EU Risk Management Plan for Skyrizi® (Risankizumab)

AbbVie

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP: Addition of pediatric psoriasis indication

Summary of significant changes in the RMP: A summary of significant changes is included in RMP Annex 8.

Administrative Information on the RMP

Part Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
Part I: Product(s) Overview	Aug 2025	7.0
Part II: Safety Specification		
SI – Epidemiology of the Indication(s) and Target Population(s)	Aug 2025	7.0
SII – Non-Clinical Part of the Safety Specification	Aug 2023	5.0
SIII – Clinical Trial Exposure	Aug 2025	7.0
SIV – Populations Not Studied in Clinical Trials	Aug 2025	7.0
SV – Post-Authorization Experience	Aug 2025	7.0
SVI – Additional EU Requirements for the Safety Specification		
SVII – Identified and Potential Risks	Aug 2025	7.0
SVIII – Summary of the Safety Concerns	Aug 2025	7.0
Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)	Apr 2026	7.2
Part IV: Plan for Post-Authorization Efficacy Studies		
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Aug 2025	7.0
Part VI: Summary of the Risk Management Plan	Aug 2025	7.0
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Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	Aug 2025	7.0
Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	Aug 2025	7.0
Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms	Apr 2026	7.2
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Annex 6 – Details of Proposed Additional Risk Minimization Activities (If Applicable)		
Annex 7 – Other Supporting Data (Including Referenced Material)	Aug 2023	5.0

Part	Module/Annex	Date last updated for submission (sign-off date)	Version number of RMP when last submitted
	Annex 8 – Summary of Changes to the Risk Management Plan Over Time	Apr 2026	7.2
	Annex 9 – Local Currently-Approved Country Labeling		
	Annex 10 – Local Risk Management/Mitigation Plan		

Other RMP versions under evaluation: not applicable

Details of the currently approved EU RMP:

Version number: v6.1

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QPPV name: Sina Schader

QPPV oversight declaration: The content of the RMP has been reviewed and approved by the marketing authorization holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

5-ASA	5-aminosalicylic acid
ACR	American College of Rheumatology
ACR/NAPF	American College of Rheumatology/National Psoriasis Foundation
ACR20	American College of Rheumatology 20% improvement criteria
ADD	average daily dose
ATC	anatomical therapeutic chemical
AUC	area under the curve
Bio-IR	biologic therapy-intolerant or inadequate responder
BMI	body mass index
CAD	coronary artery disease
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CHD	coronary heart disease
CHMP	Committee for Human Medicinal Products
CHO	Chinese hamster ovary (cells)
CI	confidence interval
CNS	central nervous system
CRP	C-reactive protein
csDMARD(s)	conventional synthetic disease-modifying anti-rheumatic drug(s)
csDMARD-IR	conventional synthetic disease-modifying anti-rheumatic drug–intolerant or inadequate responder
CVD	cardiovascular disease
CYP450	cytochrome P450
DM	diabetes mellitus
DMARD(s)	disease-modifying anti-rheumatic drug(s)
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EEA	European Economic Area
EIM	extraintestinal manifestation
EMA	European Medicines Agency
EOO	End-of-Observation (visit)
EPAR	European Public Assessment Report
ePPND	enhanced pre-/post-natal development

EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GD	gestation day
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HBV	hepatitis B virus
HCP	healthcare professional
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HTN	hypertension
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
IDV	Integrated Dataverse
Ig	immunoglobulin
IL	interleukin
IMEDS	Innovation in Medical Evidence and Development Surveillance
incl.	including
IV	intravenous(ly)
JAK	Janus kinase
KLH	keyhole limpet hemocyanin
MACE	Major Adverse Cardiovascular Events
MDA	minimal disease activity state
MI	myocardial infarction
NF	nuclear factor
NF-kB	Nuclear factor-kB
NHANES	National Health and Nutrition Examination Survey
NHP	non-human primate
NMSC	non-melanoma skin cancer
NOAEL	no-observed-adverse-effect level
NPF	National Psoriasis Foundation
NSAIDs	nonsteroidal anti-inflammatory drugs
OBI	on-body injector
PASS	post-authorization safety study
PFS	pre-filled syringe

PL	package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	psoriatic arthritis (or arthropathic psoriasis)
PSC	primary sclerosing cholangitis
PSOLAR	Psoriasis Longitudinal Assessment and Registry
PSUR	Periodic Safety Update Report
PTY	patient treatment-years
PY	patient-year(s)
q12w	every 12 weeks
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SC	subcutaneous(ly)
SLGT2	sodium-glucose co-transporter 2
SmPC	Summary of Product Characteristics
STAT	signal transducer and activator transcription
SWIBREG	Swedish Inflammatory Bowel Disease Register
TB	tuberculosis
TDAR	T-cell-dependent antibody response
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
UC	ulcerative colitis
UK	United Kingdom
US	United States
WHO	World Health Organization

Part I: Product(s) Overview

Table 1. Product Overview

Active substance(s) (INN or common name)	Risankizumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, interleukin (IL) inhibitor, ATC code: L04AC18
Marketing Authorization Applicant	AbbVie Deutschland GmbH & Co KG
Medicinal products to which this RMP refers	• Skyrizi 150 mg solution for injection in pre-filled pen • Skyrizi 150 mg solution for injection in pre-filled syringe • Skyrizi 75 mg solution for injection in pre-filled syringe • Skyrizi 55 mg solution for injection in pre-filled syringe • Skyrizi 600 mg concentrate for solution for infusion • Skyrizi 360 mg solution for injection in cartridge • Skyrizi 180 mg solution for injection in cartridge • Skyrizi 180 mg solution for injection in pre-filled syringe • Skyrizi 90 mg solution for injection in pre-filled syringe
Invented name(s) in the European Economic Area (EEA)	Skyrizi
Marketing authorization procedure	European Union (EU) Centralised Procedure
Brief description of the product	Chemical class: Humanized monoclonal antibody of the immunoglobulin (IgG) 1 subclass
	Summary of mode of action: Risankizumab selectively binds with high affinity (< 29 pM) to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor.
	Important information about its composition: The active substance, risankizumab, is produced in a mammalian cell line (Chinese hamster ovary [CHO] cells) using recombinant deoxyribonucleic acid (DNA) technology. The product is currently supplied as a solution in pre-filled pen, pre-filled syringe, or pre-filled cartridge for subcutaneous injection and concentrate for solution for infusion in vial. Each 150 mg pre-filled pen or pre-filled syringe contains 1 mL solution (150 mg/mL formulation). Each 90 mg pre-filled syringe contains

	1.0 mL solution (90 mg/mL formulation). Each 75 mg pre-filled syringe contains 0.83 mL solution (90 mg/mL formulation). Each 55 mg pre-filled syringe contains 0.37 mL solution (150 mg/mL formulation). The 360 mg/2.4 mL and 180 mg/1.2 mL presentations of the 150 mg/mL formulation will be administered by SC injection using an OBI with a pre-filled cartridge. Each 180 mg pre-filled syringe contains 1.2 mL solution (150 mg/mL formulation). Each 600 mg liquid vial contains 10.0 mL concentrate for solution for infusion (60 mg/mL formulation). The intravenous (IV) formulation is qualitatively the same as the 150 mg/mL formulation.
Hyperlink to the Product Information	https://www.ema.europa.eu/en/documents/product-information/skyrizi-epar-product-information_en.pdf
Indication(s) in the EEA	Current: Plaque Psoriasis: Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Psoriatic Arthritis: Skyrizi, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Crohn's Disease: Skyrizi is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy. Ulcerative Colitis: Skyrizi is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy. Proposed: Pediatric Plaque Psoriasis: Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

Dosage in the EEA	Current: Plaque Psoriasis and Psoriatic Arthritis: 150 mg administered by SC injection at Week 0, Week 4, and every 12 weeks thereafter. CD: Induction treatment: 600 mg administered by intravenous infusion at Week 0, Week 4, and Week 8 Maintenance treatment: 360 mg administered by subcutaneous injection at Week 12 and every 8 weeks thereafter. UC: Induction treatment: 1200 mg administered by intravenous infusion at Week 0, Week 4, and Week 8 Maintenance treatment dose based on individual patient presentation: 180 mg for patients with adequate improvement in disease activity after induction or 360 mg for patients with inadequate improvement in disease activity after induction administered by subcutaneous injection at Week 12 and every 8 weeks thereafter. Proposed for Plaque psoriasis in pediatric patients 6 to < 18 years and weighing at least 40 kg: 150 mg administered by SC injection at Week 0, Week 4, and every 12 weeks thereafter. Proposed for Plaque psoriasis in pediatric patients 6 to < 18 years and weighing less than 40 kg: 55 mg administered by SC injection at Week 0, Week 4, and every 12 weeks thereafter.

Pharmaceutical form(s) and strengths	Current: Plaque Psoriasis and Psoriatic Arthritis: 1. Skyrizi 75 mg solution for SC injection in pre-filled syringe 2. Skyrizi 150 mg solution for SC injection in pre-filled syringe and in pre-filled pen. CD and UC Induction: 1. Skyrizi 600 mg concentrate for solution for infusion CD maintenance 1. Skyrizi 360 mg solution for injection in cartridge 2. Skyrizi 180 mg solution for SC injection in pre-filled syringe 3. Skyrizi 90 mg solution for SC injection in pre-filled syringe UC maintenance 1. Skyrizi 180 mg and 360 mg solution for injection in cartridge 2. Skyrizi 180 mg solution for SC injection in pre-filled syringe Proposed: Pediatric Plaque Psoriasis: 1. Skyrizi 75 mg solution for SC injection in pre-filled syringe 2. Skyrizi 150 mg solution for SC injection in pre-filled syringe and in pre-filled pen. 3. Skyrizi 55 mg solution for SC injection in pre-filled syringe
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

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

Indication: Plaque Psoriasis (Adult and Pediatric)

Incidence: The incidence of psoriasis (per 100,000 person-years) in adults ranged from 129 to 172 in the United Kingdom (UK) (Springate 2017), from 104 to 181 in Denmark (Egeberg 2017), and from 230 to 321 in Italy (Vena 2010). In the United States (US), the incidence of psoriasis in women was approximately 91 per 100,000 person-years (Kumar 2013). The

incidence of pediatric psoriasis globally was 33.0 per 100,000 children, although the incidence in higher sociodemographic index countries was higher (70.5 per 100,000 in North America and 67.5 per 100,000 in Western Europe) (Jin 2025). In Italy, the 2019 incidence rate was 0.58 per 1,000 for 0-14 year olds and 1.60 per 1,000 for 15-17 year olds (Lapi 2023). The incidence in Taiwan in 2013 was 58.7 per 100,000, with a higher incidence in older children (27.2 per 100,000 [12-18 years]) than younger children (11.2 per 100,000 [≤12 years]) (Lin 2024).

Prevalence: In Europe, the prevalence of psoriasis ranged from 1.21% (Croatia) to 11.43% (Norway) in adults (World Health Organization 2016). The proportion of adults with moderate to severe psoriasis was 2.9% in the UK (Gelfand 2007), 12.1% in Sweden(Svedbom 2015), and 15.3% in Denmark (Egeberg 2017). In the US, approximately 6.7 million adults (3.1%) aged 20+ years have psoriasis (Helmick 2014). In patients with plaque psoriasis, approximately 80% have mild to moderate disease, and 20% have moderate to severe disease (Menter 2008). It appears that the prevalence of psoriasis is highest in Northern Europe and lowest in East Asia (Gupta 2014). There appears to be an increasing prevalence of psoriasis in Norway (Danielsen 2013).

The prevalence of pediatric psoriasis is lower than in adults, and varies by geographic location from 0.02% in East Asia to 0.21% in Western Europe (Parisi 2020). In the United States, pediatric psoriasis was diagnosed in 0.13% of children, corresponding to a prevalence rate of 128 per 100,000 children, of which 12.5% were considered moderate-to-severe (Paller 2018).

Demographics of the target population: Psoriasis incidence and prevalence in adults are similar in both sexes (Helmick 2014, Kurd 2009). However, in children the incidence of psoriasis is higher in females (Lin 2024). Prevalence is also higher among females (146 per 100,000 persons) than in males (110 per 100,000 persons) (Paller 2018). Psoriasis prevalence in adults peaks in patients aged 30 to 60 years of age (Ferrándiz 2001, Helmick 2014). In US children, prevalence increases with age as follows: 30 per 100,000 (0-3 years), 109 per 100,000 (4-11 years), and 205 per 100,000 (12-17 years) (Paller 2018). In the US, psoriasis prevalence is higher in people categorized as Caucasian/non-Hispanic white compared with people categorized as African-American/non-Hispanic black or Hispanic/other (Gelfand 2005, Helmick 2014).

Risk Factors: High body mass index (BMI), exposure to tobacco smoke at home, and stressful life events may be risk factors for paediatric psoriasis, and alcohol consumption and smoking may be risk factors for adult psoriasis (Brenaut 2013, Li 2012, Ozden 2011). Genetic predisposition (e.g., human leukocyte antigen [HLA]-Cw*06) and high latitude are also important risk factors (Springate 2017, Wu 2011).

The main treatment options: Treatment depends on the extent of disease. The traditional treatment paradigm in managing psoriasis patients is that those with limited disease are treated with topical agents such as corticosteroids, calcipotriene, or dithranol. In moderate to

severe cases, or where topical therapy has proven ineffective, phototherapy or systemic treatment are available options. Exposure to ultraviolet B phototherapy may be effective but is often inconvenient due to the frequency of treatments, which are usually administered in a physician's office. Exposure to psoralen and ultraviolet A therapy is also effective but has been associated with the development of melanoma and of squamous cell carcinoma of the skin. Chronic therapy with traditional systemic treatments for moderate and severe psoriasis, including oral retinoids, methotrexate, fumaric acid esters, and cyclosporine, can be limited by lack of efficacy or precluded by dose dependent side effects. Oral retinoids can cause hypertriglyceridemia and hepatitis; methotrexate can cause bone marrow suppression, pneumonitis, and cirrhosis; cyclosporine can cause hypertension (HTN) and renal toxicity; and fumaric acid esters can cause gastrointestinal toxicity and flush. Due to the toxicity of systemic agents, these medications are generally administered in rotation to avoid long-term or cumulative toxicities (Menter 2008, Menter 2010, Menter 2009a, Menter 2009b).

Tumor necrosis factor alpha (TNF-α) antagonists, including adalimumab, etanercept, and infliximab, are also used to treat moderate to severe plaque psoriasis. Other approved and/or recommended drugs for psoriasis include an interleukin (IL)-12 and IL-23 inhibitor ustekinumab, IL-17A inhibitors (secukinumab and ixekizumab), an IL-17 receptor A antagonist (brodalumab), IL-23 inhibitors (guselkumab and tildrakizumab), and a phosphodiesterase 4 inhibitor apremilast (Food and Drug Administration 2017, Nast 2015).

While anti-tumor necrosis factors (TNFs) have long provided an important therapeutic option for patients with moderate to severe plaque psoriasis, and newer entrants such as IL-17 and IL-12/23 inhibitors have added incremental clinical benefit, marked reduction in the extent and severity of disease, there remains an unmet medical need for adult patients with moderate to severe plaque psoriasis (Kragballe 2014). Patients can relapse because of nonadherence or treatment discontinuation due to safety risks, or inadequate treatment of symptoms such as pain or itching, leaving many patients with moderate to severe psoriasis undertreated. Plaque psoriasis is a chronic life-long disease, and patients require multiple therapeutic options including medications that are more convenient (or have longer dosing interval), and are safe and more effective (Boehncke 2017, Feldman 2016, Lambert 2018).

Treatment options for pediatric psoriasis generally mirror those used in adult psoriasis. Similar to adults, children with less severe disease may use topical medicines (such as corticosteroids, calcipotriene, or dithranol). In moderate to severe cases, or when topicals prove ineffective, phototherapy or systemic therapy (including methotrexate, cyclosporine, oral retinoids, fumaric acid esters) can be used. Biologics that are available for use in children with plaque psoriasis include TNF inhibitors (etanercept, adalimumab, and infliximab), IL-12 and IL-23 inhibitor ustekinumab, and IL-17A inhibitors (secukinumab and ixekizumab) (Diotallevi 2022, Menter 2020). The phosphodiesterase 4 inhibitor, apremilast, may also be used (Otezla (apremilast) [Summary of Product Characteristics] 2020).

Natural history of psoriasis in the population, including mortality and morbidity: Plaque psoriasis is usually chronic with intermittent remissions. In addition to cutaneous involvement, plaque psoriasis may be associated with arthritis and extra-articular manifestations such as ocular manifestations (conjunctivitis, corneal lesions and uveitis) (Basko-Plluska 2012). Mortality in psoriasis patients ranges from 11.9 to 26.0 per 1000 patient-years (PY) (Abuabara 2010, Gelfand 2007, Lee 2017, Masson 2017, Ogdie 2014, Stern 2011, Svedbom 2015). Compared with patients without psoriasis, severe psoriasis was associated with increased all-cause mortality, with hazard ratio ranging from 1.5 to 1.8, whereas mild psoriasis was found to have variable association with all-cause mortality (Gelfand 2007, Ogdie 2014, Svedbom 2015).

Pediatric psoriasis plaques may be thinner and smaller than in adults (Bronckers 2015). In infants, psoriasis most often affects the diaper areas, while the scalp, trunk and extremities are frequent areas of involved in older children(Eichenfield 2018). About 1/3 of diagnosed cases of psoriasis begin during childhood (Bronckers 2015). Mortality is not generally a concern for children with psoriasis, however, it can lead to other comorbidities.

Important co-morbidities: Obesity, metabolic syndrome, HTN, diabetes mellitus (DM), and MACE, malignancy (i.e., lymphoma, non-melanoma skin cancer [NMSC], lung cancer), autoimmune diseases (i.e., Crohn's disease and celiac disease), and psychological disorders, such as depression, anxiety, and suicidal ideation and behavior are conditions reported in adults. There is limited evidence on co-morbidities in pediatric psoriasis, but general consensus suggests that several adult comorbidities may also be experienced by children with psoriasis, including obesity, metabolic syndrome, dyslipidemia, hypertension, mental health conditions, and inflammatory bowel disease (Menter 2020). In the US, the most common comorbidities in children were anxiety, depression and obesity (Edson-Heredia 2021).

Indication: Psoriatic Arthritis

Incidence: The pooled psoriatic arthritis incidence from nine population-based studies conducted in Europe, the US, and Argentina was 8.3 per 100,000 PY (Scotti 2018). In Europe, the incidence of psoriatic arthritis per 100,000 PY has ranged from 3.0 in Greece to 41.3 in Norway (Hoff 2015, Scotti 2018). The incidence per 100,000 PY in other European countries was 3.6 in the Czech Republic (Hanova 2010), 8.0 in Sweden, 23.1 in Finland (Scotti 2018), and 7.3 to 27.3 in Denmark (Egeberg 2017).

The incidence of psoriatic arthritis has been reported to increase over the last decades with some geographic differences. In the US, the incidence rates increased from 3.6 per 100,000 PY between 1970 - 79, to 6.6 per 100,000 PY between 1982 - 91, to 9.8 per 100,000 PY between 1990 - 2000 (Shbeeb 2000, Wilson 2009). In Denmark, the incidence estimate increased from 7.3 to 27.3 per 100,000 PY from 1997 to 2010 (Egeberg 2017). In other geographic areas, the incidence of psoriatic arthritis remained stable (Eder 2018).

The incidence of psoriatic arthritis in patients with psoriasis is higher than in the general population (Solmaz 2018). Across observational and clinical studies, the incidence of psoriatic arthritis among patients with psoriasis ranged from 270 per 100,000 PY in the US and UK, to 2,700 per 100,000 PY in Canada (Alinaghi 2019), and up to 7,400 per 100,000 PY in Europe (Christophers 2010).

Prevalence: The pooled psoriatic arthritis prevalence from 26 population-based studies conducted in different countries around the world was 133 per 100,000 population (Scotti 2018). By geographic areas, the highest prevalence was reported in Asia (200 per 100,000 population), followed by Northern Europe (172 per 100,000 population), North America (138 per 100,000 population), South America (122 per 100,000 population), and Southern Europe (99 per 100,000 population). The prevalence per 100,000 population in European countries ranged from 20 in Sweden to 670 in Norway (Scotti 2018). Prevalence estimates in the US have ranged from 0.06% to 0.25% (Ogdie 2015).

Approximately 1 in 4 patients with psoriasis has psoriatic arthritis (Alinaghi 2019). Across 266 observational and clinical studies, the pooled prevalence of psoriatic arthritis among patients with psoriasis (all ages) was 19.7%; the psoriatic arthritis prevalence was 22.7% in European patients with psoriasis and 19.5% in North American patients with psoriasis (Alinaghi 2019). Among patients with moderate-to-severe psoriasis, the pooled prevalence of psoriatic arthritis was 24.6%.

