransay-Hunt)

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ One dermatome involved	☐ Disseminated vesicles	☐ Confusion	☐ Jaundice
☐ Multiple dermatomes involved	☐ Post-herpetic neuralgia	☐ Focal neurologic finding	☐ Virtual loss
☐ Other symptoms and signs:			
Relevant Past Medical History			
☐ Varicella	☐ Prior herpes zoster	☐ Smoking	☐ Corticosteroid use
☐ Prior zoster vaccination	☐ Prior varicella	☐ Malignancy	☐ Heavy alcohol use
☐ Prior varicella vaccination	☐ HIV infection	☐ Cancer chemotherapy	☐ Diabetes mellitus
☐ Other Relevant History:			
Concomitant Medications/Substances			
☐ Current alcohol use	☐ Current smoking	☐ Drug abuse	
☐ Corticosteroids (specify):			
☐ Immunomodulators (specify):			
☐ Other Medications:			

Laboratory Tests/Investigations				
Tzanck Smear	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Antigen detection (DFA; PCR)	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
HIV serology	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Ophthalmologic exam:				
Other studies:				

Laboratory Results:

Laboratory Test	Normal Range	Baseline Value	Abnormal Value	Improvement Value
		Date:	**Date:**	**Date:**
Neutrophils				
Haemoglobin				
WBC				
Platelets				
ALT				
AST				
Alkaline phosphatase				
Bilirubin				
Creatinine				
Other:				

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Eli Lilly and Company - Global Patient Safety **Case Number:**

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

⊞

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Please provide brief explanation:

Cancer/Neoplasm

Primary Diagnosis for the reported event(s):	
Hospitalization for this event? ☐ No ☐ Yes	
☐ Please specify primary site:	
☐ Neoplasm (benign mass/lesions)	☐ Possible malignant tumor – not yet confirmed
☐ Malignant tumor (please attach copy of pathology report or provide the information of Stage/Grade, Staging classification and tissue source):	
Concomitant Medications/Substances (please include prescription, OTC, and herbal)	
Relevant Tests/Studies (please attach copy of pathology report, if available)	
Study	**Result**
Histopathology (please indicate stage/grade, staging classification and tissue source)	
Ultrasound	
CAT Scan	
MRI	
Other:	
Medical History/Risk Factors	
☐ Cancer:	☐ Family history of cancer:
☐ Chemotherapy:	☐ Radiation therapy
☐ Estrogen use: years	☐ Tobacco use
☐ Diabetes mellitus	☐ Obesity
☐ Alcohol	☐ No known predisposing factors
☐ Immunosuppression:	☐ Environmental risk:
☐ Other (please describe):	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Treatment provided (please describe):

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

⊞

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Cardiac Disorders			
Primary Diagnosis for the reported event(s):			
☐ Chest Pain/Angina	☐ Myocardial Infarction	☐ Arrhythmia	☐ Other – please describe:
Hospitalization for this event? ☐ No ☐ Yes			
Presenting Signs/Symptoms			
☐ Heart Rate:		☐ Blood Pressure:	
☐ Palpitations		☐ Shortness of Breath	
☐ Syncope		☐ Chest Pain (please specify):	
☐ Cardiac Exam:			
☐ Pulmonary Exam:			
☐ Other (please specify):			
Relevant Medical History (please specify if needed)			
☐ Atrial Arrhythmia		☐ Ventricular Arrhythmia	
☐ Conduction Disorders		☐ Congenital Heart Abnormalities	
☐ Cardiovascular Disease		☐ Hypertension	
☐ Cardiovascular Infection		☐ Cardiac Surgeries	
☐ Pulmonary Disease		☐ Pulmonary Embolism	
☐ Metabolic Disorders		☐ Psychiatric/Emotional Disorders	
☐ Pericarditis		☐ Syncope	
☐ Poor compliance with BP/Cardiac Meds		☐ Dizziness	
☐ Family History of cardiac disease, congenital QT prolongation, premature cardiac death		☐ Substance Abuse	
☐ Other (please specify):			
Historic Drugs (please specify)			
☐ Antiarrhythmics:		☐ Antihypertensives:	
☐ Psychiatric Medications:		☐ Antibiotics:	
☐ Others:			
Concomitant Meds (include prescription, substance, OTC, and herbal)			
☐ Nitrates/Nitrites		☐ Alpha Blocker	
☐ ED Medication (please specify):		☐ Others:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Relevant Laboratory Tests	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Cardiac Enzyme (please specify):				
Serum Potassium				
Serum Calcium				
pO2				
O2 Saturation				

Other Diagnostic Tests	Results		
EKG (Q Waves)/EKG (QTC Interval)			
Myocardial Scan			
Echocardiogram (ECHO)			
Coronary Angiography			
Exercise Stress Test			
QT Interval (milliseconds)			
QTc (Corrected Value)			
How was QT Interval measured?	☐ Machine	☐ Manually	☐ Other
QT Correction Formula	☐ Bazett	☐ Fridericia	☐ Other
Other:			

Treatment	
☐ Cardioversion/Defibrillation	☐ Treatment not required
☐ Medication (please specify):	☐ Ablation
☐ Other (please specify):	

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Cerebrovascular Accident
Primary Diagnosis for the reported event(s):

Eli Lilly and Company - Global Patient Safety **Case Number:**

Hospitalization for this event? ☐ No ☐ Yes		
Concomitant Medications/Substances (please include prescription, OTC and herbal)		
Presenting Signs/Symptoms		
Onset Date:	End Date:	
Impairments:		
☐ Paralysis (specify):	☐ Dysarthria	☐ Impaired consciousness
☐ Weakness (specify):	☐ Visual field defect	☐ Seizure
☐ Dysphagia	☐ Aphasia	☐ Other findings:
Severity		
☐ No/Mild	☐ Moderate	☐ Severe
Relevant Medical History		
☐ Diabetes	☐ Artrial fibrillation	☐ Head trauma
☐ Smoking	☐ Hypertension	☐ Prior stroke
☐ Myocardial infarction	☐ Hyperlipidemia	☐ Other (please specify):

