EU Risk Management Plan for Rinvoq™ (Upadacitinib)

AbbVie

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

RMP Version Number: 16.0

Data lock point for this RMP: 06 February 2024

Date of final sign off: January 2025

Rationale for submitting an updated RMP: Consolidation of approved RMP version 14.0 (addition of 30 mg dose for adolescent subjects with atopic dermatitis) and RMP version 15.0 (addition of GCA 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 1: Product(s) Overview	Jun 2024	15.0
Part II: Safety Specification		
SI – Epidemiology of the Indication(s) and Target Population(s)	Jun 2024	15.0
SII – Nonclinical Part of the Safety Specification	Jun 2024	15.0
SIII – Clinical Trial Exposure	Jun 2024	15.0
SIV – Populations Not Studied in Clinical Trials	Jun 2024	15.0
SV – Post-Authorization Experience	Jun 2024	15.0
SVI – Additional European Union (EU) Requirements for the Safety Specification	Dec 2018	1.0
SVII – Identified and Potential Risks	Jun 2024	15.0
SVIII – Summary of the Safety Concerns	Jun 2024	15.0
Part III: Pharmacovigilance Plan (Including Post-Authorization Safety Studies)	Jun 2024	15.0
Part IV: Plan for Post-Authorization Efficacy Studies	May 2020	3.0
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Jun 2024	15.0
Part VI: Summary of the Risk Management Plan	Jun 2024	15.0
Part VII: Annexes		
Annex 2 – Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	Jun 2024	15.0
Annex 3 – Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	Jun 2024	15.0
Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms	Jul 2022	11.0
Annex 5 – Protocols for Proposed and Ongoing Studies in RMP Part IV	Jul 2022	10.0
Annex 6 – Details of Proposed Additional Risk Minimization Activities (If Applicable)	Jun 2024	15.0
Annex 7 – Other Supporting Data (Including Referenced Material)	Jun 2024	15.0

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	Jun 2024	15.0
	Annex 9 – Local Currently-Approved Country Labeling	Jun 2021	4.3
	Annex 10 – Local Risk Management/Mitigation Plan	Dec 2018	1.0

Other RMP versions under evaluation: Version 15.0

Details of the currently approved RMP: Version 14.0 covering indications rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non-radiographic axial spondyloarthritis (nr-axSpA), atopic dermatitis (AD), ulcerative colitis (UC) and Crohn's disease (CD).

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

ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
AD	atopic dermatitis
ADD	average daily dose
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AGA	American Gastroenterological Association
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANC	absolute neutrophil count
aRMMs	additional risk minimization measures
ARTIS	Anti-Rheumatic Treatment in Sweden
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASAS40	Assessment of SpondyloArthritis international Society 40% response
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
axSpA	axial spondyloarthritis
BCC	basal cell carcinoma
bDMARD	biologic disease-modifying anti-rheumatic drug
bDMARD-IR	biologic disease-modifying anti-rheumatic drug inadequate responder
BE	blinded extension
BID	twice daily
BIOBADASER	Spanish Registry for Adverse Events of Biological Therapy in Rheumatic Diseases
BMI	body mass index
BSRBR	British Society for Rheumatology Biologics Register
CAR	chimeric antigen receptor
CCDS	Company Core Data Sheet
CD	Crohn's disease
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum plasma concentration

CMV	cytomegalovirus
CNS	central nervous system
CRC	colorectal cancer
CRP	C-reactive protein
csDMARDs	conventional synthetic disease-modifying anti-rheumatic drugs
CV	cardiovascular
CVD	cardiovascular disease
CYP2D6	cytochrome P450 2D6 isoform subfamily
DANBIO	Danish Registry of Biological Therapy
DANIBD	Danish inflammatory bowel disease quality register
DHPC	direct healthcare professional communication
DILI	drug-induced liver injury
DMARDs	disease-modifying anti-rheumatic drugs
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase-4
EAMs	extra-articular manifestations
EC	Ethics Committee
ECCO	European Crohn's and Colitis Organisation
EEA	European Economic Area
EH	eczema herpeticum
EIM	extraintestinal manifestation
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
Eow	every other week
EPAR	European Public Assessment Report
ERA	enthesitis-related arthritis
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FLG	filaggrin
GCA	giant cell arteritis
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	glucagon-like peptide
GM-CSF	granulocyte-macrophage colony-stimulating factor

GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
GWAS	genome-wide association studies
HBV	hepatitis B virus
HCP	healthcare professional
HCV	hepatitis C virus
HDL-C	high-density lipoprotein-cholesterol
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen-B27
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HR	hazard ratio
HS	hidradenitis suppurativa
HZ	herpes zoster
IBD	inflammatory bowel disease
IL	interleukin
INN	International Nonproprietary Name
ISAAC	International Study of Asthma and Allergies in Childhood
IV	intravenous
JAK	Janus kinase
KVE	Kaposi's varicelliform eruption
LDA	low disease activity
LDL-C	low-density lipoprotein-cholesterol
LEF	leflunomide
MACE	major adverse cardiovascular event
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTX	methotrexate
NAPF	National Psoriasis Foundation
NMSC	non-melanoma skin cancer
NPR	National Patient Register
nr-axSpA	non-radiographic axial spondyloarthritis
NSAIDs	nonsteroidal anti-inflammatory drugs
OI	opportunistic infection
OLE	open-label extension
PASS	post-authorisation safety study

pcJIA	polyarticular course juvenile idiopathic arthritis
PCR	polymerase chain reaction
PCSK9	proprotein convertase subtilisin/kexin type 9
PL	package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PsA	psoriatic arthritis
PSC	primary sclerosing cholangitis
PSUR	periodic safety update report
PTD	patient treatment days
PTY	patient treatment years
PUVA	psoralen and ultraviolet A
PY	patient-years
QD	once daily
RA	rheumatoid arthritis
RABBIT	Rheumatoid Arthritis Biologics Register (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie)
RCT	randomized controlled trial
RMP	Risk Management Plan
RNA	ribonucleic acid
SAB	spontaneous abortion
SD	standard deviation
SDS	standard deviation score
SGLT2	sodium-glucose cotransporter-2
SIR	standardized incidence ratio
SLE	systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Queries
SNRI	serotonin-norepinephrine reuptake inhibitor
SpA	spondyloarthritis
SSRI	selective serotonin reuptake inhibitor
SSZ	sulfasalazine
SWIBREG	Swedish Inflammatory Bowel Disease Register
TB	tuberculosis
TCA	tricyclic antidepressant
TCS	topical corticosteroids

TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
tsDMARDs	targeted synthetic disease-modifying anti-rheumatic drugs
T2T	Treat-to-Target
UC	ulcerative colitis
UK	United Kingdom
ULN	upper limit of normal
US	United States
USPI	United States Product Insert
UV	ultraviolet
vs.	versus
VTE	venous thromboembolic event
5-HT3	serotonin receptor subtype 3
6-MP	6-mercaptopurine

Part I: Product(s) Overview

Table 1. Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Upadacitinib
Pharmacotherapeutic group(s) (anatomical therapeutic chemical [ATC] Code)	Immunosuppressants, Janus-kinase (JAK) inhibitors, ATC Code: L04AF03
Marketing Authorization Applicant	AbbVie Deutschland GmbH & Co KG
Medicinal products to which this RMP refers	Rinvoq® (upadacitinib)
Invented name(s) in the European Economic Area (EEA)	Not applicable
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** Selective and reversible Janus kinase (JAK) inhibitor
	Summary of mode of action: Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.
	Important information about its composition: Upadacitinib is a synthetic chemical entity. The excipients are pharmacologically inactive at the proposed dosages.
Hyperlink to the Product Information	https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf
Indication(s) in the EEA	**Current for rheumatoid arthritis (RA):** Rinvoq is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Rinvoq may be used as monotherapy or in combination with methotrexate. **Current for psoriatic arthritis (PsA):** Rinvoq is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more

	DMARDs. Rinvoq may be used as monotherapy or in combination with methotrexate. **Current for ankylosing spondylitis (AS):** Rinvoq is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy. **Current for non-radiographic axial spondyloarthritis (nr-axSpA):** Rinvoq is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation, as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs). **Current for atopic dermatitis (AD):** Rinvoq is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. **Current for ulcerative colitis (UC):** Rinvoq is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. **Current for Crohn's disease (CD):** Rinvoq is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent. **Proposed for giant cell arteritis (GCA):** Rinvoq is indicated for the treatment of giant cell arteritis in adult patients.
Dosage in the EEA	**Current for RA, PsA, AS, and nr-axSpA:** 15 mg once daily (QD) **Current for AD:** 15 mg QD for adolescents weighing ≥ 30 kg 15 mg QD or 30 mg QD for adults and adolescents weighing ≥ 30 kg; 15 mg QD is recommended for adults 65 years of age and older and for patients at higher risk of venous thromboembolism, major adverse cardiovascular events (MACE), and malignancy

	Current for UC and CD: Induction: 45 mg QD Maintenance: 15 mg QD or 30 mg QD 15 mg QD is recommended for adults 65 years of age and older and for patients at higher risk of venous thromboembolism, MACE, and malignancy **Proposed for GCA:** 15 mg QD with a tapering course of corticosteroids. Upadacitinib 15 mg once daily can be continued as monotherapy following discontinuation of corticosteroids
Pharmaceutical form(s) and strengths	**Current for RA, PsA, AS, and nr-axSpA:** Prolonged-release tablets, 15 mg **Current for AD:** Prolonged-release tablets, 15 mg and 30 mg **Current for UC and CD:** Prolonged-release tablets, 15 mg, 30 mg, and 45 mg **Proposed for GCA:** Prolonged-release tablets, 15mg
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

Part II: Safety Specification

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

Indication: Rheumatoid arthritis

Incidence:

The reported annual incidence of RA varies by country and region. The incidence of RA tends to be lower in Southern European countries than in Northern European countries (Alamanos 2006). The incidence of RA ranges from 8 per 100,000 patient-years (PY) in Spain to 50 per 100,000 PY in Sweden (Alamanos 2006, Carbonell 2008, Englund 2010, Rodríguez 2009b, Rossini 2014). The incidence of RA in North American countries ranges from 31 to 45 per 100,000 PY (Alamanos 2006, Myasoedova 2010). The incidence of RA was reported to be 16 per 100,000 PY in Taiwan (Kuo 2013) and 42 per 100,000 PY in South Korea (Sung 2013). Studies of time trends in incidence of RA produced inconsistent results (Minichiello 2016).

Prevalence:

Similar to incidence rates, the reported crude prevalence of RA appeared to be lower in Southern European (3.1 to 5.0 per 1,000) than in Northern European (4.4 to 8.0 per 1,000)

countries (Alamanos 2006). The prevalence of RA appeared to be lower in developing countries, ranging from 2.4 to 3.6 per 1,000. The prevalence of RA was reported to range from 7.2 to 10.7 per 1,000 in the United States (US) (Alamanos 2006, Myasoedova 2010), and 6 to 10.0 per 1,000 in Japan (Yamanaka 2014). Modelled age-standardized prevalence (using the 2001 World Health Organization standard population) for 2010 was highest in the Australasian region (0.46%), followed by Western Europe (0.44%) and North America (0.44%). The age-standardized prevalence is much lower in Asia and North Africa/Middle East (0.16%) (Cross 2014).

Approximately 36% to 74% of patients with RA have moderate to severe active disease depending on the measures of disease activity used. If limited to measurement by Disease Activity Score 28 (DAS28), the proportion of patients with moderate to severe active RA is approximately 65% to 69% (Muñoz 2017, Sengul 2015).

Demographics of the target population:

Both incidence and prevalence of RA increase with age and are approximately 2 to 3 times higher among females than among males (Alamanos 2006, Cross 2014, Myasoedova 2010). The incidence of RA peaks at 65 to 74 years of age in both sexes (Myasoedova 2010). Racial and ethnic disparities in RA disease activity may exist. Compared with white patients, Hispanic patients have higher disease activity levels and both Hispanic and African American patients reported worse functional status (Greenberg 2013).

Risk Factors:

RA results from an interaction of genetic and environmental factors (Scott 2011). Genetic factors may account for 53% to 65% of risk of developing RA according to 2 major national twin studies in the United Kingdom (UK) and Finland (Oliver and Silman 2006). Besides increased age and female gender, risk factors of RA include cigarette smoking, obesity, high birth weight, and lower socioeconomic status.

The main treatment options:

There are many treatment options for RA including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biologic disease-modifying anti-rheumatic drugs (bDMARDs), and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs). NSAIDs reduce inflammation and relieve pain, but they are not effective in slowing disease progression. Corticosteroids also improve pain and inflammation and may have a small protective benefit in slowing disease progression (Aletaha 2010), but long-term use can be associated with significant glucocorticoid-related toxicity (Miloslavsky 2017). Early therapy with csDMARDs (i.e., methotrexate [MTX], sulfasalazine [SSZ], hydroxychloroquine, chloroquine, or leflunomide [LEF]), with or without low-dose corticosteroids, is the standard of care and is recommended by European League Against Rheumatism (EULAR) and American College of

Rheumatology (ACR) (Singh 2016, Smolen 2020). However, many patients experience persistence of moderate to severe active disease despite csDMARD monotherapy or csDMARD combination therapy as evidenced by the 13% to 33% of patients who fail to achieve low disease activity (LDA) after 4 to 6 months of treatment with MTX plus a glucocorticoid (Smolen 2016).

For patients who have an inadequate response to csDMARD therapy, EULAR and ACR guidelines recommend bDMARDs in combination with csDMARDs (or as monotherapy if combination is not appropriate for an individual patient) as second-line treatment. Among patients with moderate to severe active RA who initiated bDMARD therapy, 85% received non-biologic disease-modifying anti-rheumatic drugs (DMARDs) at the time of biologics initiation (Kavanaugh 2017). Among patients treated with a bDMARD, approximately 30% fail to achieve at least 20% improvement in ACR criteria (primary failure or inefficacy) and more lose response over time (secondary failure or acquired therapeutic resistance) or experience adverse events (AEs) (Rubbert-Roth and Finckh 2009). Recently, orally administered tsDMARDs targeting Janus kinases (JAKs) (tofacitinib, baricitinib, and upadacitinib) have also been recommended as a second-line treatment in the EULAR guidelines. The EULAR guidelines placed JAK inhibitors along-side bDMARDs in the treatment algorithm, after insufficient response to csDMARDs. No preference for JAK inhibitors over bDMARDs is made (Smolen 2020). These treatments are used in combination with csDMARDs or as monotherapy if combination therapy is not appropriate for an individual patient. In the event of insufficient response to bDMARD or tsDMARD, switching to an alternative mechanism of action is preferred over cycling within a mechanism of action class (Smolen 2020).

Many clinical trials have demonstrated that RA patients in whom treatment is intensified according to clearly defined treatment goals (i.e., using a Treat-to-Target [T2T] approach) have a higher likelihood of reaching treatment goals (Eriksson 2013, Goekoop-Ruiterman 2007, Grigor 2004, Möttönen 1999, Puolakka 2004, Stoffer 2016, Verstappen 2007, Wechalekar 2017). In line with this evidence, EULAR and ACR recommend a T2T approach and to initiate therapy immediately after diagnosis of RA with a goal of achieving clinical remission or at minimum LDA, as these are associated with improved long-term outcomes (Singh 2016, Smolen 2020). Despite the number of available treatment options for RA and evidence suggesting that T2T is a feasible strategy for the treatment of RA in daily clinical practice (Vermeer 2012), the EULAR Task Force has acknowledged that a considerable proportion of patients do not reach or maintain a status of clinical remission or LDA over time or will need to discontinue treatment(s) due to safety or tolerability issues (Smolen 2017). Novel therapies are therefore needed to complement the available interventions to address the unmet need (Burmester 2014, Emery 2014, Meier and McInnes 2014).

Natural history of the indicated disease/condition in the population, including mortality and morbidity:

RA can evolve through several phases: genetic risk (Phase 1); development of asymptomatic inflammation and autoimmunity (Phase 2); development of signs and symptoms of unclassified inflammatory arthritis (Phase 3); progression to classifiable RA (Phase 4); changes in behaviour of autoimmunity and inflammation after the onset of symptomatic inflammatory arthritis, including remissions, exacerbations, response to specific therapies, evolving biomarkers, and extraarticular disease (Phase 5). Not all subjects who are at risk of developing RA progress through all of these phases, and some subjects may have resolution of inflammation, autoimmunity, and even inflammatory arthritis (Deane 2012).

Studies have consistently found increased mortality, regardless of cause, among individuals with RA compared with the general population (Naz and Symmons 2007, Sokka 2008). Median standardized mortality ratios for RA are in the range of 1.5 to 1.6 overall, 1.2 to 1.3 in inception cohort studies, and 1.6 to 1.7 in non-inception cohort studies (Sokka 2008). The distributions of the cause of death among RA patients are similar in studies conducted in the US and Western Europe. The distribution of attributed acute causes of death included: cardiovascular disease (CVD; 39.6%), cancer (16.8%), infection (14.3%), musculoskeletal disease or RA (9.4%), respiratory disease (9.0%), renal disease (5.8%), gastrointestinal (GI) disease (5.1%), accidents/intoxication (4.2%), sudden death (3.1%), and other causes (12.9%). The percentage of deaths attributable to pulmonary, GI, and renal disease and infection are more commonly observed in RA patients compared with the general population. While the risk of cardiovascular (CV) events such as myocardial infarction and stroke is higher in RA patients compared with the general population (Avina-Zubieta 2012), the percentage of deaths attributable to CVD is similar. In general, RA patients have lower lipid (total cholesterol and low-density lipoprotein-cholesterol [LDL-C]) levels than the general population, and yet the risk for CV events is higher compared with the general population due largely to chronic inflammation (Avina-Zubieta 2012, Robertson 2013).

RA may lead to joint destruction, deformity, and disability. RA is also associated with extra-articular manifestations (EAMs) including vasculitis, pericarditis, interstitial lung disease, Sjögren's syndrome, pleuritis, episcleritis, scleritis, Felty's syndrome, glomerulonephritis, interstitial nephritis, and rheumatoid nodules (Prete 2011).

Important co-morbidities:

Co-morbidities of RA include CVD, lymphoma, anaemia, interstitial lung disease, infections, and venous thromboembolic events (VTEs) (Bacani 2012, Choi 2013, Gabriel and Michaud 2009, Kim 2013, Listing 2013, Ungprasert 2014).

Indication: Psoriatic arthritis

Incidence:

The pooled PsA 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 PsA 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 PsA 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 to 79, to 6.6 per 100,000 PY between 1982 to 91, to 9.8 per 100,000 PY between 1990 to 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 PsA remained stable (Eder 2018).

The incidence of PsA in patients with psoriasis is higher than in the general population (Solmaz 2018). Across observational and clinical studies, the incidence of PsA among patients with psoriasis ranged from 270 to 2,700 per 100,000 PY (Alinaghi 2019).

Prevalence:

The pooled PsA prevalence from 26 population-based studies conducted in different countries around the world was 133 per 100,000 population. 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).

Depending on whether PsA cases were defined using medical diagnostic codes, clinical classification criteria, or self-reported diagnoses, prevalence estimates in the US have ranged from 0.06% to 0.25% (Ogdie 2015). Across observational and clinical studies, the pooled prevalence of PsA among patients with psoriasis was 19.7%; the PsA prevalence was 22.7% in European patients with psoriasis and 19.5% in North American patients with psoriasis (Alinaghi 2019).

Demographics of the target population:

PsA 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 PsA in African American patients has been found to be lower than in Caucasians (Kerr 2015).

In a population-based study in Denmark, the rheumatologist-verified PsA patient population was predominantly female (58.4%) (Tekin 2019). Among patients with mild PsA, the mean patient age was 57.0 years with a mean disease duration of 8.9 years, while among moderate and severe PsA patients, the mean patient age was 57.9 and 53.7 years, respectively, with a mean disease duration of 10.1 and 10.5 years, respectively. The socioeconomic status of patients with PsA varied from below average (23% – 30%) and average (26% – 28%) to above average (42% – 50%) (Tekin 2019).

Risk Factors:

Several risk factors for PsA have been identified, some of which are modifiable and others are not modifiable (Solmaz 2018). The main risk factors include family history of PsA, obesity, injuries/trauma, genetic risk factors, severe psoriasis, metabolic abnormalities, and smoking (Ogdie 2015).

Most patients with PsA will have psoriasis for several years prior to the development of arthritis (Solmaz 2018). Potential nonmodifiable risk factors for PsA include a family history of/genetic predisposition for PsA 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). Potential modifiable risk factors for PsA include environmental factors (injury/trauma/bone fracture, lifting cumulative loads of > 100 pounds/hour, bacterial infections requiring antibiotics, and low education level), metabolic abnormalities, smoking, alcohol use, and medication use (acetaminophen, NSAIDs) (Ogdie 2015, Solmaz 2018). Between approximately 16% and 17% of patients with PsA were smokers (Tekin 2019).

The main treatment options:

PsA patients require treatment of the entire spectrum of disease manifestations. The primary goal of treating patients with PsA 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.

Initial treatment of musculoskeletal symptoms is composed of NSAIDs and local corticosteroid injections, while topical therapies are used for the initial treatment of psoriasis. For patients who experience lack of efficacy or toxicity with these measures, for the treatment of peripheral arthritis, both the EULAR (Gossec 2016) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) (Coates 2016) recommend systemic therapy with csDMARDs (MTX, LEF, SSZ, or ciclosporin A), followed by anti-tumor necrosis factor (TNF) therapy in patients who do not respond adequately to csDMARDs, while the ACR/National Psoriasis Foundation (NAPF) recommends either anti-TNFs or csDMARDs as initial treatments (Singh 2019). Other biologic therapies (e.g., interleukin [IL]-12/23 or IL-17 inhibitors) or a tsDMARD (such as apremilast) are also recommended as alternatives to anti-TNF inhibitors in selected PsA patients, and the ACR/NAPF guidelines have incorporated a JAK inhibitor (tofacitinib) and a

T cell co-stimulation modulator (abatacept). Additional specific recommendations differ slightly between EULAR, GRAPPA, and ACR/NAPF guidelines; however, recommendations for therapeutic choice are made based on a patient's clinical presentation, as some manifestations of PsA, such as enthesitis, dactylitis, and axial disease, are either not responsive or poorly responsive to csDMARDs. Additional therapeutic options are also recommended specifically for treatment of skin disease (Coates 2016, Gossec 2016). Furthermore, patient preferences, comorbidities, and contraindications should be taken into consideration.

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 (Cimzia (certolizumab pegol) injection [prescribing information] 2016, Cosentyx (secukinumab) injection [prescribing information] 2018, Enbrel (entanercept) [prescribing information] 2015, Humira (adalimumab) injection [prescribing information]. 2020, Remicade (infliximab) [package insert] 2015, Simponi (golimumab) injection [presribing information] 2016, Stelara (ustekinumab injection) [prescribing information] 2014). The newer tsDMARDs have not increased this percentage. Importantly, all currently available drugs fail to induce a state of remission or minimal disease activity in the majority of PsA patients and do not adequately treat all disease manifestations. Thus, there remains a clear medical need for additional therapeutic options in PsA 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:

PsA is a chronic systemic inflammatory disease classified as a sub-type of spondyloarthritis (SpA) and characterized by the association of arthritis and psoriasis. PsA 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 PsA is usually characterized by flares and remissions (Duarte 2012). Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, disability, and a reduced life expectancy (Duarte 2012, Gladman and Chandran 2011). In the majority of patients (60% to 70%), the diagnosis of psoriasis precedes PsA. In 15% to 20%, arthritis precedes the onset of psoriasis, and in 15% to 20% of patients, both musculoskeletal and skin manifestations occur within a period of 1 year (Kerschbaumer 2016).

Patients with PsA 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 40 – 74% depending on the criteria used for diagnosis (Nash 2006), enthesitis in up to 72%, dactylitis in up to 59%, nail involvement in up to 92% (Pittam 2020), and anterior uveitis in 2 to 25% (Cantini 2015). Additionally, PsA patients are more likely than healthy subjects to experience the comorbid conditions of CVD, metabolic syndrome, obesity, diabetes mellitus,

fatty liver disease, inflammatory bowel disease (IBD), kidney disease, osteoporosis, fibromyalgia, depression, and anxiety, and have decreased quality of life and functional impairment (Gladman 1987, Husni 2015, Lee 2010, Magrey 2013).

Some patients with PsA 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 PsA will develop a progressive deforming arthritis with osteolysis of the digits and polyarticular involvement (Helliwell and Ruderman 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 PsA symptoms.

Among patients with rheumatologist-verified PsA in a population-based study in Denmark, 53% had mild PsA, 33% had moderate PsA, and 14% had severe PsA (Tekin 2019). Patients with relatively mild disease tend not to develop significant disability; however, in patients with moderate to severe disease, PsA 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 CVD (Helliwell and Ruderman 2015).

Important co-morbidities:

Important co-morbidities of PsA include CVD, psychiatric disorders, diabetes mellitus, obesity, osteoporosis, IBD, and ophthalmic diseases (Haddad 2017, Husted 2013, Kaine 2019, Makredes 2009, Shah 2017).

Indication: Ankylosing spondylitis

SpA is a group of diseases that share common clinical, radiographic, and genetic features. This group includes AS, PsA, reactive arthritis, enteropathic or IBD-related arthritis, and undifferentiated SpA (Dougados and Baeten 2011). A more universally consistent way of categorizing SpA patients is to define them by their primary and predominant clinical manifestation of axial or peripheral SpA (Rudwaleit 2011). Axial spondyloarthritis (axSpA) encompasses a disease spectrum with two categories, AS and nr-axSpA. The classification of AS requires the presence of sacroiliitis on plain conventional radiographs as defined by the 1984 modified New York criteria (van der Linden 1984). Clinically, patients with AS and nr-axSpA have comparable clinical manifestations and burden of disease, with the main differentiating characteristic between the two categories of axSpA being the radiographic findings meeting the classification criteria for AS (Boonen 2015, Ciurea 2013).

Incidence:

The incidence of AS per 100,000 PY has ranged from 0.44 to 5.48 in Iceland, 0.48 in Japan, 1.5 (0.4 – 2.5) in Greece, 5.8 (1.6 – 14.8) to 6.9 (6.0 – 7.8) in Finland, 6.4 (4.5 – 14.4) in

Czechoslovakia, 7.3 in the US (6.1 – 8.4) and Norway (5.3 – 9.2) (Stolwijk 2012), and up to 15.0 (age- and sex-adjusted rate) in Canada (Bohn 2018).

Prevalence:

Among studies of white Europeans and East Asians, the reported prevalence of AS has varied between 0.03% to 0.9%, depending on geographic area, patient referral, disease ascertainment, and human leukocyte antigen-B27 (HLA-B27) frequency, resulting in an overall prevalence for axSpA in the US and in the European Union (EU) of approximately up to 1% (Bohn 2018, Helmick 2008, Reveille and Weisman 2013, van Tubergen 2015).

Demographics of the target population:

In a Swedish population-based study, among a cohort of patients with AS, 66% were male and the mean age at first SpA diagnosis was 42.4 years (S.D. 13.4 years). Approximately one-third of patients (30.8%) had an education level > 12 years (Exarchou 2016). In a French cohort study, 65% of patients with AS were male, but the mean age at disease onset was younger at 23.2 years (S.D. 8.4 years) (Costantino 2017). In other AS cohorts, the proportion of male patients was approximately up to 70 to 75% and the gap between symptom onset and diagnosis ranged between approximately 7 to 10 years (Glintborg 2017, Poddubnyy and Sieper 2014, Reveille and Weisman 2013).