Demographics of the target population: Psoriatic arthritis in adults has a mean age of onset occurring in the fourth decade of life and affects men and women approximately equally (Koolaee 2013), with prevalence estimates of 150 in men and 133 in women per 100,000 population, respectively (Scotti 2018). The prevalence of psoriatic arthritis in African American patients has been found to be lower than in Caucasians (30% versus 65%, respectively) (Kerr 2015).

Risk Factors: Potential nonmodifiable risk factors for psoriatic arthritis in adults include a family history of/genetic predisposition for psoriatic arthritis and psoriasis-related factors (age of onset, severity, nail dystrophy/lesions, psoriasis lesions located on the scalp or intergluteal/perianal regions) (Ogdie 2015, Solmaz 2018).

The main treatment options: Psoriatic arthritis patients require treatment of the entire spectrum of disease manifestations. The primary goal of treating patients with psoriatic arthritis is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, normalization of function and social participation, and abrogation of inflammation.

Specific recommendations differ slightly between European League Against Rheumatism (EULAR), Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), and American College of Rheumatology/National Psoriasis Foundation (ACR/NAPF) organizations;

however, recommendations for therapeutic choice are made based on a patient's clinical presentation as some manifestations of psoriatic arthritis, such as skin, enthesitis, dactylitis, and axial disease respond differently to specific therapies. Initial treatment of musculoskeletal symptoms is composed of nonsteroidal anti-inflammatory drugs (NSAIDs) and local corticosteroid injections, while topical therapies are used for the initial treatment of psoriasis. For psoriatic arthritis patients who experience toxicity or lack of efficacy with these measures, both the EULAR (Gossec 2020) and GRAPPA (Coates 2016) recommend systemic therapy with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) (methotrexate, leflunomide, or sulfasalazine), followed by biologic therapy (TNF, IL-17, or IL-12/23 inhibitors) in patients who do not respond adequately to csDMARDs. EULAR recommends continuing methotrexate with a biologic in patients already taking and tolerating this drug; however, the csDMARDs have limited efficacy and specific risks (e.g., aplastic anemia and hepatotoxicity including liver failure). The ACR/NAPF recommends anti-TNFs primarily as initial treatments (Singh 2019). Primary or secondary non-response or intolerance to adverse effects of these available therapies; however, leaves many patients with an unmet medical need. The development of other target-specific biologic therapies (e.g., IL-23 inhibitors) or targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs) (such as Janus kinase [JAK] inhibitors) have provided additional therapy options for psoriatic arthritis patients.

The primary goal of treating patients with psoriatic arthritis is to maximize long-term health-related quality of life, and treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy (Gossec 2020). However, across randomized clinical trials with different advanced therapies, the achievement of a minimal disease activity state (MDA), or remission of disease only occurs in a minority of patients. In addition, shared decision making between the patient and the health care provider, considering efficacy, safety and costs, is consistently recommended across EULAR, GRAPPA and American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) organizations. Therefore, there is a need for additional therapeutic options in psoriatic arthritis that improve outcomes across multiple manifestations, are well tolerated, and provide convenient administration (including monitoring).

Despite the beneficial results achieved with currently available biologic agents, approximately 40% of patients who receive a biologic do not have at least a 20% improvement in ACR scores (ACR20) (Cosentyx 2016, Stelara 2014, Enbrel 2015, Remicade 2015, Humira 2019, Cimzia 2016, and Simponi 2016 package inserts). Importantly, all currently available drugs fail to induce a state of remission or minimal disease activity in the majority of psoriatic arthritis patients and do not adequately treat all disease manifestations. Thus, there remains a clear medical need for additional therapeutic options in psoriatic arthritis for patients with inadequate response to or intolerance to currently available therapies.

Natural history of the indicated disease/condition in the population, including mortality and morbidity: Psoriatic arthritis is a chronic systemic inflammatory disease classified as a sub-type of spondyloarthritis and characterized by the association of arthritis and psoriasis. Psoriatic arthritis can develop at any time, but for most people it appears between the ages of 30 and 50, and it affects men and women equally. The course of psoriatic arthritis is usually characterized by flares and remissions. Left untreated, patients with psoriatic arthritis can have persistent inflammation, progressive joint damage, disability, and a reduced life expectancy (Duarte 2012, Gladman 2011). In the majority of adult patients (60% – 70%), the diagnosis of psoriasis precedes psoriatic arthritis (Kerschbaumer 2016). In 15% – 20%, arthritis precedes the onset of psoriasis, and in 15% - 20% of patients, both musculoskeletal and skin manifestations occur within a period of 1 year (Kerschbaumer 2016).

Patients with psoriatic arthritis experience varying combinations of disease manifestations affecting the synovium, tendons, entheses, skin, and bone. These manifestations of disease range in prevalence with peripheral arthritis (mono-, oligo-, or polyarticular) and variable degrees of psoriasis observed in all patients at some point during their disease course, axial disease in 25 – 70% depending on the criteria used for diagnosis (Feld 2018), enthesitis in up to 72%, dactylitis in up to 59%, nail involvement in up to 92% (Pittam 2020), and anterior uveitis in 2 - 25% (Cantini 2015). Additionally, psoriatic arthritis patients are more likely than healthy subjects to experience the comorbid conditions of cardiovascular disease, metabolic syndrome, obesity, diabetes, fatty liver disease, inflammatory bowel disease (IBD), kidney disease, osteoporosis, fibromyalgia, depression, and anxiety, and have decreased quality of life and functional impairment (Husni 2015, Lee 2010, Magrey 2013).

Some patients with psoriatic arthritis demonstrate a mild, minimally, or non-progressive disease that requires only symptomatic treatment, including arthralgia, low-grade inflammation or oligoarthritis. The majority of patients with psoriatic arthritis will develop a progressive deforming arthritis with osteolysis of the digits and polyarticular involvement (Helliwell 2015). Patients become progressively more disabled as damaged joints are gradually accrued. Patients can develop joint deformity in their hands and feet. Markers of disease progression include erosive disease in the peripheral joints, and new symptoms or worsening of psoriatic arthritis symptoms.

Among patients with rheumatologist-verified psoriatic arthritis in a population-based study in Denmark, 53% had mild psoriatic arthritis, 33% had moderate psoriatic arthritis, and 14% had severe psoriatic arthritis (Tekin 2019). Patients with relatively mild disease tend not to develop significant disability; however, in patients with moderate to severe disease, psoriatic arthritis significantly impacts patients' function and quality of life. The additional burden of psoriatic skin disease compounds rates of disability and impaired quality of life. Patients in specialty care experience increased morbidity and mortality, most often attributable to cardiovascular disease (Helliwell 2015).

Important co-morbidities: Cardiovascular disease (CVD) (including HTN, hyperlipidaemia, ischaemic heart disease, coronary artery disease, cerebro-vascular disease, and peripheral vascular disease), atherosclerotic disease, diabetes, metabolic syndrome, obesity, liver disease, osteoporosis, IBD, uveitis, and psychological disorders (including depression and anxiety) (Haddad 2017, Husted 2013, Kaine 2019, Kimhi 2007, Makredes 2009, Shah 2017).

Indication: Crohn's Disease

Incidence: The incidence of CD worldwide has increased over the last three decades, particularly in newly industrialized countries. CD incidence is highest in North America and Europe, with estimates of 23.8 and approximately 10 to 15 per 100,000 person-years in North America and Europe, respectively (Ng 2017). In Asia and the Middle East, the incidence of CD is estimated to be up to 8.4 per 100,000 person-years (Ng 2017). The incidence of pediatric-onset CD is highest in North America (13.9 per 100,000 person-years) and in Europe (12.3 per 100,000 person-years) (Sykora 2018). The incidence of CD in children and adolescents has increased over time (Ghione 2018, Larsen 2016). Among French adolescents aged 10-16 years, the age-adjusted incidence rate of CD (per 100,000 person-years) has increased from 4.2 in 1988 to 9.5 in 2011 (Ghione 2018).

Prevalence: The burden of CD remains substantial with the highest prevalence estimates in Europe (322 per 100,000 persons in Germany) and North America (319 per 100,000). In Asia and the Middle East, prevalence may be as high as 53.1 per 100,000 (Ng 2017).

Among US children aged 2 to 17 years, the standardized prevalence of CD (per 100,000) increased from 18.5 in 2007 to 45.9 in 2016; this increase was mainly driven by a surge of CD cases among adolescents (ages 10-17 years) (Ye 2019).

Studies conducted in various geographic regions have found an increasing trend in the prevalence of CD over time (Benchimol 2014, Ye 2019, Yen 2019).

Demographics of the target population: The disease can affect persons of any age, and its onset is most common in the second and third decades. Females are affected slightly more than males, and the risk for disease is higher in some ethnic groups (Loftus 2004).

Risk Factors: Crohn's disease is an idiopathic inflammatory disorder with genetic, immunologic, and environmental influences. The etiology of the condition remains unknown. Genome-wide association studies have identified over 200 single nucleotide polymorphisms that contribute to inflammatory bowel disease (IBD) susceptibility. However, the association between these polymorphisms and disease development is relatively weak compared with twin studies and family history which suggest a stronger coefficient of heritability (Gordon 2015, Ye 2016). Environmental risk factors such as smoking, nonsteroidal anti-inflammatory drugs and oral contraceptives may increase the risk of developing CD – however the overall risk of disease

onset from these factors appears to be low (Ananthakrishnan 2012, Cornish 2008, Somerville 1984, To 2016).

The main treatment options: The long-term goal of CD treatment is to achieve clinical remission and endoscopic healing (Turner 2021). Oral 5-ASAs have not shown efficacy and are not recommended for moderate to severe CD. Corticosteroids are effective for induction of CD remission, but they are ineffective in maintaining remission and must be used sparingly given their significant short-term and long-term complications. Maintenance therapy with thiopurines or methotrexate may be considered, however clinical response may not be evident for up to 12 weeks and risks include lymphoma and hepatotoxicity (Kotlyar 2015, Lemann 2000). In moderate to severe CD, especially for patients with poor prognostic factors, the early use of TNF inhibitors may be considered. Infliximab and adalimumab have been approved in the European Union (EU). Over the past decade there is an emerging need for therapies that treat patients who do not respond to TNF inhibitors and ACG guidelines suggest that if patients do not respond to a TNF inhibitor within 2-4 weeks of initiation, drugs from another class should be used.

Since 2014, the EU has approved vedolizumab (an α4β7 integrin inhibitor), ustekinumab (an IL-12/IL-23 inhibitor) and upadacitinib (a JAK inhibitor) for the treatment of patients with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to either conventional therapy or a TNF-α antagonist.

While results from approved biologics represent progress in the treatment of CD, clinical remission rates for moderate to severe CD remain limited(Feagan 2016, Loftus 2023, Sandborn 2013, Sands 2014). Traditionally, the goals of treatment of CD centered solely on symptom control; however, it is now recognized that mucosal healing represents an important long-term treatment goal, as it has been shown to be associated with better improved long-term outcomes (e.g., reduced risk of relapse, decreased hospitalizations rates, steroid-free remission, and decreased colonic resections) (Froslie 2007, Klenske 2019, Rutgeerts 2007, Sandborn 2014).

Natural history of CD in the population, including mortality and morbidity: CD symptoms can be chronic and intermittent for many patients, but the disease course is variable. Debilitating symptoms may be associated with inflammatory Crohn's disease activity. Patients often suffer from abdominal pain, fatigue, chronic diarrhea, fecal incontinence, iron-deficiency anemia, weight loss and malnourishment. Patients with CD have been identified to suffer from higher rates of depression and anxiety (Kurina 2001). Chronic bowel inflammation can lead to complications such as strictures, fistula, or abscess and may result in surgeries and hospitalizations. At 20 years after diagnosis, the risk of developing intestinal complications among CD patients is 50 percent (Thia 2010). CD patients with disease involving the colon have an increased risk of colorectal cancer (Olen 2020). The risk of mortality in CD may be

slightly increased. In a metanalysis of 35 studies, the standardized mortality ratio for CD patients was 1.38 (95% CI 1.23-1.55) compared to the general population (Bewtra 2013).

Important co-morbidities: asthma, arthritis, arthralgia, skin disorders like erythema nodosum and pyoderma gangrenosum, uveitis, CVD, neuropsychological disorders, osteoporosis, fatigue, sexual dysfunction (Argollo 2019, Baumgart 2012, Kuenzig 2019).

Indication: Ulcerative Colitis

Incidence: The incidence of UC varies by country and region. In Europe, the incidence of UC ranges from 0.97 per 100,000 PY in Romania to 57.9 per 100,000 PY in Faroe Islands (Ng 2017). In North America, the incidence of UC ranges from 8.8 to 23.1 per 100,000 PY (Ng 2017) and in Australia from 7.3 to 11.4 (Vegh 2014). While the incidence is stabilizing in Western countries, UC is a global disease with accelerating incidence in newly industrialized countries (Ng 2017). Though once considered a rare disease in Asia, in the past two decades, in contrast to Western countries, a rapid emergence of UC in this region has been reported (Mak 2020). Most recent estimates of the incidence of UC in Asia range from 0.15 per 100,000 PY in Philippines to 6.5 per 100,000 PY in Israel (Ng 2017).

Prevalence: Similar geographic variability has been reported for the prevalence of UC. In Europe, the prevalence of UC ranged from 2.42 per 100,000 persons in Romania to 505 per 100,000 persons in Norway (Ng 2017). In North America, the prevalence of UC ranged from 140 to 322 per 100,000 persons (Coward 2019, Ng 2017, Shivashankar 2017). In Asia, the prevalence of UC ranged from 4.9 per 100,000 persons in Turkey (Ng 2017) to 173 per 100,000 persons in Japan (Murakami 2019). The prevalence of UC also varied by age groups. The prevalence of UC is estimated as 10.7 – 28.7 per 100,000 persons in children/adolescents (Benchimol 2017, Kappelman 2013), and 181 – 637 per 100,000 persons in adults (King 2020, Ye 2019).

Demographics of the target population: UC has a bimodal pattern of incidence. The main onset peaks between the ages of 15 and 30 years (Lynch 2023). Approximately 80% of patients with UC present after age 20 (Kelsen 2008). A second and smaller peak of incidence occurs between the ages of 50 and 70 years. Though some studies show a slight increase among men, most studies show no difference in UC incidence between males and females (Lynch 2023, Shah 2018). Incidence and prevalence of UC varies greatly by geographic region (Ng 2017).

UC has historically been more predominant in White populations; however, an increasing incidence of UC in non-White populations has been reported (Aniwan 2019). In the US, the incidence of UC has been increasing in previously low-incidence populations with increases among non-White races and ethnicities, which changes the population demographics of UC (Barnes 2021). The incidence of UC among Hispanics is increasing relative to Whites, and trends are similar among Asians (Afzali 2016). No major differences are seen in disease

location, behavior, and extraintestinal manifestation (EIM) among races and ethnic groups (Afzali 2016).

Risk Factors: Risk factors for UC may include environmental exposures, genetic factors, immune dysregulation, intestinal dysbiosis (Shah 2018), epigenetic factors, nutrition, and socioeconomic status. There is also a bidirectional relationship between psychologic stress and chronic inflammatory disorders (Sexton 2017).

The main treatment options: Medical treatment of UC aims is to achieve endoscopic and clinical remission through healing of the mucosa normalizing the patient's quality of life and providing absence of disability (Turner 2021).

Corticosteroids are used in patients with more severe symptoms but are not recommended for longer term therapy due to significant toxicity (Chaparro 2013, Harbord 2017, Truelove 1959). Patients with moderate to severe symptoms may derive some benefits from immunomodulatory agents (azathioprine, mercaptopurine, or methotrexate); however, up to 17% of patients on these agents experience adverse events severe enough to necessitate drug withdrawal. There are several advanced therapy drug classes for long-term management of moderate to severe UC approved in the EU, including TNF-alpha antagonists (infliximab, adalimumab, golimumab), anti-integrin agent (vedolizumab), JAK inhibitors (tofacitinib, filgotinib, upadacitinib), IL-23 antagonist (mirikizumab), IL-12/23 antagonist (ustekinumab), as well as sphingosine 1-phosphate receptor modulators like ozanimod (Pietschner 2023).

Despite the approval of additional immunomodulatory agents, clinical remission rates remain low. Additional effective and safe therapies are needed for patients with moderate to severe UC.

Natural history of UC in the population, including mortality and morbidity: The clinical course of untreated UC includes relapsing and remitting mucosal inflammation and ulceration of the large intestine, ranging from a quiescent course with prolonged periods of remission to fulminant disease requiring intensive medical treatment or surgery. The hallmark clinical symptoms include bloody diarrhea associated with rectal urgency and tenesmus. Disease outcome is often determined by relapse rates, the development of colorectal cancer and mortality rates. The most severe intestinal manifestations of UC are toxic megacolon and perforation. The 5- and 10-year cumulative risk of colectomy is 10% to 15%. Risk factors for aggressive disease course and colectomy are: young age at diagnosis (< 40 years old), extensive disease, large/deep ulcers, EIMs, early use of corticosteroids, and high inflammatory markers (Feuerstein 2020).

UC extent of disease can be divided into ulcerative proctitis, left-side colitis, and extensive/pancolitis (Satsangi 2006). At diagnosis, the majority of patients have left-sided colitis (Fumery 2018). Overall rates of progression range from 10% to 30%; UC can progress proximally in 10% to 19% of patients after 5 years and in up to 28% of patients ant 10 years

(Burisch 2017, Ungaro 2017, Vester-Andersen 2014). EIMs and elevated C-reactive protein (CRP) both at diagnosis and at 5 years of follow-up were significantly associated with extensive disease (Henriksen 2008, Vegh 2016).

Relapse: Cumulative risk of relapse ranged from 67% to 83% at 10 years (Fumery 2018, Stewénius 1996). Young age at disease onset, female sex, level of education, and smoking status have been associated with disease relapse (Höie 2007, Romberg-Camps 2009, Sjöberg 2014). Almost half of the patients with UC require hospitalization at some point during disease course (Fumery 2018). Disease extent at diagnosis, need for corticosteroids, immunomodulators, and/or anti-TNF agents have been associated with an increased risk of UC-related hospitalization (Golovics 2015, Samuel 2013). Risk of colectomy in adults with UC has been extensively studied, with 1-, 5-, 10-, and 20-year cumulative colectomy rates ranging from 0.5% to 6%, 3% to 13%, 8.5% to 19%, and 11% to 20%, respectively. Patients with extensive colitis, young age, male, and elevated CRP/erythrocyte sedimentation rate at diagnosis have been associated with an increased risk of colectomy (Fumery 2018).

Colon cancer: Patients with UC are at an increased risk for colon cancer, and the risk increases with the duration of disease as well as extent of colon affected by the disease (Ekbom 1990, Jess 2012, Rutter 2004). Young age at diagnosis, male sex, extensive colitis, disease duration, and concomitant primary sclerosing cholangitis (PSC) have been consistently identified as risk factors of colorectal cancer (Jess 2012) (Jess 2013, Karlén 1999, Lakatos 2006).

Overall mortality: Despite the increased risk of colorectal cancer, UC has not been associated with an overall increase in mortality compared with the general population (Höie 2007, Hovde 2016, Jess 2006, Manninen 2012, Masala 2004, Romberg-Camps 2010). When assessing the specific causes of death, UC may be associated with increase in the risk of gastrointestinal-related mortality, partly attributed to an increased mortality from liver diseases due to comorbid association with PSC and increase in risk of colorectal cancer-related mortality.

Important co-morbidities: EIMs most frequently affect joints (peripheral and axial arthropathies), the skin (erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, aphthous stomatitis), the hepatobiliary tract (e.g., PSC), and the eye (episcleritis, uveitis) (Vavricka 2015). Other comorbidities may include anemia from lower gastrointestinal bleeding (Høivik 2014, Ott 2012). Comorbid psychiatric conditions such as depression and anxiety have been associated with the UC diagnosis (Román 2011).

Module SII Non-Clinical Part of the Safety Specification

With regard to toxicity, it is important to keep in mind that risankizumab neutralizes both human IL-23A as well as cynomolgus monkey (non-human primate [NHP]) IL-23A but does not bind to rat IL-23A and binding to mouse IL-23A is significantly diminished. Therefore, toxicology studies in NHP can assess both potential mechanistic (on-target) and non-mechanistic (off-target) effects of risankizumab.