Relevant Laboratory Tests	Normal range for your institution	Baseline value for patient	Abnormal value	Improvement value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelet Count				
Glucose				
INR				
aPTT				
Thrombin Time				
Fibrinogen				
Other:				

Other Tests	Results
CT	
MRI	
Angiography	
EEG	
Other:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Treatment		
☐ Support and organization	☐ Thrombolytic agent	☐ Ablation
☐ Antiplatelet agent	☐ Anticoagulant	Other:

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Primary diagnosis for the reported event(s):
Hospitalization for this event? ☐ Yes ☐ No

Relevant Medical History:
Concomitant Medications/Substances (please include prescription, OTC, and herbal)
Please provide the results of any relevant laboratory test/investigations.
Treatment provided (please describe)

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Unspecified Infection	
General	
Type of Infection:	
Presenting Signs and Symptoms:	
Relevant Medical History and Risk Factors:	
Relevant Diagnostic Studies	
Cultures:	
Antigen Detection:	
Serologic Studies:	
Imaging Studies:	
Tissue Biopsy:	

Laboratory Results:				
Laboratory Test	**Normal Range**	**Baseline Value**	**Abnormal Value**	**Improvement Value**
		Date:	Date:	Date:
Neutrophils				
Haemoglobin				
WBC				
Platelets				
ALT				
AST				
Alkaline Phosphatase				
Bilirubin				
Creatinine				
Other:				

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

⊞

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Extrapulmonary Tuberculosis			
Site(s) of Infection:			
Presenting Symptoms			
☐ Cough	☐ Fever	☐ Headache	☐ Joint swelling
☐ Sputum	☐ Night sweats	☐ Confusion	☐ Skin lesions
☐ Weight loss	☐ Haemoptysis	☐ Back pain	☐ Lymphadenopathy
☐ Focal neurological findings	☐ Pyuria	☐ Nuchal rigidity	☐ Anaemia
Relevant Past Medical History			
☐ Tuberculosis	☐ Abnormal chest X-ray	☐ Smoking	☐ Corticosteroid use
☐ Positive PPD	☐ Diabetes mellitus	☐ Family member with TB	☐ Heavy alcohol use
☐ Positive IFN-y release assay	☐ From TB endemic area	☐ BCG immunization	☐ Treatment with INH
☐ HIV infection	☐ Autoimmune disorder	☐ Malignancy	☐ Cancer chemo Rx
☐ Other Relevant History:			
Concomitant Medications/Substances			
☐ Current alcohol use	☐ Current smoking	☐ Drug abuse	
☐ Corticosteroids (specify):			
☐ Immunomodulators (specify):			
☐ Other medications:			

Laboratory Tests/Investigations				
Skin test for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
IFN-y release assay	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Sputum smear for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Sputum culture for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Antigen detection	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
HIV serology	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
CSF cultures	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Urine cultures	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Bone marrow cultures	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Other cultures (site)	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Chest radiograph:				
Chest CT:				
Other studies:				

Eli Lilly and Company - Global Patient Safety **Case Number:**

Laboratory Results

Laboratory Test	Normal Range	Baseline Value	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Neutrophils				
Haemoglobin				
WBC				
Platelets				
ALT				
AST				
Alkaline Phosphatase				
Bilirubin				
Creatinine				
CSF Cell Count				
CSF Glucose				
Urinalysis				
Other:				

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pulmonary Tuberculosis			
Presenting Symptoms			
☐ Cough	☐ Fever	☐ Headache	☐ Joint swelling
☐ Sputum	☐ Night sweats	☐ Confusion	☐ Skin lesions
☐ Weight loss	☐ Haemoptysis	☐ Back pain	☐ Lymphadenopathy
Relevant Past Medical History			
☐ Tuberculosis	☐ Abnormal Chest X-ray	☐ Smoking	☐ Corticosteroid Use
☐ Positive PPD	☐ Diabetes Mellitus	☐ Family Member with TB	☐ Heavy Alcohol Use
☐ Positive IFN-γ Release Assay	☐ From TB Endemic Area	☐ BCG Immunization	☐ Treatment with INH
☐ HIV Infection	☐ Autoimmune Disorder	☐ Malignancy	☐ Cancer Chemo Rx
☐ Other Relevant History:			
Concomitant Medications / Substances			
☐ Current Alcohol Use	☐ Current Smoking	☐ Drug Abuse	
☐ Corticosteroids (specify):			
☐ Immunomodulators (specify):			
☐ Other Medications:			

Laboratory Tests / Investigations				
Skin Test for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
IFN-γ Release Assay	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Sputum Smear for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Sputum Culture for TB	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Antigen Detection	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
HIV Serology	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Chest Radiograph:				
Chest CT:				
Other Studies:				

Laboratory Results:

Laboratory Test	Normal Range	Baseline Value	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Neutrophils				
Haemoglobin				
WBC				
Platelets				

Eli Lilly and Company - Global Patient Safety **Case Number:**

ALT				
AST				
Alkaline Phosphatase				
Bilirubin				
Creatinine				
Other:				

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Candida Infection
Site(s) of Infection:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Presenting Symptoms/Signs			
☐ Oral mucosal involvement	☐ Dysphagia	☐ Vulvovaginal involvement	☐ Fever
☐ Skin involvement	☐ Stomatitis	☐ Visual loss	☐ Hepatic abnormalities
☐ Other Symptoms and Signs:			
Relevant Past Medical History			
☐ Recent antibiotic use	☐ Diabetes mellitus	☐ Malignancy	☐ HIV infection
☐ Recent neutropenia	☐ Corticosteroid use	☐ Cancer chemotherapy	☐ Antifungal treatment
☐ Other relevant history:			
Concomitant Medications/Substances			
☐ Current alcohol use		☐ Current smoking	
☐ Corticosteroids (specify name/dose):			
☐ Immunomodulators (specify name/dose):			
☐ Other medications (specify name):			

Laboratory Tests/Investigations				
Microscopic examination	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Blood culture	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
HIV Serology	☐ Positive	☐ Negative	☐ Not Done	☐ Pending
Result of fungal culture:				
Ophthalmological exam:				
Other studies:				