Risk Factors:

AS is considered to be an inherited disease. Genetic factors provide > 90% of the overall risk for developing AS; half of the genetic contribution can be attributed to HLA-B27 and other major histocompatibility complex genes (Reveille 2006). In addition, origin of the disease may be in the gut, considering approximately 40% of patients with AS have subclinical bowel inflammation (Garcia-Montoya 2018). Gut mucosal inflammation is present in approximately 70% of patients with AS and progresses to clinical IBD in 5% of patients with AS (Garcia-Montoya 2018).

In a French cohort study of SpA patients, independent risk factors associated with diagnosis of AS included age at disease onset, longer disease duration, male sex, HLA-B27, inflammatory back pain, buttock pain, uveitis, and lack of enthesitis (Costantino 2017). Factors associated with progression from nr-axSpA to AS included low-grade radiographic sacroiliitis at inclusion, buttock pain, elevated C-reactive protein (CRP), active sacroiliitis on magnetic resonance imaging (MRI), and smoking during the follow-up (Costantino 2017, Dougados 2017, Protopopov and Poddubnyy 2018); arthritis onset during the follow-up was associated with a decreased risk of developing AS (Costantino 2017).

The main treatment options:

Treatment of AS patients is based on pharmacological and non-pharmacological treatment modalities. The main treatment options for patients with AS include NSAIDs and biological DMARDs such as TNF inhibitor and IL-17 inhibitor (IL-17i) therapies.

NSAIDs and physical therapy are often the first-line therapy for AS; traditional conventional-synthetic DMARDs and corticosteroids are ineffective and therefore not recommended for the treatment of axial symptoms (van der Heijde 2017, Ward 2019). In patients with persistently high disease activity despite a course of two NSAIDs given over a total of at least 4 weeks, initiation of a bDMARD is recommended, and current practice is to start with a TNF inhibitor. If TNF inhibitor therapy fails, switching to another TNF inhibitor or an IL-17i is recommended (van der Heijde 2017, Ward 2019). Despite recent advances in the treatment of axSpA, only approximately 45% to 50% of patients achieve an Assessment of SpondyloArthritis international Society (ASAS) 40% response (ASAS40) and only approximately 15% to 20% reach a state of remission, highlighting a significant unmet medical need (Baeten 2015, Davis 2003, Inman 2008, Landewe 2014, van der Heijde 2006). The unmet need is even larger in AS patients who failed bDMARD therapy compared to patients who are bDMARD-naïve (Glintborg 2013, Ørnbjerg 2019).

In a Swedish population-based cohort study, treatment use during study follow-up among patients with AS included NSAIDs (83%), csDMARDs (38%), oral glucocorticoids (33%), and TNF inhibitors (20%) (Exarchou 2016). In a US cross-sectional study of patients with AS, history of medication use included 55% of patients with a history of bDMARD use (primarily adalimumab [32%] and etanercept [30%]), 25% csDMARD use, 75% with NSAID use, and 35% with prednisone use (Zhao 2019). It has been reported that among AS patients followed in cohorts, a significant proportion of patients discontinue a first bDMARD therapy within the first 2 years, and up to 67% of male AS patients and up to 77% of female AS patients discontinued their initial bDMARD therapy within 2 years post initiation (Hunter 2019, Ørnbjerg 2019). Recently, JAK inhibitors have been recognized in treatment guidelines as a potential treatment option (Ward 2019), and upadacitinib, with a novel mode of action, has been approved for the indication of AS in several countries including in the EU as an additional treatment option.

Natural history of the indicated disease/condition in the population, including mortality and morbidity:

Onset of axSpA occurs with chronic inflammatory back pain typically at age < 45 years. Early diagnosis is difficult, and the average diagnostic delay is estimated to be 8 to 11 years (Garg 2014). In a Swedish population-based study, prevalence of AS-related clinical manifestations among patients with AS included peripheral arthritis (21%), anterior uveitis (20%), IBD (8%), psoriasis (6%), and aorta value insufficiency (1%) (Exarchou 2016). Delays in diagnosis are

associated with delayed treatment; therefore, axSpA can cause significant symptomatic burden and loss of function in patients during productive years of life (Garg 2014).

A common feature of AS is destruction and fusion of the spinal vertebrae and sacroiliac joints (Ghasemi-Rad 2015).

Progression from nr-axSpA to AS is slow. Most of the studies report about 10 to 40% of patients with nr-axSpA progress to AS over a period of 2 to 10 years (Protopopov and Poddubnyy 2018). In a meta-analysis of 16 studies, the pooled rate of progression from undifferentiated SpA to AS was 40% after 10 years (Xia 2017). A US population-based study reported that among patients with nr-axSpA, 19% progressed to AS in a median of 5.9 years (range 2.7 to 11.8 years) (Wang 2016).

A population-based study in Sweden reported an increased risk of mortality among patients with AS compared to the general population. The crude mortality rate among patients with AS was 9.5 per 1000 PY compared to 5.6 per 1000 PY in matched general population comparators (age- and sex-adjusted hazard ratio [HR] = 1.60, 95% confidence interval [CI] 1.44 – 1.77). The estimated 6-year survival for patients with AS was 94.5%. The major cause of death was CVD (34.7%), followed by malignancy (23.4%), infections (5%), suicide (2%), and renal disease (1%). Spinal trauma was reported as an intermediate cause of death in 2.2% of patients with AS (but was never registered as the leading cause of death). In patients with AS, predictors of death included male gender, higher age, socioeconomic status, general comorbidities and hip replacement surgery (Exarchou 2016).

Patients with AS have a slightly elevated CVD risk compared to the general population (Wang and Ward 2018). The general risk for VTE is increased in patients with AS especially in the first years after diagnosis (Aviña-Zubieta 2019). HRs and 95% CIs for CV outcomes among patients with AS compared to non-AS controls have been reported for vascular mortality (1.36, 1.13 – 1.65), first acute coronary syndrome (1.3, 1.0 – 1.7), first stroke (1.5, 1.1 – 2.0), first ischemic heart disease event (1.2, 0.97 – 1.48), first acute myocardial infarction (0.91, 0.65 – 1.28), and overall CVD (1.2, 1.02 – 1.42) (Wang and Ward 2018).

Important co-morbidities:

EAMs are common in patients with AS and include anterior uveitis, bowel inflammation, and psoriasis. The prevalence of clinically overt IBD in patients with AS is estimated to be between 5% to 10% (Rosenbaum and Chandran 2012).

In a systematic review and meta-analysis, the pooled prevalence of EAMs in patients with AS included 25.8% (95% CI 24.1% to 27.6%) for uveitis, 9.3% (95% CI 8.1% to 10.6%) for psoriasis, and 6.8% (95% CI 6.1% to 7.7%) for IBD (Stolwijk 2015).

In a US cross-sectional study of patients with AS, important co-morbidities included coronary heart disease (12%), anxiety and other neuroses (11%), cancer (11%), hypertension (10%),

diabetes mellitus (7%), prostate disorders (7%), depression (7%), atrial fibrillation (6%), and irritable bowel syndrome (6%) (Zhao 2019).

Indication: Non-Radiographic Axial Spondyloarthritis

Based on the ASAS axSpA criteria, nr-axSpA is axSpA that does not meet the 1984 modified New York imaging criteria for AS (Deodhar 2016). nr-axSpA is a clinically relevant subgroup of axSpA patients without structural damage who are classified as having nr-axSpA (versus [vs.] AS) by the lack of advanced structural changes observed in the sacroiliac joints on plain radiographs (Deodhar 2016, Lopez-Medina 2019). The burden of disease and clinical presentation of nr-axSpA and AS are quite similar (Bohn 2018, Lopez-Medina 2019, Sieper 2017).

Data indicate that 23% to 80% of patients newly diagnosed with axial SpA may be patients with nr-axSpA depending on the symptom duration, selection criteria, and other parameters including interpretation of MRIs (Sieper and van der Heijde 2013).

Incidence:

There are little published data available on nr-axSpA incidence rates due to historical lack of classification criteria for this population, difficulty in diagnosis, and previous lack of a specific ICD-10 code for nr-axSpA (Bohn 2018, Deodhar 2016, Tłustochowicz 2020). Starting 01 October 2020, the diagnostic codes for nr-axSpA were indexed to an existing ICD-10 subcategory; however, the code will continue to support other specified inflammatory spondylopathies in addition to nr-axSpA (Carvalho 2020).

Prevalence

There is limited information available regarding the prevalence of nr-axSpA for reasons described above. The prevalence of nr-axSpA in Germany was estimated as 0.03% (26.2 per 100,000) using healthcare claims data (König 2018). Data from North American population studies reported the prevalence of nr-axSpA varied between 0.4% to 0.6% of the general population (Poddubnyy and Sieper 2014). In a nationwide facility survey in Japan, the prevalence of nr-axSpA was estimated as 0.0006% (0.6 per 100,000) (Matsubara 2021).

Demographics of the target population:

nr-axSpA is more prevalent among female patients though estimates range from an even gender distribution to a 2:1 female majority (Boonen 2015, Lockwood and Gensler 2017). In a meta-analysis, 54% of patients with nr-axSpA were male and 84% reported their ethnicity as Caucasian (Lopez-Medina 2019). The pooled mean age at symptom onset was 27.8 years (95% CI 26.3 to 29.4), and the pooled mean time to diagnosis was 4.2 years (95% CI 2.2 to 6.2) (Lopez-Medina 2019). In a French cohort study, 42% of patients with nr-axSpA were male, and 91% reported Caucasian ethnicity (López-Medina 2020). In a German cohort study of patients with nr-axSpA for less than 5 years, 43% of patients were

male and the mean age at disease onset was 33.2 years (standard deviation [SD] 10.5) (Rudwaleit 2009).

Risk Factors:

nr-axSpA and AS share common epidemiological, genetic, and clinical characteristics and risk factors, which support the concept of axial SpA as 1 disease (Poddubnyy and Sieper 2014). Genetic risks factors have a central role in the overall risk of developing nr-axSpA including family history of AS and HLA-B27 positivity (Lockwood and Gensler 2017, Sieper and van der Heijde 2013). One hypothesis, supported by prospective data from German Spondyloarthritis Inception Cohort (GESPIC), suggests that female patients as well as patients with low level of inflammation (i.e., CRP) have a lower likelihood of developing structural damage in the axial skeleton and thus remain longer in the non-radiographic stage of axial SpA (sometimes lifelong in the case of a self-limiting disease course) (Poddubnyy and Sieper 2014).

The main treatment options:

Similar to AS, the treatment of nr-axSpA patients is based on pharmacological and non-pharmacological treatment modalities. The main treatment options for patients with nr-axSpA include NSAIDs and bDMARDs such as TNF inhibitor and IL-17i therapies. NSAIDs and physical therapy are often the first-line therapy for nr-axSpA; traditional csDMARDs and corticosteroids are ineffective and therefore not recommended for the treatment of axial symptoms (van der Heijde 2017, Ward 2019). In patients with persistently high disease activity despite a course of 2 NSAIDs given over a total of at least 4 weeks, initiation of a bDMARD is recommended, and current practice is to start with TNF inhibitor. If TNF inhibitor therapy fails, switching to another TNF inhibitor or an IL-17i is recommended (van der Heijde 2017, Ward 2019). Despite recent advances in the treatment of axSpA, only approximately 45% to 50% of patients achieve an ASAS40 response and only approximately 15% to 20% reach a state of remission, highlighting a significant unmet medical need (Baeten 2015, Davis 2003, Deodhar 2021, Deodhar 2019, Deodhar 2020, Dougados 2014, Inman 2008, Landewe 2014, Sieper 2015, Sieper 2013, van der Heijde 2006).

In a meta-analysis of axial SpA studies, treatments used among patients with nr-axSpA included NSAIDs (69.1%), csDMARDs (28.5%), oral glucocorticoids (10.1%), and bDMARDs (26.2%) (Lopez-Medina 2019).

Natural history of the indicated disease/condition in the population, including mortality and morbidity:

nr-axSpA has been considered as an early form of AS that could, though not necessarily, progress to AS (Lopez-Medina 2019). Onset of nr-axSpA is classified by the occurrence of chronic inflammatory back pain typically at age < 45 years, in addition to being positive for HLA-B27 plus 2 additional characteristic features of AS (Sieper and van der Heijde 2013). There are currently no data to suggest that the pathogenesis of nr-axSpA disease is different

from that of AS (Lockwood and Gensler 2017). nr-axSpA is a primary axial process characterized by sacroiliac joint and spinal inflammation, though patients may also experience features of peripheral disease and EAMs (Lockwood and Gensler 2017). In a meta-analysis of 60 studies, the pooled prevalence of AS-related clinical manifestations among patients with nr-axSpA included peripheral arthritis (35.2%), uveitis (14.3%), IBD (5.6%), and psoriasis (9.3%) (Lopez-Medina 2019). In a review of 8 axial SpA studies, the mean symptom duration for nr-axSpA ranged from 1.0 years (SD 0.7) to 12.1 years (SD 8.5) (de Winter 2016).

nr-axSpA progresses to AS in about 10% to 20% of patients within 2 years and 60% of patients within 10 years, but 30% of patients remain unchanged or remit and never progress to radiographic disease (Boonen 2015, Burgos-Vargas 2016, Lopez-Medina 2019, Poddubnyy and Sieper 2014). A US population-based study reported that among patients with nr-axSpA, 19% progressed to AS in a median of 5.9 years (range 2.7 to 11.8 years); the probability that the condition would remain non-radiographic at 5, 10, and 15 years was 93.6%, 82.7% and 73.6%, respectively (Wang 2016). As noted in the AS section above, factors associated with progression from nr-axSpA to AS included low-grade radiographic sacroiliitis at inclusion, buttock pain, elevated CRP, active sacroiliitis on MRI, and smoking during the follow-up were associated with progression from nr-axSpA to AS (Costantino 2017, Dougados 2017, Protopopov and Poddubnyy 2018); arthritis onset during the follow-up was associated with a decreased risk of developing AS (Costantino 2017).

Increased mortality has been described in patients with AS compared to the general population as described in the AS section above, which can be partly explained by the higher prevalence of CVD (López-Medina and Moltó 2018, Wang and Ward 2018). It is possible that due to nr-axSpA having a shorter symptom duration or a milder disease that the CVD risk would be lower than in the AS population; however, these groups have not been studied in this manner (Lockwood and Gensler 2017).

Important co-morbidities:

In a US study using electronic medical record data for 775 patients with AS and nr-axSpA, the mean number of co-morbidities was similar in AS (mean 1.5, SD 2.2) and nr-axSpA (mean 1.3, SD 2.2) patients (Zhao 2019). EAMs are common in patients with nr-axSpA and include anterior uveitis, IBD, and psoriasis.

In a systematic review and meta-analysis, the pooled prevalence of EAMs in patients with nr-axSpA included 14.3% (95% CI 12.0% to 16.9%) for uveitis, 9.3% (95% CI 7.4% to 11.7%) for psoriasis, and 5.6% (95% CI 4.0% to 7.9%) for IBD (Lopez-Medina 2019).

Important co-morbidities among nr-axSpA patients included coronary heart disease (9%), anxiety (14%), cancer (10%), hypertension (6%), diabetes mellitus (7%), depression (10%), and irritable bowel syndrome (4%) (Zhao 2019).

Indication: Atopic Dermatitis

Incidence:

The incidence of AD is highest in early childhood and decreases in adolescence and adulthood (Abuabara 2018). The incidence rate of AD was 7.3 per 100 PY in infants and 3.4 per 100 PY among children aged less than 6 years in Norway in 2014 (Mohn 2018), and was 1.4 per 100 PY among people of all ages in the UK in 2005 (Deckers 2012). The cumulative incidence of AD in infants less than 6 months old in the US was reported to be 17.1% (Moore 2004). There is an increasing trend for the incidence of AD in industrialized countries (Bieber 2010, Mohn 2018).

Prevalence:

The lifetime prevalence of AD is estimated as 15 to 30% in children and 2 to 10% in adults (Bieber 2010).

The prevalence of AD was estimated to be 14% during the first year of life in Europe (Draaisma 2015) and 7.9% in childhood and adolescence (0 – 18 years) worldwide (Davies 2018). In children aged 13 to 14 years, the prevalence of AD ranges from 1.8% in Lithuania to 15% or higher in Denmark, Bulgaria, Finland, and Hungary (Kowalska-Oledzka 2019). Among adults, the prevalence of AD ranged from 2.2% in Switzerland to 17.6% in Estonia (Kowalska-Oledzka 2019), and the estimated prevalence in US adults is 7.3% (Chiesa Fuxench 2019).

In the US, AD prevalence was found to be higher in African American (19.3%) compared with European American (16.1%) children (Brunner and Guttman-Yassky 2019). The prevalence of AD is usually higher in females (range, 2.6% – 10%) than in males (range, 1.8% – 6.1%) (Barbarot 2018). Among adults, the prevalence of AD is highest in middle age groups (25 – 44 years), ranging from 2.1% to 9.6% (Barbarot 2018). The prevalence of AD is higher among black and Asian populations than in white populations (regardless of geographic location) (Kaufman 2018).

Approximately 30% to 66% of patients with AD have moderate to severe active disease depending on the measures of disease activity used (Barbarot 2018, Chiesa Fuxench 2019, Pawankar 2013).

Data from the International Study of Asthma and Allergies in Childhood (ISAAC) study suggest that while AD seems to have reached a plateau in countries with the highest prevalence, such as the UK and New Zealand, AD continues to increase in prevalence in young children (ages 6 – 7 as compared to ages 13 - 14 years) and in low-income countries, such as in Latin America and Southeast Asia (Nutten 2015).

Demographics of the target population:

Both the incidence and prevalence of AD decrease with age, and both are higher in females than in males, and higher in nonwhite populations, regardless of geographical location (Abuabara 2018, Barbarot 2018, Brunner and Guttman-Yassky 2019).

Risk Factors:

Risk factors for AD include genetic factors as well as environmental factors important in determining disease expression such as foetal nutrition and socioeconomic status (Williams 1999), and a bidirectional relationship exists between psychologic stress and atopic disorders (Chida 2008).

Genetic factors

The strongest known risk factor for AD is a family history of AD or any other atopic disease, including asthma, allergic rhinitis, or food allergies. The risk of having AD increases by 3-fold if one parent has AD and up to 5-fold if both parents have AD (Weidinger 2018). Null (loss-of-function) mutations of the gene encoding filaggrin (FLG), a gene located in the epidermal differentiation complex on chromosome 1q21.3, is the strongest known genetic risk factor for AD (Løset 2019). About 10% of the European and Japanese ancestry population carry a null mutation within FLG exon 3 and they have a threefold increased risk of AD compared with the general population (Løset 2019).

Candidate genes involved in epidermal differentiation, skin immunity, or systemic immunity have been studied to elucidate the genetic background of AD (Løset 2019). Highlighted genes identified by candidate gene studies comprise those encoding IL-4, the IL-4 receptor, and IL-13, all lying in the Th2 cytokine cluster on chromosome 5q31.1. This locus is also robustly associated with AD in genome-wide association studies (GWAS) (Løset 2019). The identified GWAS loci explain approximately 15% of the variance in liability (Løset 2019). Many factors could explain "missing heritability." These include effects due to marked heterogeneity of AD, the cumulative effects of multiple genetic variations, rare genetic variations, structural variations of the genome such as copy number variants, the existence of gene-gene and/or gene-environment interactions, and heritable epigenetic mechanisms (Løset 2019, Verma and Ritchie 2018).

Along with IL-4 and IL-13, AD is also driven by other pro-inflammatory cytokines (including IL-22, thymic stromal lymphopoietin (TSLP), IL-31 and interferon-γ) that transduce signals via the JAK1 pathway. Inhibiting JAK1 reduces the signaling of many mediators which drive the signs and symptoms of AD such as eczematous skin lesions and pruritus (Bao 2013, Brunner 2017a).

Environmental factors

Environmental risk factors for AD include living in urban environments and in areas with air pollution, low ultraviolet (UV) light exposure, dry climatic conditions, or in cold areas. Other risk factors for developing AD are consuming a diet high in sugars, refined cereals, red and preserved meats, and saturated and polyunsaturated fatty acids, longer duration of breastfeeding, low fish consumption during late infancy, maternal alcohol intake during pregnancy, hygiene, repeated exposure to antibiotics before 5 years of age, obesity, low physical exercise, higher socioeconomic status, higher level of family education, and smaller family size (Bonamonte 2019, Kowalska-Oledzka 2019, Nutten 2015, Weidinger 2018).

The main treatment options:

While there are no published studies comparing AD disease factors and treatment between adolescents 12 to 17 years of age and adults ≥ 18 years of age, published guidelines in both the US and EU make no distinctions in the diagnosis, assessment, and treatment of AD in adolescents and adults (Eichenfield 2014a, Eichenfield 2014b, Kunz 1997, Ring 2012, Sidbury 2014).

Food and Drug Administration (FDA)- and/or European Commission-approved treatments for AD consist of corticosteroids (topical and systemic), calcineurin inhibitors (topical), phosphodiesterase-4 (PDE-4) inhibitors (topical), cyclosporine A (systemic), IL-4 and/or -13 inhibitors (systemic; includes dupilumab and tralokinumab) and JAK inhibitors (systemic; includes baricitinib and upadacitinib). Off-label use AD treatments include systemic immunosuppressants (MTX, azathioprine, or mycophenolate mofetil); psoralen and ultraviolet A (PUVA); and alitretinoin (topical).

Treatment of AD in adolescent and adult patients depends on the extent and severity of disease. The most used topical agents are corticosteroids, calcineurin inhibitors, and moisturizers. When topical therapies are insufficient for treating AD, systemic therapy or phototherapy are generally added to topical agents. Mid-potency TCS are the first-line treatment of AD when nonpharmacologic interventions have failed; however, AD disease activity may continue despite use of TCS or patients may lose response over time (Sidbury 2014).

Treatment guidelines developed by the American Academy of Dermatology, similar to the Japanese Dermatological Association and European guidelines, recommend the use of systemic immunomodulatory agents for patients in whom optimized topical regimens or phototherapy do not adequately control the signs and symptoms of disease. These guidelines recognize that insufficient data exist to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunomodulating medication (Eichenfield 2014a, Sidbury 2014).

Importantly, in addition to the lack of well-controlled efficacy data supporting their use in moderate to severe AD, the duration of use of many traditional systemic immunomodulatory agents is limited due to cumulative toxicity. At this time, very few systemic agents are approved for AD and, of those, cyclosporin A and oral prednisone are not suitable for long-term use. Hence, there is a large unmet need for more effective therapies that provide rapid and sustained itch relief and skin clearance, with a safety profile for long-term use.

Natural history of the indicated disease/condition in the population, including mortality and morbidity:

AD is a chronic systemic inflammatory disease with symptoms most often starting during early childhood. About 60% of cases manifest first symptoms during the first year of life (Abuabara 2017, Weidinger and Novak 2016, Wollenberg 2022a, Wollenberg 2022b), with 95% experiencing onset below 5 years of age (Thomsen 2015). The majority outgrow AD in childhood or early adolescence, but around 25% continue to have AD into adulthood or experience a relapse of symptoms after some symptom-free years (Thomsen 2015).

The atopic march refers to the natural history of atopic disorders. AD is the first manifestation of the atopic march. Patients with AD may develop food allergy in early childhood, progressing to asthma and allergic rhinitis in later childhood or adult life (Spergel 2010). AD is associated with increased risk for insomnia (Billeci 2015, Brunner 2017b), reduced quality of life, and increased risk for mental health problems including depression or anxiety (Jeon 2017, Kowalska-Oledzka 2019, Silverberg 2018). Compared with disease-free adults, all-cause mortality is marginally increased in AD, with adjusted HR 1.27 (95% CI 1.11 – 1.45). The mortality rate in adults with AD in Denmark is reported to be 0.58 per 100 PYs (95% CI 0.51 – 0.66). Significant causes included CV (HR 1.45; 95% CI 1.07 – 1.96), infectious (HR 3.71; 95% CI 1.43 – 9.60), and urogenital diseases (HR 5.51; 95% CI 1.54-19.80) (Thyssen 2018). A dose-response relationship with severity of AD was found for CV death when compared with patients without AD. The HR for CV death was 1.06 (95% CI 0.98 – 1.15) for moderate disease and 1.38 (95% CI 1.17 – 1.62) for severe disease (Silverwood 2018). No increased risk for death due to cancer, endocrine, neurologic, psychiatric, respiratory, or gastroenterological disease was observed (Thyssen 2018). The risk of death in hospitalized patients with AD is also higher than the general population, with adjusted HR of 1.71 (95% CI 1.20 – 2.44) (Egeberg 2017).

Important co-morbidities:

Patients with AD are usually affected with atopic and non-atopic comorbidities. The prevalence of comorbidities in patients with AD is higher than in the general population and is particularly high among those with severe AD (Thyssen 2018).

Important co-morbidities of AD are presented below.

Other atopic diseases: Allergic rhinitis, food allergies, and asthma (Hanifin and Reed 2007).

Bacterial skin infections: Staphylococcal skin infections, impetigo (Siegfried and Hebert 2015, Simpson 2012).

Viral skin infections: Molluscum contagiosum, eczema herpeticum (EH), eczema vaccinatum, eczema coxsackium, viral exanthems (Siegfried and Hebert 2015, Simpson 2012).

Fungal skin infections: Tinea or yeast (Siegfried and Hebert 2015, Simpson 2012).

Ocular complications: blepharitis, keratoconjunctivits, keratoconus, iritis, cataract and retinal detachment (Sasoh 2015).

Psychiatric and neurodevelopmental disorders: attention deficit hyperactivity disorder (ADHD), depression, anxiety, conduct disorder, autism, sleep disturbance, and suicidality (Billeci 2015, Brunner 2017b, Chiesa Fuxench 2017, Sandhu 2019).

Autoimmune diseases: IBD, celiac disease, systemic lupus erythematosus (SLE), alopecia areata, vitiligo, and chronic urticaria (Andersen 2017, Brunner 2017b, Weidinger 2018).

Indication: Ulcerative Colitis

Incidence:

The reported annual incidence of UC varies by country and region. In Europe, the incidence of UC ranges from 4.4 per 100,000 PY in France to 17.2 per 100,000 PY in the Netherlands to 23.2 per 100,000 PY in the UK (de Groof 2016, Gower-Rousseau 2013, King 2020, Lucendo 2014, Macaluso 2019, Ng 2017, Ott 2008, Pasvol 2020, Vegh 2014). The incidence of UC ranges from 12.2 to 23.1 per 100,000 PY in North American countries (Keyashian 2019, Molodecky 2012, Ng 2017, Shivashankar 2017) and ranges from 7.3 to 11.4 in Australia (Kedia and Ahuja 2017, Vegh 2014). While the incidence is stabilizing in western countries, UC has become 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 0.18 per 100,000 PY in Malaysia and Indonesia to 6.5 per 100,000 PY in Israel (Kedia 2017, (Ng 2017).

The incidence rates for UC for men and women are similar until middle age (40 to 44 years of age), after which men have a higher incidence than women, and this pattern persists until age 70 to 74 years (Shah 2018).

Prevalence:

Similar geographic variability has been reported for the prevalence of UC. In Europe, the prevalence of UC ranged from 267 per 100,000 persons in Italy to 505 per 100,000 persons in Norway (Hein 2014, 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).