Key Safety Findings (from Non-Clinical Studies)	**Relevance to Human Usage**
Toxicity Single and repeat dose toxicity Dedicated single dose studies were not conducted but the 1st doses in the 4-week and the 26-week repeat-dose toxicity studies in NHP were well tolerated. Weekly IV doses of up to 50 mg/kg (4-week study), as well as weekly SC doses of up to 50mg/kg in the chronic 26-week study in NHP, were well tolerated. There was no evidence of an increased risk for infections or immunotoxicity. No target organs have been identified under chronic dosing; there was no evidence for opportunistic infections nor immunotoxicity (i.e., no effect on anti-keyhole limpet hemocyanin [KLH]-IgM and IgG production in the TDAR assay).	Exposure levels (serum concentrations) at the no-observed-adverse-effect level (NOAEL) of 50 mg/kg/week dosed subcutaneously (SC) in the NHP are at least 69-fold higher than exposures in plaque psoriasis patients based on the recommended dose (150 mg SC at Weeks 0 and 4, thereafter dosed every 12 weeks [q12w]). For CD, the AUC exposures at the NOAEL of 50 mg/kg/week dosed IV in the NHP were approximately 7-fold the exposures at the induction dose of 600 mg IV. For UC, the AUC exposures at the NOAEL of 50 mg/kg/week dosed IV in the NHP were approximately 3-fold the exposures at the induction dose of 1200 mg IV. For CD, the AUC exposures at the NOAEL of 50 mg/kg/week SC in the NHP were approximately 28-fold the exposures at the SC maintenance dose of 360 mg. For UC, the AUC exposures at the NOAEL of 50 mg/kg/week SC in the NHP were approximately 45- and 23-fold the exposures at the SC maintenance doses of 180 mg and 360 mg, respectively. Based on the wide toxicity margin, these studies are not indicative of specific toxicity issues in humans.
Reproductive toxicity Subcutaneous dosing of 50 mg/kg/week for 26 weeks to sexually mature male and female monkeys did not produce test item-related effects on reproductive organs or on reproductive parameters including a stage-dependent histopathological evaluation of spermatogenesis.	Non-clinical studies suggest effects on male and female fertility are low. Women of childbearing potential should use an effective method of contraception during risankizumab treatment and for at least 21 weeks (per SmPC) after risankizumab treatment. In clinical trials, there was no contraception requirement for male patients who receive risankizumab.
Developmental toxicity	Developmental toxicity studies do not suggest a teratogenic effect; however, there are limited data in humans. Risankizumab is an IgG antibody, and human immunoglobulin G (IgG) antibodies are known to cross the placenta into the serum of infants during the third trimester of pregnancy. The lack of maternal toxicity, embryotoxicity, or teratogenicity at the highest dose tested in NHP (50 mg/kg/week) suggests a low risk for humans.

Key Safety Findings (from Non-Clinical Studies)	**Relevance to Human Usage**
Subcutaneous administration of risankizumab to pregnant cynomolgus monkeys up to 50 mg/kg/week from gestation day (GD) 20 to 22 until parturition was well tolerated. No maternal toxicity, embryotoxicity, or teratogenicity was observed, and there was no effect on infant growth and development through 6 months postpartum. The observed differences in fetal/infant survival were considered consistent with normal outcomes for enhanced pre-/post-natal development (ePPND) studies in cynomolgus monkeys and were not considered test article-related. The NOAEL for both maternal and developmental outcomes was 50 mg/kg/week, the highest dose administered.	Exposure (AUC) levels at the NOAEL of 50 mg/kg/week SC in the NHP ePPND study were ≥ 99-fold the exposures in plaque psoriasis patients based on the recommended 150 mg SC dose. Based on AUC, exposure levels at the NOAEL of 50 mg/kg/week SC in the NHP ePPND study were 10-fold the exposures at the CD induction dose of 600 mg IV, 5-fold the exposures at the UC induction dose of 1200 mg IV, 39-fold the exposures at the CD 360 mg SC maintenance dose, and 65- and 32-fold the exposures at the UC 180 mg SC and 360 mg SC maintenance doses, respectively.
Nephrotoxicity There was no evidence of renal toxicity in animal studies.	Studies in NHP were not indicative of any nephrotoxicity risk for humans.
Hepatotoxicity There was no evidence of hepatotoxicity in animal studies.	Studies in NHP were not indicative of any hepatotoxicity risk for humans.
Genotoxicity Genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and, therefore, are not needed. It can be assumed that these molecules will not interact with DNA or chromosomes like small molecules can.	It is not expected that large molecules like risankizumab would interact directly with DNA or chromosomal material. Thus, no genotoxic effect is expected after dosing risankizumab to human subjects.
Carcinogenicity	Overall, the weight of evidence assessment suggests a low risk of malignancy from chronic dosing with risankizumab in humans.

Key Safety Findings (from Non-Clinical Studies)	**Relevance to Human Usage**
Genetic toxicology or traditional carcinogenicity studies have not been conducted with risankizumab due to the nature of the molecule (high specificity to its target) and species specificity (lack of a pharmacologically relevant model). Risankizumab has no known action related to the cell cycle and is not expected to have an action which influences DNA integrity. As risankizumab does not bind rodent IL-23 and is therefore not pharmacologically active in rodents, a two-year carcinogenicity study would not be informative. The toxicology assessment for risankizumab has not indicated a potential for carcinogenicity following chronic administration to cynomolgus monkeys. There was no evidence of immunotoxicity/immunosuppression, enhanced cellular proliferation or pre-neoplastic changes after six months of SC dosing to cynomolgus monkeys at dose levels up to 50 mg/kg/week. Therefore, a weight of evidence approach was followed for the evaluation of the potential carcinogenicity risk of risankizumab for human subjects.	
General Safety Pharmacology	
Cardiovascular Electrocardiogram (ECG) measurements and heart rate were measured in a 26-week chronic toxicology study in NHP at doses up to 50 mg/kg/week; dosing with risankizumab did not show any effects.	Based on the animal studies, no effects of risankizumab on cardiovascular or respiratory parameters are expected in humans.
Nervous system	Based on the animal studies, no effects of risankizumab on CNS parameters are expected in humans.

Key Safety Findings (from Non-Clinical Studies)	Relevance to Human Usage
No dedicated studies in rodents were conducted because risankizumab does not bind to rodent IL-23A. In toxicology studies in monkeys, however, no findings for potential effects on the central nervous system (CNS) were observed at the highest dose of 50 mg/kg/week, where exposures were ≥ 69-fold higher than those in plaque psoriasis patients based on the recommended 150 mg SC dose. For CD, the exposures at this dose in monkeys were approximately 7-fold higher than those at the induction dose of 600 mg IV and 28-fold higher than those at the maintenance dose of 360 mg SC. For UC, the exposures at this dose in monkeys were approximately 3-fold higher than those at the induction dose of 1200 mg IV and 45- and 23-fold higher than those at the maintenance doses of 180 mg SC and 360 mg SC, respectively.	
Mechanisms for drug interactions Cytokines (e.g., IL-6, TNF-α) have been shown to alter the expression of many cytochrome P450 (CYP450) enzymes in vitro. Thus, patients with infections or inflammatory diseases may have altered CYP450 activities due to elevated cytokine levels. No dedicated in vitro or in vivo study in animals on drug-drug interactions was conducted with risankizumab.	A dedicated drug-drug interaction study was conducted to evaluate the potential for interaction between risankizumab and drugs metabolized by CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A. Clinically relevant drug-drug interactions are not expected. Product labeling will include language with this information.
Local tolerance The 10 mg/mL formulation has been tested for local tolerance (IV and SC) in the 4-week NHP study, and the commercial formulation (90 mg/mL) was tested for local tolerance SC in the repeat-dose NHP study as well as in rabbits after single SC or intramuscular injection. In addition, local tolerance of the 150 mg/mL formulation was tested in rabbits after SC, IV and paravenous administration. There was no evidence for local intolerability in any study.	Based on animal studies, no local intolerability of risankizumab is expected in humans.
Other toxicity-related information or data	None known at this time.

Non-Clinical Safety Findings that are Included as Safety Concerns

Safety Concerns	There are no non-clinical safety findings that are considered safety concerns

Module SIII Clinical Trial Exposure

Table 2. Duration of Exposure

Cumulative for All Indications[a]	
Duration Interval Days	**All Risankizumab (N = 10064) n (%)**
< 90 days (3 months)	555 (5.5)
≥ 90 days (3 months)	9509 (94.5)
≥ 180 days (6 months)	8711 (86.6)
≥ 360 days (12 months)	7262 (72.2)
≥ 540 days (18 months)	5911 (58.7)
≥ 720 days (24 months)	5613 (55.8)
≥ 900 days (30 months)	5277 (52.4)
≥ 1080 days (36 months)	4743 (47.1)
≥ 1260 days (42 months)	4320 (42.9)
≥ 1440 days (48 months)	4021 (40.0)
≥ 1620 days (54 months)	3726 (37.0)
≥ 1800 days (60 months)	2998 (29.8)
≥ 1980 days (66 months)	1864 (18.5)
≥ 2160 days (72 months)	1020 (10.1)
≥ 2340 days (78 months)	274 (2.7)
≥ 2520 days (84 months)	210 (2.1)
≥ 2700 days (90 months)	109 (1.1)
Indication 1: Psoriasis[b]	
Duration Interval Days	**All Risankizumab (N = 4281) n (%)**
< 90 days (3 months)	193 (4.5)
≥ 90 days (3 months)	4088 (95.5)
≥ 180 days (6 months)	3873 (90.5)

≥ 360 days (12 months)	3045 (71.1)
≥ 540 days (18 months)	2325 (54.3)
≥ 720 days (24 months)	2193 (51.2)
≥ 900 days (30 months)	2075 (48.5)
≥ 1080 days (36 months)	1983 (46.3)
≥ 1260 days (42 months)	1916 (44.8)
≥ 1440 days (48 months)	1857 (43.4)
≥ 1620 days (54 months)	1792 (41.9)
≥ 1800 days (60 months)	1720 (40.2)
≥ 1980 days (66 months)	1387 (32.4)
≥ 2160 days (72 months)	914 (21.4)
≥ 2340 days (78 months)	231 (5.4)
≥ 2520 days (84 months)	170 (4.0)
≥ 2700 days (90 months)	72 (1.7)

Indication 2: Psoriatic Arthritis[c]

Duration Interval Days	**All Risankizumab (N = 1548) n (%)**
< 90 days (3 months)	15 (1.0)
≥ 90 days (3 months)	1533 (99.0)
≥ 180 days (6 months)	1448 (93.5)
≥ 360 days (12 months)	1296 (83.7)
≥ 540 days (18 months)	1136 (73.4)
≥ 720 days (24 months)	1092 (70.5)
≥ 900 days (30 months)	1056 (68.2)
≥ 1080 days (36 months)	1033 (66.7)
≥ 1260 days (42 months)	1003 (64.8)
≥ 1440 days (48 months)	961 (62.1)
≥ 1620 days (54 months)	926 (59.8)
≥ 1800 days (60 months)	589 (38.0)
≥ 1980 days (66 months)	124 (8.0)
≥ 2160 days (72 months)	5 (0.3)

Indication 3: Crohn's Disease[d]	
Duration Interval Days	**All Risankizumab (N = 1926) n (%)**
< 90 days (3 months)	162 (8.4)
≥ 90 days (3 months)	1764 (91.6)
≥ 180 days (6 months)	1604 (83.3)
≥ 360 days (12 months)	1461 (75.9)
≥ 540 days (18 months)	1346 (69.9)
≥ 720 days (24 months)	1287 (66.8)
≥ 900 days (30 months)	1225 (63.6)
≥ 1080 days (36 months)	1125 (58.4)
≥ 1260 days (42 months)	992 (51.5)
≥ 1440 days (48 months)	900 (46.7)
≥ 1620 days (54 months)	756 (39.3)
≥ 1800 days (60 months)	502 (26.1)
≥ 1980 days (66 months)	266 (13.8)
≥ 2160 days (72 months)	86 (4.5)
≥ 2340 days (78 months)	43 (2.2)
≥ 2520 days (84 months)	40 (2.1)
≥ 2700 days (90 months)	37 (1.9)

Indication 4: Ulcerative Colitis[e]	
Duration Interval Days	**All Risankizumab (N = 1523) n (%)**
< 90 days (3 months)	116 (7.6)
≥ 90 days (3 months)	1407 (92.4)
≥ 180 days (6 months)	1218 (80.0)
≥ 360 days (12 months)	1148 (75.4)
≥ 540 days (18 months)	1082 (71.0)
≥ 720 days (24 months)	1029 (67.6)
≥ 900 days (30 months)	910 (59.8)
≥ 1080 days (36 months)	592 (38.9)
≥ 1260 days (42 months)	409 (26.9)
≥ 1440 days (48 months)	303 (19.9)
≥ 1620 days (54 months)	252 (16.5)

≥ 1800 days (60 months)	187 (12.3)
≥ 1980 days (66 months)	87 (5.7)
≥ 2160 days (72 months)	15 (1.0)

a. Includes data from the following indications: Adult and pediatric Psoriasis (Studies 1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M19-973, M19-977, M20-326, M23-702, and M24-541), CD (Studies 1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885), Ankylosing Spondylitis (Study 1311_0008), Asthma (Study 1311_0014), Atopic Dermatitis (Study M16-813), Generalized Pustular PsO or Erythrodermic PsO (Study M15-988), Hidradenitis Suppurativa (Study M16-833), Palmoplantar Pustulosis (Study M19-135), PsA (Studies 1311_0005, M16-244, M15-998, M16-011, and M23-732), and UC (Studies M16-066, M16-067, and M19-974).

b. Includes data from adult and pediatric Psoriasis Studies 1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M19-973, M19-977, M20-326, M23-702, and M24-541.

c. Includes data from PsA Studies 1311_0005, M16-244, M15-998, M16-011, and M23-732.

d. Includes data from CD Studies 1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885.

e. Includes data from UC Studies M16-066, M16-067, and M19-974.

Note: Duration of treatment is defined for each subject who took Risankizumab as the minimum of: (i) the cutoff date - first dose date of Risankizumab + 1, or (ii) last dose date of Risankizumab - first dose date of Risankizumab + 84 days, or (iii) last dose date of Risankizumab - first dose date of Risankizumab + 28 days for Q4W IV, or (iv) last dose date of Risankizumab - first dose date of Risankizumab + 56 days for Q8W SC. The data cutoff for adult Psoriasis (1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M20-326, M23-702, and M24-541), CD (1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885), Ankylosing Spondylitis (1311_0008), Asthma (1311_0014), Atopic Dermatitis (M16-813), Generalized Pustular PsO or Erythrodermic PsO (M15-988), Hidradenitis Suppurativa (M16-833), Palmoplantar Pustulosis (M19-135), PsA (1311_0005, M16-244, M15-998, M16-011, and M23-732), and UC (M16-066, M16-067, and M19-974) studies is 25 March 2025. For the Psoriasis pediatric studies: The final database lock for Study M19-977 occurred on 12 December 2024 and Study M19-973 had a data cutoff of 01 January 2025.

Table 3. Exposure by Age Group and Sex

	Male		Female	
Age Group (years)	**n**	**Patient Years**	**n**	**Patient Years**
Cumulative for All Indications[a]				
< 18	86	174.3	99	210.4
18 to 64	5255	16459.4	3612	10140.6
65 to 74	495	1476.0	395	1203.3
≥ 75	63	167.1	57	118.2
Missing	1	0.1	1	0.1
Indication 1: Psoriasis[b]				
< 18	58	136.5	81	189.7
18 to 64	2477	8241.7	1159	3381.5
65 to 74	291	927.6	153	451.9
≥ 75	35	99.2	27	39.8
Indication 2: Psoriatic Arthritis[c]				
< 18	3	0.8	3	1.2
18 to 64	671	2511.8	624	2257.2
65 to 74	82	279.3	131	487.1
≥ 75	12	35.7	22	60.1
Indication 3: Crohn's Disease[d]				
< 18	24	36.3	14	19.4
18 to 64	936	3195.0	865	2720.7
65 to 74	36	90.9	41	157.7
≥ 75	6	19.1	2	8.3
Missing	1	0.1	1	0.1
Indication 4: Ulcerative Colitis[e]				
18 to 64	840	2233.4	580	1483.5
65 to 74	64	163.7	31	77.3
≥ 75	5	9.0	3	7.3

a. Includes data from the following indications: Adult and pediatric Psoriasis (Studies 1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M19-973, M19-977, M20-326, M23-702, and M24-541), CD (Studies 1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885), Ankylosing Spondylitis (Study 1311_0008), Asthma (Study 1311_0014), Atopic Dermatitis (Study M16-813), Generalized Pustular PsO or Erythrodermic PsO (Study M15-988), Hidradenitis Suppurativa (Study M16-833), Palmoplantar Pustulosis (Study M19-135), PsA (Studies 1311_0005, M16-244, M15-998, M16-011, and M23-732), and UC (Studies M16-066, M16-067, and M19-974).

b. Includes data from adult and pediatric Psoriasis Studies 1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M19-973, M19-977, M20-326, M23-702, and M24-541.

c. Includes data from PsA Studies 1311_0005, M16-244, M15-998, M16-011, and M23-732.

d. Includes data from CD Studies 1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885.

e. Includes data from UC Studies M16-066, M16-067, and M19-974.

Note: Age is calculated from the beginning of study/feeder study. The data cutoff for adult Psoriasis (1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M20-326, M23-702, and M24-541), CD (1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885), Ankylosing Spondylitis (1311_0008), Asthma (1311_0014), Atopic Dermatitis (M16-813), Generalized Pustular PsO or Erythrodermic PsO (M15-988), Hidradenitis Suppurativa (M16-833), Palmoplantar Pustulosis (M19-135), PsA (1311_0005, M16-244, M15-998, M16-011, and M23-732), and UC (M16-066, M16-067, and M19-974) studies is 25 March 2025. For the Psoriasis pediatric studies: The final database lock for Study M19-977 occurred on 12 December 2024 and Study M19-973 had a data cutoff of 01 January 2025.

Table 4. Exposure by Dose

Dose of Exposure	n	Patient Years
Cumulative for All Indications[a]		
Risankizumab 150 mg SC	5174	17258.1
Risankizumab 180 mg SC	2232	5757.7
Risankizumab 360 mg SC	1725	3460.4
Risankizumab 600 mg IV	1080	267.4
Risankizumab 1200 mg IV	2218	586.5
Risankizumab Other Dose	2004	2619.3
Indication 1: Psoriasis[b]		
Risankizumab 150 SC	3439	11435.7
Risankizumab Other Dose	842	2032.3
Indication 2: Psoriatic Arthritis[c]		
Risankizumab 150 mg SC	1526	5609.6
Risankizumab Other Dose	22	23.6
Indication 3: Crohn's Disease[d]		
Risankizumab 180 mg SC	1176	3520.7
Risankizumab 360 mg SC	991	2156.7
Risankizumab 600 mg IV	1018	253.6
Risankizumab 1200 mg IV	1087	291.3
Risankizumab Other Dose	71	25.2
Indication 4: Ulcerative Colitis[e]		
Risankizumab 180 mg SC	1056	2237.0
Risankizumab 360 mg SC	734	1303.7
Risankizumab 600 mg IV	62	13.8
Risankizumab 1200 mg IV	1131	295.3
Risankizumab Other Dose	492	124.5

a. Includes data from the following indications: Adult and pediatric Psoriasis (Studies 1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M19-973, M19-977, M20-326, M23-702, and M24-541), CD (Studies 1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885), Ankylosing Spondylitis (Study 1311_0008), Asthma (Study 1311_0014), Atopic Dermatitis (Study M16-813), Generalized Pustular PsO or Erythrodermic PsO (Study M15-988), Hidradenitis Suppurativa (Study M16-833), Palmoplantar Pustulosis (Study M19-135), PsA (Studies 1311_0005, M16-244, M15-998, M16-011, and M23-732) and UC (Studies M16-066, M16-067, and M19-974).

b. Includes data from adult and pediatric Psoriasis Studies 1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-997, M15-994, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M19-973, M19-977, M20-326, M23-702, and M24-541. Pediatric subjects received 150mg dose or a weight-based equivalent dose (55mg) if <40kg.

c. Includes data from PsA Studies 1311_0005, M16-244, M15-998, M16-011, and M23-732.

d. Includes data from CD Studies 1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885.

e. Includes data from UC Studies M16-066, M16-067, and M19-974.