Laboratory Results:

Laboratory Test	Normal Range	Baseline Value	Abnormal Value	Improvement Value
		Date:	**Date:**	**Date:**
Neutrophils				
Haemoglobin				
WBC				
ANC				
Platelets				
ALT				
AST				
Alkaline phosphatase				
Bilirubin				
Creatinine				
Urinalysis				
Other:				

Eli Lilly and Company - Global Patient Safety **Case Number:**

Laboratory Results:				
Laboratory Test	**Normal Range**	**Baseline Value**	**Abnormal Value**	**Improvement Value**
		Date:	**Date:**	**Date:**

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Pneumonia			
Presenting Symptoms			
☐ Cough	☐ Fever	☐ Weight loss	☐ Hypoxia

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Sputum	☐ Night sweats	☐ Confusion	☐ Cyanosis
☐ Dyspnoea	☐ Haemoptysis	☐ Chest pain	☐ Impaired consciousness
Relevant Past Medical History			
☐ Smoking	☐ Pneumonia	☐ Recent URI	☐ Corticosteroid use
☐ COPD	☐ Diabetes mellitus	☐ Influenza immunization	☐ Heavy alcohol use
☐ Asthma	☐ CVA	☐ Pneumonia immunization	☐ Malignancy
☐ HIV infection	☐ Autoimmune disorder	☐ Impaired consciousness	☐ Cancer chemo rx
☐ Other relevant history:			
Concomitant Medications/Substances			
☐ Current alcohol use	☐ Current smoking	☐ Proton pump inhibitors	☐ Inhaled corticosteroids
☐ Corticosteroids (specify name/dose):			
☐ Immunosuppressants (specify name/dose):			
☐ Cytotoxic chemotherapy:			
☐ Other medications (specify name):			
Laboratory Tests/Investigations			
Sputum culture:			
Antigen detection:			
Chest Radiograph:			
Chest CT:			
Other studies:			

Laboratory Results				
Laboratory Test	**Normal Range**	**Baseline Value**	**Abnormal Value**	**Improvement Value**
		Date:	**Date:**	**Date:**
Neutrophils				
Haemoglobin				
WBC				
Platelets				
ALT				
AST				
Alkaline phosphatase				
Bilirubin				
Creatinine				
Other:				

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Eli Lilly and Company - Global Patient Safety **Case Number:**

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ F ☐ M ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Viral Reactivation			
Type of Reactivation:			
Presenting Symptoms/Signs			
☐ Fever	☐ Jaundice	☐ Confusion	☐ Diarrhea
☐ Rash	☐ Visual Loss	☐ Hepatic Abnormalities	☐ Abdominal Pain
☐ Other Symptoms and Signs:			
Relevant Past Medical History			
☐ Hepatitis B infection	☐ CMV infection	☐ Malignancy	☐ HIV infection
☐ Hepatitis B infection	☐ EBV infection	☐ Cancer chemotherapy	☐ Antiviral therapy
☐ Hepatitis B immunization	☐ Cirrhosis	☐ Hepatocellular carcinoma	☐ Lymphoma
☐ Other relevant history:			
Concomitant Medications/Substances			
☐ Current alcohol use	☐ Current smoking		
☐ Corticosteroids (specify name/dose):			
☐ Immunomodulators (specify name/dose):			
☐ Other Medications (specify name):			

Laboratory Results:				
Laboratory Test	**Normal Range**	**Baseline Value**	**Abnormal Value**	**Improvement Value**
		Date:	Date:	Date:
Hepatitis B Virus Surface Antigen (HBs Ag)				
Hepatitis B Virus Surface Antigen (anti-HBs)				
Hepatitis B Virus Core Antibody IgM (anti-HBc IgM)				
Hepatitis B Virus Core Antibody IgG (anti-HBc IgG)				
Hepatitis B Virus Antibody (anti-HCV)				
Cytomegalovirus Antibody				
Hepatitis B Virus DNA (HBV DNA)				
Hepatitis C Virus RNA (HCV RNA)				
Cytomegalovirus DNA (CMV DNA)				
Epstein-Barr DNA (EBV DNA)				
Neutrophils				
Haemoglobin				
WBC				
ANC				
ALT				
AST				

Eli Lilly and Company - Global Patient Safety **Case Number:**

Laboratory Results:				
Laboratory Test	**Normal Range**	**Baseline Value**	**Abnormal Value**	**Improvement Value**
		Date:	Date:	Date:
Alkaline phosphatase				
Bilirubin				
INR				
Results of other diagnostic studies (including biopsy):				

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Hepatic Disorders
Start date of Event:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Primary Diagnosis for the Reported Event(s):
Has a Hepatologist/ Gastroenterologist been consulted? ☐ No ☐ Yes What were the results?
Hospitalization for this event? ☐ No ☐ Yes
Did the event result in a liver transplant? ☐ No ☐ Yes If yes, please provide the dates and details.

Presenting Signs/Symptoms		
☐ Fever	☐ Jaundice	☐ Abdominal Pain
☐ Rash	☐ Edema	☐ Ascites
☐ Joint Effusions	☐ Nausea	☐ Palmar Erythema
☐ Urticaria	☐ Confusion	☐ Asterixis
☐ Arthralgias	☐ Other (please specify):	
Concurrent Events and Disease(s)		
☐ Sepsis	☐ Kidney Failure	☐ Bleeding
☐ Hypotension	☐ Heart Failure	☐ Diabetes
☐ HIV	☐ Cor pulmonale	☐ Malignancy
☐ Tuberculosis	☐ Autoimmune disease	☐ Inflammatory bowel disease
☐ Other (please specify):		
Relevant Past Medical History		
☐ None	☐ Liver Toxin Exposure	☐ Budd-Chiari syndrome
☐ Hepatitis A	☐ Cirrhosis Child Pugh B or C	☐ Hepatic encephalopathy
☐ Hepatitis B	☐ Alcoholic liver disease	☐ Ascites
☐ Hepatitis C	☐ Autoimmune hepatitis	☐ Hepatorenal syndrome
☐ Gall bladder disease	☐ Hyperbilirubinemia/Jaundice	☐ Portal Hypertension
☐ Fatty liver	☐ Abnormal liver laboratory results	☐ Other:

Concomitant Medical Products (include prescription, OTC, and herbal)

Product Name	Dosage	Indication for Use	Therapy Start Date	Therapy End Date

Eli Lilly and Company - Global Patient Safety **Case Number:**

Concomitant Substances (include prescription, OTC, and herbal)	
☐ Current Alcohol	☐ Past Alcohol
What was the amount of Beer consumed? ounces/ ml (Please check the box next to the correct frequency)	☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly
What was the amount of Wine consumed? ounces/ ml (Please check the box next to the correct frequency)	☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly
What was the amount of Spirits consumed? ounces/ ml (Please check the box next to the correct frequency)	☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly
☐ Current Tobacco	☐ Past Tobacco
☐ Current Cocaine/Methamphetamine	☐ Past Cocaine/Methamphetamine
☐ Others:	

Relevant Laboratory Tests	**Normal Range for Your Institution**	**Baseline Value for Patient**	**Abnormal Value**	**Improvement Value**
		Date:	**Date:**	**Date:**
AST (SGOT)				
ALT (SGPT)				
Total Bilirubin				
Direct Bilirubin				
Alk. Phos.				
GGT				
LDH				
PT-INR				
PT				
Ammonia				
Albumin				
CPK				
Creatinine				
WBC				
Hemoglobin				
Platelet Count				
Blood Alcohol Level				
Urine Toxicology Screen				
Acetaminophen Level				

Eli Lilly and Company - Global Patient Safety **Case Number:**

Serologic Studies (check positive) (Please include values if applicable)	
☐ Anti-mitochondrial Antibody (AMA)	☐ Hepatitis A Virus Antibody IgM (anti-HAV IgM)
☐ Anti-nuclear Antibody (ANA)	☐ Hepatitis A Virus Antibody IgG (anti-HAV IgG)
☐ Anti-liver Kidney Microsomal (antiLKM)	☐ Hepatitis B Virus Core Antibody IgM (anti-HBc IgM)
☐ Anti-actin	☐ Hepatitis B Virus Surface Antibody (anti-HBs)
☐ Anti-smooth Muscle Antibody (ASMA)	☐ Hepatitis B Virus Surface Antigen (HBs Ag)
☐ Cytomegalovirus (CMV) Antibody IgM	☐ Hepatitis B Virus DNA (HBV DNA)
☐ Ebstein Barr (EBV) Serology IgM	☐ Hepatitis C Virus Antibody (anti-HCV)
☐ Ebstein Barr (EBV) Serology IgG	☐ Hepatitis C Virus RNA (HCV RNA)
☐ Other:	☐ Hepatitis E Virus Antibody IgM (anti-HEV IgM)
☐ Other:	☐ Hepatitis E Virus Antibody IgG (anti-HEV IgG)
Please list studies that were completed and were negative:	

Other Study	**Results**
Liver Biopsy	
Hepatic Ultrasound	
MRI	
Magnetic Resonance Cholangiopancreatography (MRCP)	
Magnetic Resonance Cholangiography (MRC)	
CT Scan	
Other:	

Treatment provided (please describe)

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Pregnancy Data Collection – Maternal	
Pregnancy Details	
Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)					
Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring patient's pregnancy:	Medical professional responsible for monitoring the infant:
Name:	Name:
Address:	Address:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pregnancy Data Collection – Paternal

Patient (Father) Details

Name or initials:	Date of Birth or Age:

Father's medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Pregnancy Details

Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Paternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Eli Lilly and Company - Global Patient Safety **Case Number:**

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring the father:	Medical professional responsible for monitoring the mother:
Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pregnancy Outcome Maternal

Pregnancy Details

Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Maternal Concomitant Medications/Substance (please include prescription, OTC and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Breast Feeding Information

Date the breast feeding started Date the breast feeding stopped

Breast feeding continued ? ☐ No ☐ Yes

Was the breast-feeding experience 3 months or longer while on Lilly drug ☐ No ☐ Yes

Eli Lilly and Company - Global Patient Safety **Case Number:**

Pregnancy/Fetal Outcome	
☐ Live birth/full term	☐ Premature birth (less than 37 weeks)
☐ Spontaneous/missed abortion	☐ Fetal death in utero/stillbirth
☐ Live birth with neonatal death	☐ Post natal death
☐ Elective termination (provide below the reason and the gestational age at termination):	
Were congenital or chromosomal abnormalities detected? ☐ No ☐ Yes Please define:	
Did the infant experience perinatal or post-perinatal complications? ☐ No ☐ Yes Please define:	
Was the infant admitted to the neonatal intensive care unit (NICU) at birth? ☐ No ☐ Yes Please define:	
Did the infant experience an increased incidence or severity of infection? ☐ No ☐ Yes Please define:	

Neonatal/Infant Data		
Infant name or initials:	EDC (Due Date):	Date of Delivery:
Gestational age:	Gender: ☐ Undetermined/unknown ☐ Male ☐ Female	
Apgar scores: at 1 minute at 5 minutes		
Weight: ☐ grams ☐ pounds		Length: ☐ cm ☐ inches
Infant's overall health status?		

Infant Adverse Events/Complications
Did the infant experience any problems while breast feeding? ☐ No ☐ Yes
Please describe:
Treatment:
Continuing? ☐ No ☐ Yes
Infant's overall health status:

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown	

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring patient's pregnancy:	Medical professional responsible for monitoring the infant:
Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number**

Pregnancy Outcome Paternal

Patient (Father) Details

Name or initials:	Date of Birth or Age:
Father's medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)	

Pregnancy Details

Name or initials:	Date of Birth or Age:
Due Date:	Last menstrual period:

Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)

Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				

Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)

Contraceptive method:

Exposure Period for Lilly Drug Used During Current Pregnancy

Exposure period - Weeks gestation:
☐ 0-12 weeks/1st trimester ☐ 13-24 weeks/2nd trimester ☐ 25 plus weeks/3rd trimester

Paternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)

Maternal Complications

Has the mother experienced any complications during this pregnancy? ☐ No ☐ Yes

Define complications:

Treatment:

Continuing: ☐ No ☐ Yes

Maternal Testing Performed (such as, amniocentesis, ultrasound, and so forth.)