The majority of patients with UC have a mild to moderate course, and about 10% to 15% of patients experience an aggressive course with moderate to severe active disease (Fumery 2018). However, the cumulative risk of relapse ranged from 67% to 83% at 10 years (Fumery 2018, Stewénius 1996).

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 and Hsu 2021). Approximately 80% of patients with UC present after age 20 (Kelsen and Baldassano 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 and Hsu 2021, 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 and Cross 2016). No major differences are seen in disease location and behavior, upper GI tract, and perianal involvement and extraintestinal manifestation (EIM) among races and ethnic groups (Afzali and Cross 2016).

Risk Factors:

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

The main treatment options:

There are many treatment options for UC including aminosalicylates (5-ASAs), corticosteroids, immunomodulators, JAK inhibitors, and biologic/biosimilar therapies. 5-ASAs work in the lining of the GI tract to decrease inflammation and are thought to be effective in treating mild-to-moderate UC flares and can be useful as a maintenance treatment in preventing relapses of the disease. They are often given orally in the form of delayed release tablets, or rectally as enemas or suppositories. Corticosteroids, available orally and rectally, suppress the immune system non-specifically, rather than targeting specific parts of the immune system. In

the management of mild to moderate UC, 5-ASAs (i.e., balsalazide, mesalamine, olsalazine, SSZ) are the standard of care with the option of systemic corticosteroids for patients with mild activity who do not respond to 5-ASAs, as recommended by European Crohn's and Colitis Organisation (ECCO) and American Gastroenterological Association (AGA) (Harbord 2017, Ko 2019, Raine 2022).

There are several different drug classes for long-term management of moderate to severe UC, including TNF-alpha antagonists (infliximab, adalimumab, golimumab), anti-integrin agent (vedolizumab), JAK inhibitor (tofacitinib), IL 12/23 antagonist (ustekinumab), and immunomodulators (i.e., azathioprine, cyclosporine, mercaptopurine, MTX, tacrolimus) (Ungaro 2017). Both ECCO and AGA recommends the use of biologic agents for the induction and maintenance of remission in adult patients with moderate to severe UC with infliximab and vedolizumab preferred in biologic-naïve patients (Feuerstein 2020, Harbord 2017). In patients with prior exposure to infliximab, vedolizumab or tofacitinib may be preferred over adalimumab or golimumab. Combination therapy of a biologic agent with an immunomodulator is more effective than monotherapy with either agent. Thiopurines may be considered for maintenance of remission and MTX monotherapy should not be used for induction or maintenance of remission. Orally administered tofacitinib has also been recommended in adult patients after failure of, or intolerance to, TNF-alpha antagonists in the AGA guidelines. In biologic-naïve patients, the AGA guidelines recommend any use of tofacitinib be closely monitored in a clinical or registry study. The ECCO guidelines recommend tofacitinib be used in patients with moderate to severe UC refractory to thiopurines.

Despite the approval of additional immunomodulatory agents, clinical remission rates remain limited for patients who have failed conventional therapies as well as patients who have failed biologics. Efficacy results, individualized patient safety concerns, as well as preference for route of administration (oral administration preferred) factor into the choice of an agent. The challenges in treating patients are illustrated by the real-world experience in the management of UC, including frequent dose escalation of biologics and switching between classes, to achieve and maintain patient response. Additional effective and safe therapies are needed for patients with moderate to severe UC.

Natural history of the indicated disease/condition 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 (CRC) and mortality rates. The most severe intestinal manifestations of UC are toxic megacolon and perforation. Approximately 15% of patients with UC may experience an

aggressive course, with some requiring hospitalization for severe disease activity. The 5- and 10-year cumulative risk of colectomy is 10% to 15%, mostly limited to those with moderate to severe disease activity; a subset of hospitalized patients with acute severe ulcerative colitis (ASUC) have short-term colectomy rates of 25% to 30%. 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 can be divided into ulcerative proctitis, left-side colitis, and pancolitis according to the extent of disease (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). At the end of follow-up, left-sided colitis is the most common site of disease involvement, followed by extensive colitis and proctitis. EIMs and elevated CRP both at diagnosis and at 5 years of follow-up were significantly associated with extensive disease (Henriksen 2008, Vegh 2016).

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).

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 (Rutter 2004). Since the recognition of increased risk of CRC in patients with UC, several studies have confirmed increased CRC rates in UC patients (Ekbom 1990, Jess 2012). Young age at diagnosis, male sex, extensive colitis, disease duration, and concomitant primary sclerosing cholangitis (PSC) have been consistently identified as risk factors of CRC (Jess 2013, Karlén 1999, Lakatos 2006). Population-based epidemiological studies have shown no consistent increase in the risk of overall or extraintestinal cancers in patients with UC compared with the general population (Karlén 1999, Lakatos 2006, Palli 1998, Yadav 2015), with the exception of non-melanoma skin cancer (NMSC). In a 2014 Danish population-based study, the standardized incidence ratio (SIR) for NMSC was 1.8 (95% CI: 1.7 – 2.0) in the second and subsequent years after UC diagnosis (Kappelman 2014). A 2012 US population-based study in an administrative claims

database reported an incidence rate ratio of 1.34 (95% CI: 1.26 – 1.42) for NMSC in patients with UC compared with the non-IBD population (Long 2012).

Despite the increased risk of CRC, 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 GI-related mortality, partly attributed to an increased mortality from liver diseases, and increase in risk of CRC-related mortality, as well as increased respiratory-related mortality primarily due to of asthma-related deaths, despite a decrease in risk of respiratory tract cancers. There has been no increase in risk of overall cancer-related mortality or CV mortality (Höie 2007, Jess 2006, Karlén 1999, Manninen 2012, Masala 2004, Persson 1996, Romberg-Camps 2010).

Overall risk of EIM in patients with UC is approximately 17% (Isene 2015, Vegh 2016). Articular manifestations are the most frequently observed EIMs (8.1%), including peripheral arthritis (5.5%) and AS (1%), followed by cutaneous EIMs (1.3%), PSC (0.6%), and ocular manifestations (0.6%) (Isene 2015). Other extraintestinal complications include anemia and venous thromboembolism. Approximately 20% to 24% of patients with UC are anemic at diagnosis, and disease extent and high disease activity were significantly associated with anemia (Høivik 2014, Ott 2012). Incidence rate of venous thromboembolism ranges from 1.1 to 2.0 per 1,000 PY, with a 5-year and 10-year cumulative probability of 0.8% and 1.2%, respectively (Kappelman 2011, Vegh 2015).

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 health problems or comorbidities that could alter the diagnosis, presentation, and management of the intestinal disease of UC include CVD including venous thromboembolism, and psychiatric conditions (depression and anxiety) (Román and Muñoz 2011). The complex interaction between inflammation and coagulation contributes to a shift toward a prothrombotic stat in UC (Danese 2007), leading patients with UC have an increased risk of VTE (Papa 2020).

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 to 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 to 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:

CD 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 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 and McGovern 2016). Environmental risk factors such as smoking, NSAIDs, 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, do not reduce the risk of CD relapse over a 24-month period of follow-up (Steinhart 2003), and must be used sparingly given their significant short-term and long-term complications. Maintenance therapy with thiopurines or MTX 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). The advent of biologics has revolutionized treatment of patients with moderately to severely active CD. However, despite the benefits of available biologic therapies, such as infliximab, adalimumab, vedolizumab, and ustekinumab, many patients do not respond to initial treatment or lose treatment response over time. Additionally, some patients are not candidates for available biologic therapies (e.g., patients with prior demyelinating disorders, congestive heart failure [CHF]). Furthermore, patients who have failed a biologic who are subsequently treated with a different drug of the same class or have failed multiple biologics tend to achieve lower rates of efficacy (Sandborn 2007). Lastly, all biologics require IV and/or subcutaneous administration, limiting their acceptance by some patients.

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 the indicated disease/condition 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 CD 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. Patients with CD have an increased risk of GI perforation predominantly in the small bowel (Greenstein 1985). Also, patients with moderate to severe CD demonstrate increased rates of GI perforations compared to those with mild disease (McAuliffe 2015). While free wall perforation in CD reported in the literature varies from 1% to 15.6% (Werbin 2003), the chronic inflammatory processes that induce ulceration increase the risk of fistulizing disease, which occurs in almost one-third of patients, and intra-abdominal abscesses are a common complication of disease (Lichtenstein 2018). At 20 years after diagnosis, the risk of developing intestinal complications among CD patients is 51 percent (Thia 2010). CD patients with disease involving the colon have an increased risk of CRC (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:

Co-morbidities include asthma, arthritis, arthralgia, skin disorders like erythema nodosum and pyoderma gangrenosum, uveitis, CVD, venous thromboembolism, neuropsychological disorders,

osteoporosis, fatigue, and sexual dysfunction (Argollo 2019, Baumgart and Sandborn 2012, Kuenzig 2019, Yuhara 2013).

Proposed Indication: Giant Cell Arteritis

Giant Cell Arteritis (GCA) is defined by granulomatous arteritis that affects large sized and medium sized blood vessels (Jennette 2013, Ponte 2022). GCA predominately affects those aged 50 years and older with the updated 2022 ACR/EULAR classification mandating age ≥ 50 years at diagnosis as an absolute requirement.

Incidence:

GCA incidence varies depending on the case definition used, with a lower incidence reported for temporal artery biopsy (TAB)-defined GCA (Andersen 2021, Brekke 2017). The incidence was higher in women than in men and increased with age until the 7th decade of life (Andersen 2021, Brekke 2017, Mohammad 2015, Stamatis 2021, Tomasson 2019). A 2021 meta-analysis reported an overall annual pooled incidence of GCA of 10.0 per 100,000 people over 50 years old, with the highest incidence in Scandinavia (21.57 per 100,000) followed by North and South America (10.89 per 100,000), Oceania (7.85 per 100,000), and Europe (7.26 per 100,000) (Li 2021). Different studies have reported higher incidence in populations of Northern European ancestry (Sharma 2020).

In the US, the incidence ranged from 15 to 20 per 100,000 in those > 50 years old and diagnosed since 2000 (Chandran 2015, Garvey 2021); both studies were conducted in Olmsted County, Minnesota. In Australia and New Zealand, studies evaluated only subjects who underwent TAB, and the incidence was estimated to be between 5.4 and 10.5 per 100,000 people 50 years and older (Lyne 2022, Ninan 2023). The incidence of GCA in Israel was 11.3 per 100,000 people ≥ 50 years old (Bas-Lando 2007).

Prevalence:

In nearly all published studies of patients with GCA, women were affected two to three times more often than men (Crowson and Matteson 2017, Herlyn 2014, Martínez Perez 2023, Stamatis 2021). Like GCA incidence, the prevalence increased with age (Stamatis 2021) until the 7th decade of life before declining (Martínez Perez 2023). The overall pooled prevalence of GCA from a 2021 meta-analysis was 51.7 cases per 100,000 people over 50 years old (Li 2021). In Europe, the prevalence ranged from 12 and 127 per 100,000 people 50 years and older (Catanoso 2017, Herlyn 2014, Muratore 2021, Romero-Gómez 2015, Stamatis 2021). GCA prevalence was reported to be between 204 and 235 per 100,000 people > 50 years old in North America (Barra 2020, Crowson and Matteson 2017) compared to 28.6 per 100,000 in Argentina (Martínez Perez 2023).

Demographics of the target population:

The risk of developing GCA increases with age. It occurs in adults aged 50 and older, with the highest incidence among adults age 70-79 years (Gonzalez-Gay 2009, Salvarani 2008). Women are 2 to 3 times more likely to develop GCA compared to men (Salvarani 2008). GCA is more common in northern European countries, particularly Scandinavian countries; it is less common in Black and Asian populations (Gonzalez-Gay 2009, Sharma 2020).

Risk Factors:

Although the exact underlying cause is unknown, it is believed that a combination of genetic and environmental risk factors contribute to GCA risk (Salvarani 2008). The human leukocyte antigen (HLA) region is strongly associated with GCA, particularly *HLA-DRB1*04* alleles (Carmona 2014, Greigert 2022). Given that it occurs exclusively in older adults, it is thought that immunosenescence, or immune dysfunction due to aging, also contributes to the development of GCA (Gloor 2022, Mohan 2011). Caucasian populations are also at a greater risk of developing GCA (Gonzalez-Gay 2009, Sharma 2020).

Associations have been observed between GCA and cytomegalovirus, herpes simplex virus, human parvovirus B19, human parainfluenzae virus 1, Epstein-Barr virus, and *Chlamydia pneumoniae*, although these findings have not been replicated (Duhaut 2004, Ly 2010). More recently, varicella zoster virus has been studied as a possible cause, but results are inconclusive (Ostrowski 2019). To date, no definitive environmental trigger for GCA has been identified.

The main treatment options:

Oral glucocorticoids are the primary treatment option for GCA. Initial large doses of 40-60 mg/day of prednisone equivalent are recommended, followed by a slow taper in dose over weeks or months to a goal of ≤ 5 mg/day prednisone equivalent after 1 year (Hellmich 2020, Maz 2021). High-dose pulse IV methylprednisolone may also be used prior to oral glucocorticoids in patients with acute visual loss (Hellmich 2020, Maz 2021).

Other medications may be used in combination with glucocorticoids to treat GCA. Tocilizumab used with glucocorticoids has been shown to increase the time to first disease flare and reduce cumulative glucocorticoid exposure compared to placebo (Stone 2022, Stone 2017, Villiger 2016). Methotrexate in combination with glucocorticoid therapy may also be used in patients unable to take tocilizumab, although evidence for the efficacy of methotrexate in GCA is mixed (Hoffman 2002, Jover 2001, Maz 2021, Spiera 2001).

Natural history of the indicated disease/condition in the population, including mortality and morbidity:

GCA is a systemic vasculitis affecting large and medium-sized arteries in adults aged 50 and older, with a preponderance for affecting the cranial arteries (Salvarani 2008). It is

characterized by granulomatous infiltrate of mononuclear and giant cells into the arterial wall, resulting in stenosis and occlusion of the vascular lumen (Greigert 2022, Weyand 2012). Patients typically present with symptoms including new-onset temporal headache (62.8%), scalp tenderness (34.4%), jaw (47.1%) or tongue (2.8%) claudication, sudden vision loss (13.5%), morning stiffness in the shoulders (23.0%) and neck (11.6%), and elevated acute phase inflammatory markers (73.8-90.3%) (Ponte 2022). Once visual loss is established, it is rarely reversible (Danesh-Meyer 2005). Other symptoms typically improve or resolve with treatment.

Nearly half of patients experience a relapse in disease activity, ranging from 32% by 1 year after diagnosis to 47% by 5 years after diagnosis; multiple relapses occur in 30% of patients (Mainbourg 2020, Moreel 2023). Shorter duration of initial glucocorticoid treatment after diagnosis is associated with an increased risk of relapse, as well as female gender, and younger age (Mainbourg 2020, Moreel 2023).

Comorbidities associated with glucocorticoid exposure are common in GCA patients, including diabetes, osteoporosis, glaucoma, fractures, and serious infections (Gale 2018). Vascular comorbidities are also common. Patients with GCA have an increased risk of stroke compared to the general population, with an RR of 1.40 (1.27, 1.56); however, risk of coronary artery disease is not elevated with an RR of 1.51 (0.88, 2.61) (Ungprasert 2015, Ungprasert 2016). Risk of VTE is also increased compared to the general population, with an RR of 2.26 (1.38, 3.71) (Ungprasert 2014).

Evidence on mortality risk in GCA is mixed, although several meta-analyses have not found an increased overall risk of mortality compared to the general population (Hill 2017, Lee and Song 2018). In two studies, the most common cause of death in GCA patients were cardiovascular-related (Brekke 2019, Chazal 2018).

Important co-morbidities:

Polymyalgia rheumatica (PMR) occurs in 40-60% of GCA patients, and may be caused by the same underlying disease process (Salvarani 2008). Patients with GCA have an increased risk of aortic arch syndrome (10-15% of patients) and thoracic aortic aneurysm (17 times more likely) compared to the general population (Salvarani 2008).

Glucocorticoid-related comorbidities are common among GCA patients, including diabetes, osteoporosis, fractures, glaucoma/cataract, and serious infections (Best 2019, Broder 2016, Gale 2018, Lai 2018, Mohammad 2017, Paskins 2018, Wilson 2017).

Module SII Nonclinical Part of the Safety Specification

A high-level summary of the key nonclinical findings and the relevance of the findings to use in humans are provided in the following table.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Toxicity	
Repeated-dose toxicity: Immunosuppressive effects in dogs were observed in a 39-week toxicity study. Findings included the occurrence of demodicosis at the high dose. Demodicosis, or demodectic mange, is a common skin disease in dogs often associated with immunosuppression. Decreases in circulating lymphocytes and decreased cellularity of lymphoid tissues were observed in rats and dogs and were consistent with the expected pharmacologic activity of a selective and reversible JAK inhibitor. Effects were generally mild and reversible. Suppression of erythropoiesis, resulting in reversible decreases in red cell mass and reticulocytes, was observed in rats and dogs. Administration of upadacitinib to juvenile Sprague-Dawley rats resulted in pharmacologic effects on the lymphoid system and exposures similar to those observed in adult rats but did not result in renal tubular degeneration/regeneration or any additional target organ toxicity. No evidence of effects on bone during postnatal development of the skeletal system in juvenile or adult rats or dogs has been observed following administration of upadacitinib.	Nonclinical evidence suggests that there may be a risk of decreases in red cell parameters and circulating lymphocytes as well as a risk of infections in humans. Immunosuppressive effects in dogs occurred at exposures 2 times the exposures at the clinical dose of 15 mg, at similar exposures to the expected exposure at the clinical dose of 30 mg, and at 0.9 times the expected exposure at 45 mg. Across the upadacitinib clinical programs, data support minimal impact of upadacitinib on hemoglobin and lymphocyte counts with the 15, 30, and 45 mg doses. Impact of immunosuppression observed during nonclinical studies is relevant for the risk of infections in humans. In clinical trials, upadacitinib was generally associated with an increased risk of serious infection and herpes zoster. Thus, serious and opportunistic infections including tuberculosis (TB) and herpes zoster are important identified risks for upadacitinib (see Module SVII).
Reproductive toxicity: Results from a fertility and early embryonic development study in male and female rats indicated that upadacitinib had no effect on fertility in either male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females. In a pre-/postnatal development study in rats, there were no maternal effects, no effects on parturition, lactation, or maternal behaviour, and no effects on the offspring (sexual maturation, behaviour, mating and fertility, or ovarian and uterine parameters). No effects were observed at exposures in rats at approximately the same exposure expected at	The potential for effects on fertility is low based on nonclinical data; effects in humans have not been evaluated.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
the clinical dose of 45 mg, at 1.4 times the exposures at the clinical dose of 30 mg, and at 2.8 times the exposures at the clinical dose of 15 mg.	
Developmental toxicity: Embryofetal development studies with upadacitinib indicated that upadacitinib is teratogenic in both rats and rabbits. Upadacitinib administration was associated with skeletal malformations in rats at ≥ 4 mg/kg/day in the absence of maternal toxicity and cardiac malformations in rabbits concurrent with maternal toxicity (only at the high dose of 25 mg/kg/day). In rats and rabbits, teratogenicity occurred at exposure multiples (on an area under the concentration-time curve [AUC] basis) of 0.6 and 6 times the exposures at the clinical dose of 45 mg, respectively, 0.8 and 7.6 times the exposures at the clinical dose of 30 mg, respectively, and 1.6 and 15 times the exposures at the clinical dose of 15 mg, respectively.	Teratogenic effects in nonclinical species suggest there is a potential risk for fetal malformation following exposure in utero. Based on limited data available in the upadacitinib development program through 15 August 2023, in the 100 clinical trial pregnancies for studies which have been unblinded (RA, PsA, AS, nr-axSpA, AD, UC, CD, hidradenitis suppurativa [HS], and SLE), in which a pregnant woman had received upadacitinib within 1 month prior to conception and at least during the first trimester, the pregnancy outcomes are as follows: 1 live birth with congenital anomaly (35 week gestation premature infant with an atrial septal defect), 42 live births without congenital anomaly (including 2 infants born premature at 28 and 34 weeks gestation, neither with complications), 19 spontaneous abortions (SABs), 18 elective terminations (without report of fetal defects or unknown), 1 ectopic pregnancy, 5 ongoing pregnancies, and 14 pregnancies lost to follow up. In 9 of the 19 SABs, pregnant mothers were taking concomitant MTX or used MTX within 1 month prior to conception (background MTX was allowed in RA and PsA studies). Fetal malformation following exposure in utero is an important potential risk for upadacitinib (see Module SVII). The Summary of Product Characteristics (SmPC) includes pregnancy as a contraindication.
Nephrotoxicity: Renal tubular degeneration/regeneration was observed in rats in the 4-week and 26-week toxicity studies. This finding occurred at exposures at least 12, 15, or 30 times the exposures at the clinical dose of 45, 30, and 15 mg, respectively. No increases in serum blood urea nitrogen or creatinine were observed in rats, except in one moribund	Nonclinical evidence suggests that there is a low risk of nephrotoxicity in humans. (See Module SVII).

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
animal with marked kidney findings in the 4-week toxicity study. Renal tubular degeneration/regeneration has not been observed in dogs administered upadacitinib.	
Hepatotoxicity: Hepatic necrosis was observed in a 4-week rat study only at the highest doses where mortality was observed. This finding occurred only in early mortality animals (males) experiencing poor clinical condition and moribundity/death. Exposures in male rats at this dose were 41 times the exposures at the clinical dose of 45 mg, more than 50 times the exposures at the clinical dose of 30 mg, and more than 100 times the exposures at the clinical dose of 15 mg. No increases in serum hepatic enzymes have been observed in nonclinical studies in dogs or at non-lethal doses in rats.	Based on the moribund condition of rats with hepatic necrosis in the 4-week toxicity study, the relevance to humans is uncertain. In upadacitinib clinical trials, asymptomatic transaminase elevations have been observed in subjects treated with upadacitinib. Drug-induced liver injury (DILI) is an important potential risk for upadacitinib (see Module SVII).
Genotoxicity: The results of all genetic toxicology testing indicate that upadacitinib is not genotoxic.	Upadacitinib is not genotoxic.
Carcinogenicity: Upadacitinib was not carcinogenic in a 2-year rat study at exposure levels up to 1.7 and 4 times the exposures at the clinical dose of 45 mg, up to 2 and 5 times the exposures at the clinical dose of 30 mg, and up to 4 and 10 times the exposures at the clinical dose of 15 mg (on an AUC basis) for male and female rats, respectively. Upadacitinib was also not carcinogenic in a 26-week study in CByB6F1-Tg(HRAS)2Jic mice.	Upadacitinib is not expected to be carcinogenic in humans. (See Module SVII).
General Safety Pharmacology	
Cardiovascular: Upadacitinib produced moderate dose-dependent effects on mean arterial pressure and heart rate in dogs beginning at a maximum plasma concentration (C_{max}) of 0.42 µg/mL, which is approximately 3.4 times the C_{max} at 45 mg, 5 times the C_{max} at the clinical dose of 30 mg, and 10 times the C_{max}	Nonclinical evidence suggests that there is a low risk of effects on mean arterial pressure and heart rate in humans.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
at the clinical dose of 15 mg.	
Nervous system: In an activity assay in rats, oral administration of upadacitinib produced no consistent effects on motor activity. In a Good Laboratory Practices functional observational battery assay in rats, upadacitinib had no neurobehavioral effects at oral doses of 10 mg/kg and 50 mg/kg (C_{max} = 5.2 µg/mL), which is approximately 42 times the C_{max} at the clinical dose 45 mg, 62 times the C_{max} at the clinical dose of 30 mg, and 125 times the C_{max} at the clinical dose of 15 mg. Upadacitinib produced a significant decrease in motor activity at the highest dose of 100 mg/kg (C_{max} = 13.5 µg/mL, approximately 108 times the C_{max} at the clinical dose of 45 mg, 161 times the C_{max} at the clinical dose of 30 mg, and 326 times the C_{max} at the clinical dose of 15 mg), doses that also results in morbidity/lethality in rats.	No adverse central nervous system (CNS) effects of upadacitinib are anticipated with human usage.
Respiratory system: Upadacitinib did not produce any effects on respiratory function in rats through the highest dose of 100 mg/kg, which resulted in a C_{max} of 3.9 µg/mL, approximately 31 times the C_{max} at the clinical dose of 45 mg, 46 times the C_{max} at the clinical dose of 30 mg, and approximately 94 times the C_{max} at the clinical dose of 15 mg.	No adverse respiratory effects of upadacitinib are anticipated with human usage.
Mechanisms for drug interactions:	
Other toxicity-related information or data: Upadacitinib was negative for phototoxicity potential in a neutral red uptake phototoxicity assay in Balb/c 3T3 mouse fibroblasts.	Upadacitinib is not expected to be phototoxic in humans.