Note: Risankizumab 150 mg SC includes subjects randomized to Risankizumab 150 mg or placebo and switched to 150 mg and remained on this dose. Pediatric Psoriasis subjects received 150mg SC or a weight-based equivalent dose (55mg SC) if <40kg. Risankizumab Other Dose includes doses by indication as follows: Psoriasis (≤ 90 mg SC), CD (200 and 1800 mg IV), Ankylosing Spondylitis (≤ 90 mg SC), Asthma (90 mg SC), Atopic Dermatitis (300 mg SC), Generalized Pustular PsO/Erythrodermic PsO (75 mg SC), PsA (75 mg SC), and UC (1800 mg IV). The data cutoff for adult Psoriasis (1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M20-326, M23-702, and M24-541), CD (1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885), Ankylosing Spondylitis (1311_0008), Asthma (1311_0014), Atopic Dermatitis (M16-813), Generalized Pustular PsO or Erythrodermic PsO (M15-988), Hidradenitis Suppurativa (M16-833), Palmoplantar Pustulosis (M19-135), PsA (1311_0005, M16-244, M15-998, M16-011 and M23-732) and UC (M16-066, M16-067, and M19-974) studies is 25 March 2025. For the Psoriasis pediatric studies: The final database lock for Study M19-977 occurred on 12 December 2024 and Study M19-973 had a data cutoff of 01 January 2025. CD and UC subjects may receive multiple doses during treatment, so the subject numbers are not mutually exclusive across doses.

Table 5. Exposure by Ethnic Origin

Ethnic Origin	n	Patient Years
Cumulative for All Indications[a]		
White	8030	23706.5
Black or African American	304	610.3
Asian	1587	5215.9
American Indian or Alaska Native	36	101.0
Native Hawaiian or Other Pacific Islander	25	94.1
Other	65	208.9
Missing	17	12.7
Indication 1: Psoriasis[b]		
White	3442	10204.7
Black or African American	146	336.0
Asian	620	2708.3
American Indian or Alaska Native	26	86.0
Native Hawaiian or Other Pacific Islander	17	64.6
Other	23	66.3
Missing	7	2.0
Indication 2: Psoriatic Arthritis[c]		
White	1448	5317.6
Black or African American	10	39.6
Asian	60	168.9
American Indian or Alaska Native	2	3.8
Native Hawaiian or Other Pacific Islander	4	19.0
Other	18	78.8
Missing	6	5.5
Indication 3: Crohn's Disease[d]		
White	1560	4963.0
Black or African American	62	141.8
Asian	282	1079.8
American Indian or Alaska Native	3	5.2
Native Hawaiian or Other Pacific Islander	3	10.3
Other	12	42.3
Missing	4	5.2

Ethnic Origin	n	Patient Years
Indication 4: Ulcerative Colitis[e]		
White	1135	2919.7
Black or African American	27	55.1
Asian	352	977.2
American Indian or Alaska Native	1	2.9
Native Hawaiian or Other Pacific Islander	0	-
Other	8	19.4

a. Includes data from the following indications: Adult and pediatric Psoriasis (Studies 1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M19-973, M19-977, M20-326, M23-702, and M24-541), CD (Studies 1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885), Ankylosing Spondylitis (Study 1311_0008), Asthma (Study 1311_0014), Atopic Dermatitis (Study M16-813), Generalized Pustular PsO or Erythrodermic PsO (Study M15-988), Hidradenitis Suppurativa (Study M16-833), Palmoplantar Pustulosis (Study M19-135), PsA (Studies 1311_0005, M16-244, M15-998, M16-011, and M23-732), and UC (Studies M16-066, M16-067, and M19-974).

b. Includes data from adult and pediatric Psoriasis Studies 1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16_177, M16-178, M16-766, M19-164, M19-973, M19-977, M20-326, M23-702, and M24-541.

c. Includes data from PsA Studies 1311_0005, M16-244, M15-998, M16-011 and M23-732.

d. Includes data from CD Studies 1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885.

e. Includes data from UC Studies M16-066, M16-067, and M19-974.

Note: The data cutoff for adult Psoriasis (1311_0001, 1311_0002, 1311_0003, 1311_0004, 1311_0013, 1311_0028, 1311_0030, 1311_0038, M15-994, M15-997, M15-999, M16-005, M16-007, M16-176, M16-177, M16-178, M16-766, M19-164, M20-326, M23-702, and M24-541), CD (1311_0006, M15-989, M15-991, M16-000, M16-006, M16-194, M19-974, M20-259, M24-144, and M24-885), Ankylosing Spondylitis (1311_0008), Asthma (1311_0014), Atopic Dermatitis (M16-813), Generalized Pustular PsO or Erythrodermic PsO (M15-988), Hidradenitis Suppurativa (M16-833), Palmoplantar Pustulosis (M19-135), PsA (1311_0005, M16-244, M15-998, M16-011 and M23-732), and UC (M16-066, M16-067, and M19-974) studies is 25 March 2025. For the Psoriasis pediatric studies: The final database lock for Study M19-977 occurred on 12 December 2024 and Study M19-973 had a data cutoff of 01 January 2025.

Exposure for special populations here is limited to pregnancies. Exposure data for patients ≥ 75 years old is included in Table 3.

Table 6. Exposure for Special Populations (Pregnancies)

Cumulative for All Indications and Healthy Volunteers	Patients
Pregnant women	104
Indication 1: Plaque Psoriasis	
Pregnant women	31
Indication 2: Psoriatic Arthritis	
Pregnant women	2
Indication 3: Crohn's Disease	
Pregnant women	33
Indication 4: Ankylosing Spondylitis	
Pregnant women	1
Indication 5: Hidradenitis Suppurativa	
Pregnant women	2
Indication 6: Ulcerative Colitis	
Pregnant women	29
Indication 7: Generalized Pustular Psoriasis/Erythrodermic Psoriasis	
Pregnant women	1
Healthy Volunteers	
Pregnant women	5

Notes: This table uses a data cutoff of 25 March 2025.

All pregnancies occurred while the women were receiving risankizumab treatment, and consequently the subjects were discontinued from the study per protocol. Drug exposure presented here is limited to maternal exposure.

Module SIV Populations Not Studied in Clinical Trials

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

Criterion 1: Woman who is pregnant, nursing, or who plans to become pregnant
Reason for exclusion: The effects of risankizumab on human fetal development and lactation are not known.
Is it considered to be included as missing information?: Yes
Rationale: Not applicable

Criterion 2: Patient with known chronic or relevant acute infections including active tuberculosis (TB), human immunodeficiency virus (HIV), or viral hepatitis
Reason for exclusion: Allow for interpretability of safety findings and ensure subject safety.
Is it considered to be included as missing information?: No
Rationale: Was previously considered missing information; however as no new significant information has been identified following review in Periodic Safety Update Reports (PSURs), it is no longer considered missing information (EMEA/H/C/PSUSA/00010765/202103).

Criterion 3: Patient with any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix
Reason for exclusion: Allow for interpretability of safety findings and ensure subject safety.
Is it considered to be included as missing information?: No
Rationale: Was previously considered missing information; however as no new significant information has been identified following review in PSURs, it is no longer considered missing information (EMEA/H/C/PSUSA/00010765/202103).

Criterion 4: Use of live virus vaccinations within 6 weeks prior to randomization
Reason for exclusion: Since risankizumab is an immunomodulator, response to live virus vaccinations prior to initiation of risankizumab is not known.
Is it considered to be included as missing information?: No
Rationale: Product labeling will guide against the use of live vaccines in the treated population.

Criterion 5: Use in patients < 18 years of age (PsA)
Reason for exclusion: Clinical trial development program designed to evaluate safety and efficacy in adults.
Is it considered to be included as missing information?: No
Rationale: Clinical trial evaluation to date and proposed indication will be in adults. Data specific to pediatrics will be evaluated as part of the Paediatric Investigation Plan per regulatory requirement.

SIV.2 Limitations to Detect Adverse Reactions in the Clinical Development Program

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

SIV.3 Limitations in Respect to Populations Typically Under Represented in Clinical Development Program

Table 7. Exposure of Special Populations Included or Not in the Clinical Development Program

Type of special population	Exposure	Implications
Pregnant or nursing women	Women who were pregnant, nursing, or who planned to become pregnant while in a risankizumab study, were excluded from participation in the clinical development program. As of 25 March 2025, 104 female subjects became pregnant during study participation and were exposed to risankizumab. The pregnancy outcomes were as follows: 51 live births without congenital anomalies, 16 spontaneous abortions, 18 elective terminations (no known fetal defects), 2 elective terminations (with fetal defects)*, 14 subjects lost to follow-up, and 3 ongoing pregnancies. No nursing women were exposed to risankizumab as women were discontinued from risankizumab upon knowledge of pregnancy.	Product labeling includes language to indicate that the effects of risankizumab on human fetal development, lactation, and breast-fed infants are not known. A population-based, non-interventional, cohort study of women with moderate-to-severe psoriasis who are exposed to risankizumab or comparator biologic during pregnancy is ongoing (see Section III.2 for additional details on study design). A non-interventional cohort study will be conducted to describe risankizumab exposure in pregnant patients with Crohn's disease or UC, and compare pregnancy and infant outcomes to pregnant patients with Crohn's disease or UC who were treated with alternative therapies (see Section III.2 for additional details on study design).
Patients ≥ 75 years	As of 25 March 2025, in the risankizumab PsO, PsA, CD, and UC programs, 62, 34, 8, and 8 subjects ≥ 75 years of age, respectively, received risankizumab.	There is a limited number of subjects ≥ 75 years of age. Since it is not anticipated that use in this population would be associated with specific safety issues, this is not considered missing information.

Type of special population	Exposure	Implications
Patients with hepatic impairment	These patients were not specifically excluded from clinical trials; however, no specific studies were conducted to assess the effect of hepatic impairment on the pharmacokinetics of risankizumab.	Risankizumab, as an IgG1 monoclonal antibody, is not expected to undergo metabolism by hepatic metabolic enzymes. Hepatic impairment is not expected to impact risankizumab's safety profile. Based on method of metabolism and clinical data to date, this is not considered to be missing information.
Patients with cardiovascular impairment	These patients were not specifically excluded from clinical trials.	Cardiovascular impairment is not expected to impact risankizumab's safety profile based on clinical data to date. This is not considered missing information.
Patients with renal impairment	These patients were not specifically excluded from clinical trials; however, no specific studies were conducted to assess the effect of renal impairment on the pharmacokinetics of risankizumab.	Risankizumab, as an IgG1 monoclonal antibody, is not expected to undergo renal elimination. Renal impairment is not expected to impact risankizumab's safety profile. Based on method of metabolism and clinical data to date, this is not considered to be missing information.
Immunocompromised patients	Patients with HIV were excluded from clinical trials.	Use in patients with a history of HIV will be excluded from missing information since this group would include patients with known HIV infection who are receiving chronic anti-retroviral therapy and should have suppression of HIV replication. Use of any immunomodulatory product in this setting may not be different from that of a population not infected with HIV.

* There was 1 elective termination(s) with foetal cystic hygroma and early hydrops fetalis and 1 elective termination with a chromosome 21 defect in a high-risk patient. Both events were deemed to be not related to risankizumab by the sponsor. Being a monoclonal antibody, risankizumab is not genotoxic and product administration would not be expected to cause chromosomal mutations. Further, IgG placental transfer is minimal in the first trimester, limiting large molecule drug transfer to the fetus during the period of organogenesis (between gestational Weeks 3 and 8).

Module SV Post-Authorization Experience

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

Post-marketing exposure to risankizumab is estimated to be 1,124,512 patient treatment-years (PTY) cumulatively as of 25 March 2025.

Risankizumab post-marketing patient exposure from 26 March 2019 through 25 March 2025 was estimated from AbbVie sales and distribution data from 01 April 2019 through 25 March 2025 using the following formula.

Number of PTY =

$$\frac{\text{Number of packages sold x number of units per package}}{\text{Average daily dose (ADD)} \times 365.25 \text{ days per year}}$$

where the ADD is the average number of drug-units taken per day for a treatment indication.

ADD is calculated as the dose divided by the recommended dosing interval (in days).

The 75 mg, 150 mg, 180 mg, 360 mg, 600 mg, and 1,200 mg doses are approved for risankizumab, though 75 mg is approved in Japan only. Of note, the loading dose administered in psoriasis and the induction dose for CD and UC are not included in the PTY calculation.

Dosage Forms and Strengths (A)	Recommended Dosing Interval (days) (B)	ADD (A÷B)	1 PTY (ADD x 365.25)	Estimated Number of Units per Year (PTY ÷ A)
150 mg PFS/pen	84	1.79 mg	653.80 mg	4.3
2 × 75 mg PFS	84	1.79 mg	653.80 mg	8.7[a]
75 mg PFS	84	0.89 mg	325.07 mg	4.3
180 mg cartridge	56	3.21 mg	1,172.45 mg	6.5
360 mg cartridge	56	6.43 mg	2,348.56 mg	6.5

ADD = average daily dose; PFS = pre-filled syringe; PTY = patient treatment-years

a. Accounts for 2 units per package.

SV.1.2 Exposure

Post-Authorization (Non-Clinical Trial) Exposure by Dose

Patient exposure was also estimated by dose. Based on available data, the following estimates were calculated.

Table 8. Post-Authorization Exposure by Dose

Estimated Cumulative Patient Exposure from 26 March 2019 through 25 March 2025 from AbbVie Sales			
Dose	**Total Amount (syringe/vial/cartridge)**	**Total Amount (mg)**	**PTY**
75 mg/0.83 mL	88,114	6,608,550	20,265
75 mg/mL x 2	1,775,845	133,188,375	204,120
150 mg/0.83 mL	3,561,776	534,266,400	819,176
180 mg/1.2 mL	21,216	3,818,880	3,264
360 mg/2.4 mL	504,965	181,787,400	77,687
600 mg/10 mL[a]	391,670	234,983,700	-
Total	**6,343,586**	**1,094,653,305**	**1,124,512**

PTY = patient treatment-years

a. PTY were not applicable for the 600 mg/10 mL induction dose. The 1,200 mg induction dose is administered via 2 intravenous infusions of 600 mg/10 mL.

Post-Authorization (Non-Clinical Trial) Exposure by Geographic Region

Patient exposure was also estimated by geographic region. Based on available data, the following estimates were calculated.

Table 9. Post-Authorization Exposure by Geographic Region

Estimated Cumulative Patient Exposure from 26 March 2019 through 25 March 2025 from AbbVie Sales by Region	
Region	**PTY**
EU[a]	196,919
UK	[redacted]
Non-EU/UK European countries	10,460
Middle East & Africa	31,611
JAPAC[b]	77,755
Latin America	28,153
US	[redacted]
Canada	[redacted]
Grand total	**1,124,512**

EU = European Union; JAPAC = Japan and Asian Pacific; PTY = patient treatment-years; UK = United Kingdom; US = United States

a. EU countries.

b. Japan, Asia Pacific countries.

Post-Authorization (Non-Clinical Trial) Exposure by Indication

Exposure data derived from AbbVie sales and distribution data cannot provide exposure by indication, age, and gender. Symphony Health Solutions Integrated Dataverse (IDV) was used to generate exposure data by age, gender and indication. The Symphony Health Solutions IDV is an integrated database that consists of health care billing transactions between payers, hospitals, pharmacies, and physicians. The dataset consists of 1.9 million prescribers in the IDV representing over 317 million unique patients in 2021. All payers in the US are represented in the data source (health plans, and government and public organizations). Only approved claims (not rejected or reversible claims) are used for the analysis.

Patient exposure was estimated by indication. Based on available data, the following estimates were calculated.

Table 10. Post-Authorization Exposure by Indication

Cumulative Exposure by Patient Indication from Symphony Health Solutions* from 01 April 2019 through 25 March 2025

	01 April 2019 – 25 March 2025	
Indication[a]	**Count**	**%**
Plaque Psoriasis[b]	127,125	48.0%
Psoriatic Arthritis[c]	47,814	18.0%
Crohn's Disease[d]	32,625	12.3%
Ulcerative Colitis[e]	16,501	6.2%
Not Reported	92,337	34.8%
Total[f]	**264,994**	**100.0%**

* Symphony Health Solutions is representative of > 90% of the patient exposure in the US.

a. Patients who received risankizumab during this reporting interval may have used risankizumab in the previous periods.

b. Plaque Psoriasis was defined by using International Classification of Diseases (ICD) codes: (ICD-9-CM 696.1, ICD-10-CM L40.0).

c. PsA was defined by using ICD codes: (ICD-9-CM 696.0, ICD-10-CM L40.5).

d. CD was defined by using ICD codes: (ICD-9-CM 555, ICD-10-CM K50).

e. UC was defined using ICD codes: (ICD-9-CM 556, ICD-10 K51)

f. The total is less than the direct sum of the column above because otherwise duplicates will be counted across diagnosis for patients who have more than 1 indication.

Note: Diagnosis in this table allows for patients to have more than 1 diagnosis of interest. "Not reported" is the count of patients with claims where patient diagnosis is not available in the database.

Post-Authorization (Non-Clinical Trial) Exposure by Age Group and Gender

Based on Symphony Health solutions IDV from 01 April 2019 through 25 March 2025, the following post-authorization patient exposure by age group and gender were obtained.

Table 11. Post-Authorization Exposure by Age Group and Gender

Risankizumab Cumulative Exposure by Patient Age and Gender from Symphony Health Solutions[a] (Excluding Clinical Trials) from 01 April 2019 through 25 March 2025						
	Females		Males		Total	
Age (Years Old)	Number of Patients	%	Number of Patients	%	Number of Patients	%
0 – ≤ 17	242	0.2%	241	0.2%	483	0.2%
18 – 44	49,672	36.3%	50,211	39.1%	99,883	37.7%
45 – 64	62,717	45.9%	57,496	44.8%	120,213	45.4%
65 – 74	19,176	14.0%	16,442	12.8%	35,618	13.4%
75 +	4,903	3.6%	3,894	3.0%	8,797	3.3%
Total[b]	**136,710**	**51.6%**	**128,284**	**48.4%**	**264,994**	**100.0%**

a. Symphony Health Solutions is representative of > 90% of the patient exposure in the US.

b. The total might not equal the sum of each category due to rounding.

Post-Authorization Exposure (Non-Clinical Trial) in Special Populations

AbbVie is not aware of any study findings from observational studies or registries on the use of risankizumab in special patient populations.

Other Post-Authorization (Non-Clinical Trial) Use

AbbVie is not aware of any pattern of use of risankizumab that is relevant for the interpretation of safety data.

Module SVI Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

No cases consistent with misuse or abuse were reported during clinical development. It is highly unlikely that risankizumab has a potential for abuse, as it does not cross the blood-brain barrier, and its pharmacological target is not associated with pathways associated with reward.

Module SVII Identified and Potential Risks

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

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

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Non-serious infections (upper respiratory tract infections, tinea infections, folliculitis)
- Fatigue
- Injection site reactions
- Headache

SVII.1.2 Risks/Missing Information Considered Important for Inclusion in the RMP

Identified risk 1: Serious hypersensitivity reactions Reason for Inclusion: Some monoclonal antibody products carry a risk of immune reactions against the small nonhuman part of the antibody. Additionally, anaphylactic reaction has been added as an adverse drug reaction for Risankizumab.

Potential risk 1: MACE Reason for Inclusion: Currently there is no evidence of an increased risk of MACE with risankizumab; however, there is an increased risk of cardiovascular disease (CVD) (e.g., myocardial infarction [MI] and stroke) among the patient populations in the approved indications for risankizumab (i.e., psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, etc.).
Potential risk 2: Serious infections Reason for Inclusion: Currently there is no evidence of an increased risk of serious infection with risankizumab; however, immunomodulatory products have the potential to increase the risk of infections.
Potential risk 3: Malignancies Reason for Inclusion: Currently there is no evidence of an increased risk of malignancy with risankizumab; however, there is a theoretical possibility of decreased immune surveillance against malignancies with alteration of immune pathways.

Missing Information

Information 1: Use during pregnancy and lactation Reason for Inclusion: Pregnant women, nursing women, and women who planned to become pregnant were excluded from the clinical trials, and effective contraception was mandated. Data in pregnant women in the clinical trials are limited to 104 women who became pregnant during study participation and were exposed to risankizumab as of 25 March 2025. The pregnancy outcomes were as follows: 51 live births without congenital anomalies, 16 spontaneous abortions, 18 elective terminations (no known fetal defects), 2 elective terminations (with fetal defects), 14 subjects lost to follow-up, and 3 ongoing pregnancies. No nursing women were exposed to risankizumab as women were discontinued from risankizumab upon knowledge of pregnancy. Data to be Collected Post-Authorization: Routine pharmacovigilance data. A population-based, non-interventional, cohort study of women with moderate-to-severe psoriasis who are exposed to risankizumab or comparator biologic during pregnancy is ongoing (see Section III.2 for additional details on study design). A non-interventional cohort study will be conducted to describe risankizumab exposure in pregnant patients with Crohn's disease or UC and compare pregnancy and infant outcomes to pregnant patients with Crohn's disease or UC who were treated with alternative therapies (see Section III.2 for additional details on study design).
Information 2: Long-term safety Reason for Inclusion: Long-term safety data on events with a low frequency and/or long latency are not available. Data to be Collected Post-Authorization: Data from routine pharmacovigilance activities, long-term comparative cohort studies, and the long-term extension portion of Phase 3 risankizumab trials (see Section III.2 for additional details on study design).