Eli Lilly and Company - Global Patient Safety **Case Number**

Pregnancy/Fetal Outcome	
☐ Live birth/full term	☐ Premature birth (less than 37 weeks)
☐ Spontaneous/missed abortion	☐ Fetal death in utero/stillbirth
☐ Live birth with neonatal death	☐ Post natal death
☐ Elective termination (provide below the reason and the gestational age at termination):	
Were congenital or chromosomal abnormalities detected? ☐ No ☐ Yes Please define:	
Did the infant experience perinatal or post-perinatal complications? ☐ No ☐ Yes Please define:	
Was the infant admitted to the neonatal intensive care unit (NICU) at birth? ☐ No ☐ Yes Please define:	
Did the infant experience an increased incidence or severity of infection? ☐ No ☐ Yes Please define:	

Neonatal/Infant Data		
Infant name or initials:	EDC (Due Date):	Date of Delivery:
Gestational age:	Gender: ☐ Undetermined/unknown ☐ Male ☐ Female	
Apgar scores: at 1 minute at 5 minutes		
Weight: ☐ grams ☐ pounds	Length: ☐ cm ☐ inches	
Infant's overall health status?		

Infant Adverse Events/Complications
Did the infant experience any problems while breast feeding? ☐ No ☐ Yes
Please describe:
Treatment:
Continuing? ☐ No ☐ Yes
Infant's overall health status:

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome:	

Eli Lilly and Company - Global Patient Safety **Case Number**

☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring the father:	Medical professional responsible for monitoring the mother:
Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

⊞

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Breast Feeding	
Pregnancy Details	
Name or initials:	Date of Birth or Age:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Due Date:			Last menstrual period:		
Previous pregnancies and outcomes of the pregnancies (please indicate if exposed to a Lilly Drug during pregnancy or breast feeding and any complications.)					
Birth Date	Male or Female	Birth Weight	Weeks Gestation	Lilly Drug Used	Mother or baby complications?
	☐ M ☐ F				
Maternal medical history/risk factors (for example, hypertension, seizure disorder, smoking, alcohol use, drug abuse, family history, and so forth.)					
Contraceptive method:					
Maternal Lilly Drug Information					
Drug name:					
Infant's age at first use:			Date of first use:		
Infant's age at last use:			Date of last use:		
Maternal Concomitant Medications/Substance (please include prescription, OTC, and herbal)					
Breast Feeding Information					
Date the breast feeding started:			Date the breast feeding stopped:		
Breast feeding continued? ☐ No ☐ Yes					
Was the breast feeding experience 3 months or longer while on Lilly drug? ☐ No ☐ Yes					
Infant Adverse Events/Complications					
Did the infant experience any problems while breast feeding? ☐ No ☐ Yes Please describe:					
Treatment:					
Continuing? ☐ No ☐ Yes					
Infant's overall health status:					

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Additional Contact Information	
Medical professional responsible for monitoring the mother:	Medical professional responsible for monitoring the infant:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Name:	Name:
Address:	Address:
Phone:	Phone:
Fax:	Fax:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Fistula and/or Gastrointestinal Perforation	
General Questions: What was the anatomic site?	
Primary Diagnosis for the Reported Event(s):	
Hospitalization for this event? ☐ No ☐ Yes	
Presenting Signs and Symptoms:	
Medical History	
☐ Prior GI Bleeding (site):	☐ Renal Impairment
☐ Cancer (site):	☐ Cirrhosis
☐ Peptic Ulcer Disease	☐ Chronic Liver Disease
☐ GERD	☐ Esophageal Varices
☐ Hiatal Hernia	☐ Portal Hypertension
☐ Inflammatory Bowel Disease	☐ AV Malformation
☐ Colonic Polyps	☐ C Difficile Colitis
☐ Bleeding Disorder (specify):	☐ Alcohol Overuse
☐ Recent Surgery (specify date and type):	
☐ Other (specify):	

Other Study	**Results**
Endoscopy	
Ultrasound	
CT/MRI	
Biopsy	
Other:	

Concomitant Medications/Substances:	
☐ NSAIDs:	☐ Antiplatelet Agent:
☐ Corticosteroids:	☐ Antibiotics:
☐ Warfarin:	☐ Proton Pump Inhibitors:
☐ Heparin:	☐ Other:

Laboratory Tests:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Treatment:		
☐ Intravenous Fluids	☐ RBC Transfusion (units):	☐ Antibiotics
☐ Surgery, please describe:		
☐ Other:		

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Mortality	
Date of Death:	**Underlying Cause of Death:**
Was an autopsy performed? ☐ No ☐ Yes Please provide a copy of the death certificate or autopsy report, if available.	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member), please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide a brief explanation:	
Please provide circumstances surrounding the patient's death and include what symptoms were experienced just prior to death (for example, chest pain, dyspnea, headache, syncope, and so forth)	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Medical History:
Concomitant Medications/Substances (please include prescription, OTC, and herbal)

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ F ☐ M ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Blood and Bone Marrow Disorders		
Primary Diagnosis for the Reported Events:		
☐ Aplastic Anemia	☐ Bone Marrow Aplasia	☐ Bone Marrow Depression
☐ Bone Marrow Failure	☐ Bone Marrow Hypoplasia	☐ Polycythemia
☐ Pancytopenia	☐ Neutropenia	☐ Other
Hospitalization for this event? ☐ Yes ☐ No		
Concomitant Medications/Substances (please include prescription, OTC and herbal)		

Clinical Findings:	
☐ Fever ≥ 101°	☐ Hypotension (systolic < 90 mmHg)
☐ Fever < 101°	☐ Sore throat
☐ Sepsis	☐ Petechiae
☐ Chemotherapy within last 30 days	☐ Recent viral illness:
☐ Radiotherapy within last 30 days	
☐ Other (please specify):	