Nonclinical Safety Findings that are Included as Safety Concerns

Safety Concerns	
Important identified risks	Serious infections and herpes zoster based on clinical trial data.
Important potential risks	• Foetal malformation following exposure in utero based on nonclinical findings. • DILI based on clinical trial data.
Missing information	None

Module SIII Clinical Trial Exposure

Table 2. Upadacitinib Duration of Exposure

	Upadacitinib									
	15 mg QD (N = 8906)		30 mg QD (N = 5616)		45 mg QD (N = 1925)		Other Doses[a] Tablets (N = 752)		Other Doses[b] oral solution (N = 51)	
Duration of Exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
Cumulative for All Indications[c]										
≥ 1 day	8906	25971.9	5616	16063.3	1925	379.5	752	799.0	51	71.7
≥ 4 weeks (28 days)	8771	25967.3	5520	16060.1	1884	378.1	720	798.1	50	71.6
≥ 12 weeks (84 days)	8373	25910.9	5182	16007.7	768	191.5	592	775.4	47	71.2
≥ 24 weeks (168 days)	7736	25702.3	4781	15881.5	0	--	303	699.5	41	69.2
≥ 36 weeks (252 days)	7270	25447.8	4573	15761.4	0	--	265	677.4	36	66.5
≥ 48 weeks (336 days)	6945	25192.8	4336	15574.9	0	--	235	655.6	30	61.7
≥ 52 weeks (364 days)	6742	24996.1	4229	15473.3	0	--	204	625.4	29	60.8
≥ 72 weeks (504 days)	5995	24156.0	3923	15108.0	0	--	145	565.1	24	54.7
≥ 96 weeks (672 days)	5418	23207.8	3659	14687.3	0	--	134	547.6	15	40.2
≥ 120 weeks (840 days)	4758	21878.0	3421	14198.5	0	--	103	485.7	11	31.5
≥ 144 weeks (1008 days)	4453	21109.6	3127	13456.1	0	--	100	478.1	6	19.0
≥ 168 weeks (1176 days)	3987	19728.2	2696	12176.4	0	--	96	465.8	3	10.6

	Upadacitinib									
	15 mg QD (N = 8906)		30 mg QD (N = 5616)		45 mg QD (N = 1925)		Other Doses[a] Tablets (N = 752)		Other Doses[b] oral solution (N = 51)	
Duration of Exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
Indication 1: Rheumatoid arthritis										
Pooled[c]										
≥ 1 day	4108	13999.9	1569	4992.8	--	--	380	549.1	--	--
≥ 4 weeks (28 days)	4041	13997.5	1538	4991.9	--	--	376	549.0	--	--
≥ 12 weeks (84 days)	3873	13974.6	1440	4976.7	--	--	305	535.1	--	--
≥ 24 weeks (168 days)	3571	13877.5	1292	4932.6	--	--	114	490.2	--	--
≥ 36 weeks (252 days)	3312	13740.6	1240	4901.9	--	--	112	489.2	--	--
≥ 48 weeks (336 days)	3191	13646.3	1183	4857.0	--	--	110	487.6	--	--
≥ 52 weeks (364 days)	3116	13574.4	1159	4834.4	--	--	109	486.7	--	--
≥ 72 weeks (504 days)	2755	13159.8	1112	4779.0	--	--	107	484.5	--	--
≥ 96 weeks (672 days)	2611	12932.8	1042	4668.1	--	--	102	476.5	--	--
≥ 120 weeks (840 days)	2501	12709.2	979	4538.3	--	--	99	470.5	--	--
≥ 144 weeks (1008 days)	2418	12501.4	938	4434.4	--	--	96	462.9	--	--
≥ 168 weeks (1176 days)	2311	12185.6	905	4335.9	--	--	93	453.6	--	--

	Upadacitinib									
	15 mg QD (N = 8906)		30 mg QD (N = 5616)		45 mg QD (N = 1925)		Other Doses[a] Tablets (N = 752)		Other Doses[b] oral solution (N = 51)	
Duration of Exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
Indication 2: Psoriatic arthritis										
Pooled[e]										
≥ 1 day	907	2942.8	921	2908.7	--	--	--	--	--	--
≥ 4 weeks (28 days)	896	2942.4	911	2908.4	--	--	--	--	--	--
≥ 12 weeks (84 days)	873	2938.9	877	2903.0	--	--	--	--	--	--
≥ 24 weeks (168 days)	826	2924.1	833	2888.8	--	--	--	--	--	--
≥ 36 weeks (252 days)	798	2908.0	793	2866.2	--	--	--	--	--	--
≥ 48 weeks (336 days)	755	2874.3	753	2835.3	--	--	--	--	--	--
≥ 52 weeks (364 days)	747	2866.6	745	2827.5	--	--	--	--	--	--
≥ 72 weeks (504 days)	717	2830.8	710	2785.3	--	--	--	--	--	--
≥ 96 weeks (672 days)	678	2767.8	678	2732.3	--	--	--	--	--	--
≥ 120 weeks (840 days)	652	2712.6	644	2662.0	--	--	--	--	--	--
≥ 144 weeks (1008 days)	587	2550.8	573	2484.7	--	--	--	--	--	--
≥ 168 weeks (1176 days)	470	2207.5	456	2141.2	--	--	--	--	--	--

	Upadacitinib									
	15 mg QD (N = 8906)		30 mg QD (N = 5616)		45 mg QD (N = 1925)		Other Doses[a] Tablets (N = 752)		Other Doses[b] oral solution (N = 51)	
Duration of Exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
Indication 3: Ankylosing spondylitis										
Pooled[f]										
≥ 1 day	596	1012.4	--	--	--	--	--	--	--	--
≥ 4 weeks (28 days)	590	1012.3	--	--	--	--	--	--	--	--
≥ 12 weeks (84 days)	581	1010.8	--	--	--	--	--	--	--	--
≥ 24 weeks (168 days)	564	1004.9	--	--	--	--	--	--	--	--
≥ 36 weeks (252 days)	540	991.3	--	--	--	--	--	--	--	--
≥ 48 weeks (336 days)	531	983.8	--	--	--	--	--	--	--	--
≥ 52 weeks (364 days)	521	974.1	--	--	--	--	--	--	--	--
≥ 72 weeks (504 days)	496	944.5	--	--	--	--	--	--	--	--
≥ 96 weeks (672 days)	251	523.8	--	--	--	--	--	--	--	--
≥ 120 weeks (840 days)	25	72.2	--	--	--	--	--	--	--	--
≥ 144 weeks (1008 days)	13	41.4	--	--	--	--	--	--	--	--
≥ 168 weeks (1176 days)	5	17.8	--	--	--	--	--	--	--	--

	Upadacitinib									
	15 mg QD (N = 8906)		30 mg QD (N = 5616)		45 mg QD (N = 1925)		Other Doses[a] Tablets (N = 752)		Other Doses[b] oral solution (N = 51)	
Duration of Exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
Indication 4: Non-radiographic axial spondyloarthritis[g]										
≥ 1 day	286	379.3	--	--	--	--	--	--	--	--
≥ 4 weeks (28 days)	283	379.3	--	--	--	--	--	--	--	--
≥ 12 weeks (84 days)	274	377.8	--	--	--	--	--	--	--	--
≥ 24 weeks (168 days)	256	372.2	--	--	--	--	--	--	--	--
≥ 36 weeks (252 days)	243	365.4	--	--	--	--	--	--	--	--
≥ 48 weeks (336 days)	235	359.4	--	--	--	--	--	--	--	--
≥ 52 weeks (364 days)	198	323.1	--	--	--	--	--	--	--	--
≥ 72 weeks (504 days)	125	248.2	--	--	--	--	--	--	--	--
≥ 96 weeks (672 days)	119	238.6	--	--	--	--	--	--	--	--
≥ 120 weeks (840 days)	1	3.1	--	--	--	--	--	--	--	--
≥ 144 weeks (1008 days)	1	3.1	--	--	--	--	--	--	--	--
≥ 168 weeks (1176 days)	0	--	--	--	--	--	--	--	--	--

	Upadacitinib									
	15 mg QD (N = 8906)		30 mg QD (N = 5616)		45 mg QD (N = 1925)		Other Doses[a] Tablets (N = 752)		Other Doses[b] oral solution (N = 51)	
Duration of Exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
Indication 5: Atopic dermatitis										
Pooled[h]										
≥ 1 day	1518	4552.9	1600	4955.0	--	--	60	16.4	--	--
≥ 4 weeks (28 days)	1501	4552.4	1587	4954.6	--	--	43	15.9	--	--
≥ 12 weeks (84 days)	1467	4547.5	1554	4949.6	--	--	36	14.9	--	--
≥ 24 weeks (168 days)	1382	4518.3	1490	4927.3	--	--	7	5.1	--	--
≥ 36 weeks (252 days)	1331	4489.3	1453	4906.7	--	--	2	2.5	--	--
≥ 48 weeks (336 days)	1275	4445.4	1411	4873.8	--	--	1	1.7	--	--
≥ 52 weeks (364 days)	1260	4430.8	1389	4852.9	--	--	1	1.7	--	--
≥ 72 weeks (504 days)	1181	4337.7	1266	4702.1	--	--	1	1.7	--	--
≥ 96 weeks (672 days)	1092	4195.7	1166	4544.3	--	--	0	--	--	--
≥ 120 weeks (840 days)	1024	4056.8	1105	4419.8	--	--	0	--	--	--
≥ 144 weeks (1008 days)	942	3847.1	1039	4251.6	--	--	0	--	--	--
≥ 168 weeks (1176 days)	778	3355.9	871	3750.6	--	--	0	--	--	--

	Upadacitinib									
	15 mg QD (N = 8906)		30 mg QD (N = 5616)		45 mg QD (N = 1925)		Other Doses[a] Tablets (N = 752)		Other Doses[b] oral solution (N = 51)	
Duration of Exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
Indication 6: Ulcerative colitis										
Pooled[i]										
≥ 1 day	875	2065.5	698	1700.8	987	169.2	47	23.4	--	--
≥ 4 weeks (28 days)	862	2065.0	684	1700.3	968	168.5	47	23.4	--	--
≥ 12 weeks (84 days)	766	2050.9	597	1687.2	126	39.0	20	19.4	--	--
≥ 24 weeks (168 days)	678	2021.7	560	1674.8	0	--	15	17.7	--	--
≥ 36 weeks (252 days)	626	1991.9	537	1661.6	0	--	12	16.1	--	--
≥ 48 weeks (336 days)	583	1956.9	498	1630.4	0	--	11	15.2	--	--
≥ 52 weeks (364 days)	541	1916.1	483	1615.9	0	--	9	13.2	--	--
≥ 72 weeks (504 days)	462	1831.9	445	1572.8	0	--	1	4.9	--	--
≥ 96 weeks (672 days)	439	1795.4	418	1530.9	0	--	1	4.9	--	--
≥ 120 weeks (840 days)	402	1721.0	385	1462.3	0	--	1	4.9	--	--
≥ 144 weeks (1008 days)	369	1638.4	344	1358.4	0	--	1	4.9	--	--
≥ 168 weeks (1176 days)	333	1531.8	283	1174.7	0	--	1	4.9	--	--

	Upadacitinib									
	15 mg QD (N = 8906)		30 mg QD (N = 5616)		45 mg QD (N = 1925)		Other Doses[a] Tablets (N = 752)		Other Doses[b] oral solution (N = 51)	
Duration of Exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
Indication 7: Crohn's disease										
Pooled[j]										
≥ 1 day	324	670.3	774	1467.2	938	210.3	154	84.0	--	--
≥ 4 weeks (28 days)	317	670.0	753	1466.2	916	209.6	148	83.8	--	--
≥ 12 weeks (84 days)	284	665.6	671	1453.1	642	152.5	132	81.3	--	--
≥ 24 weeks (168 days)	232	647.9	568	1421.6	0	--	83	66.3	--	--
≥ 36 weeks (252 days)	213	637.2	516	1390.7	0	--	60	52.3	--	--
≥ 48 weeks (336 days)	186	616.2	468	1353.8	0	--	35	34.6	--	--
≥ 52 weeks (364 days)	182	612.3	452	1338.5	0	--	15	15.1	--	--
≥ 72 weeks (504 days)	158	585.4	389	1264.7	0	--	0	--	--	--
≥ 96 weeks (672 days)	149	571.3	354	1207.7	0	--	0	--	--	--
≥ 120 weeks (840 days)	137	546.7	307	1112.0	0	--	0	--	--	--
≥ 144 weeks (1008 days)	114	488.0	232	922.9	0	--	0	--	--	--
≥ 168 weeks (1176 days)	81	390.3	180	770.0	0	--	0	--	--	--

	Upadacitinib									
	15 mg QD (N = 8906)		30 mg QD (N = 5616)		45 mg QD (N = 1925)		Other Doses[a] Tablets (N = 752)		Other Doses[b] oral solution (N = 51)	
Duration of Exposure	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**	**n**	**PYs**
Indication 8: Giant cell arteritis[k]										
≥ 1 day	209	245.7	--	--	--	--	107	115.5	--	--
≥ 4 weeks (28 days)	203	245.5	--	--	--	--	102	115.3	--	--
≥ 12 weeks (84 days)	183	242.9	--	--	--	--	95	114.2	--	--
≥ 24 weeks (168 days)	167	237.6	--	--	--	--	81	109.8	--	--
≥ 36 weeks (252 days)	162	235.0	--	--	--	--	76	107.1	--	--
≥ 48 weeks (336 days)	157	230.8	--	--	--	--	75	106.2	--	--
≥ 52 weeks (364 days)	146	219.9	--	--	--	--	67	98.4	--	--
≥ 72 weeks (504 days)	78	148.2	--	--	--	--	33	63.7	--	--
≥ 96 weeks (672 days)	60	119.3	--	--	--	--	28	55.9	--	--
≥ 120 weeks (840 days)	0	--	--	--	--	--	0	--	--	--
≥ 144 weeks (1008 days)	0	--	--	--	--	--	0	--	--	--
≥ 168 weeks (1176 days)	0	--	--	--	--	--	0	--	--	--

a. Other doses (tablets) include upadacitinib 1.6, 2, 3, 3.2, 4, 8, 18, and 24 mg BID, and 7.5 and 24 mg QD.

b. Other doses (oral solution) include upadacitinib 1.5, 2, 3, 4, 6, and 8 mg BID from Study pcJIA (Study M15-340).

c. Includes data from the following indications: RA (Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557, and M15-925), PsA (Studies M15-554 and M15-572), CD (Studies M13-740, M14-327, M14-431, M14-433, and M14-430), UC (Studies M14-234, M14-675, and M14-533), AD (Studies M16-045, M16-047, M16-048, M16-049, M17-377, and M18-891), AS (Studies M16-098 and M19-944 [Study 1; biologic disease modifying anti-rheumatic drug inadequate responder (bDMARD-IR) AS]), nr-axSpA (Study M19 944 [Study 2]), HS (Study M20-040), GCA (Study M16-852), and pcJIA (Study M15-340).

d. Includes data from RA Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557, and M15-925.

e. Includes data from PsA Studies M15-554 and M15-572.

f. Includes data from AS Studies M16-098 and M19-944 (Study 1; bDMARD-IR AS).

g. Includes data from nr-axSpA Study M19-944 (Study 2).

h. Includes data from AD Studies M16-045, M16-047, M16-048, M16-049, M17-377, and M18-891.

i. Includes data from UC Studies M14-234, M14-533, and M14-675.

j. Includes data from CD Studies M13-740, M14-327, M14-431, M14-433, and M14-430.

k. Includes data from GCA Study M16-852.

Note: Table represents available exposure for unblinded studies. Data are from ongoing and completed trials. The data cutoff for RA, PsA, AS, nr-axSpA, CD, UC, AD and pcJIA studies is 15 February 2024. The data cutoff for GCA Study M16-852 is 06 February 2024. The data for HS Study M20-040 and CD Studies M13-740, M14-431, and M14-433 are considered final.

Table 3. Upadacitinib Exposure by Age Group and Sex

	Male		Female	
Age Group (years)	**n**	**PYs**	**n**	**PYs**
Cumulative for All Indications[a]				
0 to 11	26	25.9	62	70.0
12 to 17	254	765.3	286	834.9
≥ 18	5638	16387.5	8157	25164.7
18 to 49	3392	9905.7	3627	11035.2
50 to 64	1600	4852.3	3134	10297.6
65 to 74	546	1396.8	1148	3295.4
75 to 84	97	221.8	239	516.5
≥ 85	3	10.9	9	20.0
Indication 1: Rheumatoid arthritis				
Pooled[b]				
0 to 11	0	--	0	--
12 to 17	0	--	0	--
≥ 18	1127	3892.9	4452	15648.9
18 to 49	313	1186.0	1418	5249.5
50 to 64	530	1895.5	2137	7614.9
65 to 74	230	660.9	761	2414.1
75 to 84	52	141.6	130	354.5
≥ 85	2	8.9	6	15.9
Indication 2: Psoriatic arthritis				
Pooled[c]				
0 to 11	0	--	0	--
12 to 17	0	--	0	--
≥ 18	846	2751.0	982	3100.5
18 to 49	411	1464.0	369	1242.7
50 to 64	323	998.4	451	1402.7
65 to 74	100	263.2	140	399.7
75 to 84	12	25.3	22	55.4
≥ 85	0	--	0	--

	Male		Female	
Age Group (years)	**n**	**PYs**	**n**	**PYs**
Indication 3: Ankylosing spondylitis				
Pooled[d]				
0 to 11	0	--	0	--
12 to 17	0	--	0	--
≥ 18	434	752.8	162	259.6
18 to 49	321	560.5	92	141.5
50 to 64	97	165.9	54	88.6
65 to 74	13	20.4	15	27.9
75 to 84	3	6.0	1	1.7
≥ 85	0	--	0	--
Indication 4: Non-radiographic axial spondyloarthritis[e]				
0 to 11	0	--	0	--
12 to 17	0	--	0	--
≥ 18	119	162.0	167	217.3
18 to 49	85	122.5	115	149.7
50 to 64	31	36.9	47	61.1
65 to 74	3	2.6	4	4.5
75 to 84	0	--	1	2.0
≥ 85	0	--	0	--
Indication 5: Atopic dermatitis				
Pooled[f]				
0 to 11	9	0.8	13	1.3
12 to 17	241	745.5	258	795.5
≥ 18	1565	4958.8	1032	3022.3
18 to 49	1227	3945.3	808	2366.1
50 to 64	266	833.6	166	498.8
65 to 74	70	173.2	54	146.5
75 to 84	2	6.7	4	10.9
≥ 85	0	--	0	--

	Male		Female	
Age Group (years)	**n**	**PYs**	**n**	**PYs**
Indication 6: Ulcerative colitis				
Pooled[g]				
0 to 11	0	--	0	--
12 to 17	5	4.2	4	7.7
≥ 18	809	2430.3	496	1516.8
18 to 49	523	1542.2	339	1002.3
50 to 64	220	699.5	110	372.3
65 to 74	62	175.8	43	130.9
75 to 84	4	12.7	4	11.4
≥ 85	0	--	0	--
Indication 7: Crohn's disease				
Pooled[h]				
0 to 11	0	--	0	--
12 to 17	0	--	0	--
≥ 18	643	1335.1	579	1096.7
18 to 49	502	1077.8	440	852.1
50 to 64	118	209.2	115	200.8
65 to 74	22	46.0	24	43.8
75 to 84	1	2.2	0	--
≥ 85	0	--	0	--
Indication 8: Giant cell arteritis[i]				
0 to 11	0	--	0	--
12 to 17	0	--	0	--
≥ 18	80	93.3	236	267.8
18 to 49	0	--	0	--
50 to 64	11	10.4	50	55.6
65 to 74	45	53.6	106	127.5
75 to 84	23	27.4	77	80.6
≥ 85	1	2.0	3	4.1

a. Includes data from the following indications: RA (Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557, and M15-925), PsA (Studies M15-554 and M15-572), CD (Studies M13-740, M14-327, M14-431, M14-433, and M14-430), UC (Studies M14-234, M14-675, and M14-533), AD (Studies M16-045, M16-047, M16-048, M16-049, M17-377, and M18-891), AS (Studies M16-098 and M19-944 [Study 1; bDMARD-IR AS]), nr-axSpA (Study M19-944 [Study 2]), and HS (Study M20-040), GCA (Study M16-852), and pcJIA (Study M15-340).

b. Includes data from RA Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557, and M15-925.

c. Includes data from PsA Studies M15-554 and M15-572.

d. Includes data from AS Studies M16-098 and M19-944 (Study 1; bDMARD-IR AS).

e. Includes data from nr-axSpA Study M19-944 (Study 2).

f. Includes data from AD Studies M16-045, M16-047, M16-048, M16-049, M17-377, and M18-891.

g. Includes data from UC Studies M14-234, M14-533, and M14-675.

h. Includes data from CD Studies M13-740, M14-327, M14-431, M14-433, and M14-430.

i. Includes data from GCA Study M16-852.

Note: Table represents available exposure for unblinded studies. Data are from ongoing and completed trials. The data cutoff for RA, PsA, AS, nr-axSpA, CD, UC, AD and pcJIA studies is 15 February 2024. The data cutoff for GCA Study M16-852 is 06 February 2024. The data for HS Study M20-040 and CD Studies M13-740, M14-431, and M14-433 are considered final.

Table 4. Upadacitinib Exposure by Dose

Dose of Exposure	n	PYs
Cumulative for All Indications[a]		
Upadacitinib 15 mg QD	8906	25971.9
Upadacitinib 30 mg QD	5616	16063.3
Upadacitinib 45 mg QD	1925	379.5
Upadacitinib other doses (tablets)[b]	752	799.0
Upadacitinib other doses (oral solution)[b]	51	71.7
Indication 1: Rheumatoid arthritis		
Pooled[c]		
Upadacitinib 15 mg QD	4108	13999.9
Upadacitinib 30 mg QD	1569	4992.8
Upadacitinib Other Doses[b]	380	549.1
Indication 2: Psoriatic arthritis		
Pooled[d]		
Upadacitinib 15 mg QD	907	2942.8
Upadacitinib 30 mg QD	921	2908.7
Indication 3: Ankylosing spondylitis		
Pooled[e]		
Upadacitinib 15 mg QD	596	1012.4
Indication 4: Non-radiographic axial spondyloarthritis[f]		
Upadacitinib 15 mg QD	286	379.3
Indication 5: Atopic dermatitis		
Pooled[g]		
Upadacitinib 15 mg QD	1518	4552.9
Upadacitinib 30 mg QD	1600	4955.0
Upadacitinib other doses (tablets)[b]	60	16.4
Indication 6: Ulcerative colitis		
Pooled[h]		
Upadacitinib 15 mg QD	875	2065.5
Upadacitinib 30 mg QD	698	1700.8
Upadacitinib 45 mg QD	987	169.2
Upadacitinib other doses (tablets)[b]	47	23.4

Dose of Exposure	n	PYs
Indication 7: Crohn's disease		
Pooled[i]		
Upadacitinib 15 mg QD	324	670.3
Upadacitinib 30 mg QD	774	1467.2
Upadacitinib 45 mg QD	938	210.3
Upadacitinib other doses (tablets)[b]	154	84.0
Indication 8: Giant cell arteritis[j]		
Upadacitinib 15 mg QD	209	245.7
Upadacitinib other doses (tablets)[b]	107	115.5

a. Includes data from the following indications: RA (Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557, and M15-925), PsA (Studies M15-554 and M15-572), CD (Studies M13-740, M14-327, M14-431, M14-433, and M14-430), UC (Studies M14-234, M14-675, and M14-533), AD (Studies M16-045, M16-047, M16-048, M16-049, M17-377, and M18-891), AS (Studies M16-098 and M19-944 [Study 1; bDMARD-IR AS]), nr-axSpA (Study M19-944 [Study 2]), and HS (Study M20-040), GCA (Study M16-852), and pcJIA (Study M15-340).

b. Other doses (tablets) include upadacitinib 1.6, 2, 3, 3.2, 4, 8, 18, and 24 mg BID, and 7.5 and 24 mg QD. Other doses (oral solution) include upadacitinib 1.5, 2, 3, 4, 6 and 8 mg BID.

c. Includes data from RA Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557, and M15-925.

d. Includes data from PsA Studies M15-554 and M15-572.

e. Includes data from AS Studies M16-098 and M19-944 (Study 1; bDMARD-IR AS).

f. Includes data from nr-axSpA Study M19-944 (Study 2).

g. Includes data from AD Studies M16-045, M16-047, M16-048, M16-049, M17-377, and M18-891.

h. Includes data from UC Studies M14-234, M14-533, and M14-675.

i. Includes data from CD Studies M13-740, M14-327, M14-431, M14-433, and M14-430.

j. Includes data from GCA Study M16-852.

Note: Table represents available exposure for unblinded studies. Data are from ongoing and completed trials. The data cutoff for RA, PsA, AS, nr-axSpA, CD, UC, AD and pcJIA studies is 15 February 2024. The data cutoff for GCA Study M16-852 is 06 February 2024. The data for HS Study M20-040 and CD Studies M13-740, M14-431, and M14-433 are considered final.

Table 5. Upadacitinib Exposure by Ethnic Origin

Ethnic Origin	n	PYs
Cumulative for All Indications[a]		
White	10977	33395.8
Black or African American	611	1515.5
Asian	2586	7508.4
American Indian or Alaska Native	74	234.3
Native Hawaiian or Other Pacific Islander	28	79.3
Multiple	167	552.2
Indication 1: Rheumatoid arthritis		
Pooled[b]		
White	4389	16050.8
Black or African American	260	744.8
Asian	815	2346.1
American Indian or Alaska Native	39	133.7
Native Hawaiian or Other Pacific Islander	7	32.0
Multiple	69	234.3
Indication 2: Psoriatic arthritis		
Pooled[c]		
White	1627	5209.7
Black or African American	23	58.7
Asian	155	507.3
American Indian or Alaska Native	6	11.2
Native Hawaiian or Other Pacific Islander	4	2.9
Multiple	13	61.7
Indication 3: Ankylosing spondylitis		
Pooled[d]		
White	484	831.8
Black or African American	7	6.7
Asian	105	174.0

Ethnic Origin	n	PYs
Indication 4: Non-radiographic axial spondyloarthritis[e]		
White	244	326.5
Black or African American	3	3.3
Asian	37	47.1
American Indian or Alaska Native	1	2.0
Multiple	1	0.5
Indication 5: Atopic dermatitis		
Pooled[f]		
White	1945	5921.1
Black or African American	196	444.8
Asian	889	2874.1
American Indian or Alaska Native	22	73.0
Native Hawaiian or Other Pacific Islander	14	37.7
Multiple	52	173.5
Indication 6: Ulcerative colitis		
Pooled[g]		
White	916	2704.0
Black or African American	40	123.1
Asian	336	1063.0
American Indian or Alaska Native	3	10.2
Native Hawaiian or Other Pacific Islander	2	5.7
Multiple	17	53.0
Indication 7: Crohn's disease		
Pooled[h]		
White	934	1821.1
Black or African American	61	120.0
Asian	212	463.6
American Indian or Alaska Native	2	3.3
Multiple	13	23.8
Indication 8: Giant cell arteritis[i]		
White	298	339.2
Black or African American	1	0.2
Asian	16	20.7
Native Hawaiian or Other Pacific Islander	1	1.0

a. Includes data from the following indications: RA (Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557 and M15-925), PsA (Studies M15-554 and M15-572), CD (Studies M13-740, M14-327, M14-430, M14-431, and M14-433), UC (Studies M14-234, M14-675 and M14-533), AD (Studies M16-045, M16-047, M16-048, M16-049, M17-377 and M18-891), AS (Study M16-098 and M19-944 [Study 1; bDMARD-IR AS]), HS (Study M20-040), nr-axSpA (Study M19-944 [Study 2]), GCA (Study M16-852), and pcJIA (Study M15-340).
b. Includes data from RA Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557, and M15-925.
c. Includes data from PsA Studies M15-554 and M15-572.
d. Includes data from AS Studies M16-098 and M19-944 (Study 1; bDMARD-IR AS).
e. Includes data from nr-axSpA Study M19-944 (Study 2).
f. Includes data from AD Studies M16-045, M16-047, M16-048, M16-049, M17-377, and M18-891.
g. Includes data from UC Studies M14-234, M14-533, and M14-675.
h. Includes data from CD Studies M13-740, M14-327, M14-431, M14-433, and M14-430.
i. Includes data from GCA Study M16-852.

Note: Table represents available exposure for unblinded studies. Data are from ongoing and completed trials. The data cutoff for RA, PsA, AS, nr-axSpA, CD, UC, AD and pcJIA studies is 15 February 2024. The data cutoff for GCA Study M16-852 is 06 February 2024. The data for HS Study M20-040 and CD Studies M13-740, M14-431, and M14-433 are considered final.

Table 6. Upadacitinib Exposure for Special Populations

Special Population	Subjects[a]
Cumulative for All Indications[b]	
Pregnant women	99[b,c]
Indication 1: Rheumatoid arthritis	
Pregnant women	
Pooled[d]	38[c]
Indication 2: Psoriatic arthritis	
Pregnant women	
Pooled[e]	6
Indication 3: Ankylosing spondylitis	
Pregnant women	
Pooled[f]	1
Indication 4: Non-radiographic axial spondyloarthritis[g]	
Pregnant women	0

Special Population	Subjects[a]
Indication 5: Atopic dermatitis	
Pregnant women	
Pooled[h]	31
Indication 6: Ulcerative colitis	
Pregnant women	
Pooled[i]	13
Indication 7: Crohn's disease	
Pregnant women	
Pooled[j]	8

a. All subjects were exposed to upadacitinib during pregnancy.

b. Includes data from the following indications: RA (Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557, and M15-925), PsA (Studies M15-554 and M15-572), CD (Studies M13-740, M14-327, M14-431, M14-433, and M14-430), UC (Studies M14-234, M14-675, and M14-533), AD (Studies M16-045, M16-047, M16-048, M16-049, M17-377, M18-891, and M19-850), AS (Studies M16-098 and M19-944 [Study 1; bDMARD-IR AS]), nr-axSpA (Study M19 944 [Study 2]), HS (Study M20-040) (2 pregnancies not listed above), and pcJIA (Study M15-340).

c. One subject had 2 pregnancies on upadacitinib treatment during an RA study.

d. Includes data from RA Studies M13-537, M13-550, M13-538, M13-545, M13-549, M14-465, M15-555, M13-542, M14-663, M15-557, and M15-925.

e. Includes data from PsA Studies M15-554 and M15-572.

f. Includes data from AS Study M16-098 and M19-944 (Study 1; bDMARD-IR AS).

g Includes data from nr-axSpA Study M19-944 (Study 2).

h. Includes data from AD Studies M16-045, M16-047, M16-048, M16-049, M17-377, M18-891, and M19-850.

i. Includes data from UC Studies M14-234, M14-533, and M14-675.

j. Includes data from CD Studies M13-740, M14-327, M14-431, M14-433, and M14-430.