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

With this first addition of a pediatric indication, the important potential risk of MACE was initially specified as applicable only to adults. In response to the CHMP Day 120 Assessment Report - List of Questions (EMA/X/0000296763) the important potential risk of MACE was updated to remove the restriction of MACE as an important potential risk to only the adult population.

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 Risk 1: Serious hypersensitivity reactions
Potential Mechanisms:
Biological drugs have been reported to cause hypersensitivity reactions, including anaphylaxis (Corominas 2014). The hypersensitivity reactions might be immediate onset (possible IgE mediated) or delayed onset (due to IgG formation, and T-cell mediated). Immediate reactions appear during the first hours after administration and are very heterogeneous in etiology and presentation (nausea, vomiting, skin reactions, respiratory symptoms, hypotension). Some reactions involve release of cytokines by immune system cells due to activation by the drug itself, other cases involve the participation of an IgE-mediated mechanism. Delayed hypersensitivity reactions can appear between 1 to 2 hours and 14 days after administration, often with serum sickness–like symptoms. As a biologic protein, systemic or subcutaneous administration of risankizumab may be associated with immunogenicity (i.e., development of anti-drug antibodies) as well as hypersensitivity reactions.
Evidence Sources and Strength of Evidence:
The risk varies depending on the biologic used and is reflected in the individual biologic labels. Integrated risankizumab clinical trial data were used to assess the risk with risankizumab therapy.
Characterization of the Risk:
Psoriasis: As of 25 March 2025, the cumulative rate of serious hypersensitivity reactions across any risankizumab exposure was < 0.1 events/100 PY (95% CI: 0.03 - 0.13). In the pediatric PsO trials specifically (M19-977 and M19-973), there were no treatment-emergent serious hypersensitivity reactions through the data cut off of 01 January 2025 for M19-973 and end of study for M19-977. **Psoriatic Arthritis:** As of 25 March 2025, the cumulative rate of serious hypersensitivity reactions across any risankizumab exposure was < 0.1 events/100 PY (95% CI: 0.02 – 0.18). **Crohn's Disease**: As of 25 March 2025, the cumulative rate of serious hypersensitivity reactions across any risankizumab exposure was < 0.1 events/100 PY (95% CI: 0.01 – 0.13). **Ulcerative Colitis:** As of 25 March 2025, the cumulative rate of serious hypersensitivity reactions across any risankizumab exposure was < 0.1 events/100 PY (95% CI: 0.00 – 0.13).
Risk Factors and Risk Groups:
Several factors influence the propensity towards development of hypersensitivity reactions including degree of humanization of the antibody, cell line from which the drug is obtained (CHO produces virtually no 1,3-galactosyltransferase, resulting in a glycosylation pattern much different from that of other drugs such as cetuximab [derived from the murine cell line SP2/O], thereby reducing the risk of hypersensitivity reactions) and the excipients used (Corominas 2014). Host factors include the indication for the treatment (e.g., atopic tendencies in patients with asthma), patient's immune status, and concomitant medications.

Preventability:
A patient should not be rechallenged with the drug in the case of a systemic hypersensitivity reaction judged related to the product.
Impact on the Risk-Benefit Balance of the Product:
With appropriate risk minimization measures, the risk benefit balance remains positive.
Public Health Impact:
Biologics, being proteins, are known to have a risk of hypersensitivity. Serious hypersensitivity reactions with use of risankizumab in the clinical trial program were rare. Therefore, a significant impact on public health is not anticipated.

Important Potential Risk 1: MACE
Potential Mechanisms: The rationale for a correlation between psoriasis, psoriatic arthritis, Crohn's Disease, and atherosclerotic disease is not well understood. Although the increased prevalence of risk factors for CVD (obesity, HTN, DM, hyperlipidemia, metabolic syndrome, and cigarette smoking) in patients with psoriasis and psoriatic arthritis likely contributes to the elevated risk for atherosclerosis, the role of chronic inflammation in the pathogenesis of these disorders may also be a key factor (Argollo 2019, Reich 2012).
Evidence Sources and Strength of Evidence: Adjudicated MACE in the integrated risankizumab clinical trial was used to assess the risk with risankizumab therapy.
Characterization of the Risk:
Psoriasis: Evaluating the long-term safety of all subjects with plaque psoriasis who received risankizumab treatment at any dose or time, the cumulative rate of MACE was 0.5 events/100 PY (95% confidence interval [CI] 0.43 – 0.68) as of 25 March 2025; across the pediatric PsO studies, no events of MACE were reported. It is in the range of MACE rates (0.37 – 0.84 events/100 PY) reported for other non-TNF biologic products at the time of their initial submission: brodalumab (0.7, 22 events/3373 PY, 95% CI 0.43 – 1.02) (Food and Drug Administration 2017), ixekizumab (0.72, 31 events/4322 PY, 95% CI 0.5 – 1.02) (Therapeutic Goods Administration 2017), secukinumab (0.37, 10 events/2725 PY, 95% CI 0.18 – 0.68) (Novartis 2014), ustekinumab (0.61, 9 events/1467 PY, 95% CI 0.28 – 1.16) (Centocor 2008), and guselkumab (0.84, 10 events/1191 PY, 95% CI 0.4 – 1.54) (Center for Drug Evaluation and Research 2017). In addition, this rate is consistent with the MACE rates reported in the Psoriasis Longitudinal Assessment and Registry (PSOLAR), including the long-term rate of overall MACE in patients with psoriasis (0.57 events/100 PY) and in patients with psoriasis treated with non-biologics (0.64 events/100 PY) (Papp 2020). **Psoriatic Arthritis**: Across all risankizumab PsA studies, the cumulative rate of MACE with risankizumab therapy as of 25 March 2025 was 0.4 events/100 PY (95% CI: 0.27 - 0.62), consistent with the reported rate of MACE for the patient population (0.46 per 100 PY) (Li 2015), and within the range of adjudicated MACE rates of 0.5 events/100 PY with ixekizumab (Sesin 2021) and 0.5 events/100 PY with secukinumab Phase 3 long-term exposure in PsA (Gottlieb 2022).

Crohn's Disease: Across all risankizumab CD studies, the cumulative rate of MACE with rizankizumab therapy as of 25 March 2025 was 0.2 events/100 PY (95% CI: 0.08 – 0.30), consistent with the reported rate of MACE for the CD patient population (0.82/100 PY) (Kristensen 2013).

Ulcerative Colitis: Considering the rarity of CV events across the risankizumab UC program (i.e., all doses, induction, maintenance) and the latency of CV events, patients exposed to any risankizumab was considered the most appropriate for this assessment. Across all risankizumab UC studies as of 25 March 2025, a total of 5 events of MACE and the cumulative rate of MACE (0.1/100 PY) was not higher than the background rate for this patient population based on published estimates (1.10/100 PY) (Kristensen 2013).

Risk Factors and Risk Groups:

Patients with traditional cardiac risk factors, i.e., age, sex, family history of premature coronary artery disease (CAD), current smoking, HTN, low high-density lipoprotein, are at higher risk of CAD. Other risk factors include DM (insulin resistance, hyperinsulinemia, and elevated blood glucose are associated with atherosclerotic CVD) (Almdal 2004, Gerstein 1999, Kannel 1979a, Kannel 1979b, Zavaroni 1989), chronic kidney disease (increased coronary heart disease [CHD] risk in patients with end-stage renal disease has been well described, but there is now clear evidence that mild to moderate renal dysfunction is also associated with a substantial increase in CHD risk) (Gansevoort 2013), other lifestyle factors (lack of exercise, psychosocial factors), and metabolic syndrome.

Preventability:

As is known for the general population, interventions geared towards the modifiable cardiac risk factors cited above (HTN, DM, hyperlipidemia, obesity, smoking) can be influential in reducing the MACE/CV risk.

Impact on the Risk-Benefit Balance of the Product:

With appropriate risk minimization measures, the risk benefit balance remains positive.

Public Health Impact:

MACE is a well-recognized co-morbidity with immune-mediated inflammatory diseases. Given the comparable incidence rates of MACE with other biologics at the time of their initial submission and consistency of long-term rates with real world data, long-term epidemiologic data from literature within the approved and proposed indications of risankizumab, no adverse public health impact due to risankizumab is anticipated.

Important Potential Risk 2: Serious infections

Potential Mechanisms:

Binding of risankizumab to IL-23 p19 inhibits the action of IL-23 to induce and sustain T helper (Th) 17 type cells, innate lymphoid cells, γδT cells, and natural killer cells responsible for tissue inflammation, destruction and aberrant tissue repair. Due to the immunomodulatory effects of risankizumab, there is a risk for serious infections.

Evidence Source and Strength of Evidence:

Integrated risankizumab clinical trial data were used to assess the risk with risankizumab therapy, and epidemiologic data were used to contextualize the risankizumab data.

Characterization of the Risk:

Psoriasis: As of 25 March 2025, the cumulative (long-term all risankizumab psoriasis exposure) rate of serious infections in clinical trials was 1.2 events/100 PY (95% CI: 1.02 – 1.39). In the pediatric PsO trials specifically (M19-977 and M19-973), there were no treatment-emergent serious infections through the data cut off of 01 January 2025 for M19-973 and end of study for M19-977. The rate for serious infections with risankizumab treatment in plaque psoriasis patients was in the range (1.02 – 2.0 events/100 PY) reported for other non-TNF biologics at the time of their initial submission: brodalumab (1.3, 95% CI 1.02 – 1.62) (European Medicines Agency 2017), ustekinumab (1.02, 95% CI 0.57 – 1.69) (Centocor 2008), ixekizumab (2.0, 95% CI 1.53 – 2.51) (Center for Drug Evaluation and Research 2016a, TALTZ 2017), secukinumab (1.47, 95% CI 1.05 – 2.01) (van de Kerkhof 2016), and guselkumab (1.17, 95% CI 0.56 – 2.16) (Center for Drug Evaluation and Research 2016b).

Psoriatic Arthritis: Across all risankizumab PsA studies, the cumulative rate of serious infections with risankizumab therapy as of 25 March 2025 was 1.6 events/100 PY (95% CI: 1.26 – 1.93) and is within the expected range for this patient population based on published estimates (3.98 events/100 PY) (Shah 2017). The types of serious infections reported were consistent with those anticipated in a population of patients with PsA.

Crohn's Disease:

12-Week Induction

In the induction period, serious infections were reported at a lower percentage and rate among subjects in the risankizumab group (0.9%, 3.4 events/100 PY in the 600 mg IV group) compared to subjects in the placebo group (3.6%, 16.7 events/100 PY). The higher rate of serious infections in the placebo group was driven primarily by more events of gastrointestinal abscess.

Maintenance up to 52 Weeks

The rate of serious infection was 6.0 events/100 PY and 5.0 events/100 PY for the risankizumab 360 mg SC arm and the withdrawal (placebo SC) arm, respectively.

Any Risankizumab

Across all risankizumab CD studies, the cumulative rate of serious infections with risankizumab therapy as of 25 March 2025 was 2.6 events/100 PY (95% CI: 2.26 – 3.06) and is within the expected range for this patient population based on published estimates.

CD is associated with increased risk of infection (Irving 2021). In a nationwide population-based study conducted in France, incidence rate (per 100 PY) among patients with inflammatory bowel disease (IBD), including CD and UC, was 0.94 for serious infections (Kirchgesner 2018).

Treatment of IBD may be associated with an increased risk of serious infection (Kirchgesner 2018). The incidence rate of serious infections (per 100 PY) varied by treatment options with 0.84 in patients with IBD unexposed to thiopurines and anti-TNFs, 1.89 in those treated with anti-TNF monotherapy, and 2.24 in patients treated with thiopurine/anti-TNF combination therapy (Kirchgesner 2018). In a nationwide population-based study in Denmark, using a broader definition of serious infection, the incidence rate (per 100 PY) for serious infections was 8 and 6 among patients with IBD exposed and unexposed to anti-TNF, respectively, within a year of treatment start (Nyboe Andersen 2015). Integrated safety analyses of ustekinumab Phase 2/3 CD studies found that the rate of serious infections through 1 year follow-up was similar across treatment groups: 6.64 per 100 PY in placebo and 6.06 per 100 PY in the ustekinumab-treated group (Sandborn 2021). The most common serious infections in IBD patients (both treated and untreated) affected the lungs (24.2%) with pneumonia being the most prevalent diagnosis (20.2%) (Kirchgesner 2018).

Overall, the data did not suggest an increased risk of serious infection with risankizumab treatment in subjects with CD. The types of serious infections reported were consistent with those anticipated in a population of patients with CD.

Ulcerative Colitis:

12-Week Induction

In the induction period, serious infections were reported at a similar percentage among subjects in the risankizumab group (0.7%) compared to subjects in the placebo group (1.1%).

Maintenance up to 52 Weeks

The rates of serious infection in both risankizumab arms were similar to the placebo arm:
1.1 events/100 PY in the risankizumab 180 mg SC arm, 0.6 events/100 PY in the risankizumab 360 mg SC arm, and 2.3 events/100 PY in the placebo arm.

Any Risankizumab

Across all risankizumab UC studies, the incidence rate of serious infections with risankizumab therapy as of 25 March 2025 was 1.7/100 PY and not higher than the expected range for this patient population based on published estimates.

Patients with UC are at increased risk for serious infections, due in part to background immunomodulatory treatment (Bonovas 2016, Irving 2021). The incidence rate of serious infections (per 100 PY) varied by treatment options in patients with IBD and ranged from 0.84 to 2.4 (Kirchgesner 2018) and 6 to 8 (Nyboe Andersen 2015), with details summarized under CD above.

Overall, the data did not suggest an increased risk of serious infection with risankizumab treatment in subjects with UC. The types of serious infections reported were consistent with those anticipated in a population of patients with UC.

Risk Factors and Risk Groups:

The elderly and patients with other risk factors compromising immunity such as diabetes or chronic renal insufficiency are at increased risk.

Preventability:

Early detection of serious systemic infection can improve outcomes. There are no laboratory correlates such as white blood cell or neutrophil counts that can influence early detection/prevention.

Impact on the Risk-Benefit Balance of the Product:

With appropriate risk minimization measures, the risk benefit balance remains positive.

Public Health Impact:

Serious infections evolving to sepsis can be associated with major morbidity and mortality. Adequate precautions have been outlined in the labeling for early identification and mitigation of serious infections. Therefore, a significant impact on public health is not anticipated.

Important Potential Risk 3: Malignancies

Potential Mechanisms:

Inflammation is now accepted as a hallmark and an enabling characteristic of cancer (Langan 2012). Upregulation of pro-inflammatory cytokines associated with anti-bacterial responses, particularly in a chronic inflammation setting, has been shown to be contributing factors to tumorigenesis (Voiculescu 2014). Chronic inflammation promotes tumorigenesis through the activation of the nuclear factor (NF)-kB (NF-kB) and signal transducer and activator transcription (STAT)3 pathways (Azfar 2012, Qureshi 2009). Prolonged STAT3 signaling in malignant cells controls survival and proliferation through upregulation of Bcl-Xl (Gelfand 2006), Mcl1, and c-Myc levels. In the local tumor environment, STAT3 activation leads to the expression of IL-23, and elevated levels of IL-23 can be found in several human carcinomas and correlated with a poor prognosis (Aratari 2008, Gelfand 2006, Huerta 2007). Moreover, genome-wide association studies identified 2 variants of IL-23R that may increase the risk of cancer development (Ahlehoff 2012).

While the pro-tumorigenic role of IL-23 has been shown in a number of studies, there are also reports supporting a tumor suppressive function of IL-23. One possible explanation is that the amount of IL-23 expressed in the tumor environment might determine the pro- or anti-tumorigenic role of the cytokine. In the latter case, blocking IL-23 could potentially increase the risk of carcinogenesis. Furthermore, IL-23 is unlikely to increase the risk for cancer, as expression of IL-23 is increased in human tumors. Preclinical data have, moreover, demonstrated beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction models (Langowski 2006).

Evidence Sources and Strength of Evidence:

Integrated risankizumab clinical trial data were used to assess the risk with risankizumab therapy.

Characterization of the Risk:

Psoriasis: As of 25 March 2025, the cumulative (long-term all risankizumab psoriasis exposure) rates of malignancies excluding NMSC and NMSC were 0.6 events/100 PY (95% CI: 0.49 – 0.76) and 0.5 events/100 PY (95% CI: 0.43 – 0.68), respectively. In the pediatric PsO trials specifically (M19-977 and M19-973), there were no treatment-emergent malignancies through the data cut off of 01 January 2025 for M19-973 and end of study for M19-977.

The cumulative rate of malignancies excluding NMSC for risankizumab in the plaque psoriasis population is consistent with that reported for other non-TNF biologics (brodalumab rate not publicly available) in psoriasis population at the time of their initial submission: ustekinumab (0.34, 95% CI 0.11 – 0.7) (Centocor 2008), ixekizumab (0.49, 95% CI 0.31 – 0.70) (Center for Drug Evaluation and Research 2016a), secukinumab (0.48, 95% CI 0.25 – 0.82) (van de Kerkhof 2016), guselkumab (0.31, 95% CI 0.06 – 0.90) (Center for Drug Evaluation and Research 2016b). Further, these rates are consistent with the rate in the PSOLAR; the rates of malignancies excluding NMSC in subjects treated with ustekinumab, infliximab, and other biologics are 0.48 events/100 PY (95% CI 0.37 – 0.61), 0.79 events/100 PY (95% CI 0.57 – 1.05), and 0.73 events/100 PY (95% CI 0.6 – 0.86), respectively (Papp 2020). The cumulative rate of NMSC (0.6 events/100 PY) was lower than that reported in a MarketScan® claims database cohort study of 40,788 US patients with psoriasis with varying disease severity with 1.80/100 PY (95% CI 1.73 – 1.88) for the overall psoriasis population and 1.99/100 PY (95% CI 1.70 – 2.27) for the non-biologic arm (Kimball 2015).

Psoriatic Arthritis: Across all risankizumab PsA studies, the cumulative rate for malignant tumors excluding NMSC with risankizumab therapy as of 25 March 2025 was 0.5 events/100 PY (95% CI: 0.35 - 0.75), which is within the epidemiologic reference rate in the PsA population

(0.48 events/100 PY) (Vaengebjerg 2020). The rate of NMSC with long-term risankizumab exposure was 0.4 events/100 PY (95% CI: 0.28 – 0.64) and is within the epidemiological reference rate in the PsA population (0.61 events/100 PY) (Vaengebjerg 2020).

Crohn's Disease: Across all risankizumab CD studies, the cumulative rates of malignancies excluding NMSC and NMSC with risankizumab therapy as of 25 March 2025 were 0.4 events/100 PY (95% CI: 0.28 – 0.61) and 0.2 events/100 PY (95% CI: 0.13 – 0.37), respectively.

Patients with CD have a modestly increased risk of cancer overall partially due to an increased risk of gastrointestinal cancers, especially colorectal cancer (Lo 2021, Long 2012). Long-lasting exposures to immunosuppressive therapies, underlying disease, and lifestyle factors may contribute to the development of cancer in patients with CD (Taborelli 2020). In a population-based cohort study conducted in northeastern Italy linking local healthcare databases and the cancer registry from 1995 to 2013, with a total follow-up time of 10,558 PY for CD, incidence rate (per 100 PY) was 0.98 for cancer excluding NMSC and 0.36 for NMSC among patients with CD; standardized incidence ratio was 1.07 (95% CI: 0.87-1.30) for cancer excluding NMSC and 1.86 (95% CI: 1.32-2.55) for NMSC (Taborelli 2020). Another population-based cohort study conducted in Denmark and Sweden found that the incidence rate (per 100 PY) of colorectal cancer was 0.08 in patients with CD and 0.06 in the general population, resulting in an adjusted hazard ratio of 1.40 (95% CI: 1.27-1.53) (Olen 2020). Gastrointestinal cancer risk in CD, particularly colorectal cancer, has been decreasing over time partly due to earlier and more frequent use of immunosuppressive agents and biologics, which may be more effective in controlling inflammation (Kappelman 2014).

The rates of malignancies in the risankizumab-treated CD population are within the expected range for this patient population based on published estimates.

Ulcerative Colitis: Considering the rarity of malignancies across the risankizumab UC program (i.e., all doses, induction, maintenance) and the latency of malignancy events, patients exposed to any risankizumab was considered the most appropriate for this assessment. Across all risankizumab UC studies, the cumulative rates of malignancies excluding NMSC and NMSC with risankizumab therapy as of 25 March 2025 were 0.5 events/100 PY (95% CI: 0.34 – 0.81) and 0.4 events/100 PY (95% CI: 0.23 - 0.64), respectively. Patients with UC have a modestly increased risk of cancer overall (Kappelman 2014). Long-lasting exposures to immunosuppressive therapies, underlying disease, and lifestyle factors may contribute to the development of cancer in patients with UC (Taborelli 2020). In a population-based cohort study conducted in northeastern Italy linking local healthcare databases and the cancer registry from 1995 to 2013, with a total follow-up time of 18,299 PY for UC, the incidence rate (per 100 PY) was 1.06 (95% CI: 0.92 – 1.22) for malignancies excluding NMSC and 0.28 (95% CI: 0.21 – 0.37) for NMSC among patients with UC (Taborelli 2020).