Past Medical History:	
☐ Bone marrow transplantation	☐ Paroxysmal Nocturnal Hemoglobinuria
☐ Hematologic malignancy	☐ Solid tumor
☐ Renal insufficiency	☐ Toxic agent exposure
☐ Myelodysplastic syndrome	☐ Autoimmune disease (please specify):
☐ Neutropenia	☐ Hematologic disorder (please specify):
☐ Chronic obtrusive lung disease	☐ Liver disease (please specify):
☐ Thrombocytopenia	☐ Other allergic disease (please specify):
☐ Viral illness (HIV, CMV, EBV)	☐ Other (please specify):

Laboratory Tests/Investigations

	Normal Range for your institution	**Baseline Value for patient**	**Abnormal Value**	**Improvement Value**
		Date:	Date:	Date:
WBC				
Neutrophil Count				
Hemoglobin				
MCV				
Platelets				
ALT				
Viral Studies (CMV, EBV, HIV)				
Hematocrit				

Eli Lilly and Company - Global Patient Safety **Case Number:**

Other:				

Other Studies	
Study	Results
Bone marrow examination	
Imaging studies (CXR, CT)	
Microbiologic studies	
Serologic studies (HIV, EBV, CMV, other)	
Other:	

Treatment Provided	
☐ Antibiotics	☐ G-CSF
☐ RBC transfusion (units):	☐ Platelet transfusion (units):
☐ Other (please specify):	

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender:	Race:	Weight:	Height:
☐ M ☐ F ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Please provide brief explanation:

Clotting and/or Coagulation Disorders	
Primary Diagnosis for the Reported Event(s)	
☐ Disseminated Intravascular Coagulopathy	☐ Thrombotic Microangiopathy
☐ Hemolytic Uremic Syndrome	☐ Thrombotic Thrombocytopenia
☐ Thrombocytopenia	☐ Other:
Hospitalization for this event? ☐ Yes ☐ No	

Presenting Signs and Symptoms	
☐ Petechiae	☐ Recent Chemotherapy
☐ Bleeding (site):	☐ Recent Massive Trauma
☐ Recent Viral Infection (for example, CMV, HIV, EBV)	☐ Recent Pregnancy
☐ Recent Sepsis	☐ Clinical DIC
☐ Neurologic Findings:	☐ Renal Failure
☐ Pseudothrombocytopenia ruled out	☐ Thrombosis (site):
☐ Anemia	☐ Diarrhea
☐ Other (please specify):	☐ Cardiac Symptoms

Medical History/Risk Factors	
☐ Thrombocytopenia	☐ Hypersplenism
☐ Idiopathic Thrombocytopenic Purpura	☐ Liver Disease
☐ Hematologic Disorder	☐ Renal Failure
☐ Bleeding Disorder	☐ Alcohol Abuse
☐ Cancer Chemotherapy	☐ Myelodysplasia
☐ Autoimmune Disorder	☐ Other (please specify):

Concomitant Meds/Substances (include OTC, herbal, recently discontinued drugs)	
☐ Heparin/LMWH	☐ Aspirin
☐ Glycoprotein IIb/IIIa Inhibitor:	☐ Chemotherapy

Eli Lilly and Company - Global Patient Safety **Case Number:**

☐ Other Antiplatelet Agents:	☐ Radiation Therapy
☐ Oral Anticoagulant:	☐ NSAIDs
☐ Quinine	☐ Hydrochlorothiazide
☐ Immunosuppressants	☐ Other (please specify):

Laboratory Tests/Investigation				
	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Hemoglobin				
WBC				
Platelets				
INR/Prothrombin Time				
aPTT				
d-Dimer				
Serum Creatinine				
Lactate Dehydrogenase				
Platelet-associated IgG				
Antinuclear Antibodies				
Hemoglobin				
Anti-PF4 Antibodies				
ATAMTS13 Assay				
Other:				

Test	**Result (include units of measurement)**
Peripheral Smear	Schistocytes ☐ Present ☐ Absent ☐ Unknown
	Other:
Bone Marrow Examination	Megakaryocytes ☐ Normal ☐ Increased ☐ Decreased ☐ Unknown
	Other:
Other:	

☐ Platelet Transfusion (units):	☐ RBC Transfusion (units):
☐ Plasmapheresis	☐ Fresh Frozen Plasma (units):
☐ Other:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Treatment Provided (please describe):

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown
Event outcome: ☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown ☐ Recovered with Sequella (Please provide details):	

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided by: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender	Race	Weight:	Height:
☐ F ☐ M ☐ Unknown	☐ Caucasian ☐ Asian ☐ Black ☐ Other	☐ lb ☐ kg	☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Thromboembolism		
Primary Diagnosis for the Reported Event(s):		
☐ Pulmonary Embolism	☐ Deep Vein Thrombosis	☐ Other:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Please provide type of thromboembolism: ☐ Venous ☐ Arterial	
Hospitalization for this event? ☐ No ☐ Yes	
Medical History	
☐ Family history of thromboembolic events	☐ Personal history of smoking (please specify):
☐ Recent immobilization/hospitalization/long distance travel	☐ Recent surgery (for example, varicose veins) (please specify):
☐ Pulmonary embolism	☐ Deep vein thrombosis
☐ Chronic venous stasis, for example, varicose veins	☐ Peripheral vascular disease
☐ Hormone replacement therapy	☐ Recent pelvic/lower extremity fracture
☐ Recent trauma	☐ Cancer
☐ Obesity	☐ Hypercoagulability (please specify):
☐ Recent myocardial infarction	☐ Congestive heart failure
☐ Recent infection	☐ Chronic renal disease/Nephrotic syndrome
☐ Inflammatory bowel disease	
☐ Recent childbirth	
☐ Other (please specify):	
Concomitant Meds/Substances	
☐ Heparin (please specify):	☐ Oral contraceptives/Estrogen (please specify):
☐ Other (please specify):	☐ Anti-psychotic drugs (please specify):