Note: Only maternal drug exposure is presented in this table. Data are from unblinded ongoing and complete trials as of 15 August 2023.

Module SIV Populations Not Studied in Clinical Trials

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

Criterion 1: **For RA, PsA, AS, nr-axSpA, and CD: Subjects < 18 years of age** **For AD: Subjects < 12 years of age, Subjects 12 to < 18 years of age weighing < 40 kg** **For UC: Subjects < 16 years of age** **For GCA: Subjects < 50 years of age**
Reason for exclusion: As patients < 18 years of age are a vulnerable patient population, the safety, tolerability, and efficacy were first characterized in clinical trials with adult subjects (≥ 18 years of age). With the known early onset and high prevalence of AD in a younger population, safety, tolerability, and efficacy were first characterized in adult and adolescent subjects (12 years and older) weighing ≥ 40 kg. With the possibility of early onset of UC in a younger population, and with the minimum allowable age of 16 years for patients in UC clinical trials, safety, tolerability, and efficacy were also characterized in adolescent subjects 16 years and older (weighing ≥ 40 kg) with UC. GCA generally occurs in patients ≥ 50 years of age.
Is it considered to be included as missing information?: No
Rationale: RA, PsA, AS, nr-axSpA, CD, and GCA clinical trial evaluation to date has been in adults. AD clinical trial evaluation included adults and adolescents (aged 12 years and older weighing > 40 kg). UC clinical trial evaluation included adults and older adolescents (aged 16 years and older weighing ≥ 40 kg). Data specific to paediatrics will be evaluated as part of a Paediatric Investigation Plan that has been agreed with the Paediatric Committee of the European Medicines Agency (EMA) focusing on the treatment of juvenile idiopathic arthritis in patients from 1 to < 18 years of age, in AD in patients from 2 to < 18 years of age, and in UC in patients from 2 < 18 years of age.

Criterion 2: **Female who is pregnant, breastfeeding, or is considering becoming pregnant**
Reason for exclusion: Upadacitinib is teratogenic in both rats and rabbits. The risk of upadacitinib administration in human pregnancy is unknown.
Is it considered to be included as missing information?: No

Rationale:

Based on nonclinical studies, foetal malformation following exposure in utero is considered an important potential risk. The SmPC includes pregnancy as a contraindication and advises female patients of childbearing potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib. Upadacitinib should not be used during breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue upadacitinib therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Criterion 3:

Receipt of any live vaccine within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug

Reason for exclusion:

The impact of upadacitinib treatment on administration of live vaccines is not yet known. Live vaccinations were prohibited throughout the studies, including 4 weeks prior to the first dose and 30 days after the last dose, to ensure subject safety.

Is it considered to be included as missing information?:

No

Rationale:

Upadacitinib is an immunomodulatory agent that has the potential to impact the efficacy and safety of live vaccinations. The SmPC includes language that upadacitinib is not recommended to be administered during, or immediately prior to, live, attenuated vaccines, and additional risk minimization measures (aRMMs) for serious infections includes language on avoidance of live vaccines based on SmPC language. The package leaflet (PL) also warns that patients who have recently received or plan to receive a vaccination (immunization) should consult their doctor or pharmacist before and during treatment.

Criterion 4:

For RA: History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA

For PsA: History of fibromyalgia, any arthritis with onset prior to age 17 years, or concurrent diagnosis of inflammatory joint disease other than PsA

For AS and nr-axSpA: History of any arthritis with onset prior to age 17 years or history of inflammatory arthritis of different etiology other than axial SpA

For CD: Ongoing known complications of CD:

- **abscess (abdominal or peri-anal);**
- **symptomatic bowel strictures;**
- **fulminant colitis;**
- **toxic megacolon;**
- **ostomies or ileoanal pouch; or**
- **short gut or short bowel syndrome or multiple (> 3) bowel resections**

For GCA: History of chronic use of systemic CS for > 4 years or if ≤ 4 years, an inability, in the opinion of the investigator, to withdraw from CS treatment through the protocol-defined taper regimen.
Reason for exclusion: To exclude potential confounding factors in the assessment of RA, PsA, AS, nr-axSpA, CD, or GCA disease activity during upadacitinib clinical trials in these conditions.
Is it considered to be included as missing information?: No
Rationale: The SmPC specifies the intended population who can be treated with upadacitinib.

Criterion 5: **Chronic, recurring, or active viral infection including active hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated herpes zoster, disseminated herpes simplex (including EH for AD), and active human immunodeficiency virus (HIV) or immunodeficiency syndrome**
Reason for exclusion: The effects of upadacitinib on these pre-existing viral conditions, which pose a risk for reactivation of disease, are not known. Subjects with active or recurrent viral infection or immunodeficiency syndrome were excluded in studies due to the potential for an immunomodulatory drug to increase susceptibility to infection/viral reactivation.
Is it considered to be included as missing information?: Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C will be considered missing information. Patients with any active or recurrent viral infection including recurrent or disseminated herpes zoster, disseminated herpes simplex, known history of HIV, and HIV or immunodeficiency syndrome will not be considered missing information.
Rationale: Serious and opportunistic infections including active TB are considered an important identified risk, as is herpes zoster. The SmPC indicates that upadacitinib should not be initiated in patients with an active, serious infection, including localized infections. Prescribers will need to consider the risks and benefits of treatment prior to initiating upadacitinib in patients with chronic or recurrent infection. The PL also warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. This would include herpes zoster or herpes simplex. Use in patients with a history of HIV is excluded from missing information since patients who are known to be HIV+ should be receiving chronic anti-retroviral therapy and should have suppression of HIV replication. With appropriate anti-retroviral therapy, CD4 counts should be in the normal range and the expectation is that these patients should no longer be immunocompromised due to the HIV infection. Use of an immunomodulatory product, such as upadacitinib, in this setting should not be different from patients not infected with HIV. Prescribers will need to determine whether the benefit of treatment outweighs any risks for an individual patient with HIV infection.

Criterion 6: **Subject has active TB or meets TB exclusionary parameters**
Reason for exclusion: The effect of upadacitinib on subjects with active TB is not known. Subjects with active TB or with untreated latent TB who met exclusionary TB parameters were not enrolled in studies due to the potential of an immunomodulatory drug to affect the disease course.
Is it considered to be included as missing information?: No
Rationale: Serious and opportunistic infections including active TB are considered an important identified risk. The SmPC indicates that upadacitinib is contraindicated in patients with active TB. The SmPC has language on the need for screening for TB (active or latent) prior to initiation of upadacitinib and includes language that upadacitinib should not be given to patients with active TB. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with previously untreated latent TB or in patients with risk factors for TB infection.

Criterion 7: **Laboratory values meeting the following criteria within the screening period prior to the first dose of study drug:** • **Serum aspartate transaminase (AST) > 2 × upper limit of normal (ULN);** • **Serum alanine transaminase (ALT) > 2 × ULN.**
Reason for exclusion: JAK inhibitors are known to be associated with increases in transaminase levels. Subjects meeting exclusion criteria were not enrolled in studies to properly evaluate the effects of upadacitinib on liver transaminase levels.
Is it considered to be included as missing information?: Use in patients with moderate hepatic impairment will be considered missing information. Use in patients with severe hepatic impairment will not be considered missing information.
Rationale: The SmPC states that upadacitinib is contraindicated for use in patients with severe hepatic impairment.

Criterion 8: **Laboratory values meeting the following criteria within the screening period prior to the first dose of study drug:** **Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73 m^2, < 30 mL/min/1.73 m^2 for bDMARD-IR AS, nr-axSpA, UC, CD, and GCA.**
Reason for exclusion: To properly evaluate the effects of upadacitinib on serum creatinine and as a precaution until more information is available regarding potential effects of upadacitinib on renal function

Is it considered to be included as missing information?: Yes (use in patients with severe renal impairment to be considered missing information)
Rationale: Not applicable

Criterion 9: **Laboratory values meeting the following criteria within the screening period prior to the first dose of study drug:** • **Total white blood cell count < 2,500/µL;** • **Absolute neutrophil count (ANC) < 1,500/µL for GCA, < 1,200/µL for bDMARD-IR AS, nr-axSpA, UC, and CD;** • **Platelet count < 100,000/µL;** • **Absolute lymphocyte count (ALC) < 800/µL, < 750/µL for bDMARD-IR AS, nr-axSpA, UC, CD, and GCA;** • **Hemoglobin < 10 g/dL, < 9 g/dL for bDMARD-IR AS, nr-axSpA, UC, CD, and GCA.**
Reason for exclusion: To properly evaluate the effects of upadacitinib on hematologic parameters
Is it considered to be included as missing information?: No
Rationale: The effects of upadacitinib on hematologic parameters (including white blood cell count, ANC, platelet count, ALC, and hemoglobin) were assessed in upadacitinib clinical trials. The SmPC has language proposing when upadacitinib should not be initiated or when interruptions are recommended based on ANC, ALC, and hemoglobin values. Baseline hematologic parameters tend to be lower in UC (particularly ANC and ALC, and hemoglobin) and CD (particularly ANC and ALC) patients based on direct pathophysiologic effects of blood loss, disease activity, and concomitant medications.

Criterion 10: **History of any malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix** **For UC and CD: Prior or current GI dysplasia, other than completely removed low-grade dysplastic lesion**
Reason for exclusion: The effect of upadacitinib treatment on malignancies is not known. Subjects with a history of any malignancy except for successfully treated NMSC or localized carcinoma in situ of the cervix were not enrolled to ensure their safety. For patients with UC and CD, there is an increased risk of intestinal malignancy.
Is it considered to be included as missing information?: No

Rationale:

NMSC is considered an important identified risk and malignancies excluding NMSC are considered an important potential risk. Prescribers need to determine whether the benefit of treatment outweighs any risks for an individual patient. The SmPC specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Long-term safety data will be collected in post-marketing long-term comparative cohort studies which will include follow-up for malignancies.

Criterion 11:

History of any of the following CV conditions:

- **Moderate to severe CHF (New York Heart Association class III or IV) in RA studies and in PsA Study M15-572 which included an adalimumab comparator;**
- **Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;**
- **Uncontrolled hypertension as defined by a confirmed systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg, for RA, PsA, AS, nr-axSpA, AD, and GCA;**
- **Prior history of thrombotic events, including deep vein thrombosis and pulmonary embolism for UC and CD;**
- **Known inherited conditions that predispose to hypercoagulability for UC and CD.**

Reason for exclusion:

To avoid potential confounding effects of these co-morbidities on safety assessment of upadacitinib and due to label warnings for active comparators included in the studies. Patients with IBD, including UC and CD, have an increased risk of thrombosis, reported to be 2- to 4-fold higher in patients with IBD compared to those without IBD. Thus, patients with risk factors for thrombosis were excluded from upadacitinib UC and CD studies.

Is it considered to be included as missing information?:

No

Rationale:

MACE and VTE are considered important potential risks. Patients with New York Heart Association class III or IV CHF were excluded from upadacitinib RA studies and PsA Study M15-572 where adalimumab was used as the active comparator; however, cardiac function was not evaluated at baseline. Patients with moderate to severe CHF and uncontrolled hypertension were not specifically excluded from the AS and AD studies.

Prescribers will need to weigh the benefits and risks of using upadacitinib in patients with known cardiac impairment, prior history of thrombotic events, or predisposition to hypercoagulability. The SmPC specifies patient populations and risk factors for MACE and VTE to be aware of. Long-term safety data will be collected in post-marketing long-term comparative cohort studies which will include follow-up for MACE and VTE.

Criterion 12: **History of GI perforation (other than appendicitis or penetrating injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment**
Reason for exclusion: The effect of upadacitinib treatment on GI perforation is not known. Lower GI tract perforations have been associated with treatment with the IL-6 inhibitor, tocilizumab. JAK inhibitors also affect the IL-6 signaling pathway; consequently, a risk of GI perforation is being evaluated for this class of products. Subjects with a history of GI perforation, diverticulitis, or significantly increased risk for GI perforation were not enrolled to ensure their safety until more information is available.
Is it considered to be included as missing information?: No
Rationale: GI perforation is considered an important identified risk (See Module SVII.2).

Criterion 13: **Prior exposure to any JAK inhibitor for RA, PsA, AD, AS, nr-axSpA, UC, CD, and GCA.**
Reason for exclusion: To prevent bias in the studies by enrolling individuals who had either a positive or negative response to other compounds in the JAK inhibitor class
Is it considered to be included as missing information?: No
Rationale: Due to the short half-life of marketed JAK inhibitors (e.g., ~3 hours for tofacitinib [(Xeljanz (tofacitinib) [summary of product characteristics] 2019)] and ~12 hours for baricitinib [(FDA 2018, Olumiant (baricitinib) Tablets [prescribing information] 2022)]), no safety concerns are expected with consecutive use of different JAK inhibitors. Prescribers will need to determine whether an individual patient may benefit from use of another JAK inhibitor once a product from this class of drugs has been discontinued by the patient.

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 women Breastfeeding women	Based on limited data available in the upadacitinib development program through 15 August 2023, in 100 clinical trial pregnancies for studies which have been unblinded (RA, PsA, AS, nr-axSpA, AD, UC, CD, HS, and SLE) in which a pregnant woman had received upadacitinib within 1 month prior to conception and at least during the first trimester, the pregnancy outcomes are as follows: 1 live birth with congenital anomaly (35-week gestation premature infant with an atrial septal defect), 42 live births without congenital anomaly (including 2 infants born premature at 28 and 34 weeks gestation, neither with complications), 19 SABs, 18 elective terminations (without report of fetal defects or unknown), 1 ectopic pregnancy, 5 ongoing pregnancies, and 14 pregnancies lost to follow up. In 9 of the 19 SABs, pregnant mothers were taking concomitant MTX or used MTX within 1 month prior to conception (background MTX was allowed in RA and PsA studies).	The target population will include female patients of childbearing potential. Based on limited data, the risk of teratogenicity in humans is not yet known. The SmPC includes pregnancy as a contraindication and advises female patients of childbearing potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib and that upadacitinib should not be used during breastfeeding. Fetal malformation following exposure in utero is considered an important potential risk. Information on pregnancies and pregnancy outcomes will be collected in the long-term extension portion of Phase 3 upadacitinib trials.
Patients with hepatic impairment	Study M13-539 assessed the pharmacokinetics of upadacitinib following oral administration of a single 15 mg dose of upadacitinib in subjects with normal hepatic function and in subjects with mild (Child-Pugh Category A) and moderate (Child-Pugh Category B) hepatic impairment. A total of 18 subjects (6 in each hepatic function group) were enrolled in the study. Data from Study M13-539	The SmPC states that no dose adjustment is required for patients with mild or moderate hepatic impairment and that upadacitinib is contraindicated for use in patients with severe hepatic impairment. Based on exclusion criteria from

Type of special population	Exposure	Implications
	indicate that no dose adjustment is needed for patients with mild or moderate hepatic impairment. Upadacitinib was not studied in patients with severe (Child-Pugh Category C) hepatic impairment. Subjects were not excluded from upadacitinib RA, PsA, AS, nr-axSpA, AD, UC, CD, or GCA clinical trials based on hepatic functional status; however, patients with serum AST or ALT > 2 × ULN were excluded.	Phase 3 upadacitinib clinical trials, safety data in subjects with moderate hepatic impairment are limited. Use in patients with moderate hepatic impairment will be considered as missing information. Long-term safety data will be collected in post-marketing comparative cohort studies.
Patients with renal impairment	Study M13-551 evaluated the pharmacokinetics of upadacitinib following oral administration of a single 15 mg dose of upadacitinib in subjects with normal renal function and in subjects with mild, moderate, and severe renal impairment. A total of 24 subjects (8 in each renal function group) were enrolled in the study. Data from Study M13-551 indicate that mild or moderate renal impairment has no clinically relevant effect on upadacitinib exposure for the 15 or 30 mg QD dosing regimens. Subjects with baseline estimated GFR of < 40 mL/min/1.73 m^2 were excluded from upadacitinib clinical trials. Rheumatoid arthritis: Across the global Phase 2 and Phase 3 RA studies, 2231 subjects (40.0%) with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 257 subjects (4.6%) with moderate (30 to < 60 mL/min/1.73 m^2) renal impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib. Psoriatic arthritis: Across the Phase 3 PsA studies, 418 subjects (46.1%) with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 49 subjects (5.4%) with moderate (30 to < 60 mL/min/1.73 m^2) renal	The SmPC states that no dose adjustment is required for patients with mild or moderate renal impairment. Upadacitinib should be used with caution in patients with severe renal impairment. The SmPC specifies that for RA, PsA, AS, nr-axSpA, and AD, the recommended dose is 15 mg for patients with severe renal impairment and that for patients with UC and CD, the recommended dose is 30 mg QD for induction treatment and 15 mg QD for maintenance treatment, for patients with severe renal impairment. Based on exclusion criteria from upadacitinib clinical trials, use in patients with severe renal impairment will be considered missing information. Long-term safety data will be collected in post-marketing comparative cohort studies.

Type of special population	Exposure	Implications
	impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib 15 mg. Ankylosing spondylitis: In the Phase 2/3 bDMARD-naïve AS study, 55 subjects (30.2%) with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 3 subjects (1.6%) with moderate (30 to < 60 mL/min/1.73 m^2) renal impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib 15 mg. In the Phase 3 trial involving bDMARD-IR AS (Study 1), 138 subjects (33.3%) with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 11 subjects (2.7%) with moderate (30 to < 60 mL/min/1.73 m^2) renal impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib 15 mg. Non-radiographic axial spondyloarthritis: In Study 2 of the Phase 3 trial, 89 subjects (47.6%) with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 4 subjects (2.1%) with moderate (30 to < 60 mL/min/1.73 m^2) renal impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib 15 mg. Atopic dermatitis: Across the Phase 3 AD studies, 393 subjects (35.2%) with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 28 subjects (2.5%) with moderate (40 to < 60 mL/min/1.73 m^2) renal impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib 30 mg. One subject had an eGFR of < 40 mL/min/1.73 m2 at screening Across the Phase 3 AD studies, 388 subjects (35.2%) with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 19 subjects	

Type of special population	Exposure	Implications
	(1.7%) with moderate (40 to < 60 mL/min/1.73 m^2) renal impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib 15 mg. Ulcerative colitis: Across the Phase 2 and Phase 3 UC studies, 538 subjects (41.3%) with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 41 subjects (3.1%) with moderate (30 to < 60 mL/min/1.73 m^2) renal impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib. Crohn's disease: Across the Phase 3 studies and among subjects who responded to upadacitinib or placebo induction or extended induction treatment, 318 (38.2%) with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 25 (3.0%) with moderate (30 to < 60 mL/min/1.73 m^2) renal impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib. Giant cell arteritis: A total of 189 subjects with mild (≥ 60 to < 90 mL/min/1.73 m^2) and 78 subjects with moderate (30 to < 60 mL/min/1.73 m^2) renal impairment based on estimated GFR values at screening were enrolled and received at least 1 dose of upadacitinib. Review of safety data from these subjects suggests there is no novel upadacitinib-related safety risk for subjects with mild or moderate renal impairment.	
Patients with cardiovascular impairment	Subjects with a history of moderate to severe CHF were excluded from RA study participation and from PsA studies with adalimumab as the active comparator, and subjects with uncontrolled hypertension were excluded from study participation. Rheumatoid arthritis:	Patients with New York Heart Association Class III or IV CHF were excluded from specific upadacitinib clinical trials; however, cardiac function was not evaluated at baseline.

Type of special population	Exposure	Implications
	Across the global Phase 2 and Phase 3 RA studies, 618 subjects (11.1%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib. The following subjects received upadacitinib and were enrolled with prior or ongoing CV risk factors: 2135 subjects (38.3%) with hypertension, and 868 subjects (15.6%) with diabetes mellitus. Psoriatic arthritis: Across the Phase 3 PsA studies, 115 subjects (12.7%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib 15 mg. The following subjects received upadacitinib and were enrolled with prior or ongoing CV risk factors: 402 subjects (44.3%) with hypertension, and 43 subjects (4.7%) with Type 2 diabetes mellitus. Patients with moderate to severe CHF and uncontrolled hypertension were not specifically excluded from the AS and AD studies. Ankylosing spondylitis: In the Phase 2/3 bDMARD-naïve AS study, 19 subjects (10.4%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib 15 mg. The following subjects received upadacitinib and were enrolled with prior or ongoing CV risk factors: 34 subjects (18.7%) with hypertension, 4 subjects (2.2%) with Type 2 diabetes mellitus. In the Phase 3 trial involving bDMARD-IR AS (Study 1), 40 subjects (9.7%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib 15 mg. The following subjects received upadacitinib and were enrolled with prior or ongoing CV risk factors: 82 subjects (19.8%) with hypertension, 9 subjects (2.2%) with Type 2 diabetes	Possible surrogates for cardiac functional status may include prior CV history and co-morbidities such as diabetes and hypertension which are risk factors for CVD. Baseline demographics across the global Phase 2 and Phase 3 studies in RA indicate that although there were few subjects treated with upadacitinib with a prior history of a CV event, up to almost 40% of subjects treated with upadacitinib were enrolled with CV co-morbidities such as diabetes mellitus or hypertension. Across the Phase 3 PsA studies, over 40% of subjects were enrolled with CV co-morbidities such as diabetes mellitus or hypertension. In the Phase 2/3 bDMARD-naïve AS study and Phase 3 bDMARD-IR AS study, about 20% of subjects were enrolled with CV co-morbidities such as diabetes mellitus or hypertension. In the Phase 3 nr-axSpA study, approximately 20% of subjects were enrolled with CV co-morbidities such as diabetes mellitus or hypertension. Across the Phase 3 AD studies, up to nearly 12% of subjects were enrolled with CV co-morbidities such

Type of special population	Exposure	Implications
	mellitus. Non-radiographic axial spondyloarthritis: In Study 2 of the Phase 3 trial, 11 subjects (5.9%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib 15 mg. The following subjects received upadacitinib and were enrolled with prior or ongoing CV risk factors: 37 subjects (19.8%) with hypertension, 2 subjects (1.1%) with Type 2 diabetes mellitus. Atopic dermatitis: Across the Phase 3 AD studies, 71 subjects (5.3%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib 30 mg; the following subjects received upadacitinib 30 mg and were enrolled with prior or ongoing CV risk factors: 126 subjects (9.4%) with hypertension, and 27 subjects (2.0%) with Type 2 diabetes mellitus. Across the Phase 3 AD studies, 71 subjects (5.3%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib 15 mg; the following subjects received upadacitinib and were enrolled with prior or ongoing CV risk factors: 149 subjects (11.1%) with hypertension, and 26 subjects (1.9%) with Type 2 diabetes mellitus. Ulcerative colitis: Across the Phase 2 and Phase 3 UC studies, 100 subjects (7.7%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib. The following subjects received upadacitinib and were enrolled with prior or ongoing CV risk factors: 202 subjects (15.5%) with hypertension, and 33 subjects (2.5%) with Type 2 diabetes mellitus. Crohn's disease: Across the Phase 3 studies and among subjects who responded to upadacitinib or	as diabetes or hypertension. Across the Phase 2 and Phase 3 UC studies, up to approximately 20% of subjects were enrolled with CV co-morbidities such as diabetes or hypertension. Across the Phase 3 CD studies, approximately 15% of subjects were enrolled with CV co morbidities such as diabetes or hypertension. Prescribers will need to weigh the benefits and risks of using upadacitinib in patients with known cardiac impairment. MACE is considered an important potential risk. The SmPC specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Long-term safety data will be collected in post-marketing comparative cohort studies which will include follow-up for MACE.

Type of special population	Exposure	Implications
	placebo induction or extended induction treatment, 71 (8.5%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib. The following subjects received upadacitinib and were enrolled with prior or ongoing CV risk factors: 99 subjects (11.9%) with hypertension, and 22 subjects (2.6 %) with diabetes mellitus. Giant cell arteritis: A total of 96 subjects (30.4%) were enrolled with a prior history of cardiac events and received at least 1 dose of upadacitinib. The following subjects received upadacitinib and were enrolled with prior or ongoing CV risk factors: 174 subjects (55%) with hypertension or essential hypertension, 6 subjects (1.9%) with deep vein thrombosis, 5 subjects (1.6%) with pulmonary embolism, and 13 subjects (4.1%) with Type 2 diabetes mellitus. Review of safety data from these RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA subjects suggests there is no novel upadacitinib-related safety risk for MACE for subjects with prior or ongoing CV risk factors.	
Immunocompromised patients	Concomitant use of azathioprine, ciclosporin, tacrolimus, and bDMARDs or other JAK inhibitors with upadacitinib were prohibited in upadacitinib clinical trials. During combination therapy in upadacitinib clinical trials, upadacitinib was evaluated on a background of other potentially immunosuppressive treatments. Patients with a known history of HIV were excluded from upadacitinib clinical trials.	Indication for use of upadacitinib for treatment of moderate to severe active RA includes use of upadacitinib in combination with MTX. The SmPC includes language that combination of potent immunosuppressants such as azathioprine, ciclosporin, tacrolimus, and bDMARDs or other JAK inhibitors with upadacitinib is not recommended as a risk of additive immunosuppression cannot

Type of special population	Exposure	Implications
		be excluded. Patients who are known to be HIV+ should be receiving chronic anti-retroviral therapy and should have suppression of HIV replication. With appropriate anti-retroviral therapy, CD4 counts should be in the normal range and the expectation is that these patients should no longer be immunocompromised due to the HIV infection. Use of an immunomodulatory product, such as upadacitinib, in this setting should not be different from patients not infected with HIV. Prescribers will need to determine whether the benefit of treatment outweighs any risks for an individual patient with HIV infection.
Population with relevant different ethnic origin	Upadacitinib has been studied in subject populations that included men and women of a variety of ethnic origins in clinical trials. Across the global Phase 2 RA, UC, and CD, Phase 3 RA, PsA, AD, AS, nr-axSpA, UC, CD, and GCA, and Phase 2/3 AS studies, most subjects reported their race as white. Review of safety data from these trials suggests there is no upadacitinib-related safety concern based on race and ethnicity.	There are no safety concerns for upadacitinib based on race and ethnicity.
Subpopulations carrying relevant genetic polymorphisms	The effect of cytochrome P450 enzyme 2D6 (CYP2D6) metabolic phenotype (based on determination of CYP2D6 genotype) on upadacitinib pharmacokinetics has been evaluated through population pharmacokinetic analyses of Phase 1 and RA Phase 2 studies and oral clearance is	There are no known concerns based on subpopulations carrying relevant genetic polymorphisms.