The rates of malignancies in the risankizumab-treated UC population are similar to the background rate for this patient population based on published estimates.

Risk Factors and Risk Groups:

Multiple factors may contribute to an increased rate of malignancy in patients using immunosuppressive or immunomodulatory therapies, which are used in immune-mediated inflammatory diseases. The traditional systemic therapies, methotrexate, cyclosporine A, and mycophenolate mofetil, may be associated with an increased risk of lymphoproliferative disorders during treatment, demonstrated in clinical trials in patients with rheumatoid arthritis and CD documented in case reports. However, the majority of studies examining this carcinogenic risk suggest that TNF-α inhibitors may cause a slightly increased risk of cancer, including NMSC and hematologic malignancies.

Preventability: Routine standard of care for early detection of malignancy can be followed. In addition, patients may be under close care of dermatologists, skilled towards early detection of skin cancers.
Impact on the Risk-Benefit Balance of the Product: With appropriate risk minimization measures, the risk benefit balance remains positive.
Public Health Impact: Given the comparable incidence rates of malignancies and malignancies excluding NMSC with other biologics at the time of their initial submission and consistency of long-term rates with real world data and epidemiologic reference data, no adverse public health impact due to risankizumab is anticipated.

SVII.3.2 Presentation of the Missing Information

Missing information 1: Use during pregnancy and lactation
• Population in need of further characterization Pregnant women, nursing women, and women who planned to become pregnant were excluded from the clinical trials. Further characterization of pregnancy outcomes in women who become pregnant while receiving risankizumab will be needed. Routine pharmacovigilance data will be collected. A population-based, non-interventional, cohort study of women with moderate-to-severe psoriasis who are exposed to risankizumab or comparator biologic during pregnancy is ongoing (see Section III.2 for additional details on study design). A non-interventional cohort study will be conducted to describe risankizumab exposure in pregnant patients with Crohn's disease or UC and compare pregnancy and infant outcomes to pregnant patients with Crohn's disease or UC who were treated with alternative therapies.

Missing information 2: Long-term safety
• Population in need of further characterization Long-term risankizumab clinical safety data are currently limited. Psoriasis, psoriatic arthritis, Crohn's Disease, and UC are chronic diseases requiring long-term treatment. Therefore, further characterization of the safety profile is needed for events with a low frequency and/or long latency. Data from routine pharmacovigilance activities will be collected as well as data from multiple long-term cohort studies in real world settings in subjects with plaque psoriasis, PsA, CD, and UC, and data from the long-term extension portions of Phase 3 trials in subjects with PsA and pediatric psoriasis.

Module SVIII Summary of the Safety Concerns

Table 12. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Serious hypersensitivity reactions
Important potential risks	• MACE • Serious infections • Malignancies
Missing information	• Use during pregnancy and lactation • Long-term safety

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

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include:

- Biweekly line listing review of all post-marketing reports, serious and nonserious, received from all sources (including literature) and includes serious adverse events from clinical trials.
- Quarterly review of data mining scores generated from FDA Adverse Event Reporting System database.
- Periodic reports to agencies (e.g., periodic safety update reports, development safety update reports, periodic adverse drug experience reports) with inclusion of sections outlining findings for adverse events of interest. These will occur per mandated timelines.

Specific adverse reaction follow-up questionnaires for pregnancy:

AbbVie has a standardized global process for the use of follow-up questionnaires within the pharmacovigilance system as part of post-marketing surveillance. This process includes contact to the healthcare professional (HCP) or reporter using the questionnaire via phone, fax or send letter/form. The follow-up to consumer will include an attempt to obtain consent to contact the HCP. A minimum number of queries are made depending on the seriousness of the case; medical judgment or local regulations are applied to determine if further attempts (above the minimum) should be made. Data collection using the questionnaires will be done as described in Annex 4.

Other forms of routine pharmacovigilance activities:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Additional pharmacovigilance studies are proposed to evaluate safety risks including malignancies, MACE, serious infections, serious hypersensitivity reactions, use in pregnancy, and long-term safety.

Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting

Study Short Name and Title: A long term registry-based prospective cohort study of long-term safety of risankizumab in Denmark and Sweden (Study P19-633)

Rationale and Study Objectives: Clinical trials of risankizumab did not allow us to fully characterize the risk of malignancies, MACE, serious infections and serious hypersensitivity reactions. Therefore, they are considered potential risks. These potential risks will be studied via a post-marketing long term cohort comparison study. The aim of the study is to estimate the risks of malignancy, MACE, serious infections, and serious hypersensitivity reactions, among individuals who were exposed to risankizumab for the treatment of psoriasis, relative to comparative cohorts, that is, similar patients treated with: i) TNF-α inhibitors; ii) other IL inhibitors; and iii) non-biological systemic treatments.

Study Design: A cohort study will be carried out utilizing linked data from the Danish and Swedish national registers to estimate rates of malignancy, MACE, serious infections, and serious hypersensitivity reactions in patients treated with risankizumab for psoriasis and to estimate event risks relative to those treated with other systemic therapies.

Study Population: All psoriasis patients (which includes patients with arthropathic psoriasis (PsA) [ICD-10-CM L40.5x]) who have filled at least one prescription of a biological drug (IL inhibitors [L04AC] and/or TNF-α inhibitors [L04AB]), or have been administrated a biological drug in the hospital (e.g., infliximab), as well as all psoriasis patients who have filled at least one prescription of non-biological systemic treatment (methotrexate, ciclosporin, and acitretin) or have been treated with phototherapy (procedure codes from the patient registers) will be identified from the prescription and other databases in Denmark and Sweden from January 01, 2020 and enrolled for a prospective follow-up. The study will accrue patients from April 2019 through 31 December 2024 and then follow up the patients through 31 December 2032. Based on the use of ustekinumab and secukinumab within the Danish and Swedish databases, the estimated number of patients with psoriasis identified as risankizumab users will range from 1656 to 3384 over a 12-year period.

Using an exploratory analysis of these Danish and Swedish databases from 2006 to 2013, it is expected that at minimum, the number of PsA patients will be one-third of all psoriasis

patients. This will result in a range of 552 to 1128 patients with PsA exposed to risankizumab. The main statistical analysis for each outcome as defined in the P19-633 protocol will also be conducted for this subset of individuals with PsA.

Milestones:

- Start of data collection (incl. data up to December 2019): January 2020
- Study Progress report: Q3 2023
- 1st Interim report of study results (incl. data up to December 2024): December 2026
- 2nd Interim report of study results (incl. data up to December 2028): December 2030
- End of data collection (incl. data up to December 2032): December 2033
- Final report of study results: December 2034

Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting

Study Short Name and Title: A comparative cohort study of long-term safety of risankizumab in patients with ulcerative colitis and Crohn's disease (Study P23-654)

Rationale and Study Objectives: The clinical trial program was not able to fully characterize the safety profile of risankizumab in the ulcerative colitis and Crohn's disease populations. Additional long-term data are needed from the real-world experience of patients with ulcerative colitis and Crohn's disease treated with risankizumab to assess product potential risks.

Study Design: A comparative cohort study will be conducted to estimate rates of malignancy (malignancy excluding NMSC, NMSC), serious infections, serious hypersensitivity reactions, and MACE in risankizumab treated patients with ulcerative colitis or Crohn's disease, relative to alternative systemic therapies (e.g., biologics). The study will be conducted within the Swedish Inflammatory Bowel Disease Register (SWIBREG) and the National Registers of Sweden and Denmark. Validated disease and outcome definitions, and appropriate methods for confounding control will be utilized.

Study Population: All patients with ulcerative colitis or Crohn's disease (with age per labeled indication) who have filled at least one prescription for risankizumab or comparator treatment will be identified in the data source after a specified start date and included in the study.

Milestones:

- Start data collection period: Q1 2025
- Interim report: Q4 2029
- End data collection period: Q1 2034

- Final report: Q4 2034

Pregnancy Exposure and Outcomes for Women with Psoriasis Treated with Risankizumab

Study Short Name and Title: Pregnancy Exposures and Outcomes in Women with Psoriasis Treated with Risankizumab: A Cohort Study Utilizing Large Electronic Healthcare Databases with Mother-Baby Linkage in the United States (Study P16-751)

Rationale and Study Objectives: Available clinical trial data is inadequate to assess whether there is a risk for women receiving risankizumab while pregnant. Based on available data regarding the number of pregnant women who have received other biologic treatments including adalimumab for the treatment of moderate to severe plaque psoriasis, the Sponsor predicts that use of risankizumab by women who become pregnant will be rare. Therefore, a traditional pregnancy registry will not afford an adequate assessment of pregnancy outcomes. This study will compare pre-specified pregnancy, birth and infant outcomes among women exposed to risankizumab versus comparators during pregnancy (anti-TNF-α, IL-17 biologics or their biosimilars [comparator biologic-exposed group] for moderate to severe psoriasis).

Study Design: The study will be a population-based, non-interventional, cohort study of women with moderate-to-severe psoriasis who are exposed to risankizumab or comparator biologic during pregnancy. The study will leverage the longitudinal nature of healthcare databases that have complete longitudinal capture of medical encounters and prescription medication exposures for large cohorts. Pregnancies with outcomes occurring during the period 01 May 2019 to 31 December 2026, and infant outcomes identified from these pregnancies for a 1-year period ending in Q4 2027 (i.e., the end of the study period for infant outcomes will be Q4 2027) will be included, with a provision to extend the period with additional years of data to reach the desired sample size.

Study Population: Women of child-bearing age (ages 15 to 55 years at the start of pregnancy) with psoriasis or arthropathic psoriasis (PsA) will serve as the study population. There will be two specific cohorts of women included in this study: 1) women exposed to risankizumab but not exposed to other biologic therapies at any time during pregnancy (risankizumab-exposed cohort); and 2) women exposed to an anti-TNF-α, IL-17 biologics or their biosimilars for moderate-to-severe psoriasis at any time during pregnancy (comparator biologic-exposed cohort). In addition, women with psoriasis unexposed to treatment under investigation will serve as a frame of reference and be included for descriptive analysis only to provide context to the rates of outcomes observed in the risankizumab-exposed and comparator biologic-exposed groups. Women with PsA will be captured and analyzed in a subgroup analysis.

Milestones: Approximate dates for important milestones for this study are listed below. Additionally, annual surveillance (i.e., progress) reports will be submitted.

- Estimated start of data collection (when Q2 2019 data become available): Q1 2021
- Study progress report: Q3 2024
- Study progress report: Q3 2027
- End of data collection: Q3 2029
- Final study report: Q3 2030

Pregnancy Exposure and Outcomes for Women with Inflammatory Bowel Disease Treated with Risankizumab

Study Short Name and Title: Pregnancy exposures and outcomes in women with Inflammatory Bowel Disease treated with risankizumab: A Cohort Study Utilizing Large Electronic Healthcare Databases with Mother-Baby Linkage in the United States (Study P23-653)

Rationale and Study Objectives: The clinical trial programs did not assess the safety of risankizumab use during pregnancy. In addition to the study of risankizumab exposure in psoriasis patients, a study of pregnancy outcomes in patients with IBD (Crohn's disease and ulcerative colitis) who are exposed to risankizumab, compared to alternative biologic treatments, will be conducted.

Study Design: A comparative cohort study will be conducted to describe risankizumab exposure in pregnant patients with IBD (Crohn's disease and ulcerative colitis) and compare pregnancy and infant outcomes to pregnant patients with IBD who were treated with alternative therapies (e.g., biologics). In addition, descriptive analyses of pregnancy outcomes in IBD patients without exposure to any treatments under investigation will also be conducted.

Study Population: Women of child-bearing age with IBD will comprise the study population. Patients (with age per labeled indication) who have filled at least one prescription for risankizumab or comparator treatment and are considered to be exposed to treatment during pregnancy will be included in the study. The study will be conducted within the network of administrative claims data with mother-baby linkage within the FDA Sentinel Distributed Database.

Milestones:

- Start data collection period: Q3 2025
- Progress report: Q3 2028
- End data collection period: Q2 2032
- Final report: Q2 2033

Risankizumab Psoriatic Arthritis Studies

Study Title: A Phase 3, Randomized, Double-Blind, Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis (PsA) Who Have a History of Inadequate Response to or Intolerance to at Least One Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy (KEEPsAKE 1) (Study M16-011)

Rationale: To evaluate the treatment of moderately to severely active psoriatic arthritis in subjects who have a demonstrated inadequate response (lack of efficacy after a minimum 12-week duration of therapy) or intolerance to at least 1 csDMARD therapy (csDMARD-IR).

Objective: The primary objective in Period 1 is to compare the efficacy of risankizumab 150 mg versus placebo for the treatment of signs and symptoms of psoriatic arthritis in subjects with active psoriatic arthritis who have a history of inadequate response to or intolerance to at least one DMARD therapy. The objective in open-label Period 2 is to evaluate the long-term safety, tolerability, and efficacy of risankizumab 150 mg in subjects with psoriatic arthritis who have completed Period 1.

Study Design: Phase 3, 2-period, multicenter study designed to investigate the long-term safety and efficacy of 150 mg risankizumab for the treatment of moderately to severely active psoriatic arthritis. Nine hundred sixty-four subjects were randomized in Study M16-011.

During double-blind, placebo-controlled Period 1, study visits occurred at Week 0, Week 4, Week 8, Week 12, Week 16, Week 24, and dosing in Period 1 occurred at Week 0, Week 4, and Week 16. During open-label Period 2, all subjects receive risankizumab 150 mg subcutaneously every 12 weeks from Week 28 and for the remaining dosing visits (to Week 208). For all subjects continuing to participate in Period 2, the open-label portion of the study, dosing visits will be scheduled to Week 208 unless they discontinue study drug or study participation earlier in the study. The Follow-up Period consists of a completion visit 12 weeks after the last study drug dose. An additional follow-up phone call will occur 8 weeks later, 20 weeks after last study drug dose, to determine the status of any ongoing adverse events/serious adverse events or the occurrence of any new adverse events/serious adverse events.

An independent adjudication committee will adjudicate all observed cardio-vascular and cerebro-vascular events, including MACE, in a blinded manner. In addition, an anaphylactic adjudication committee will adjudicate any serious hypersensitivity reactions.

Milestones:

- Original protocol approved: 26 July 2018
- Current protocol version 7.0 approved: 10 October 2024
- End of Period 1: 08 October 2020
- Estimated final report approval: Q1 2027

Study Title: A Phase 3, Randomized, Double-Blind Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis Including Those Who Have a History of Inadequate Response or Intolerance to Biologic Therapy(ies) (KEEPsAKE 2) (Study M15-998)

Rationale: To evaluate the treatment of moderately to severely active psoriatic arthritis. The subject population will consist of no more than 50% of subjects with a demonstrated inadequate response (lack of efficacy after a minimum 12-week duration of therapy) or intolerance to 1 or 2 biologic therapies (Bio-IR). The remaining study population will be subjects who have a demonstrated inadequate response (lack of efficacy after a minimum 12 week duration of therapy) or intolerance to at least 1 csDMARD (csDMARD-IR).

Objective: The primary objective in Period 1 is to compare the efficacy of risankizumab 150 mg versus placebo for the treatment of signs and symptoms of subjects with active psoriatic arthritis including those who have a history of inadequate response or intolerance to biologic therapy(ies). The objective in open-label Period 2 is to evaluate the long-term safety, tolerability, and efficacy of risankizumab 150 mg in subjects who have completed Period 1.

Study Design: Phase 3, 2-period, multicenter study designed to investigate the long-term safety and efficacy of 150 mg risankizumab in the treatment of moderately to severely active psoriatic arthritis. Four hundred forty-four subjects were randomized in Study M15-998.

During double-blind, placebo-controlled Period 1, study visits occurred at Week 0, Week 4, Week 8, Week 12, Week 16, Week 24, and dosing in Period 1 occurred at Week 0, Week 4, and Week 16 for each study. During open-label Period 2 of each study, all subjects receive risankizumab 150 mg subcutaneously every 12 weeks from Week 28 and for the remaining dosing visits (to Week 208). For all subjects continuing to participate in Period 2, the open-label portion of the study, dosing visits will be scheduled to Week 208 unless they discontinue study drug or study participation earlier in the study. The Follow-up Period consists of a completion visit 12 weeks after the last study drug dose. An additional follow-up phone call will occur 8 weeks later, 20 weeks after last study drug dose, to determine the status of any ongoing adverse events/serious adverse events or the occurrence of any new adverse events/serious adverse events.

An independent adjudication committee will adjudicate all observed cardio-vascular and cerebro-vascular events, including MACE, in a blinded manner. In addition, an anaphylactic adjudication committee will adjudicate any serious hypersensitivity reactions.

Milestones:

- Original protocol approved: 26 July 2018
- Current protocol version 8.0 approved: 10 October 2024
- End of Period 1: 21 June 2020
- Estimated final report approval: Q4 2026

Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis

Study Title: OptIMMize-2: A Phase 3 multicenter, single-arm, open-label extension study to assess the safety, tolerability, and efficacy of risankizumab in subjects with moderate to severe plaque psoriasis who have completed participation in Study M19-977 (OptIMMize-1) (Study M19-973)

Rationale and Study Objectives: There is an unmet medical need for effective treatment in pediatric patients with plaque psoriasis. This study is being conducted to assess long-term safety, tolerability, and efficacy of risankizumab in pediatric subjects with moderate to severe plaque psoriasis.

Study Design: A Phase 3 multicenter, single-arm, open-label extension (OLE) study designed to investigate the long-term safety, tolerability, and efficacy of risankizumab 150 mg or 55 mg by weight every 12 weeks (Q12W) in the treatment of moderate to severe plaque psoriasis in eligible subjects who have completed all assessments in Study M19-977 and elect to participate in Study M19-973.

This study has a duration of up to 224 weeks with the last dose of study drug scheduled at Week 204 and last visit at Week 216.

Study Population: Pediatric patients with moderate to severe plaque psoriasis who have completed all assessments in Study M19-977 and elect to participate in Study M19-973.