Laboratory Test	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	**Date:**	**Date:**
D-dimer				
Platelet Count				
INR				
Hemoglobin/Hematocrit				
Testosterone Level				
Factor V Leiden				
Prothrombin G20210A				
MTHRF C677T-A129C				
Factor VIII				
Factor XI				
Antiphospholipid Antibody Level				
Protein S				
Protein C				

Eli Lilly and Company - Global Patient Safety **Case Number:**

Laboratory Test	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
4G49 Plasminogen Activator Inhibitor				
Antithrombin Level				
Sedimentation Rate				
Activated Protein C				
Other:				

Other Relevant Studies	Results
CT Chest	
Duplex Ultrasonography	
Impedance Plethysmography	
Venogram	
CT/MRI	
Ventilation/Perfusion Scan	
Angiography	
Other:	

Treatment	
☐ Heparin	☐ Oral Anticoagulant
☐ Antiplatelet Agents:	☐ Thrombolytic Agent
☐ Angioplasty	☐ Vena Cava Filter
☐ Embolectomy	☐ Arterial Bypass
☐ Other (please specify):	

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Eli Lilly and Company - Global Patient Safety **Case Number:**

Spontaneous Follow-up Form

Reported Events:

Date: Lilly Case #:

Information Provided By: Signature/Initials: Fax:

Patient's Name or Initials: Patient's Birth Date or Age:

Gender: ☐ M ☐ F ☐ Unknown	Race: ☐ Caucasian ☐ Asian ☐ Black ☐ Other	Weight: ☐ lb ☐ kg	Height: ☐ in ☐ cm

Reported Drug:

Lot/Control Number (if available): Indication:

Dose: Frequency: Formulation:

Start Date: Dose when event occurred: Route:

Drug D/C? ☐ No ☐ Yes Date D/C: If Discontinued, did the event resolve? ☐ No ☐ Yes

Drug Restarted? ☐ No ☐ Yes Date Restarted: If Restarted, did the event occur? ☐ No ☐ Yes

Date of Death:	Underlying Cause of Death:
Was an autopsy performed? ☐ No ☐ Yes **Please provide a copy of the death certificate or autopsy report, if available.**	Source of above cause of death: ☐ Listed as underlying cause on death certificate ☐ Suspected cause of death from physician directly involved in patient's care ☐ Other source (for example, family member) – please specify: ☐ Listed on autopsy report
Possible Relatedness	
Is the reported cause of death related to drug? ☐ No ☐ Unlikely ☐ Likely ☐ Yes ☐ Unknown	
Please provide brief explanation:	

Eli Lilly and Company - Global Patient Safety **Case Number:**

Rhabdomyolysis	
Primary diagnosis for the reported event(s):	
Hospitalization for this event? ☐ No ☐ Yes	
Presenting Signs and Symptoms	
☐ Muscle pain	☐ Weakness
☐ Myoglobinuria	☐ Tenderness
☐ Other:	

Medical History/Risk Factors (please check and specify):	
☐ Antipsychotic use:	☐ Muscle rigidity
☐ Use of illicit drugs	☐ Alcohol use
☐ Recent infections	☐ Involvement in increased muscular activity or injury
☐ Hyperthermia	☐ Seizures, burns, electric shock
Others:	
Concomitant Medications/Substances (please include prescription, OTC and herbal)	

Laboratory Test	Normal Range for Your Institution	Baseline Value for Patient	Abnormal Value	Improvement Value
		Date:	Date:	Date:
Creatine Phosphokinase				
Serum Creatine				
Serum Sodium				
Serum Potassium				
Serum Calcium				
Serum Magnesium				
Serum Phosphate				
BUN				
Myoglobin				
Lactate dehydrogenase				
Aldolace				
Creatinine Clearance				
Other:				

Eli Lilly and Company - Global Patient Safety **Case Number:**

Was this event related to a Lilly drug?	☐ Yes ☐ No ☐ Unknown

Event outcome:
☐ Recovered ☐ Not recovered ☐ Recovering ☐ Worsened ☐ Unknown
☐ Recovered with Sequella (Please provide details):

Please provide rationale for relatedness assessment:

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if applicable)

Approved key messages of the additional risk minimisation measures

Physician educational material:

- The Summary of Product Characteristics
- Healthcare professionals training material (2 separate materials are available: 1 for RA and JIA, and 1 for AD, paediatric AD, and AA)
- Patient alert card

Healthcare professionals training material:

- Patient Alert Card (PAC) will be provided to the patient as part of the initial discussion in which the rheumatologist or dermatologist is instructed to:
    - Provide a PAC to each patient
    - Advise them that the card should be read in conjunction with the Patient Information Leaflet

Advise the patients:

- Indication and posology statements provided to reinforce in whom baricitinib should be used.
- That baricitinib increases the potential risk of infections. Patients should be instructed to seek immediate medical attention, if signs or symptoms suggesting infection appear. As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. Baricitinib should only be used in patients 65 years of age and older if no suitable treatment alternatives are available.
- That baricitinib use should be stopped in case of herpes zoster or any other infection that doesn't respond to standard treatment until the event resolves. Patients should not be immunised using live attenuated vaccines shortly before or during treatment with baricitinib.
- Prior to initiating Olumiant, it is recommended that all patients, particularly paediatric patients, be brought up to date with all immunisations in agreement with local current immunisation guidelines.
- Prescribers should screen the patients for viral hepatitis before commencing baricitinib treatment. Active tuberculosis should also be ruled out.
- That baricitinib use is associated with hyperlipidaemia; prescribers should monitor the patient's lipid parameters and manage the hyperlipidaemia, if detected.
- Baricitinib increases the risk of venous thrombosis and pulmonary embolism. Baricitinib should be used with caution in patients with known risk factors for DVT/PE other than cardiovascular or malignancy risk factors. Patients should be instructed to seek immediate medical attention if signs or symptoms of DVT/PE appear.