Type of special population	Exposure	Implications
	not affected by CYP2D6 metabolic phenotype (based on genotype). Upadacitinib has not been studied in subpopulations with common genetic polymorphisms. There are known genetic polymorphisms related to the susceptibility of RA (Viatte 2013), PsA (Loft 2018) AS (Reveille 2006), AD (Rodríguez 2009a), UC (Anderson 2011), CD (Gordon 2015, Ye and McGovern 2016), and GCA (Greigert 2022); however, no genetic polymorphisms have been linked to a drug response for inhibition of the JAK pathway in general.	
Other • Use in very elderly (≥ 75 years of age) • Children < 12 years of age	Use in very elderly (≥ 75 years of age): **Experience with upadacitinib in subjects ≥ 75 years of age is limited**. Rheumatoid arthritis: In the global RA Phase 2 and Phase 3 studies, in total, 190 subjects ≥ 75 years of age received at least 1 dose of upadacitinib. This represents 3.4% of all RA subjects studied. Psoriatic arthritis: In the Phase 3 PsA studies, in total, 34 subjects ≥ 75 years of age received at least 1 dose of upadacitinib. This represents 3.7% of all PsA subjects studied. Ankylosing spondylitis: In the Phase 2/3 bDMARD-naïve AS study, there were no subjects ≥ 75 years of age. In the Phase 3 Study involving bDMARD-IR AS (Study 1), there were 4 subjects ≥ 75 years of age. Non-radiographic axial spondyloarthritis: In the Phase 3 Study involving nr-axSpA (Study 2), there was 1 subject ≥ 75 years of age. Atopic dermatitis: In the Phase 3 AD studies, in total, 5 subjects ≥ 75 years of age received at least 1 dose of upadacitinib. This	Patients ≥ 75 years of age may be at higher risk for infections and other safety concerns. Use in this population will be considered missing information. Long-term safety data (for all patient populations including adolescent subjects with AD) will be collected in post-marketing comparative cohort studies.

Type of special population	Exposure	Implications
	represents 0.4% of all AD subjects studied. Ulcerative colitis: In the Phase 2 and 3 UC studies, in total, 8 subjects ≥ 75 years of age received at least 1 dose of upadacitinib. This represents 0.6% of all UC subjects studied. Crohn's disease: In the Phase 2 and 3 CD studies, in total, 1 subject ≥ 75 years of age received at least 1 dose of upadacitinib. This represents < 0.1% of all CD subjects studied. Giant cell arteritis: During Period 1, in total, 140 subjects (32.7%) ≥ 75 years of age were enrolled and received at least 1 dose of upadacitinib, and in the long term, 70 subjects were ≥ 75 years of age. <u>Children < 12 years of age:</u> <u>Atopic dermatitis:</u> The safety and efficacy of RINVOQ in children below the age of 12 years have not been established. Adolescents (≥ 12 to < 18 years, n = 541) weighing ≥ 40 kg were included in the AD clinical program. Safety in the adolescent population was evaluated separately in AD subjects and was consistent with safety in the overall AD population. No clinical exposure data are available in adolescents < 40 kg. The posology in adolescent patients 30 kg to < 40 kg was determined using population pharmacokinetic modelling and simulation.	

Module SV Post-Authorization Experience

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

Since the approval of upadacitinib for RA in the US in August 2019 and in the EU in December 2019, global post-marketing exposure has begun to accrue.

An estimate of the patients treated with upadacitinib was calculated from internal AbbVie sales. Available data span from 16 August 2019 through 29 February 2024. The sales data is only available for the full month. The difference between available sales data through 31 July 2023 and data lock through 15 August 2023 is unlikely to affect calculations significantly.

Using the total number of tablets distributed and dividing by the average daily dose (ADD) determined from the upadacitinib label, an estimate of the number of patient treatment days (PTD) was obtained. The PTD were further divided by 365.25 days to obtain the estimated number of patient treatment years (PTY).

SV.1.2 Exposure

Below are data for exposure including by region. Numbers may not sum due to rounding.

Estimated Cumulative Patient Exposure from 16 August 2019 through 29 February 2024 from AbbVie Sales

Formulation	Amount Distributed (A)	mg/tablet (B)	ADD (mg) (C)	PTD (A×B/C)	PTY (PTD/365.25)
15 mg tablets	197,791,892	15	15	197,791,892	541,525
30 mg tablets	12,452,209	30	30	12,452,209	34,092
45 mg tablets	4,454,407	45	45	4,454,407	12,196
Total	**214,698,508**			**214,698,508**	**587,812**

Estimated Cumulative Patient Exposure from 16 August 2019 through 29 February 2024 from AbbVie Sales by Region

Region	PTY
EU and UK[a]	153,758
JAPAC[b]	105,660
Latin America	17,509
North America[c]	285,400
Middle East, Africa, and Other[d]	25,485
Total	**587,812**

a. Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, **Luxembourg**, **Malta**, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden, (countries with no usage reported in **bold**).

b. Japan, Asia Pacific Countries.

c. US and Canada.

d. Other includes Bosnia, Montenegro, Norway, Russia, Serbia, Switzerland, and Ukraine.

Estimated Cumulative Patient Exposure from 16 August 2019 through 29 February 2024 from AbbVie Sales by EU Countries

Country	PTY
Austria	[redacted]
Belgium	
Bulgaria	
Croatia	
Cyprus	
Czechia	
Denmark	
Estonia	
Finland	
France	
Germany	
Greece	
Hungary	
Ireland	
Italy	
Latvia	
Lithuania	
Netherlands	
Poland	
Portugal	
Romania	
Slovakia	
Slovenia	
Spain	
Sweden	
United Kingdom†	
Norway‡	
Switzerland*	

† UK left the EU on 31 January 2020. UK (Northern Ireland) remains part of the EU regulatory framework. UK (Great Britain) is now nationally governed and not part of the EU.

‡ Norway is not part of the EU but is part of the EEA.

* Switzerland is not an EU or EEA member but is part of the single market.

Notes: EU Member States: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and UK.

Iceland and Liechtenstein do not have sales recorded during this time frame.

Module SVI Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

The potential for illicit use of upadacitinib for illegal purposes is not considered to be a risk. There have been no reports of abuse or dependence leading to addiction for other JAK inhibitors such as tofacitinib and baricitinib. There is no evidence for and no anticipation of drug abuse with upadacitinib treatment based on upadacitinib clinical trials.

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):

- Elevations in creatine phosphokinase

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and AE reporting, and for which the risk minimization messages in the product information are adhered to by prescribers:

- Neutropenia
- Lymphopenia
- Decreases in hemoglobin

Known risks that do not impact the risk-benefit profile:

- Acne
- Pyrexia
- Cough
- Nausea

- Weight increased

Known risk for which a possible outcome is included as an important potential risk:

- Hyperlipidaemia (major adverse cardiovascular event [MACE] included as an important potential risk)
- Increases in transaminases (aspartate transaminase [AST] and alanine transaminase [ALT]) (drug-induced liver injury [DILI] included as an important potential risk)

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

Important Identified Risks

Identified risk 1: Serious and opportunistic infections including TB

Reason for Inclusion:

Approved therapies of the JAK inhibitor class are associated with or are being investigated for risk of serious infections and opportunistic infections.

See Module SVII.3 for additional details.

Identified risk 2: Herpes zoster

Reason for Inclusion:

Approved therapies of the JAK inhibitor class are associated with an increased risk of herpes zoster.

See Module SVII.3 for additional details.

Identified risk 3: NMSC

Reason for Inclusion:

Review of the longer-term pooled data across indications as of 15 August 2021 demonstrated that the overall crude incidence rate of NMSC was higher with upadacitinib 30 mg (N = 4,179; PY = 8,565.8; 0.62 events per 100 PY) compared with upadacitinib 15 mg (N = 6,848; PY = 15,408.5; 0.38 events per 100 PY), with a hazard ratio (HR) of 1.76 (95% CI, 1.20 to 2.58; stratified by indication, p = 0.004). The increased risk of NMSC with upadacitinib 30 mg compared to the 15 mg dose was more apparent after approximately 1 year of upadacitinib treatment and continued to increase beyond 1 year. Subjects on upadacitinib 30 mg had more frequent recurrence of NMSC than upadacitinib 15 mg over time. NMSC has been added as an adverse drug reaction for upadacitinib.

Identified risk 4: GI perforation

Reason for Inclusion:

To align with inclusion of GI perforation in Section 4.8 of the SmPC.

Important Potential Risks

Potential risk 1: Malignancies excluding NMSC

Reason for Inclusion:

Approved therapies in the JAK inhibitor class are being investigated for potential risk of malignancies (Cohen 2017). Results of the post-marketing ORAL Surveillance trial involving RA patients ≥ 50 years of age with underlying CV risk factors, comparing tofacitinib vs. TNF inhibitors, showed higher rates of malignancy excluding NMSC in patients on tofacitinib. Differences in the risk were more pronounced in patients 65 years of age or older than in younger patients (Ytterberg 2022).

Although there is no evidence of an increased risk of malignancies excluding NMSC with upadacitinib during clinical trials to date (see Module SVII.3), immunomodulatory drugs may increase a person's susceptibility to develop malignancies. Malignancies have a long latency of onset, so longer-term follow-up is needed.

Potential risk 2: MACE

Reason for Inclusion:

Approved therapies in the JAK inhibitor class are being investigated for potential risk of MACE.

In upadacitinib clinical trials, treatment with upadacitinib increased LDL-C and high-density lipoprotein-cholesterol (HDL-C). In the Phase 2/3 and Phase 3 AS trial, both LDL-C and HDL-C also increased with upadacitinib 15 mg therapy; the ratio of LDL-C/HDL-C remained constant throughout the treatment period. Although there is no clear evidence of an increased risk of MACE with upadacitinib and no evidence to suggest that elevated cholesterol was associated with the occurrence of treatment-emergent MACE during upadacitinib clinical trials to date (see Module SVII.3), JAK inhibitors are known to increase lipid levels and the long-term effects of the changes are unknown. Results of the post-marketing ORAL Surveillance trial in RA patients ≥ 50 years of age with underlying CV risk factors showed higher rates of adjudicated MACE in patients on tofacitinib compared to TNF inhibitors. Differences in the risk were more pronounced in patients 65 years of age or older than in younger patients (Ytterberg 2022). MACE resulting from atherosclerotic plaque disease may take years to develop, so longer-term follow up is needed.

Potential risk 3: VTEs (deep venous thrombosis and pulmonary embolus)

Reason for Inclusion:

Baricitinib, a JAK1 and JAK2 inhibitor, was the first JAK inhibitor for RA associated with VTEs (includes deep venous thrombosis and/or pulmonary embolus) based on results from Phase 3 RA clinical trials.

A United States Product Insert (USPI) warning for dose-related increased risk of mortality and thrombosis in RA subjects with one or more CV risk factors has been communicated for tofacitinib (Xeljanz (tofacitinib) Safety announcement [25 Feb 2019] 2019), and final results of the post-marketing ORAL Surveillance trial showed increased risk of blood clots with tofacitinib compared to TNF inhibitors (Ytterberg 2022).

In upadacitinib clinical trials, adjudicated VTEs were reported at comparable rates in subjects receiving upadacitinib 15 mg, 30 mg, or 45 mg and subjects on placebo and/or active comparators (i.e., MTX and adalimumab). No VTEs have been reported to date in the global AS clinical program. Although there is no evidence of an increased risk of VTE with upadacitinib during clinical trials to date (see Module SVII.3), evaluation with longer duration follow-up is needed to confirm this finding.

Potential risk 4: DILI

Reason for Inclusion:

Approved therapies in the JAK inhibitor class are being investigated for DILI.

Although ALT increased and AST increased are considered adverse reactions for upadacitinib, there is no clear evidence of an increased risk of DILI (i.e., hepatic transaminase elevations in association with elevations in bilirubin, or severe hepatic outcomes) during upadacitinib administration to date (see Module SVII.3), further characterization of this potential risk is needed in larger patient cohorts.

Potential risk 5: Fetal malformation following exposure in utero

Reason for Inclusion:

Approved therapies in the JAK inhibitor class are being investigated for potential risk of fetal malformation following exposure in utero.

Upadacitinib is teratogenic in both rats and rabbits. Upadacitinib administration was associated with skeletal malformations in rats at ≥ 4 mg/kg/day in the absence of maternal toxicity and cardiac malformations in rabbits concurrent with maternal toxicity (only at the high dose of 25 mg/kg/day). In rats and rabbits, teratogenicity occurred at exposure multiples (on an AUC basis) of 0.6 and 6 times the exposures at the clinical dose of 45 mg, respectively, 0.8 and 7.6 times the exposures at the clinical dose of 30 mg, respectively, and 1.6 and 15 times the exposures at the clinical dose of 15 mg, respectively. Teratogenic effects in nonclinical species suggest there is a potential risk for fetal malformation in humans following exposure in utero.

Potential risk 6: Fractures

Reason for Inclusion:

Administration of abrocitinib, another JAK inhibitor with specificity toward JAK1, to juvenile rats (comparable to a 3-month-old human) resulted in macroscopic and microscopic bone findings. When dosing was initiated at postnatal Day 10 (at exposures ≥ 0.8 times the human AUC at the maximum recommended human dose of 200 mg), macroscopic bone findings (malrotated and/or impaired use of forelimbs or hindlimbs or paws, fractures, and/or femoral head abnormalities) were noted. Only the microscopic bone dystrophy finding (similar to that observed in rat general toxicity studies of up to 1 month) was fully reversible after cessation of treatment. In juvenile rats administered upadacitinib, no evidence of effects on bone during postnatal development of the skeletal system in juvenile or adult rats or dogs in nonclinical studies were observed. Results of a post hoc analyses of the post-marketing ORAL Surveillance trial involving RA patients ≥ 50 years of age with underlying CV risk factors showed numerically higher risk for fractures with tofacitinib vs. TNF inhibitors (Hansen 2022), and based on findings from ORAL Surveillance, the SmPC of tofacitinib was updated. Although there are some signals for fractures from the upadacitinib randomized controlled trials (RCTs), the increased risk is not currently consistent across indications and comparators; therefore, there is need for further characterization of the risk. Given the totality of existing data, fracture is considered a potential risk for upadacitinib.

Missing Information

Information 1: Use in very elderly (≥ 75 years of age)

Reason for Inclusion:

There is limited experience with upadacitinib in subjects ≥ 75 years of age. Further data collection is warranted as this age range is within the target population.

Data to be Collected Post-Authorization:

Data from routine pharmacovigilance activities and long-term comparative cohort studies.

Information 2: Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C

Reason for Inclusion:

Experience with upadacitinib in subjects with evidence of chronic infection with untreated hepatitis B or hepatitis C is limited. Subjects who are hepatitis B surface antigen positive or hepatitis B DNA PCR positive or hepatitis C RNA PCR positive were excluded from clinical trials with upadacitinib.

HCV and HBV are non-cytopathic, thus the host immune system has a crucial role in inducing liver disease, including immune-mediated disease pathogenesis or viral clearance. Following immune suppression, viral reactivation may occur with an increase in viral replication and resultant signs and symptoms of hepatitis (Di Bisceglie 2015, Lee 2017).

Data to be Collected Post-Authorization:

Data from routine pharmacovigilance activities and long-term comparative cohort studies.

Information 3: Use in patients with moderate hepatic impairment

Reason for Inclusion:

Based on exclusion criteria from upadacitinib clinical trials, safety data in subjects with moderate hepatic impairment are limited, and there are no data in subjects with severe hepatic impairment. The SmPC states that no dose adjustment is required for patients with mild or moderate hepatic impairment and that upadacitinib is contraindicated for use in patients with severe hepatic impairment; consequently, use in patients with severe hepatic impairment is not included as missing information.

Data to be Collected Post-Authorization:

Data from routine pharmacovigilance activities and long-term comparative cohort studies.

Information 4: Use in patients with severe renal impairment

Reason for Inclusion:

Based on exclusion criteria from upadacitinib clinical trials (excluded with baseline estimated GFR of < 40 mL/min/1.73 m^2), use in patients with severe renal impairment will be considered missing information. The SmPC states that no dose adjustment is required for patients with mild or moderate renal impairment and upadacitinib should be used with caution in patients with severe renal impairment. The SmPC also states that for RA, PsA, AS, nr-axSpA, and AD, the recommended dose is 15 mg QD for patients with severe renal impairment. For UC and CD, the recommended induction treatment dose is 30 mg QD and the recommended maintenance treatment dose is 15 mg QD for patients with severe renal impairment. Upadacitinib has not been studied in subjects with end stage renal disease.

Data to be Collected Post-Authorization: Data from routine pharmacovigilance activities and long-term comparative cohort studies.
Information 5: Long-term safety Reason for Inclusion: Limited long-term safety data are available on events with a low frequency and/or long latency in patients receiving upadacitinib therapy. 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 upadacitinib trials.
Information 6: Long-term safety in adolescents with AD Reason for Inclusion: The safety database in adolescents is still small in terms of long-term treatment, compared with that in adults. The available nonclinical data for upadacitinib do not suggest a risk associated with bone development in adolescent patients 12 to 17 years old. However, clinical data are too limited to draw any conclusions on potential effects of upadacitinib on height in growing children. Further characterization of long-term safety in adolescents will include data from adolescent subjects who continue in the long-term extension of the Phase 3 AD clinical trials (Studies M16-045, M18-891, and M16-047), the long-term safety study of upadacitinib use in AD patients (Study P20-390), and in the additional long-term pharmacovigilance study of growth in adolescents with AD who receive upadacitinib (Study P21-824). 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 upadacitinib trials.

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

There are no new or removed safety concerns or reclassification of safety concerns in this RMP revision.

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 and opportunistic infections including TB Medical Dictionary for Regulatory Activities (MedDRA) terms: See Annex 1
Potential Mechanisms: Upadacitinib affects cytokine signaling pathways such as IL-6 and INF-gamma. Upadacitinib may also affect other pathways such as IL-7, IL-15, and granulocyte-macrophage colony-stimulating factor (GM-CSF). These pathways are known to be involved in host defense against bacterial and viral pathogens; thus, inhibition of these pathways may be associated with increased risk of infections.
Evidence Source and Strength of Evidence: Approved therapies of the JAK inhibitor class are associated with or are being investigated for risk of serious infections and opportunistic infections. Serious and opportunistic infections including TB were assessed in data from upadacitinib clinical trials described below.
Characterization of the Risk: Rheumatoid Arthritis: *Serious infections:* In the placebo-controlled periods of Phase 3 RA trials the percentage of subjects with serious infections was higher in the upadacitinib 15 mg group (1.2%) compared with the placebo group (0.6%). In the MTX-controlled study, Study M13-545, the event rate (long-term all exposure) of serious infections was higher for upadacitinib 15 mg monotherapy (4.1 E/100 PY) compared with MTX monotherapy (2.9 E/100 PY) through the data cutoff. In contrast, the long-term event rates (all study drug exposure) observed were similar for upadacitinib 15 mg (plus background MTX) (3.7 E/100 PY) and adalimumab (plus background MTX) (4.3 E/100 PY) in the adalimumab-controlled study, Study M14-465, through the data cutoff. *Across the Phase 3 RA trials as of the 31 December 2019 cutoff:* The event rate (long-term all exposure) of serious infections was 3.2 E/100 PY for upadacitinib 15 mg, which is below the range reported (3.42 – 4.24 E/100 PY) for clinical development programs of other immunomodulatory therapies for RA, including tocilizumab, tofacitinib, and sarilumab (FDA 2010, FDA 2012, FDA 2017). *Opportunistic infections excluding TB and herpes zoster:* There were 3 subjects who experienced serious opportunistic infections (bronchopulmonary aspergillosis, pneumonia cryptococcal, and sinusitis aspergillus) while receiving upadacitinib 15 mg. *Across the RA clinical program (Phase 2 and Phase 3 trials) as of the 31 December 2019 cutoff:* The types of serious infections reported for subjects receiving upadacitinib were generally consistent with those anticipated in a population of patients with moderate to severe active RA.

The majority of opportunistic infections (excluding TB and herpes zoster) reported for subjects treated with upadacitinib were nonserious mucosal candida infections. There was 1 death due to an opportunistic infection (listeriosis) in a subject treated with upadacitinib.

Active TB:

There have been 9 events in 8 subjects of active TB reported on upadacitinib. Based on 9 events of active TB on upadacitinib in 11201.0 PY, the event rate was < 0.1 E/100 PY. All but 2 subjects were receiving concomitant csDMARDs and/or corticosteroids. Of the 8 subjects receiving upadacitinib, 6 subjects were noted to have latent TB at study screening and 1 subject was cohabitating with a TB positive individual. Five subjects presented with extrapulmonary disease. No subject treated with upadacitinib died due to TB infection.

Psoriatic Arthritis:

Serious infections:

In the placebo-controlled periods of the Phase 3 PsA trials, the percentage of subjects with serious infections was similar in the upadacitinib 15 mg and placebo groups (0.9% and 0.8%, respectively). In the adalimumab-controlled study, Study M15-572, the event rate (long-term all exposure) of serious infections was 2.1 E/100 PY in the upadacitinib 15 mg group and 1.5 E/100 PY in the ADA group, through the data cutoff. Across the Phase 3 PsA trials, the event rate (long-term all exposure) of serious infections was 2.2 E/100 PY for subjects treated with upadacitinib 15 mg.

Opportunistic infections excluding TB and herpes zoster:

Across the Phase 3 PsA trials, the majority of opportunistic infections (excluding TB and herpes zoster) reported for subjects treated with upadacitinib were nonserious infections; however, coccidioidomycosis (1 event) and bronchopulmonary aspergillosis (1 event) have been reported for subjects treated with upadacitinib 15 mg. There was no death due to an opportunistic infection in subjects treated with upadacitinib.

Active TB:

There was no case of active TB reported in subjects treated with upadacitinib.

Ankylosing Spondylitis:

Serious infections:

In the placebo-controlled period of the Phase 2/3 bDMARD-naïve AS trial, the percentage of subjects with serious infections was the same in the upadacitinib 15 mg and placebo groups (each had no serious infections). In subjects with bDMARD-IR AS in the placebo-controlled period (14 weeks) of Study 1 of the Phase 3 trial, the percentage of subjects with serious infections was 2.4% in the upadacitinib 15 mg group, and there were none reported in the placebo group. The long-term event rate (any upadacitinib) of serious infections was 6.0 E/100 PY through the data cutoff and over half of the serious infection events were coronavirus disease 2019 (COVID-19)-related events, none of which were considered related to upadacitinib.

Opportunistic infections excluding TB and herpes zoster:

In the placebo-controlled period of the Phase 2/3 bDMARD-naïve AS study, 2 nonserious events of oesophageal candidiasis were reported in one subject treated with upadacitinib 15 mg. No subjects with bDMARD-IR AS reported events of opportunistic infection (excluding TB and herpes zoster) in Study 1 of the Phase 3 trial through the data cutoff.

Active TB:

There have been no cases of active TB reported on upadacitinib in the AS clinical program.

Non-Radiographic Axial Spondyloarthritis:

Serious infections:

In the placebo-controlled period of Study 2 of the Phase 3 trial, the percentage of subjects with nr-axSpA with serious infections through 14 weeks was 1.3% in the upadacitinib 15 mg group and 0.6% in the placebo group. The long-term event rate (any upadacitinib) of serious infections was 1.7 E/100 PY.

Opportunistic infections excluding TB and herpes zoster:

There were no events of opportunistic infections reported by subjects in the study up to the data cutoff.

Active TB:

There have been no cases of active TB reported by subjects in the study up to the data cutoff.

Atopic Dermatitis:

Serious infections:

Placebo-controlled period:

Overall (adults and adolescents), in the placebo-controlled periods of the Phase 2 and 3 Phase 3 Pivotal AD trials, the percentage of all subjects with serious infections was similar across the upadacitinib 30 mg, 15 mg, and placebo groups (0.4%, 0.8%, and 0.6%, respectively). In adult subjects (Phase 2 and 3 trials), the percentage with serious infections was similar across the upadacitinib 30 mg, 15 mg, and placebo groups (0.5%, 0.8%, and 0.5%, respectively). In adolescent subjects (Phase 3 trials), no serious infections were reported in the upadacitinib 30 mg group, and the percentage with serious infections was the same in the upadacitinib 15 mg and placebo groups (0.6% for both groups).

Long-term exposure:

Overall, across all Phase 2 and 3 AD trials, the event rate for serious infection was 2.4 E/100 PY in all upadacitinib treated subjects. Overall, in the Phase 3 trials (adults and adolescents), the event rate of serious infections was 2.6 E/100 PY and 2.2 E/100 PY for subjects treated with upadacitinib 30 mg and 15 mg, respectively. The most common serious infection was COVID-19 pneumonia. In adult subjects (Phase 3 trials), the event rate of serious infections was 2.9 E/100 PY and 2.2 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively. In adolescent subjects (Phase 3 trials), the event rate was not higher in the upadacitinib 30 mg group (1.4 E/100 PY) compared with the upadacitinib 15 mg group (2.5 E/100 PYs). Rates of serious infections in adolescent subjects were generally similar to those observed in adult subjects.

Opportunistic infections excluding TB and herpes zoster:

Placebo-controlled period:

Overall (adults and adolescents), in the placebo-controlled periods of the Phase 2 and 3 Phase 3 Pivotal AD trials, the percentage of subjects with opportunistic infections (excluding TB and herpes zoster) was similar across the upadacitinib 30 mg, 15 mg, and placebo groups (0.8%, 0.7%, and 0.4%, respectively). For adults, (Phase 2 and 3 trials), the percentage of subjects with opportunistic infections (excluding TB and herpes zoster) was similar across the upadacitinib 30 mg, 15 mg, and placebo groups (0.9%, 0.8%, and 0.5%, respectively). For adolescents, (Phase 3 trials), no subjects reported opportunistic infections (excluding TB and herpes zoster).

Long-term exposure:

Overall, across all Phase 2 and 3 AD trials, the event rate of opportunistic infections (excluding TB and herpes zoster) was 2.1 E/100 PY in all upadacitinib treated subjects. There was no death due to an opportunistic infection. Across the Phase 3 AD trials (adults and adolescents), the event rate was 2.2 events/100 PY and 1.7 events/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively. In

adults (Phase 3 trials), the event rate of opportunistic infections was 2.6 E/100 PY and 1.7 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively, with rates of serious events of 0.2 E/100 PY in both the upadacitinib 30 mg group and 15 mg group. In adolescents (Phase 3 trials), the event rate of opportunistic infections was 0.5 E/100 PY for upadacitinib 30 mg, and 1.5 E/100 PY for upadacitinib 15 mg. The rate of serious events was 0.1 E/100 PY in both the upadacitinib 30 mg and 15 mg group.

Active TB:

Placebo-controlled period:

No active TB was reported in subjects during the placebo-controlled periods of the Phase 2 and 3 Phase 3 Pivotal AD trials.

Long-term exposure:

Across all Phase 2 and 3 AD trials, the event rate for active TB was < 0.1 E/100 PY in all patients treated with upadacitinib. In the Phase 3 trials (adults), 1 event of active TB was reported in the upadacitinib 30 mg group and 2 events in the upadacitinib 15 mg group; all events were considered serious. In adolescents (Phase 3 trials), no events of active TB were reported.

Ulcerative Colitis:

Serious infections:

In the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials, the percentage of subjects with serious infections was the same in the upadacitinib 45 mg and placebo groups (1.3% in both groups). In the extended induction period (16 weeks, upadacitinib 45 mg) for nonresponders, the percentage of subjects with serious infections was 0.8%; no additional events were reported in the extended induction period.