Milestones:

- Original protocol approved: 26 February 2021
- Current protocol version 5.0 approved: 18 July 2025
- Estimated final report approval: Q2 2029

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 13. Ongoing and Planned Additional Pharmacovigilance Activities

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 – Required additional pharmacovigilance activities				
P19-633: Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting/Ongoing	Estimate the risks of the following events in individuals with psoriasis exposed to risankizumab relative to individuals with psoriasis (including patients with arthropathic psoriasis [PsA]) exposed to other systemic psoriasis treatments: i) TNF-α inhibitors; ii) other IL inhibitors; and iii) non-biological systemic treatments: • overall malignancy excluding NMSC • NMSC • MACE (defined as a composite of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) • serious infections (incl. opportunistic infections) • serious hypersensitivity reactions	Risks of serious hypersensitivity reactions, malignancies, MACE, and serious infections among moderate to severe plaque psoriasis patients exposed to risankizumab and comparators. Missing information: long-term safety	Study Progress report	Q3 2023
			1st Interim report of study results (incl. data up to December 2024)	December 2026
			2nd Interim report of study results (incl. data up to December 2028)	December 2030
			Final study report	December 2034

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
P16-751: Pregnancy Exposures and Outcomes in Women with Psoriasis Treated with Risankizumab: A Cohort Study Utilizing Large Electronic Healthcare Databases with Mother-Baby Linkage in the United States/Ongoing	The specific objectives of this study are to: - Evaluate the rate of major congenital malformations in infants born to women exposed to risankizumab during pregnancy compared to those exposed to other systemic treatments (primary outcome for sample size estimation). - Evaluate and compare pregnancy outcomes (i.e., live birth, spontaneous abortion, elective abortion, stillbirth) among women exposed to risankizumab versus comparators during pregnancy - Assess and compare infant outcomes (neonatal deaths, serious infections up to 1 year of age) among infants born to women exposed to risankizumab during pregnancy compared to those exposed to other biologic treatments.	Missing information on the use during pregnancy.	Study progress report Final study report	Q3 2024 Q3 2027 Q3 2030
P23-653: Pregnancy Exposure and Outcomes for Women with Inflammatory Bowel Disease Treated with Risankizumab/ Ongoing		Missing information: use during pregnancy.	Progress report	Q3 2028

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	The clinical trial programs did not assess the safety of risankizumab use during pregnancy. In addition to the study of risankizumab exposure in psoriasis patients, a study of pregnancy outcomes in patients with IBD (Crohn's disease and ulcerative colitis) who are exposed to risankizumab, compared to alternative biologic treatments, will be conducted. A comparative cohort study will be conducted to describe risankizumab exposure in pregnant patients with IBD, and compare pregnancy and infant outcomes to pregnant patients with IBD who were treated with alternative therapies (e.g., biologics). In addition, descriptive analyses of pregnancy outcomes in patients with IBD without exposure to any treatments under investigation will also be conducted.		Final report	Q2 2033
P23-654: Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting/	The clinical trial program was not able to fully characterize the safety profile of risankizumab in the ulcerative colitis and Crohn's disease populations. Additional long-term data are needed from the real-world experience of patients with ulcerative colitis and Crohn's disease treated with	Risks of serious hypersensitivity reactions, malignancies, serious infections, and MACE. Missing information: long-term safety	Interim report	Q4 2029

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Planned	risankizumab to assess product potential risks. A comparative cohort study will be conducted to estimate rates of malignancy (malignancy excluding NMSC, NMSC), serious infections, serious hypersensitivity reactions, and MACE in risankizumab treated patients with ulcerative colitis or Crohn's disease, relative to alternative systemic therapies (e.g., biologics).		Final report	Q4 2034
M16-011: A Phase 3, Randomized, Double-Blind, Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis (PsA) Who Have a History of Inadequate Response to or Intolerance to at Least One Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy (KEEPsAKE 1)/ Ongoing	The primary objective of the open-label Period 2 of Study M16-011 is to evaluate the long-term safety, tolerability and efficacy of risankizumab 150 mg in subjects with psoriatic arthritis who have completed the double-blind period.	Risks of serious hypersensitivity reactions, malignancies, MACE, and serious infections Missing information: long-term safety	Final report	Q1 2027

Study Name/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
M15-998: A Phase 3, Randomized, Double-Blind Study Comparing Risankizumab to Placebo in Subjects with Active Psoriatic Arthritis Including Those Who Have a History of Inadequate Response or Intolerance to Biologic Therapy(ies) (KEEPsAKE 2)/Ongoing	The primary objective of the open-label Period 2 of Study M15-998 is to evaluate the long-term safety, tolerability and efficacy of risankizumab 150 mg in subjects with psoriatic arthritis who have completed the double-blind period.	Risks of serious hypersensitivity reactions, malignancies, MACE, and serious infections Missing information: long-term safety	Final report	Q4 2026
M19-973: OptIMMize-2: A Phase 3 multicenter, single-arm, open-label extension study to assess the safety, tolerability, and efficacy of risankizumab in subjects with moderate to severe plaque psoriasis who have completed participation in Study M19-977 (OptIMMize-1)/Ongoing	The objective of this study is to assess the long-term safety, tolerability, and efficacy of risankizumab in pediatric subjects with moderate to severe plaque psoriasis who have completed participation in the preceding study (Study M19-977).	Risks of serious hypersensitivity reactions, malignancies, MACE, and serious infections Missing information: long-term safety	Final report	Q2 2029

Part IV: Plans for Post-Authorization Efficacy Studies

Not applicable.

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

Risk Minimization Plan

Currently there are no additional risk minimization activities beyond labeling.

V.1 Routine Risk Minimization Measures

Table 14. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Serious hypersensitivity reactions	Routine risk communication: SmPC Section 4.3 indicates contraindication if known hypersensitivity to the active substance or to any of the excipients listed in SmPC Section 6.1. SmPC Section 4.4 specifies that serious hypersensitivity reactions, including anaphylaxis, have been reported with use of risankizumab. SmPC Section 4.8 includes anaphylactic reactions as an ADR. Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 states if a serious hypersensitivity reaction occurs, administration of risankizumab should be discontinued immediately and appropriate therapy initiated. Other routine risk minimization measures: Prescription-only medicine
MACE	Routine risk communication: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription-only medicine
Serious infections	Routine risk communication: Summary of Product Characteristics (SmPC) Section 4.3 indicates contraindication for clinically important active infections such as active TB. SmPC Section 4.4 includes language that risankizumab may increase the risk of infections, that prescribers should consider the risks and benefits in patients with a chronic infection, a history of recurrent infection, known risk factors for infection, and language specific to TB. Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4 includes language regarding:

Safety Concern	Routine Risk Minimization Activities
	• Treatment with risankizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. • Patient instructions to seek medical advice for signs or symptoms suggestive of clinically important chronic or acute infection. • Closely monitor a patient who develops an infection or is not responding to standard treatment for the infection • Interrupt risankizumab until infection resolves • Evaluate patients for TB infection prior to treatment • Monitor patients for TB infection during treatment • Consider anti-TB therapy for patients with a past history of latent or active TB which was not adequately treated. Other routine risk minimization measures: Prescription-only medicine
Malignancies	Routine risk communication: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription-only medicine
Use during pregnancy and lactation	Routine risk communication: SmPC Section 4.6 states there are limited data from the use of risankizumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of risankizumab during pregnancy. Women of childbearing potential should use an effective method of contraception during treatment and for at least 21 weeks after treatment. It is unknown whether risankizumab is excreted in human milk and a decision should be made to discontinue or abstain from risankizumab therapy. The effect of risankizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility. SmPC Section 5.3 states animal studies do not indicate direct or indirect harmful effects with respect to pre- and post-developmental toxicity. Routine risk minimization activities recommending specific clinical measures to address the risk: Product labeling will be determined based on local regulatory requirements. Other routine risk minimization measures: Prescription-only medicine
Long-term safety	Routine risk communication: None Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription-only medicine

V.2 Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of risankizumab.

Additional Risk Minimization: None

Removal of Additional Risk Minimization Activity: Not applicable

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table 15. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious hypersensitivity reactions	Routine risk minimization measures: SmPC Section 4.3 indicates contraindication if known hypersensitivity to the active substance or to any of the excipients listed in SmPC Section 6.1. SmPC Section 4.4 specifies that serious hypersensitivity reactions, including anaphylaxis, have been reported with use of risankizumab. SmPC Section 4.8 includes anaphylactic reactions as an ADR. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2 • Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis
MACE	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: None	• Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2 • Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis
Serious infections	Routine risk minimization measures: Product labeling (SmPC Section 4.3, Contraindications and Section 4.4, Special warnings and precautions for use) Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2 • Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis
Malignancies	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Psoriasis Patients in Real World Setting • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		• Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis
Use during pregnancy and lactation	Routine risk minimization measures: SmPC Section 4.6 Fertility, pregnancy, and lactation Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire Additional pharmacovigilance activities: • Pregnancy Exposure and Outcomes for Women with Psoriasis Treated with Risankizumab • Pregnancy Exposure and Outcomes for Women with Inflammatory Bowel Disease Treated with Risankizumab
Long-term safety	Routine risk minimization measures: None. Other routine risk minimization measures: Prescription-only medicine Additional risk minimization measures: None	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2 • Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Skyrizi® (risankizumab)

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

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

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

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

I The Medicine and What it Is Used For

Skyrizi is authorized for treatment of

- Moderate to severe plaque psoriasis in adults
- Psoriatic arthritis alone or in combination with methotrexate in adults
- Moderately to severely active Crohn's disease in adults
- Moderately to severely active ulcerative colitis (UC) in adults
- Moderate to severe plaque psoriasis in children and adolescents from the age of 6 years

See the SmPC for the full indication statements. Skyrizi contains risankizumab as the active substance and is given by subcutaneous (SC) injection and IV infusion.

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

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

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

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

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

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed 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 Skyrizi is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of Skyrizi are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Skyrizi. 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	• Serious hypersensitivity reactions
Important potential risks	• MACE • Serious infections • Malignancies
Missing information	• Use during pregnancy and lactation • Long-term safety

II.B Summary of Important Risks

Important identified risk 1: Serious hypersensitivity reactions	
Evidence for linking the risk to the medicine	The risk varies depending on the biologic used and is reflected in the individual biologic labels. Integrated risankizumab clinical trial data were used to assess the risk with risankizumab therapy.
Risk factors and risk groups	Several factors influence the propensity towards development of hypersensitivity reactions including degree of humanization of the antibody, cell line from which the drug is obtained (Chinese hamster ovary [CHO] cells produce virtually no 1,3-galactosyltransferase, resulting in a glycosylation pattern much different from that of other drugs such as cetuximab [derived from the murine cell line SP2/O], thereby reducing the risk of hypersensitivity reactions) and the excipients used (Corominas 2014). Host factors include the indication for the treatment (e.g., atopic tendencies in patients with asthma), patient's immune status, and concomitant medications.
Risk minimization measures	Routine risk minimization measures: Product labeling
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2 • Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk 1: MACE	
Evidence for linking the risk to the medicine	Adjudicated MACE in the integrated risankizumab clinical trial was used to assess the risk with risankizumab therapy.
Risk factors and risk groups	Patients with traditional cardiac risk factors, i.e., age, sex, family history of premature coronary artery disease (CAD), current smoking, hypertension (HTN), low high-density lipoprotein, are at higher risk of CAD. Other risk factors include DM (insulin resistance, hyperinsulinemia, and elevated blood glucose are associated with atherosclerotic cardiovascular disease [CVD]) (Almdal 2004, Gerstein 1999, Kannel 1979a, Kannel 1979b, Zavaroni 1989), chronic kidney disease (increased coronary heart disease [CHD] risk in patients with end-stage renal disease has been well described, but there is now clear evidence that mild to moderate renal dysfunction is also associated with a substantial increase in CHD

	risk) (Gansevoort 2013), other lifestyle factors (lack of exercise, psychosocial factors), and metabolic syndrome.
Risk minimization measures	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2 • Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 2: Serious infections	
Evidence for linking the risk to the medicine	As with many immune-modulating agents, risankizumab may impair immune function, resulting in a risk of serious infection. In patients with psoriasis not treated with biologics, the incidence rates of serious infections ranged from approximately 0.3 to 2.1 per 100 PY (Gottlieb 2014, Reich 2015). In patients with psoriatic arthritis, the incidence rate of serious infections was (3.98 events per 100 PY) (Shah 2017). Among patients with inflammatory bowel disease (IBD), including CD and UC, the incidence rate (per 100 PY) was 0.94 for serious infections (Kirchgesner 2018). Integrated risankizumab clinical trial data were used to assess the risk with risankizumab therapy, and epidemiologic data were used to contextualize the risankizumab data.
Risk factors and risk groups	The elderly and patients with other risk factors compromising immunity such as diabetes or chronic renal insufficiency are at increased risk.
Risk minimization measures	Routine risk minimization measures: Product labeling

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2 • Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 3: Malignancies	
Evidence for linking the risk to the medicine	Integrated risankizumab clinical trial data were used to assess the risk with risankizumab therapy.
Risk factors and risk groups	Multiple factors may contribute to an increased rate of malignancy in patients with psoriasis, Crohn's Disease, and/or UC, including the effects of immunosuppressive or immunomodulatory therapies. Psoralen and ultraviolet A, when given long-term, is associated with increased risks of cutaneous squamous cell carcinoma and malignant melanoma. Reviews of studies on ultraviolet B, both narrowband and broadband, do not indicate any increased risk of non-melanoma skin cancer or melanoma (Patel 2009). The traditional systemic therapies, methotrexate, cyclosporine A, and mycophenolate mofetil, may be associated with an increased risk of lymphoproliferative disorders during treatment, demonstrated in clinical trials in patients with rheumatoid arthritis and Crohn's disease documented in case reports concerning psoriasis patients The risk of malignancy with biologic therapy is still unclear. However, the majority of the studies examining this carcinogenic risk suggest that tumor necrosis factor alpha inhibitors may cause a slightly increased risk of cancer, including non-melanoma skin cancer and hematologic malignancies.
Risk minimization measures	Routine risk minimization measures: No specific measures are required for patients receiving risankizumab; standard of care is adequate.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2 • Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate

	to Severe Psoriasis See Section II.C of this summary for an overview of the post-authorization development plan.

Missing information 1: Use during pregnancy and lactation	
Risk minimization measures	Routine risk minimization measures: Product labeling
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Pregnancy Exposure and Outcomes for Women with Psoriasis Treated with Risankizumab • Pregnancy Exposure and Outcomes for Women with Inflammatory Bowel Disease Treated with Risankizumab See Section II.C of this summary for an overview of the post-authorization development plan.
Missing information 2: Long-term safety	
Risk minimization measures	Routine risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting • Risankizumab Psoriatic Arthritis Studies KEEPsAKE 1 and KEEPsAKE 2 • Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting • Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis See Section II.C of this summary for an overview of the post-authorization development plan.

II.C Post-Authorization Development Plan

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

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

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

Long-Term Prospective Cohort Study in Patients with Psoriasis in Real World Setting

A prospective cohort study of population-based patients in the real-world is being conducted to monitor the incidence of safety outcomes coincident with exposure to risankizumab in patients

with psoriasis (which includes patients with arthropathic psoriasis [ICD-10-CM L40.5x]) in two European national registers with linkage data from national quality registers. The aim of Study P19-633 is to estimate the risks of overall malignancy excluding NMSC, NMSC, MACE, serious infections, and serious hypersensitivity reactions among individuals who were exposed to risankizumab for the treatment of psoriasis, relative to similar patients on other systemic treatments (biologics and non-biologics). In addition, a separate cohort study will be conducted (synopsis below) to assess pregnancy exposures and outcomes utilizing large electronic healthcare databases with mother-baby linkage in the United States.

Pregnancy Exposure and Outcomes in Women with Psoriasis Treated with Risankizumab

A population-based, non-interventional, cohort study of women with moderate-to-severe psoriasis (which includes patients with arthropathic psoriasis [ICD-10-CM L40.5x]) who are exposed to risankizumab or comparator biologic during pregnancy is ongoing. The specific objectives of Study P16-751 are (1) to evaluate the rate of major congenital malformations in infants born to women exposed to risankizumab during pregnancy compared to those exposed to comparator treatments (primary outcome for sample size estimation); (2) to evaluate and compare pregnancy outcomes (i.e., live birth, spontaneous abortion, elective abortion, stillbirth) among women exposed to risankizumab versus comparators during pregnancy; and (3) to assess and compare additional infant outcomes (premature birth, small for gestational age, neonatal deaths, serious infections up to 6 months of age) among infants born to women exposed to risankizumab during pregnancy compared to those exposed to other biologic treatments. Adult women of child-bearing years with moderate-to-severe psoriasis will serve as the study population. There will be 3 specific cohorts of women included in this study:
1) women exposed to risankizumab but not exposed to other biologic therapies at any time during pregnancy (risankizumab-exposed cohort); 2) women exposed to an anti-TNF, IL-17 biologics or their biosimilars for moderate-to-severe psoriasis at any time during pregnancy (comparator biologic-exposed cohort); and, 3) women with psoriasis who received no psoriasis therapy, or treatment for psoriasis other than risankizumab or comparator biologics (e.g., phototherapy or nonbiologic therapy). This untreated psoriasis group was chosen to serve as a frame of reference and provide context to the rates of outcomes observed in the risankizumab-exposed and comparator biologic-exposed groups. This study will be conducted using administrative claims data in the Innovation in Medical Evidence Development and Surveillance System (IMEDS) Distributed Databases (IMEDS-DD).

Risankizumab Psoriatic Arthritis Studies

Study M15-998 is a 2-part, multicenter study assessing the long-term safety and efficacy of risankizumab in subjects with moderately to severely active psoriatic arthritis who have a history of inadequate response or intolerance to at least 1 disease-modifying anti-rheumatic drug or to biologic therapy(ies). The primary objective of the open-label period of the study is

to evaluate the long-term safety, tolerability, and efficacy of risankizumab 150 mg in subjects who have completed the double-blind period of the study.

Study M16-011 is a 2-part, multicenter study assessing the long-term safety and efficacy of risankizumab with moderately to severely active psoriatic arthritis who have a history of inadequate response to or intolerance to at least 1 disease-modifying antirheumatic drug therapy. The primary objective of the open-label period of the study is to evaluate the long-term safety, tolerability, and efficacy of risankizumab 150 mg in subjects who have completed the double-blind period of the study.

Pregnancy Exposure and Outcomes for Women with Inflammatory Bowel Disease Treated with Risankizumab

Study Short Name and Title: Pregnancy exposures and outcomes in women with Inflammatory Bowel Disease treated with risankizumab: A Cohort Study Utilizing Large Electronic Healthcare Databases with Mother-Baby Linkage in the United States (Study P23-653)

Rationale and Study Objectives: The clinical trial programs did not assess the safety of risankizumab use during pregnancy. In addition to the study of risankizumab exposure in psoriasis patients, a study of pregnancy outcomes in patients with IBD (Crohn's disease and ulcerative colitis) who are exposed to risankizumab, compared to alternative biologic treatments, will be conducted.

Study Design: A comparative cohort study will be conducted to describe risankizumab exposure in pregnant patients with IBD (Crohn's disease and ulcerative colitis), and compare pregnancy and infant outcomes to pregnant patients with IBD who were treated with alternative therapies. In addition, descriptive analyses of pregnancy outcomes in IBD patients without exposure to any treatments under investigation will also be conducted.

Study Population: Women of child-bearing age with IBD will comprise the study population. Patients (with age per labeled indication) who have filled at least one prescription for risankizumab or comparator treatment and are considered to be exposed to treatment during pregnancy will be included in the study. The study will be conducted within the network of administrative claims data with mother-baby linkage within the FDA Sentinel Distributed Database.

Long-Term Comparative Cohort Study in Patients with Ulcerative Colitis and Crohn's Disease in a Real World Setting

Study Short Name and Title: A comparative cohort study of long-term safety of risankizumab in patients with ulcerative colitis and Crohn's disease (Study P23-654)

Rationale and Study Objectives: The clinical trial program was not able to fully characterize the safety profile of risankizumab in the ulcerative colitis and Crohn's disease populations.

Additional long-term data are needed from the real-world experience of patients with ulcerative colitis and Crohn's disease treated with risankizumab to assess product potential risks.

Study Design: A comparative cohort study will be conducted to estimate rates of malignancy (malignancy excluding NMSC, NMSC), serious infections, serious hypersensitivity reactions, and MACE in risankizumab treated patients with ulcerative colitis or Crohn's disease, relative to alternative systemic therapies (e.g., biologics). The study will be conducted within the Swedish Inflammatory Bowel Disease Register (SWIBREG) in Sweden and the National Registers within Sweden and Denmark. Validated disease and outcome definitions, and appropriate methods for confounding control will be utilized.

Study Population: All patients with ulcerative colitis or Crohn's disease (with age per labeled indication) who have filled at least one prescription for risankizumab or comparator treatment will be identified in the data source after a specified start date and included in the study.

Open-Label Extension Study in Pediatric Patients with Moderate to Severe Psoriasis

Study Title: OptIMMize-2: A Phase 3 multicenter, single-arm, open-label extension study to assess the safety, tolerability, and efficacy of risankizumab in subjects with moderate to severe plaque psoriasis who have completed participation in Study M19-977 (OptIMMize-1) (Study M19-973)

Rationale and Study Objectives: There is an unmet medical need for effective treatment in pediatric patients with plaque psoriasis. This study is being conducted to assess long-term safety, tolerability, and efficacy of risankizumab in pediatric subjects with moderate to severe plaque psoriasis.

Study Design: A Phase 3 multicenter, single-arm, open-label extension (OLE) study designed to investigate the long-term safety, tolerability, and efficacy of risankizumab 150 mg or 55 mg by weight every 12 weeks (Q12W) in the treatment of moderate to severe plaque psoriasis in eligible subjects who have completed all assessments in Study M19-977 and elect to participate in Study M19-973.

This study has a duration of up to 224 weeks with the last dose of study drug scheduled at Week 204 and last visit at Week 216.

Study Population: Pediatric patients with moderate to severe plaque psoriasis who have completed all assessments in Study M19-977 and elect to participate in Study M19-973.

Part VII: Annexes

Annex 2	Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program
Annex 3	Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan
Annex 4	Specific Adverse Drug Reaction Follow-Up Forms
Annex 5	Protocols for Proposed and Ongoing Studies in RMP Part IV
Annex 6	Details of Proposed Additional Risk Minimization Activities (If Applicable)
Annex 7	Other Supporting Data (Including Referenced Material)
Annex 8	Summary of Changes to the Risk Management Plan Over Time
Annex 9	Local Currently Approved Country Labeling
Annex 10	Local Risk Management/Mitigation Plan

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms included:

Pregnancy Outcome Letter Mother version 1

Pregnancy Outcome Letter Father version 1

Thank you for taking the time to answer this questionnaire. Please read each question and answer honestly.
If you are a patient, answer the questions in the section starting on page 1.
If you are a healthcare professional, answer the questions in the section starting on page 5

Case Number:

Patient Questionnaire

We want to learn more about you, your pregnancy, the baby, and the baby's father. If you have suffered the loss of your baby, please accept our deepest sympathies. You are welcome to skip any questions that might be difficult or uncomfortable for you to answer.