- That there is a potentially increased risk of MACE in patients with certain risk factors using JAK inhibitor treatment, including baricitinib. In patients 65 years of age and older, patients who are current or past long-term smokers, and patients with other cardiovascular risk factors, baricitinib should only be used if no suitable treatment alternatives are available.
- That lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including baricitinib. In patients over 65 years of age, patients who are current or past long-term smokers, or with other malignancy risk factors (for example, current malignancy or history of malignancy) baricitinib should only be used if no suitable treatment alternatives are available.
- That baricitinib is contraindicated in pregnancy as pre-clinical data showed reduced foetal growth and malformations. Physicians should advise women of child-bearing potential to use contraception during treatment and for a week after its ending. If a planned pregnancy is considered, baricitinib treatment should be stopped.

Patient alert card:

- That treatment with baricitinib may increase the risk of infections and viral re-activation, which can become serious if not treated.
- Signs or symptoms of infections including general symptoms, and specifically tuberculosis and herpes zoster signs and symptoms; and a warning for the patients to seek immediate medical attention if signs or symptoms suggesting infection appear.
- Patients should seek immediate medical attention if signs and symptoms of myocardial infarction or stroke occur.
- That baricitinib should not be taken while pregnant and that women should inform their doctor should they become (or wish to become) pregnant.
- That baricitinib may cause a blood clot in the leg that may travel to the lungs; a description of signs and symptoms is provided, along with a warning for the patients to seek immediate medical attention if signs or symptoms suggesting a blood clot appear.
- That baricitinib may cause non-melanoma skin cancer and that the patients should talk to their doctor if new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.
- That the Patient Alert Card should be carried by the patient at any time and to share it with other health care professionals involved in their treatment.

Name and contact details of the Olumiant prescriber.

Name of the patient.

Direct Healthcare Professional Communication (DHPC)

< Month > 2022

Cibinqo® (abrocitinib), Jyseleca® (filgotinib), Olumiant® (baricitinib), Rinvoq® (upadacitinib) and Xeljanz® (tofacitinib) – Updated recommendations to minimise the risk of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality with use of Janus Kinase (JAK) inhibitors.

Dear Healthcare Professional,

AbbVie, Galapagos, Lilly and Pfizer in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following:

Summary

- **An increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality has been observed in patients with rheumatoid arthritis (RA) with certain risk factors using JAK inhibitor treatment compared to TNFα inhibitors.**
- **These risks are considered class effects and relevant across all approved indications of JAK inhibitors in inflammatory and dermatologic diseases.**
- **These JAK inhibitors should only be used if no suitable treatment alternatives are available in patients:**
    - **65 years of age and older;**
    - **who are current or past long-time smokers;**
    - **with other cardiovascular or malignancy risk factors.**
- **JAK inhibitors should be used with caution in patients with VTE risk factors other than those listed above.**
- **Dosing recommendations are revised for some patient groups with risk factors.**
- **Periodic skin examination is recommended for all patients.**
- **Prescribers should discuss with patients the risks associated with the use of JAK inhibitors.**

Background on the safety concern

Janus kinase (JAK) inhibitors Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) are approved for the treatment of several chronic inflammatory disorders (rheumatoid arthritis (RA), psoriatic arthritis, juvenile

idiopathic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, ulcerative colitis, atopic dermatitis, and alopecia areata). The approved use differs for the different products, as outlined in the respective product information.

In March 2021, a Direct Healthcare Professional Communication (DHPC) for Xeljanz (tofacitinib) was sent to healthcare professionals, informing them that data from a completed clinical trial (A3921133) in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, suggest a higher risk of major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer (NMSC)) with tofacitinib as compared to patients treated with a TNF-alpha inhibitor.

An additional DHPC was sent in July 2021 to inform about an increased incidence of myocardial infarction, lung cancer, and lymphoma with tofacitinib compared to TNF-alpha inhibitors observed in the same clinical trial, as well as adopted recommendations for the product information of tofacitinib.

Preliminary findings from an observational study (B023) involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of major cardiovascular events and VTE in patients with RA treated with Olumiant compared with those treated with TNF-alpha inhibitors.

Following the finalization of a review procedure of the available data across these five JAK inhibitors by the EMA, recommendations have been adopted as specified in the "summary" above. The product information and the educational materials for healthcare professional and patients is being updated accordingly.

This letter is not intended as a complete description of the benefits and risks related to the use of these products. For further details, please refer to the updated SmPC for the respective products.

Call for reporting_

Healthcare providers and patients are encouraged to report adverse reactions in accordance with the national spontaneous reporting system. <to be filled nationally>

Please find the relevant contact for each product in the table below:

Product	Cibinqo® (abrocitinib)	Jyseleca® (filgotinib)	Olumiant® (baricitinib)	Rinvoq® (upadacitinib)	Xeljanz® (tofacitinib)
MAH	Pfizer	Galapagos	Lilly	AbbVie	Pfizer
Telephone number					
Email address					

Company contact point

<to be filled nationally>

Product	Cibinqo® (abrocitinib)	Jyseleca® (filgotinib)	Olumiant® (baricitinib)	Rinvoq® (upadacitinib)	Xeljanz® (tofacitinib)
MAH	Pfizer	Galapagos	Lilly	AbbVie	Pfizer
Website address					
Postal address					
Telephone number					
Email address					

Annexes

<Link/reference to other available relevant information, such as information on the website of a competent authority

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Cibinqo® (abrocitinib), Jyseleca® (filgotinib), Olumiant® (baricitinib), Rinvoq® (upadacitinib) and Xeljanz® (tofacitinib)
Marketing authorisation holder(s)	AbbVie, Galapagos, Lilly and Pfizer
Safety concerns and purpose of the communication	Inform about important updates in the SmPC for JAK inhibitors which concern warnings and actionable advice regarding malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality.
DHPC recipients	Allergologists, dermatologists, gastroenterologists, rheumatologists, paediatricians

	The target group should be further defined at national level, in agreement with the respective national competent authority.
Member States where DHPC will be distributed	All EU/EEA member states

Timetable	**Date**
DHPC and communication plan (in English) agreed by PRAC	27/10/2022
DHPC and communication plan (in English) agreed by CHMP	10/11/2022
Submission of translated DHPCs to national competent authorities for review	24/11/2022
Agreement of translations by national competent authorities	1/12/2022
Dissemination of DHPC	EC decision + 5 calendar days