In the Phase 3 UC maintenance trials (up to 52 weeks) for clinical responders to the induction dose, the event rate of serious infections was 3.0 E/100 PY and 4.9 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively, and 6.2 E/100 PY in the placebo group.

The long-term event rate for serious infection was 4.3 E/100 PY and 4.7 E/100 PY in the upadacitinib 45 mg induction/30 mg maintenance (45/30 mg) and 45 mg induction/15 mg maintenance (45/15 mg) cohorts, respectively. There were no deaths due to a serious infection.

Opportunistic infections excluding TB and herpes zoster:

In the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials, the percentage of subjects with opportunistic infections (excluding TB and herpes zoster) was 0.4% in the upadacitinib 45 mg group and 0.3% in the placebo group. Events were either cytomegalovirus (CMV) colitis, CMV infection, or oral fungal infection. In the extended induction period (16 weeks, upadacitinib 45 mg) for nonresponders, the percentage of subjects with opportunistic infections was 1.6%; no additional events were reported in the extended induction period.

In the Phase 3 UC maintenance trials (up to 52 weeks) for clinical responders to the induction dose, the event rate of opportunistic infections (excluding TB and herpes zoster) was 0.5 E/100 PY and 1.1 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively, and 1.6 E/100 PY in the placebo group.

The long-term event rate for opportunistic infections (excluding TB and herpes zoster) was 0.5 E/100 PY and 0.4 E/100 PY in the upadacitinib 45/30 mg and 45/15 mg cohorts, respectively.

Active TB:

No active TB was reported in subjects during the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials or in the extended induction period (16 weeks, upadacitinib 45 mg) for nonresponders.

No active TB was reported in subjects during the Phase 3 UC maintenance trials (up to 52 weeks) for clinical responders to the induction dose.

No events of active TB were reported (long-term event rates) in the upadacitinib 45/30 mg and 45/15 mg cohorts.

Crohn's Disease:

Serious infections:

In the placebo-controlled induction period (12 weeks) of the Phase 3 CD trials, the percentage of subjects with treatment-emergent serious infections was similar in the upadacitinib 45 mg and placebo groups (1.9% and 1.7%, respectively).

During placebo-controlled maintenance treatment in the Phase 3 CD trials, for clinical responders to the induction dose, the event rates of treatment-emergent serious infections were lower in the upadacitinib 30 mg (5.7 E/100 PY) and 15 mg (4.0 E/100 PY) groups compared with the placebo group (7.2 E/100 PY).

The long-term event rates for treatment-emergent serious infection were 7.3 E/100 PY and 5.1 E/100 PY in the upadacitinib 45 mg induction/30 mg maintenance (45 mg/30 mg) and 45 mg induction/15 mg maintenance (45 mg/15 mg) cohorts, respectively.

Opportunistic infections excluding TB and herpes zoster:

In the placebo-controlled induction period (12 weeks) of the Phase 3 CD trials, 2 subjects in the upadacitinib 45 mg group and no subjects in the placebo group reported a treatment-emergent opportunistic infection (excluding TB and herpes zoster). The events were CMV infection and pneumocystis jirovecii pneumonia.

During placebo-controlled maintenance treatment in the Phase 3 CD trials, for clinical responders to the induction dose, 2 treatment-emergent opportunistic infection (excluding TB and herpes zoster) were reported in the 30 mg group (oesophageal candidiasis and CMV reactivation) and one in the upadacitinib 15 mg group (pneumocystis jirovecii pneumonia), while no event was reported in the placebo group.

The long-term event rates for treatment-emergent opportunistic infections (excluding TB and herpes zoster) were 0.4 E/100 PY and 0.7 E/100 PY in the upadacitinib 45 mg/30 mg and 45 mg/15 mg cohorts, respectively. There was no death due to an opportunistic infection.

Active TB:

There have been no cases of treatment-emergent active TB in the upadacitinib CD global clinical development program up to the data cutoff.

Giant cell arteritis:

Serious infections:

During Period 1 (52 weeks) the EAER of TEAEs of serious infections were similar in the upadacitinib groups (7.9 E/100 PYs each), both of which were lower than the placebo group (12.7 E/100 PYs). By PT, no more than 1 subject reported an event for any given treatment group, with the exception of pneumonia (5 subjects in the placebo group and 3 subjects in the upadacitinib 7.5 mg group); and COVID-19 pneumonia and ophthalmic herpes zoster (2 subjects each in the upadacitinib 15 mg group).

Similar trends to Period 1 were generally observed with the long-term data, with lower rates of serious infections in the upadacitinib groups (upadacitinib 15 mg: 2.9 E/100 PYs, upadacitinib 7.5 mg: 4.1 E/100 PYs) than in the placebo group (6.9 E/100 PYs)

Opportunistic infections excluding TB and herpes zoster:

During Period 1, treatment-emergent opportunistic infections excluding TB and herpes zoster were only

reported in the upadacitinib 15 mg (2.2 E/100 PYs) and placebo groups (1.1 E/100 PYs). Events reported were oral fungal infection (2 subjects) and esophageal candidiasis and PJP (1 subject each) in the upadacitinib 15 mg group; and esophageal candidiasis (1 subject) in the placebo group. In the long term, opportunistic infections excluding TB and herpes zoster were only reported in the upadacitinib 15 mg (0.6 E/100 PYs; 1 event of esophageal candidiasis) and placebo (1.4 E/100 PYs; 1 event of aspergillus infection) groups with none in the upadacitinib 7.5 mg group. *Active TB:* No TEAE of active TB was reported.
Risk Factors and Risk Groups: Advanced age and background immunosuppressive medications such as concomitant csDMARDs and prednisone are common in the moderate to severe active RA, PsA, and GCA populations and can also be found in the AS and nr-axSpA populations, although to a lesser extent, and systemic corticosteroids such as prednisone are common in the moderate to severe active AD, UC, CD, and GCA populations, placing these populations at increased risk. Corticosteroids and csDMARDs are not recommended for axial symptoms in AS and nr-axSpA; therefore, immunosuppressive medication burden is smaller than in RA, PsA, or GCA. EH is an infection that has been associated with AD and is the most commonly recognized viral complication in patients with AD (Beck 2009)
Preventability: Serious infections may be prevented using typical measures to prevent transmission of infectious agents. The SmPC includes language on clinical measures which can help reduce the risk of infections with upadacitinib (See Table 10). The SmPC also specifies populations who have a higher incidence of infections and that in patients 65 years of age and older, upadacitinib should only be used if no suitable treatment alternatives are available.
Impact on the Risk-Benefit Balance of the Product: With appropriate risk minimization measures, the risk-benefit balance remains positive.
Public Health Impact: It is anticipated that risk will be reduced by risk minimization activities targeting specific screening and encouragement of routine vaccination and that the public health impact will be minimal.

Important Identified Risk 2: Herpes zoster

MedDRA terms: See Annex 1

Potential Mechanisms:

The specific mechanism for this important identified risk is not known; however, upadacitinib affects cytokine signaling pathways (including those for IL-7, IL-15, GM-CSF, and the Type 1 and Type 2 interferon) and is associated with modest reductions in NK cells, particularly at doses greater than 15 mg QD, which are known to be involved in host defense against viral pathogens. Thus, inhibition of these pathways may be associated with increased risk of varicella zoster viral reactivation.

Evidence Source and Strength of Evidence:

Approved therapies of the JAK inhibitor class show increased risk of herpes zoster in patients with RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA.

Herpes zoster was assessed in data from upadacitinib clinical trials described below.

Characterization of the Risk:

Rheumatoid Arthritis:

In the placebo-controlled periods of Phase 3 RA trials, the percentage of subjects with herpes zoster was higher in the upadacitinib 15 mg group (0.7%) compared with the placebo group (0.3%). In the MTX-controlled study, Study M13-545, the event rate (long-term all exposure) of herpes zoster was higher for upadacitinib 15 mg monotherapy (5.6 E/100 PY) compared with MTX monotherapy (1.1 E/100 PY) through the data cutoff. Likewise, the long-term event rate (all study drug exposure) of herpes zoster was higher for upadacitinib 15 mg (plus background MTX) (3.1 E/100 PY) compared with adalimumab (plus background MTX) (1.2 E/100 PY) through the data cutoff in the adalimumab-controlled study (Study M14-465).

Across the Phase 3 RA trials as of the 31 December 2019 cutoff:

The event rate (long-term all exposure) of herpes zoster was 3.3 E/100 PY for upadacitinib 15 mg. Most of the herpes zoster events reported for subjects treated with upadacitinib involved a single dermatome and were nonserious. Cases of disseminated cutaneous and ophthalmic zoster have been reported in the 15 mg upadacitinib group (11 subjects [5.9%] and 10 subjects [5.4%], respectively, across the global Phase 2 and Phase 3 studies). No cases of CNS involvement were reported for subjects treated with upadacitinib. No fatal event of herpes zoster was reported for subjects treated with upadacitinib.

Psoriatic Arthritis:

In the placebo-controlled periods of the Phase 3 PsA trials, the percentage of subjects with herpes zoster was similar in the upadacitinib 15 mg group (1.1%) compared with the placebo group (0.8%). In the adalimumab-controlled study, Study M15-572, the event rate (long-term all exposure) of herpes zoster was higher for the upadacitinib 15 mg group (3.4 E/100 PY) compared with ADA (0.5 events/100 PY) through the data cutoff. Across the Phase 3 PsA trials, the event rate (long-term all exposure) of herpes zoster was 3.2 events/100 PY for upadacitinib 15 mg.

Across the Phase 3 PsA trials, most of the herpes zoster events reported for subjects treated with upadacitinib 15 mg involved a single dermatome and were nonserious. No cases of CNS involvement were reported for subjects treated with upadacitinib. No fatal event of herpes zoster was reported for subjects treated with upadacitinib.

Ankylosing Spondylitis:

No subjects had herpes zoster during the placebo-controlled period of the Phase 2/3 bDMARD-naïve AS trial. In Period 2 (open-label, long-term extension), among 4 subjects on upadacitinib 15 mg,

5 nonserious events of herpes zoster (2.1 E/100 PY) were reported. All 5 of these events were mild (3 events) or moderate (2 events) in severity and were limited to one dermatome.

In subjects with bDMARD-IR AS in the placebo-controlled period (14 weeks) of Study 1 of the Phase 3 trial, the percentage of subjects with herpes zoster was 0.9% in the upadacitinib 15 mg group compared with none in the placebo group. The long-term event rate (any upadacitinib) of herpes zoster was 4.1 E/100 PY. All events of herpes zoster were mild (6 events) or moderate (4 events) in severity, nonserious, and most were limited to 1 dermatome, except for 1 subject who had an SAE of severe disseminated herpes zoster with no extracutaneous manifestations.

Non-Radiographic Axial Spondyloarthritis:

In the placebo-controlled period of Study 2 of the Phase 3 trial, the percentage of subjects with herpes zoster through 14 weeks was 1.3% in the upadacitinib 15 mg and 0.6% in the placebo group. The long-term event rate (any upadacitinib) of herpes zoster was 3.4 E/100 PY. All events of herps zoster were mild (3 events) or moderate (1 event) in severity and were limited to 1 dermatome.

Atopic Dermatitis:

Placebo-controlled period:

Overall (adults and adolescents), in the placebo-controlled periods of the Phase 2 and 3 Phase 3 Pivotal AD trials, the percentage of subjects with herpes zoster was similar in the upadacitinib 30 mg and 15 mg groups (1.5% and 1.6%, respectively) and higher than the placebo group (0.6%). In adult subjects, (Phase 2 and 3 trials), the percentage with herpes zoster was similar in the upadacitinib 30 mg and 15 mg groups (1.4% and 1.7%, respectively) and higher than the placebo group (0.6%). In adolescents, (Phase 3 trials), 1.7% and 0.6% of subjects in the upadacitinib 30 mg group and 15 mg group, respectively, had herpes zoster compared with none in the placebo group.

Long-term exposure:

Overall, across all Phase 2 and 3 AD trials, the event rate for herpes zoster was 4.9 E/100 PY in all upadacitinib-treated subjects.

Overall, across the Phase 3 AD trials (adults and adolescents), the event rate of herpes zoster was 5.5 E/100 PY and 3.1 E/100 PY for upadacitinib 30 mg and 15 mg, respectively. No CNS, liver, or lung involvement was reported. No fatal event of herpes zoster was reported for subjects treated with upadacitinib. In adults, the event rate of herpes zoster was 6.2 E/100 PY and 3.5 E/100 PY for upadacitinib 30 mg and 15 mg, respectively. In adolescents, the event rate of herpes zoster was 2.5 E/100 PY and 1.8 E/100 PY for upadacitinib 30 mg and 15 mg, respectively.

Ulcerative Colitis:

In the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials, the percentage of subjects with herpes zoster was 0.6% in the upadacitinib 45 mg group and 0% in the placebo group. In the extended induction period (16 weeks, upadacitinib 45 mg) for nonresponders, the percentage of subjects with herpes zoster was 3.9%.

In the Phase 3 UC maintenance trials (up to 52 weeks) for clinical responders to the induction dose, the event rate of herpes zoster was 6.0 E/100 PY in both the upadacitinib 30 mg and 15 mg groups, and 0 E/100 PY in the placebo group.

The long-term event rate for herpes zoster was 5.0 E/100 PY and 6.4 E/100 PY in the upadacitinib 45/30 mg and 45/15 mg cohorts, respectively. Most of the herpes zoster events for subjects treated with upadacitinib involved a single dermatome and were nonserious. Overall, 5.1% of subjects had herpes zoster events that involved 3 or more dermatomes, 2.6% had ophthalmic involvement, and none had herpes zoster oticus. No CNS, liver, or lung involvement was reported. No fatal event of

herpes zoster was reported.

Crohn's Disease:

In the placebo-controlled induction period (12 weeks) of the Phase 3 CD trials, the percentages of subjects with treatment-emergent herpes zoster were 2.2% in the upadacitinib 45 mg group and 0% in the placebo group.

During placebo-controlled maintenance treatment in the Phase 3 CD trials, for clinical responders to the induction dose, the event rate of treatment-emergent herpes zoster was higher in the upadacitinib 30 mg (5.4 E/100 PY) compared with the upadacitinib 15 mg (4.0 E/100 PY) and placebo (3.6 E/100 PY) groups.

The long-term event rates for treatment-emergent herpes zoster were 5.7 E/100 PY and 5.1 E/100 PY in the upadacitinib 45 mg/30 mg and 45 mg/15 mg cohorts, respectively. Among subjects exposed to at least 1 dose of upadacitinib, slightly over half had herpes zoster events reported during exposure to upadacitinib involved a single dermatome and all but 1 herpes zoster event was nonserious. Overall, 12.9% of subjects had herpes zoster events that involved 3 or more dermatomes, 4.8% had ophthalmic involvement, and none had herpes zoster oticus. No CNS, liver, or lung involvement was reported. No fatal event of herpes zoster was reported.

Giant cell arteritis:

During Period 1 (52 weeks) the EAER of herpes zoster was higher on upadacitinib 15 mg (7.3 E/100 PYs) compared placebo (4.2 E/100 PYs) and upadacitinib 7.5 mg (4.5 E/100 PYs) groups, which had similar rates. For those subjects with extent of involvement reported, the majority of herpes zoster events involved 1 dermatome. Four subjects had events involving 2 or 3 dermatomes and no events involved CNS, liver, or lung. There were 2 subjects with events of ophthalmic herpes zoster.

In the long term, the EAERs of herpes zoster were higher in the upadacitinib treatment groups (upadacitinib 15 mg: 4.1 E/100 PYs, upadacitinib 7.5 mg: 5.5 E/100 PYs) compared to the placebo group (2.8 E/100 PYs). Overall, the extent of involvement of the herpes zoster events were similar to that reported for Period 1.

Risk Factors and Risk Groups:

Herpes zoster is caused by reactivation of latent varicella zoster virus; therefore, it can only occur in patients who have previously been infected with varicella zoster virus. Herpes zoster can also occur in people who have received the varicella vaccine. Herpes zoster occurs most frequently among older adults and immunocompromised persons such as patients using immunomodulatory products or immunosuppressive products. Advanced age and background immunosuppressive medications such as concomitant csDMARDs and prednisone are common in the moderate to severe active RA, PsA, and GCA populations, and can also be found in the AS and nr-axSpA, populations, and prednisone is common in the moderate to severe active AD, UC, CD, and GCA populations, placing these populations at increased risk. As anticipated based on published literature regarding herpes zoster in patients with these conditions, prior herpes zoster and advanced age were risk factors for the development of herpes zoster while receiving upadacitinib. Additionally, a higher rate of herpes zoster was seen in the Asian region, as reported with other JAK inhibitors (Winthrop 2014).

Preventability:

Varicella zoster vaccine is available and may be administered prior to initiation of immunomodulatory products as per local standard practice.

Patients should be monitored for signs/symptoms (e.g., painful dermatomal rash) of herpes zoster while receiving upadacitinib therapy. The SmPC advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Occurrences of herpes zoster should be promptly managed, as clinically indicated, to try and reduce severity of disease and complications.

Impact on the Risk-Benefit Balance of the Product:

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

Public Health Impact:

It is anticipated that the risk difference between upadacitinib vs. comparators will be reduced by risk minimization activities targeting specific vaccination and that public health impact will be minimal.

Important Identified Risk 3: NMSC

MedDRA terms: See Annex 1

Potential Mechanisms:

The mechanism for this risk is not fully understood. Immunosuppressant medications have been hypothesized to impact malignancy immunosurveillance although evidence has been inconclusive. Upadacitinib has inhibitory activity on IL-15 signaling. It has been hypothesized that inhibition of IL-15 signaling will attenuate natural killer cell number and possibly function, thereby affecting the host immune surveillance against malignancies (Imai 2000, Vivier 2008).

Evidence Source and Strength of Evidence:

NMSC was assessed in data from upadacitinib clinical trials described below and from the company post-marketing database.

Characterization of the Risk:

An analysis of NMSC was performed to evaluate NMSC using the pooled data from all unblinded and open label extension upadacitinib studies (RA, PsA, AS, AD, UC, and CD [only Phase 2]) as of 15 August 2021. The data analysis showed that the overall rate of NMSC was higher with upadacitinib 30 mg (0.62 E/100 PY) compared with upadacitinib 15 mg (0.38 E/100 PY), with a hazard ratio of 1.76 (95% CI, 1.20 to 2.58; p = 0.004). No NMSC were reported in adolescent subjects in the AD studies.

The higher incidence of NMSC with upadacitinib 30 mg emerged after approximately 1 year of upadacitinib treatment as compared to the 15 mg dose and continued to increase beyond 1 year. Additionally, the proportion of subjects with recurrent NMSC was higher with upadacitinib 30 mg as compared to upadacitinib 15 mg. These observations further suggest a potential higher risk of NMSC over long-term exposure with upadacitinib 30 mg compared with upadacitinib 15 mg.

Giant cell arteritis:

During Period 1 (52 weeks), the EAIRs of NMSC were similar in the upadacitinib 15 mg (2.8 n/100 PYs) and placebo (2.1 n/100 PYs) groups and lower in the upadacitinib 7.5 mg group (1.1 n/100 PYs).

In the long term, TEAEs of NMSC were only reported in the upadacitinib 15 mg (3.5 n/100 PYs) and placebo (2.8 n/100 PYs) groups.

Overall, the events of NMSC reported in the upadacitinib program were generally nonserious, clinically managed by surgical removal on an outpatient basis, and did not lead to study drug discontinuation.

Risk Factors and Risk Groups:

Inflammation is considered a key process in skin tumorigenesis (Neagu 2019). Patients with inflammatory diseases such as RA and IBD have higher risks of NMSC than the general population (Raaschou 2016, Singh 2011). Immunosuppressive medications, such as MTX and TNF inhibitors, have been found to be associated with a higher risk of NMSC (Assassi 2016).

Basal cell carcinoma (BCC) (a type of NMSC) develops primarily on sun-exposed skin; thus, UV radiation plays a critical role in the pathogenesis of BCC. The occurrence of BCC increases as the population ages and approximately 80% of all BCC's are diagnosed above age 55 years (Ciążyńska 2021). The most critical risk factor for squamous cell carcinoma (a type of NMSC) is UV radiation from sunlight exposure (Fagan 2023).

Traditional risk factors of NMSC such as cumulative UV exposure, radiation therapy, prolonged immunosuppression, human papillomavirus infection, smoking, lower Fitzpatrick skin types, and other genetic risk factors also apply in patients with RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA.

Preventability:

The SmPC specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. The SmPC also advises on periodic skin examination.

Impact on the Risk-Benefit Balance of the Product:

With appropriate risk minimization measures, the risk-benefit balance remains favorable.

Public Health Impact:

It is anticipated that public health impact is minimal.

Important Identified Risk 4: GI perforation

MedDRA terms: See Annex 1

Potential Mechanisms:

The mechanism for this important identified risk is not fully understood. GI perforations have been reported in RA in association with the disease itself or in association with certain medications (Jagpal and Curtis 2018), most of which are also used for PsA and many of which are also used for or have been tried in AS, nr-axSpA, AD, UC, CD, and GCA. For example, lower GI tract perforations have been associated with treatment with the IL-6 inhibitor, tocilizumab (Monemi 2016, Strangfeld 2017). Historically, RA patients more frequently developed upper GI perforations in a setting of NSAID intake (Xie 2016). In UC, risk of intestinal perforation is high based on inflammatory processes that induce ulceration and disrupted neuromuscular function (Autenrieth and Baumgart 2012, Chang and Cohen 2004, Gan and Beck 2003). Patients with CD have an increased risk of GI perforation with vast majority cases involving a solitary perforation of the small bowel (Greenstein 1985). Also, patients with moderate to severe CD demonstrate increased rates of GI perforations compared to those with mild disease (McAuliffe 2015). While free wall perforation in CD reported in the literature varies from 1% to

15.6% (Werbin 2003), the chronic inflammatory processes that induce ulceration contribute to an increased risk of fistulizing disease, which occurs in almost one-third of patients, and intra-abdominal abscesses are a common complication of disease (Lichtenstein 2018). Bowel stricture in patients with CD was identified as one of the most significant risk factors associated with GI perforation (Doh 2015).

Evidence Source and Strength of Evidence:

Adjudicated GI perforation was assessed in data from upadacitinib clinical trials described below.

Characterization of the Risk:

Rheumatoid Arthritis:

In the placebo-controlled periods of Phase 3 RA trials and active comparator-controlled Phase 3 trials, GI perforation, identified by the Standard MedDRA Queries (SMQ) search, was uncommon, precluding any meaningful quantitative comparison between treatment groups.

Across the Phase 3 RA trials as of the 31 December 2019 cutoff:

The event rate (long-term all exposure) of adjudicated GI perforation across all upadacitinib doses was 0.1 E/100 PY. Fourteen events were reported, and 5 of the 14 events were reported by subjects who received upadacitinib 15 mg for an event rate (long-term all exposure) of < 0.1 E/100 PY for upadacitinib 15 mg.

Across the RA clinical program (Phase 2 and Phase 3 trials) as of the 31 December 2019 cutoff:

The majority of subjects who experienced events of GI perforation had risk factors per medical history, concomitant medications, or concurrent medical conditions that pose an increased risk of for GI perforation. One event (peritonitis), which occurred in the setting of a concurrent gastric ulcer, was fatal in a subject with a history of bleeding gastric ulcer who received upadacitinib 30 mg. The peritonitis was assessed as a perforation of the GI tract and was likely due to the gastric ulcer.

Psoriatic Arthritis:

In the placebo-controlled periods of Phase 3 PsA trials, no adjudicated GI perforations were identified by the SMQ search.

Across the Phase 3 PsA trials, the event rate (long-term all exposure) of GI perforation across 15 mg upadacitinib was 0.1 E/100 PY. There was a single event of adjudicated GI perforation (gastric ulcer perforation) reported in a subject who received upadacitinib 15 mg; the event was serious. The event was considered by the investigator to have no possibility of being related to study drug and likely related to concomitant use of NSAIDs and MTX.

Ankylosing Spondylitis:

No adjudicated GI perforations have been reported during the Phase 2/3 bDMARD-naïve AS trial.

No adjudicated GI perforations have been reported in subjects with bDMARD-IR AS in Study 1 of the Phase 3 trial.

Non-Radiographic Axial Spondyloarthritis:

No adjudicated GI perforations have been reported in subjects with nr-axSpA in Study 2 of the Phase 3 trial up to the data cutoff.

Atopic Dermatitis:

Placebo-controlled period:

Across all Phase 2 and 3 Phase 3 Pivotal AD trials, no event of adjudicated GI perforation was reported by upadacitinib-treated adult or adolescent subjects.

Long-term exposure:

Overall, across the Phase 2 and 3 AD trials, the event rate of adjudicated GI perforation was

< 0.1 E/100 PY in all upadacitinib treated subjects. Overall, across the Phase 3 AD trials (adults and adolescents), and in adults (Phase 3 trials), the event rate of adjudicated GI perforation was < 0.1 E/100 PY for upadacitinib 30 mg with no event of adjudicated GI perforation reported for upadacitinib 15 mg. No event of adjudicated GI perforation occurred in adolescent subjects. Ulcerative Colitis: In the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials, the percentage of subjects with adjudicated GI perforation was 0% in the upadacitinib 45 mg group and 0.3% in the placebo group. In the extended induction period (16 weeks, upadacitinib 45 mg) for nonresponders, no events were reported. In the Phase 3 UC maintenance trials (up to 52 weeks) for clinical responders to the induction dose, there were no adjudicated GI perforation events reported in the upadacitinib 30 mg and 15 mg groups and the event rate was 1.6 E/100 PY in the placebo group.
Across all Phase 2 and 3 UC trials, no events of adjudicated GI perforation were reported in the 45/30 mg and 45/15 mg cohorts. One subject who received upadacitinib 30 mg as an induction dose and upadacitinib 15 mg as maintenance treatment experienced an event of adjudicated GI perforation that was considered not related to upadacitinib. Crohn's Disease: In the placebo-controlled induction period (12 weeks) of the Phase 3 CD trials, the percentage of subjects with treatment-emergent adjudicated GI perforation was 0.1% (1 subject) in the upadacitinib 45 mg group and 0% in the placebo group. During extended treatment with upadacitinib 45 mg (up to 12 weeks) after not responding to placebo, 3 additional subjects reported TEAEs of adjudicated GI perforation. During placebo-controlled maintenance treatment in the Phase 3 CD trials, for clinical responders to the induction dose, treatment-emergent adjudicated GI perforations were reported in 1 subject each in the upadacitinib 30 mg (0.4 E/100 PY), upadacitinib 15 mg (0.4 E/100 PY), and placebo (0.7 E/100 PY) groups. The long-term event rates for treatment-emergent adjudicated GI perforation were 0.4 E/100 PY each in the upadacitinib 45 mg/30 mg and 45 mg/15 mg cohorts. Additionally, 3 subjects who received upadacitinib 30 mg as rescue therapy after not responding to maintenance or long-term extension treatment with placebo or upadacitinib 15 mg experienced GI perforations. Overall, all subjects with GI perforation had active CD at the time of event occurrence, stricture/penetrating CD, or fistulizing disease. Most of the GI perforations reported in subjects who received upadacitinib were attributed to CD progression. All perforations were at the site of active CD or proximal to a stricture. Giant Cell Arteritis: No TEAE of adjudicated GI perforation was reported.