If you have details about your pregnancy from your health records, please attach it to this form. **All of the information you share will be kept strictly confidential**. You can find this medical information in a doctor's note, visit summary, hospital discharge summary, laboratory results, or medication list from your patient app or online health portal. The information in your health records can help you answer the questions below.

Mother Patient:

1. When did you use the AbbVie medicine? Select all that apply.
   - ☐ I stopped the medicine before I got pregnant. If stopped, about how many days or months before getting pregnant did you stop taking the medicine?
   - ☐ During my first trimester (0-12 weeks pregnant)
   - ☐ During my second trimester (13-26 weeks pregnant)
   - ☐ During my third trimester (27-40 weeks pregnant)
   - ☐ During breastfeeding _____
   - ☐ Unknown

2. What is the due date of the baby/babies, or if they have already been born, when were they born?
   _____ /_____/_____ (day/month/year)

   If the baby was born, how old is the baby now? _____

3. What happened with your most recent pregnancy?
   - ☐ I am still pregnant
   - ☐ I had twins, triplets, or more. Please check the outcome of baby A below and fill in the outcome of baby B (and baby C etc.) in the space below.
   - ☐ Baby born at or after 37 weeks
   - ☐ Baby born premature, before 37 weeks
   - ☐ I had a miscarriage (loss before 20 weeks)
   - ☐ I had a stillbirth (loss 20 weeks or after)
   - ☐ I had an elective abortion, and the baby did not have any known birth defects
   - ☐ I had an elective abortion because the baby had birth defects
   - ☐ I had an ectopic pregnancy (baby starts to grow outside the womb)

4. If your baby/babies have been born, did they have any birth defects or syndromes? Select all that apply. If you had twins or triplets, answer for baby A below and fill in the outcome of baby B (and baby C etc.) in the space below.
   - ☐ Congenital heart (issues in the structure of the heart)
   - ☐ Cleft lip and palate (openings or splits in the upper lip or top of the mouth)
   - ☐ Down syndrome
   - ☐ Other: _____

5. Were there any issues affecting the baby/babies at birth? Select all that apply. If you had twins or triplets, answer for baby A below and fill in the outcome of baby B (and baby C etc.) in the space below.
   - ☐ My baby had an infection. List name the infection_____
   - ☐ My baby was hospitalized. Please explain_____
   - ☐ I had an emergency C-section (birth surgery)
   - ☐ Other: _____
   - ☐ No
   - ☐ Not sure

6. If you had any issues at the time of delivery, did you take any medicine for it?
   - ☐ Yes (please list medicine name and dose): _____
   - ☐ No, I had an issue at birth, but I didn't take medicine for it
   - ☐ No, I didn't have any birth issues
   - ☐ Not sure

7. What other medicines did you use during this pregnancy? Select all that apply and list the name and dose of each medicine.
   - ☐ Prescription medicines: _____
   - ☐ Over-the-counter (non-prescription) medicines: _____
   - ☐ Vitamins: _____
   - ☐ Herbal or dietary supplements: _____
   - ☐ Birth control (contraception), if any: _____
   - ☐ Street drugs, alcohol, or tobacco: _____
   - ☐ Other: _____
   - ☐ None

8. Do you have any long-term (chronic) medical conditions?
   - ☐ Obesity
   - ☐ Diabetes
   - ☐ High blood pressure (hypertension)
   - ☐ Asthma
   - ☐ Thyroid problems
   - ☐ Other: _____
   - ☐ No
   - ☐ Not sure

9. Have you had any of the following problems with your pregnancy?
   - ☐ Gestational diabetes (high blood sugar that usually goes away after birth)
   - ☐ Hypertension (high blood pressure during pregnancy, like pre-eclampsia)
   - ☐ Placenta previa (when the placenta covers part or all of the cervix)
   - ☐ Placenta abruption (when the placenta separates from the womb too early)
   - ☐ Other: _____
   - ☐ No
   - ☐ Not sure

10. Did you have any abnormal labs or tests during the pregnancy?
    - ☐ Yes, I had genetic testing that indicated potential genetic concerns or conditions in the developing baby. Please explain:_____
    - ☐ Yes, I tested positive for an infection. List name of infection_____
    - ☐ Other: _____
    - ☐ No
    - ☐ Not sure

11. Has your doctor ever told you that your baby is not growing or developing as expected? This could mean your baby is not gaining weight, or they are reaching milestones like sitting and walking later than expected. If you had twins or triplets, answer if any of the babies have not been growing or developing as expected.
    - ☐ Yes (please describe): _____
    - ☐ No
    - ☐ Not sure

12. Are you currently breastfeeding your baby/ babies?
    - ☐ Yes
    - ☐ No

13. Do you or the baby's father have a family history of genetic conditions or birth defects? This could include conditions like cystic fibrosis, sickle cell disease, Down syndrome, or heart defects.

    Your family**:**
    - ☐ Yes (please describe): _____
    - ☐ No
    - ☐ Not sure

    Baby's father's family:
    - ☐ Yes (please describe): _____
    - ☐ No
    - ☐ Not sure

14. Have you had any problems with your past pregnancies? Check all that apply.
    - ☐ Baby born at or after 37 weeks
    - ☐ Baby born premature, before 37 weeks
    - ☐ I had a miscarriage (loss before 20 weeks)
    - ☐ I had a stillbirth (loss 20 weeks or after)
    - ☐ I had an abortion
    - ☐ I had an ectopic pregnancy (baby starts to grow outside the womb)
    - ☐ No
    - ☐ Not sure

15. What is the sex of your baby?
    - ☐ Male
    - ☐ Female

    For twins, what is the sex of your 2nd baby?
    - ☐ Male
    - ☐ Female

    For triplets, what is the sex of your 3rd baby?
    - ☐ Male
    - ☐ Female

16. Your date of Birth (month/year): ____/_____

17. Please describe your race or ethnicity

    _____

18. What is the lot number and expiration date listed on your AbbVie medicine? The lot number is usually 8 or 9 numbers on your medicine packaging. You can find it near the expiration date, bar code, or instructions. If you can't find the lot number or expiration date, please select "unknown".

Lot Number:	Lot number: _____ ☐ Unknown
Expiration Date:	____ /_____/_____ (day/month/year) ☐ Unknown

If you can't find the lot number and/or expiration date of your medicine, list the reason below:

- ☐ AbbVie medication packaging thrown out
- ☐ I did not receive the AbbVie medication in the original packaging
- ☐ Not able to read the numbers clearly on the AbbVie medication packaging
- ☐ Other: _____

Health Care Provider Questionnaire

If available, please attach relevant information from the patient's chart (such as doctor's notes, hospital discharge summary, medication lists, laboratory results) to this form to answer the following questions. Any information provided will be kept confidential.

1. When did the patient use the AbbVie medicine? Select all that apply.
   - ☐ During the first trimester (0-12 weeks pregnant)
   - ☐ During the second trimester (13-26 weeks pregnant)
   - ☐ During the third trimester (27-40 weeks pregnant)
   - ☐ Patient stopped the medicine before they got pregnant
     if checked: How many days/months prior to getting pregnant did the patient stop the medicine?
     _____
   - ☐ During breastfeeding _____
   - ☐ Unknown

2. What is the due date of the baby/babies, or if they have already been born, when were they born?
_____ /_____/_____ (dd/mm/year)

   If the baby was born, how old is the baby now? _____

3. What was the pregnancy outcome?
   - ☐ Patient is still pregnant
   - ☐ Patient had twins, triplets, or more. Please check the outcome of baby A below and fill in the outcome of baby B (and baby C etc.) in the space below
   - ☐ Live Birth-full term (born at or after 37 weeks) without birth defect
   - ☐ Live birth full term (born at or after 37 weeks) with birth defect(s)
   - ☐ Premature birth (born before 37 weeks) without birth defect. What was the gestational age of the baby at birth?_____
   - ☐ Premature birth (born before 37 weeks) with birth defect(s) What was the gestational age of the baby at birth?_____
   - ☐ Miscarriage (fetal loss prior to 20 weeks)
   - ☐ Stillbirth (fetal loss 20 weeks or after)
   - ☐ Elective abortion
   - ☐ Ectopic pregnancy

4. If the baby/fetus was diagnosed with any birth defects or syndromes, please list below, If twins or greater number, write for baby A and baby B (and baby C if triplets).

5. If there were any complications (e.g. infection, hospitalization, emergency C-section) affecting the baby at birth, please describe the event and treatment given. If twins, write for baby A and baby B (and baby C if triplets).

6. List the medications that the patient was taking during the pregnancy. Please include prescription and over-the-counter medicines, herbal or dietary supplements, and contraception methods.

☐ Medication list provided as attachment from patient's chart

7. Did the patient use any substances, such as street drugs, alcohol, tobacco during their pregnancy?

☐ No
☐ If Yes, please list which substances were used_____
☐ Unknown

8. Provide a list of the patient's chronic medical conditions:

☐ Medical conditions provided as attachment from patient's chart

9. List any complications the patient had with her pregnancy:

☐ Patient had no pregnancy complications

10. List any abnormal labs or tests the patient had during the pregnancy, including amniocentesis, CVS, genetic testing or infections:

☐ Patient had no abnormal labs or tests

11. Has the baby met their expected mental and physical developmental milestones (e.g., crawling, standing, walking, etc.)?

☐ Yes
☐ No If no, please describe_____
☐ Unknown

12. Has the baby been growing (height, weight, head size) as expected since birth? If no, please describe.

☐ Yes
☐ No If no, please describe _____
☐ Unknown

13. Is the patient currently breastfeeding the baby?

☐ Yes
☐ No
☐ Unknown

14. Does the patient have any family history of genetic conditions or congenital malformations?

☐ Yes
☐ No
☐ Unknown

15. Has the patient had any problems with past pregnancies? Select all that apply.

☐ Premature delivery
☐ Miscarriage
☐ Stillbirth
☐ Ectopic pregnancy
☐ Fetal malformations
☐ Other: _____

16. What is the sex of the baby?

☐ Male
☐ Female
☐ Unknown

17. Patient's Date of Birth (mm/yyyy): ___/_____

18. Please describe the patient's race or ethnicity. _____

19. Please provide the lot number and the expiration date of the AbbVie medication. If you are unable to locate the lot number or expiration date, please select N/A

Lot Number:	Lot #: _____ ☐ N/A
Expiration Date	(dd/mmm/yyyy):____ /_____/_____ ☐ N/A

If N/A, please indicate reason below:

☐ Patient has thrown out AbbVie medication packaging
☐ Patient did not receive AbbVie medication in original packaging
☐ Not legible on AbbVie medication packaging
☐ Not in patient's file
☐ Other: _____

Thank you for taking the time to answer this questionnaire. Please read each question and answer honestly.
If you are a patient, answer the questions in the section starting on page 1.
If you are a healthcare professional, answer the questions in the section starting on page 5

Case Number:

Patient Questionnaire

Father Patient:

We want to learn more about you, the mother of your child and her pregnancy, and the baby or unborn baby. If you, or the mother of your child, have suffered the loss of your baby, please accept our deepest sympathies. You are welcome to skip any questions that might be difficult or uncomfortable for you to answer.
If you have details about the mother's pregnancy from her health records, please attach it to this form. **All of the information you share will be kept strictly confidential**. You can find this medical information in a doctor's note, visit summary, hospital discharge summary, laboratory results, or medication list from your patient app or online health portal. The information in your health records can help you answer the questions below.

1. When did you use the AbbVie medicine? Select all that apply
   ☐ During the mother's first trimester (0-12 weeks pregnant)
   ☐ During the mother's second trimester (13-26 weeks pregnant)
   ☐During the mother's third trimester (27-40 weeks pregnant)
   ☐ I stopped the medicine before the mother got pregnant
   If stopped, about how long before the mother got pregnant did you stop taking the medicine _____
   ☐ Unknown

2. What happened with your partner's most recent pregnancy?
   ☐ The mother is still pregnant
   ☐ The mother had twins, triplets, or more. Please answer for baby A below and fill in the outcome of baby B (and baby C etc.) in the space below
   ☐ Baby born at or after 37 week.
   ☐ Baby born premature, before 37 weeks
   ☐ The mother had a miscarriage (loss before 20 weeks)
   ☐ The mother had a stillbirth (loss 20 weeks or after)
   ☐ The mother had an abortion
   ☐ The mother had an ectopic pregnancy (baby starts to grow outside the womb)
   ☐ Not sure

3. What is the due date of the baby/babies, or if they have already been born, when were they born?
   ____ /_____/_____ (day/month/year), If the baby was born, how old is the baby now? _____
   If your baby/babies were born, did they have any birth defects or syndromes? Select all that apply. If you had twins or triplets, answer for baby A below and fill in the outcome of baby B (and baby C etc.) in the space below
   ☐ Congenital heart (issues in the structure of the heart)
   ☐ Cleft lip and palate (openings or splits in the upper lip or top of the mouth)
   ☐ Down syndrome
   ☐ Other: _____

4. Were there any issues affecting the baby/babies at birth? Select all that apply. If you had twins or triplets, answer for baby A below and fill in the outcome of baby B (and baby C etc.) in the space below
   ☐ My baby had an infection. List name of infection_____
   ☐ My baby was hospitalized.
   ☐ My partner had an emergency C-section (birth surgery).
   ☐ Other: _____
   ☐ No
   ☐ Not sure

5. If the mother had any problems during delivery, did she take any medicines for it?
   ☐ Yes (please list):_____
   ☐ No, the mother had a problem at birth, but she did not take medicines for it.
   ☐ No, the mother didn't have any birth problems.
   ☐ Not sure

6. What medicines or substances were you using around the time the mother got pregnant? Select all that apply and then list the medicines in the blanks.
   ☐ Prescription medicines: _____
   ☐ Over-the-counter medicines: _____
   ☐ Vitamins: _____
   ☐ Herbal or dietary supplements: _____
   ☐ Birth control (contraception): _____
   ☐ Street drugs, alcohol, or tobacco: _____
   ☐ Other: _____
   ☐ None
   ☐ Not sure

7. What medicines did the mother use during their pregnancy? Select all that apply and then list the medicines in the blanks.
   ☐ Prescription medicines: _____
   ☐ Over-the-counter medicines: _____
   ☐ Vitamins: _____
   ☐ Herbal or dietary supplements: _____
   ☐ Birth control (contraception): _____
   ☐ Street drugs, alcohol, or tobacco: _____
   ☐ Other: _____
   ☐ None
   ☐ Not sure

8. Does the mother have any long-term (chronic) medical conditions?
   ☐ Obesity
   ☐ Diabetes
   ☐ High blood pressure (hypertension)
   ☐ Asthma
   ☐ Thyroid problems
   ☐ Other: _____
   ☐ No
   ☐ Not sure

9. Has the mother had any problems with her pregnancy?
   ☐ Gestational diabetes (high blood sugar that usually goes away after birth)
   ☐ Hypertension (high blood pressure during pregnancy, like pre-eclampsia)
   ☐ Placenta previa (when the placenta covers part or all of the cervix)
   ☐ Placenta abruption (when the placenta separates from the womb too early)
   ☐ Other: _____
   ☐ No
   ☐ Not sure

10. Did the mother have any abnormal labs or tests during the pregnancy?
    ☐ Yes, we had genetic testing that indicated potential genetic concerns or conditions in the developing baby. Please describe____
    ☐ Yes, she tested positive for an infection. List name of infection_____
    ☐ Other: _____
    ☐ No
    ☐ Not sure

11. Has your doctor or nurse ever told you that your baby is not growing or developing as expected? This could mean your baby is not gaining weight, or they are reaching milestones like sitting and walking much later than expected. If you had twins, triplets, or more, answer if any of the babies have been not growing or developing as expected.
    ☐ Yes (please describe): _____
    ☐ No
    ☐ Not sure

12. Do you or the mother have a family history or other children with genetic conditions or birth defects? This could include conditions like cystic fibrosis, sickle cell disease, Down syndrome, or heart defects.

    Your family:
    ☐ Yes (please describe): _____
    ☐ No
    ☐ Not sure

    The mother's family:
    ☐ Yes (please describe): _____
    ☐ No
    ☐ Not sure

13. Has the mother had any problems with past pregnancies? Select ALL that apply.
    - ☐ Baby born at or after 37 weeks
    - ☐ Baby born premature, before 37 weeks
    - ☐ She had a miscarriage (loss before 20 weeks)
    - ☐ She had a stillbirth (loss 20 weeks or after)
    - ☐ She had an ectopic pregnancy (baby starts to grow outside the womb)
    - ☐ Not sure

14. What is the sex of your baby?
    - ☐ Male
    - ☐ Female
    - ☐ Unknown

    For twins, what is the sex of your 2nd baby?
    - ☐ Male
    - ☐ Female

    For triplets, what is the sex of your 3rd baby?
    - ☐ Male
    - ☐ Female

15. Your Date of Birth (month/year): ____/_____

16. Please describe your race or ethnicity

    _____

17. What is the lot number and expiration date listed on your AbbVie medicine? The lot number is usually 8 or 9 numbers on your medicine packaging. You can find it near the expiration date, bar code, or instructions. If you can't find the lot number or expiration date, please select "unknown".

Lot Number:	Lot number: _____ ☐ Unknown
Expiration Date	____ /_____/_____ (day/month/year) ☐ Unknown

If you can't find the lot number and/or expiration date of your medicine, list the reason below:

- ☐ AbbVie medication packaging thrown out
- ☐ I did not receive the AbbVie medication in the original packaging
- ☐ Not able to read the numbers clearly on the AbbVie medication packaging
- ☐ Other: _____

Health Care Provider Questionnaire

If available, please attach relevant information from the father as a patient's chart (such as doctor's notes, medication lists, laboratory results) to this form to answer the following questions. Any information provided will be kept confidential.

1. When did the father, as a patient, use the AbbVie medicine in relation to the pregnancy? Select all that apply.
   ☐ Just prior to the insemination/pregnancy
   ☐ During the first trimester (0-12 weeks)
   ☐ Second trimester (13-26 weeks)
   ☐ Third trimester (27-40 weeks)
   ☐ The father stopped the medicine before their female partner got pregnant
   if checked: How many days/months prior to getting pregnant did the patient stop the medicine?
   _____
   ☐ Unknown

2. Provide a list of the father's chronic medical conditions:

❑ Medical conditions provided as attachment from patient's chart

3. Does the father have any family history or other children with genetic conditions or congenital malformations ?
   ☐ Yes
   ☐ No
   ☐ Unknown

4. If known, what is the due date of the baby/babies, or if they have already been born, when were they born?
   ____ /_____/_____ (dd/mmm/yyyy). If the baby was born, how old is the baby now? _____

5. What was the pregnancy outcome?
   ☐ Patient is still pregnant
   ☐ Patient had twins, triplets, or more. Please check the outcome of baby A below and fill in the outcome of baby B (and baby C etc.) in the space below
   ☐ Live Birth-full term (born at or after 37 weeks) without birth defect
   ☐ Live birth full term (born at or after 37 weeks) with birth defect(s)
   ☐ Premature birth (born before 37 weeks) without birth defect. What was the gestational age of the baby at birth?
   _____
   ☐ Premature birth (born before 37 weeks) with birth defect(s) What was the gestational age of the baby at birth?
   _____
   ☐ Miscarriage (fetal loss prior to 20 weeks)
   ☐ Stillbirth (fetal loss 20 weeks or after)
   ☐ Elective abortion
   ☐ Ectopic pregnancy
   ☐ Unknown

6. If the baby/fetus was diagnosed with any birth defects or syndromes, please list below, If twins or greater number, write for baby A and baby B (and baby C if triplets).

7. If there were any complications (e.g. infection, hospitalization, emergency C-section) affecting the baby at birth, please describe the event and treatment given. If twins, write for baby A and baby B (and baby C if triplets).

8. What is the sex of the baby?
   ☐ Male
   ☐ Female
   ☐ Unknown

9. Patient's Date of Birth (mm/yyyy): ___/_____

10. Please describe the patient's race or ethnicity. _____

11. Please provide the lot number and the expiration date of the AbbVie medication. If you are unable to locate the lot number or expiration date, please select N/A

Lot Number:	Lot #: _____ ☐ N/A
Expiration Date	____/_____/_____ (dd/mm/yyyy) ☐ N/A

If N/A, please indicate reason below:

☐ Patient has thrown out AbbVie medication packaging
☐ Patient did not receive AbbVie medication in original packaging
☐ Not legible on AbbVie medication packaging
☐ Not in patient's file
☐ Other: _____

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

Not applicable.

Annex 7. Other Supporting Data (Including Referenced Material)

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