Risk Factors and Risk Groups:

Risk factors for GI perforations include history of diverticulitis, use of glucocorticoids, exposure to NSAIDs, increasing age, and higher levels of co-morbidity (Curtis 2012). Advanced age is common for RA, PsA, and GCA patients, background immunosuppressive medications and NSAIDS are common in the moderate to severe active RA, PsA, AS, nr-axSpA, and GCA populations, and background immunosuppressive medications are common in the moderate to severe AD, UC, CD, and GCA populations placing these populations at increased risk. Patients with moderate to severe IBDs (UC and CD) have an increased risk of GI perforation compared to the general population (McAuliffe 2015). In CD, patients with moderate to severe disease have a higher risk of intestinal/gastric perforations compared to those with mild disease (McAuliffe 2015).

Preventability:

Since advanced age is common for RA, PsA, and GCA patients and background immunosuppressive medications are common in the moderate to severe active RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA populations, and place these populations at increased risk, patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or GI perforation. Usual care and vigilance in patients with signs/symptoms which may be suggestive of GI perforation are needed to quickly diagnose and treat patients.

Impact on the Risk-Benefit Balance of the Product:

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

Public Health Impact:

It is anticipated that public health impact will be minimal.

Important Potential Risk 1: Malignancies excluding NMSC

MedDRA terms: See Annex 1

Potential Mechanisms:

The mechanism for this risk is not fully understood. Immunosuppressant medications have been hypothesized to impact malignancy immunosurveillance although evidence has been inconclusive. Upadacitinib has inhibitory activity on IL-15 signaling. It has been hypothesized that inhibition of IL-15 signaling will attenuate natural killer cell number and possibly function, thereby affecting the host immune surveillance against malignancies (Imai 2000, Vivier 2008).

Evidence Source and Strength of Evidence:

Results of the post-marketing ORAL Surveillance trial involving RA patients ≥ 50 years of age with underlying CV risk factors, comparing tofacitinib vs. TNF inhibitors, showed higher rates of adjudicated malignancies excluding NMSC in patients on tofacitinib. Differences in the risk were more pronounced in patients 65 years of age or older than in younger patients (Ytterberg 2022).

Malignancies were assessed in data from upadacitinib clinical trials described below.

Characterization of the Risk:

Rheumatoid Arthritis:

Malignancy excluding NMSC:

In the placebo-controlled periods of Phase 3 RA trials, there were few malignancies reported, precluding any meaningful quantitative comparison between treatment groups. In the MTX-controlled study, Study M13-545, the incidence rate (long-term all exposure) of malignancies excluding NMSC was

similar between upadacitinib 15 mg monotherapy (0.8 n/100 PY) and MTX monotherapy (0.6 n/100 PY) through the data cutoff. In the adalimumab-controlled study (Study M14-465), the long-term incidence rate (all study drug exposure) of malignancies excluding NMSC was similar for the upadacitinib 15 mg (plus background MTX) (0.4 n/100 PY) and adalimumab (plus background MTX) (0.8 n/100 PY) groups through the data cutoff. With long-term exposure, the rate of malignancies excluding NMSC in subjects receiving upadacitinib 15 mg remained stable and did not increase over time.

Across the Phase 3 RA trials as of the 31 December 2019 cutoff:

The incidence rate (long-term all exposure) of malignancies excluding NMSC was 0.8 n/100 PY for upadacitinib 15 mg which is within the range reported (0.51 – 1.44 n/100 PY) for clinical development programs of other immunomodulatory therapies for RA including sarilumab, tocilizumab, baricitinib, and tofacitinib (FDA 2018, FDA 2010, FDA 2012, FDA 2017). An SIR analysis for malignancy excluding NMSC using age-gender specific malignancy data from the Surveillance, Epidemiology, and End Results (SEER) 18 Registry Research Data 2000 – 2015 for the general population yielded an SIR estimate of 1.05 (95% CI: 0.66, 1.60) for the treatment-emergent adverse event (TEAE) malignancies in the upadacitinib 15 mg group. The age-gender adjusted SIR for malignancies other than NMSC indicates that the malignancy risk with upadacitinib 15 mg is within the expected range for the general population.

Across the RA clinical program (Phase 2 and Phase 3 trials) as of the 31 December 2019 cutoff:

No notable pattern of types of malignancies other than NMSC was observed and the types observed reflected those expected in a study population of patients with moderate to severe active RA (Simon 2015).

Lymphoma:

Across the Phase 3 RA trials as of the 31 December 2019 cutoff:

One subject receiving upadacitinib 15 mg reported lymphoma (< 0.1 n/100 PY; long-term all exposure). There is no evidence to suggest an increased risk of lymphoproliferative disorders in subjects with RA who received upadacitinib 15 mg therapy.

Psoriatic Arthritis:

Malignancy excluding NMSC:

In the placebo-controlled periods of the Phase 3 PsA trials there were few malignancies reported, precluding any meaningful quantitative comparison between treatment groups. In the adalimumab-controlled study, Study M15-572, the event rate (long-term all exposure) of malignancies excluding NMSC was lower for upadacitinib 15 mg group (0.6 events/100 PY) compared with ADA (1.0 events/100 PY) through the data cutoff. Across the Phase 3 PsA trials, the event rate (long-term all exposure) of malignancies excluding NMSC was 0.9 events/100 PY for upadacitinib 15 mg.

Lymphoma:

Across the Phase 3 PsA trials, no subjects receiving upadacitinib 15 mg reported lymphoma.

Ankylosing Spondylitis:

No malignancies were reported during the placebo-controlled period of the Phase 2/3 bDMARD-naïve AS trial. In Period 2 (open-label, long-term extension), one malignancy was reported (0.4 events/100 PY) in 1 subject (squamous cell carcinoma of tongue). No subjects receiving upadacitinib 15 mg reported events of lymphoma.

In subjects with bDMARD-IR AS, in the placebo-controlled period (14 weeks) of Study 1 of the Phase 3 trial, malignancy excluding NMSC was reported in 1 subject (0.5%) in the placebo group, and no events were reported in the long-term data (any upadacitinib) up to the cutoff. No events of lymphoma were

reported in the placebo-controlled period, and no confirmed lymphoma was reported in the long-term data up to the data cutoff.

Non-Radiographic Axial Spondyloarthritis:

No events of malignancy other than NMSC, or lymphoma, were reported in subjects receiving upadacitinib 15 mg, up to the data cutoff.

Atopic Dermatitis:

Malignancy excluding NMSC:

Placebo-controlled period: In the placebo-controlled periods of the Phase 2 and 3 Phase 3 Pivotal AD trials, malignancy excluding NMSC was reported in four adult subjects (0.4%) in the upadacitinib 30 mg group, and no subjects in the upadacitinib 15 mg and placebo groups. No malignancy excluding NMSC was reported in adolescent subjects in the PBO-controlled Phase 3 AD adolescent analysis set.

Long-term exposure:

Overall, across all Phase 2 and 3 AD trials, the incidence rate for malignancy excluding NMSC was 0.5 n/PY in all upadacitinib treated subjects. Overall, across the Phase 3 AD trials (adult and adolescent), the incidence rate of malignancies excluding NMSC was 0.4 n/100 PY and 0.3 n/100 PY for the upadacitinib 30 mg and 15 mg group, respectively. There was no pattern to the types of malignancies reported. In adults the incidence rate of malignancy excluding NMSC was 0.5 n/100 PY and 0.3 n/100 PY for upadacitinib 30 mg and 15 mg, respectively. In adolescents, the incidence rate of malignancy excluding NMSC was 0 and 0.1n/100 PY for upadacitinib 30 mg and 15 mg, respectively. One event of medulloblastoma was reported in the upadacitinib 15 mg group. The serious event occurred on Study Day 267, considered not to have a reasonable possibility of being related to study drug, and resulted in study drug being withdrawn.

Lymphoma:

Placebo-controlled period:

In the placebo-controlled periods of the Phase 2 and 3 Phase 3 Pivotal AD trials, 1 case of cutaneous T-cell lymphoma was reported in an adult on upadacitinib 30 mg and it was not considered by the investigator to be related to upadacitinib.

Long-term exposure:

Overall, across all Phase 2 and 3 AD trials, the incidence rate for lymphoma was < 0.1 n/100 PY in all upadacitinib treated subjects. Overall, across the Phase 3 trials (adults and adolescents) and in adults (Phase 3 trials), the event rate of lymphoma was <0.1 n/100 PY for both upadacitinib 30 mg (2 events) and 15 mg (2 events). No lymphoma was reported in adolescent subjects.

Ulcerative Colitis:

Malignancy excluding NMSC:

No events of malignancy excluding NMSC were reported in subjects in the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials or in the extended induction period (16 weeks, upadacitinib 45 mg) for nonresponders.

In the Phase 3 UC maintenance trials (up to 52 weeks) for clinical responders to the induction dose, the incidence rate of malignancies excluding NMSC was 1.0 n/100 PY and 0.5 n/100 PY for the upadacitinib 30 mg and 15 mg groups, respectively, and 0.8 n/100 PY in the placebo group.

The long-term incidence rate for malignancy excluding NMSC was 0.9 n/100 PY and 0.4 n/100 PY in the upadacitinib 45/30 mg and 45/15 mg cohorts, respectively. There was no pattern to the types of malignancies reported and no temporal association with upadacitinib use.

Lymphoma:

Across all Phase 2 and 3 UC trials, no events of lymphoma were reported.

Crohn's Disease:

Malignancy excluding NMSC:

During the Phase 3 CD trials, no subjects had treatment-emergent malignancy excluding NMSC in the upadacitinib 45 mg and placebo groups in the placebo-controlled induction period (12 weeks) or during any portion of induction or extended treatment with upadacitinib 45 mg.

During placebo-controlled maintenance treatment in the Phase 3 CD trials, for clinical responders to the induction dose, the incidence rates of treatment-emergent malignancies excluding NMSC were 1.1 n/100 PY and 0.4 n/100 PY for the upadacitinib 30 mg and 15 mg groups, respectively, and 0.7 n/100 PY in the placebo group.

The long-term incidence rates for treatment-emergent malignancy excluding NMSC were 1.0 n/100 PY and 0.4 n/100 PY in the upadacitinib 45/30 mg and 45/15 mg cohorts, respectively. There was no pattern to the types of malignancies reported.

Lymphoma:

Across the Phase 3 CD trials, 1 case of treatment-emergent lymphoma (Burkitt's lymphoma) was reported. The subject was on rescue treatment with upadacitinib 30 mg during the long-term extension period at the time of the event. The long-term incidence rate was < 0.1 n/100 PY in the any upadacitinib cohort.

Giant cell arteritis:

Malignancy excluding NMSC:

During Period 1 (52 weeks), EAIRs of malignancies excluding NMSC were only reported in the upadacitinib 15 mg and placebo groups, and the incidence rates were similar (upadacitinib 15 mg: 2.3 n/100 PYs, placebo: 2.1 n/100 PYs).

In the long term, TEAEs of malignancies excluding NMSC were only reported in the upadacitinib groups with a higher incidence rate in the upadacitinib 7.5 mg group (upadacitinib 15 mg: 1.2 n/100 PYs, upadacitinib 7.5 mg: 2.8 n/100 PYs).

Lymphoma:

During Period 1 and the long term, no event of lymphoma was reported.

Risk Factors and Risk Groups:

There is evidence that RA, PsA, AD, UC, CD, and GCA patients have a higher occurrence of certain malignancies compared to the general population. The etiology of this finding may include immune dysregulation and/or chronic immune activation, as seen in RA patients (Shah 2015), AD patients (Wang 2019), and UC and CD patients (Ullman and Itzkowitz 2011). Lymphoproliferative disorders occur with increased frequency in patients with RA and PsA (Smitten 2008), and patients with UC or CD exposed to specific therapies are at increased risk of lymphoproliferative disease (Beaugerie 2009, Kandiel 2005). The lymphoma incidence increases as active RA persists and correlates with the severity of disease activity (Baecklund 2006, Naschitz and Rosner 2008). In addition to lymphoma, RA patients are at increased risk for lung cancer, and patients with CD are at increased risk of CRC (Olen 2020). Patients with AS or nr-axSpA have not been reported to have an increased risk of malignancy, with the exception of those exposed to spinal radiation treatment, which is no longer used (Exarchou 2016). There is mixed evidence on the risk of malignancy among patients with GCA. Chronic inflammation associated with GCA may be a potential driver of malignancy pathogenesis and progression, while an increased risk of hematologic malignancies in GCA may be attributed to shared environmental triggers (e.g., viral infections) (Dar 2021).

Preventability:

The SmPC specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available.

Impact on the Risk-Benefit Balance of the Product:

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

Public Health Impact:

It is anticipated that public health impact will be minimal.

Important Potential Risk 2: MACE

MedDRA terms: See Annex 1

Potential Mechanisms:

The mechanism for this important potential risk is not fully understood. In general, patients with RA and UC have lower lipid (total cholesterol and LDL-C) levels than the general population, and yet the risk for CV events is higher compared with the general population due largely to chronic inflammation (Avina-Zubieta 2012, Robertson 2013). Therefore, the relationship between serum lipid levels and CVD risk in RA appears to be inversely related. Patients with AS have been found to have higher LDL-C and lower HDL-C levels (Malesci 2007), and increased arterial wall inflammation, which is reduced by statin therapy (van der Valk 2016). While inflammation, which contributes to CVD risk, is decreased with various therapies including JAK inhibitors, lipid levels are increased to varying degrees across DMARDs. The overall effect of JAK inhibitor-mediated increases in lipid parameters on CV morbidity and mortality is unclear.

Evidence Source and Strength of Evidence:

Results of the post-marketing ORAL Surveillance trial involving RA patients ≥ 50 years of age with underlying CV risk factors, comparing tofacitinib vs. TNF inhibitors, showed higher rates of adjudicated MACE in patients on tofacitinib. Differences in the risk were more pronounced in patients 65 years of age or older than in younger patients (Ytterberg 2022).

Adjudicated MACE was assessed in data from upadacitinib clinical trials described below.

Characterization of the Risk:

Rheumatoid Arthritis:

In the placebo-controlled periods of Phase 3 RA trials, there were few subjects with treatment-emergent adjudicated MACE (1 in the upadacitinib 15 mg group and 3 in the placebo group). In the MTX-controlled study, Study M13-545, the incidence rate (long-term all exposure) of adjudicated MACE was 0.5 n/100 PY for upadacitinib 15 mg monotherapy and 0.6 n/100 PY MTX monotherapy through the data cutoff. Likewise, similar results were observed through the data cutoff in the adalimumab-controlled study (Study M14-465) (all study drug exposure) when comparing upadacitinib 15 mg (plus background MTX) to adalimumab (plus background MTX) (0.4 n/100 PY and 0.6 n/100 PY, respectively).

Across the Phase 3 RA trials as of the 31 December 2019 cutoff:

The incidence rate (long-term all exposure) of adjudicated MACE was 0.4 n/100 PY for upadacitinib 15 mg, which is below the range of that reported (0.44 n/100 PY [95% CI: 0.12, 1.13] to 0.50 n/100 PY [95% CI: 0.10, 1.45]) for clinical development programs of other immunomodulatory therapies for RA, including baricitinib, sarilumab, and tofacitinib (FDA 2018, FDA 2017, FDA 2012).

Across the RA clinical program (Phase 2 and Phase 3 trials) as of the 31 December 2019 cutoff:

The majority of the adjudicated MACE for subjects treated with upadacitinib did not lead to discontinuation of study drug and occurred in subjects with at least 1 known CV risk factor in addition to underlying RA. There was no evidence to suggest that elevated lipids were associated with the occurrence of treatment-emergent MACE. Seventeen subjects on upadacitinib experienced treatment-emergent CV death; all 17 subjects had multiple CV risk factors. Additionally, 1 subject on placebo, 1 subject on MTX, and 1 subject on adalimumab experienced CV death.

Psoriatic Arthritis:

In the placebo-controlled periods of the Phase 3 PsA trials, there were few subjects with treatment-emergent adjudicated MACE (1 in the upadacitinib 15 mg group and 1 in the placebo group). In the adalimumab-controlled study, Study M15-572, the incidence rate (long-term all exposure) of adjudicated MACE was similar for the upadacitinib 15 mg group (0.6 events/100 PY) compared with the ADA group (0.8 events/100 PY) through data cutoff.

Across the Phase 3 PsA trials, the incidence rate (long-term all exposure) of adjudicated MACE was 0.5 n/100 PY for upadacitinib 15 mg. The majority of the adjudicated MACE for subjects treated with upadacitinib did not lead to discontinuation of study drug and occurred in subjects with at least 1 known CV risk factor in addition to underlying PsA. There was no evidence to suggest that elevated lipids were associated with the occurrence of treatment-emergent MACE. Across the Phase 3 PsA trials, no subjects on upadacitinib treatment experienced CV death. One subject on placebo experienced CV death.

Ankylosing Spondylitis:

No MACE were reported during the Phase 2/3 bDMARD-naïve AS trial.

No adjudicated MACE were reported by subjects with bDMARD-IR AS during Study 1 of the Phase 3 trial up to the data cutoff.

Non-Radiographic Axial Spondyloarthritis:

No adjudicated MACE were reported in subjects with nr-axSpA in Study 2 of the Phase 3 study up to the data cutoff.

Atopic Dermatitis:

Placebo-controlled period:

In the placebo-controlled periods of the Phase 2 and 3 Phase 3 Pivotal AD trials, no subjects had treatment-emergent adjudicated MACE.

Long-term exposure:

Overall, across all Phase 2 and 3 AD trials, the incidence rate of adjudicated MACE was 0.1 n/100 PY in all upadacitinib treated subjects. Overall across the Phase 3 trials (adults and adolescents), the incidence rate of adjudicated MACE was < 0.1 n/100 PY (2 events) and 0.2 n/100 PY (6 events) in the upadacitinib 30 mg and 15 mg groups, respectively. All adjudicated MACE events were reported in adults and none were reported in adolescents. Seven out of 8 events of MACE led to discontinuation of study drug.

All subjects with MACE had at least 1 known CV risk factor. There was no evidence to suggest that elevated lipids were associated with the occurrence of treatment-emergent MACE.

Ulcerative colitis:

In the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials, no subjects had adjudicated MACE in the upadacitinib 45 mg and placebo groups or in the extended induction period (16 weeks, upadacitinib 45 mg) for nonresponders.

In the Phase 3 UC maintenance trials (up to 52 weeks) for clinical responders to the induction dose, the incidence rate for MACE was 0.5 n/100 PY and 0 n/100 PY for the upadacitinib 30 mg and 15 mg groups, respectively, and 0.8 n/100 PY in the placebo group.

The long-term incidence rate for MACE was 0.7 n/100 PY in the upadacitinib 45/30 mg cohort, and no MACE was reported in the 45/15 mg cohort.

Most subjects with MACE had at least 1 known CV risk factor in addition to underlying UC. All MACE led to discontinuation of study drug. There was no evidence to suggest that elevated lipids were associated with the occurrence of treatment-emergent MACE. There was no death due to adjudicated MACE.

Crohn's Disease:

During the Phase 3 CD trials, no subjects had treatment-emergent adjudicated MACE during the placebo-controlled induction period (12 weeks) or any portion of induction or extended treatment with upadacitinib 45 mg or placebo-controlled maintenance treatment for clinical responders to the induction dose.

No subjects had treatment-emergent adjudicated MACE in the upadacitinib 45 mg/15 mg and 45 mg/30 mg cohorts with long-term treatment. Adjudicated MACE were reported in 2 subjects during rescue treatment with upadacitinib 30 mg. One of the 2 subjects discontinued study drug. All subjects with MACE receiving upadacitinib had at least 1 known CV risk factor. There was no evidence to suggest that elevated lipids were associated with the occurrence of treatment-emergent MACE. There were no deaths due to MACE.

Giant cell arteritis:

During Period 1, no TEAEs of adjudicated MACE were reported in the upadacitinib groups. Two TEAEs of adjudicated MACE (2.1 n/100 PYs; cerebrovascular accident and myocardial ischemia) were reported in the placebo group.

In the long term, no TEAEs of adjudicated MACE were reported in the upadacitinib groups.

Risk Factors and Risk Groups:

Traditional CV risk factors such as prior CV events, smoking, dyslipidaemia, obesity, hypertension,

diabetes mellitus, and age also apply to patients with RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA. The potential for MACE in these patients as a result of elevations of lipid levels while on a JAK inhibitor or other therapies for these conditions remains unclear.
Preventability: As is known for the general population, interventions geared towards modifiable CV risk factors (e.g., hypertension, diabetes mellitus, hyperlipidaemia, obesity, smoking, etc.) can be influential in reducing the risk of MACE. Prescribers should inform patients of a potential risk for MACE and provide recommendations for reducing CV risk (e.g., smoking cessation, maintaining a healthy weight, physical activity, treatment of hyperlipidaemia, etc.). The SmPC recommends that lipid parameters be monitored and managed 12 weeks after initiation of upadacitinib and thereafter according to international clinical guidelines for hyperlipidaemia. The SmPC specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available.
Impact on the Risk-Benefit Balance of the Product: With appropriate risk minimization measures, the risk-benefit balance remains positive.
Public Health Impact: It is anticipated that public health impact will be minimal.
Important Potential Risk 3: VTEs (deep venous thrombosis and pulmonary embolus) MedDRA terms: See Annex 1
Potential Mechanisms: A potential mechanism for this important potential risk is not known. In UC and CD, the complex interaction between inflammation and coagulation contributes to a shift toward a prothrombotic state (Danese 2007).
Evidence Source and Strength of Evidence: Baricitinib, an approved JAK inhibitor with similar selectivity for JAK1 and JAK2, is being investigated for potential risk of thromboembolic events. It is not yet known if there is a role of JAK inhibition in the potential for developing VTEs. A USPI warning for dose-related increased risk of mortality and thrombosis in RA subjects with one or more CV risk factors has been communicated for tofacitinib (Xeljanz (tofacitinib) Safety announcement [25 Feb 2019] 2019) and final results of the post-marketing ORAL Surveillance trial showed increased risk of blood clots with tofacitinib compared to TNF inhibitors (Ytterberg 2022). Adjudicated VTEs (deep venous thrombosis and pulmonary embolus) were assessed in data from upadacitinib clinical trials described below.
Characterization of the Risk: <u>Rheumatoid Arthritis:</u> In the placebo-controlled periods of Phase 3 RA trials, the percentage of subjects with adjudicated VTE was similar in the upadacitinib 15 mg group (0.2%) compared with the placebo group (< 0.1%). In the MTX-controlled study, Study M13-545, the incidence rate (long-term all exposure) of adjudicated VTE through the data cutoff was 0 n/100 PY (no events) for upadacitinib 15 mg monotherapy compared with 0.6 n/100 PY for MTX monotherapy. In the adalimumab-controlled study (Study M14-465), through the data cutoff, the long-term incidence rate (all study drug exposure) of adjudicated VTE was 0.3 n/100 PY for upadacitinib 15 mg (plus background MTX) compared with 1.0 n/100 PY for adalimumab (plus background MTX).

Across the Phase 3 RA trials as of the 31 December 2019 cutoff:

Through the data cutoff of 31 December 2019, across the Phase 3 RA trials, the incidence rate (long-term all exposure) of adjudicated VTE was 0.5 n/100 PY for upadacitinib 15 mg, which is within the range of VTE rates reported (0.3 to 0.8 n/100 PY) for the general RA population (Choi 2013, Holmqvist 2012, Scott 2018).

Across the RA clinical program (Phase 2 and Phase 3 trials) as of the 31 December 2019 cutoff:

Among subjects treated with upadacitinib, approximately half of the adjudicated VTEs led to discontinuation of study drug, and all of the subjects who had VTEs had underlying risk factors such as prior history of thrombotic event, obesity, hormonal therapy, hypertension, or recent surgery. No pattern in the time to onset of VTEs was noted with upadacitinib treatment. Specifically, there were no clinically meaningful differences seen for treatment with upadacitinib compared to placebo, adalimumab, or MTX for changes in platelet counts, for subjects meeting criteria for potentially clinically significant values for platelet counts, for shift analysis from baseline to post-baseline in platelet counts, or for TEAEs representing changes in platelet counts.

Psoriatic Arthritis:

In the placebo-controlled periods of Phase 3 PsA trials, the percentage of subjects with adjudicated VTE was the same in the upadacitinib 15 mg group and the placebo group (0.2% each). In the adalimumab-controlled study, Study M15-572, the incidence rate (long-term all exposure) of adjudicated VTE through the data cutoff was 0.6 n/100 PY (3 events) for upadacitinib 15 mg compared with 0.5 n/100 PY for adalimumab.

Across the Phase 3 PsA trials, the incidence rate (long-term all exposure) of adjudicated VTE was 0.5 n/100 PY for upadacitinib 15 mg. Among subjects treated with upadacitinib, the majority of the adjudicated VTEs led to discontinuation of study drug, and most the subjects who had VTEs had underlying risk factors such as prior history of thrombotic event, obesity, hormonal therapy, hypertension, or recent surgery. No pattern in the time to onset of VTEs was noted with upadacitinib treatment.

Ankylosing Spondylitis:

No VTEs were reported during the Phase 2/3 bDMARD-naïve AS trial.

No VTEs were reported during the placebo-controlled period (14 weeks) of Study 1 (bDMARD-IR AS) from the Phase 3 trial. The long-term (any upadacitinib) incidence rate of VTE (1 event of pulmonary embolism) was 0.4 n/100 PY; the subject had underlying risk factors including overweight (BMI > 25) and hypertriglyceridemia.

Non-Radiographic Axial Spondyloarthritis:

In the placebo-controlled period of Study 2 of the Phase 3 trial, no subjects had adjudicated VTE. Up to the data cutoff, no subjects on upadacitinib 15 mg had adjudicated VTE.

Atopic Dermatitis

Placebo-controlled period:

In the placebo-controlled periods of the Phase 2 and 3 Phase 3 Pivotal AD trials, no subjects in the upadacitinib 30 mg or 15 mg treatment groups, and 1 subject (0.1%) in the placebo group, had adjudicated VTE.

Long-term exposure:

Overall, across all Phase 2 and 3 trials, the incidence rate of adjudicated VTE was 0.1 n/100 PY in all upadacitinib treated subjects.

Overall, across the Phase 3 AD trials (adults and adolescents), the incidence rate of adjudicated VTE

was 0.1 n/100 PY for both upadacitinib 30 mg (6 subjects) and 15 mg (4 subjects), respectively. In adults, the incidence rate of adjudicated VTE was 0.2 n/100 PY and 0.1 n/100 PY in the upadacitinib 30 mg and 15 mg, respectively. The majority of subjects with VTE had underlying risk factors including prior history of thrombotic event, obesity, hyperlipidemia, hypertension or co-morbid Covid-19.

In adolescents, no adjudicated VTE was reported.

Ulcerative Colitis:

In the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials, the percentage of subjects with adjudicated VTE was 0.1% in the upadacitinib 45 mg group and 0.3% the placebo group. In the extended induction period (16 weeks, upadacitinib 45 mg) for nonresponders, no additional events were reported.

In the Phase 3 UC maintenance trials (up to 52 weeks) for clinical responders to the induction dose, the incidence rate for adjudicated VTE was 1.0 n/100 PY and 1.1 n/100 PY for the upadacitinib 30 mg and 15 mg groups, respectively, and 0 n/100 PY in the placebo group.

The long-term incidence rate for adjudicated VTE was 0.5 n/100 PY and 0.6 n/100 PY in the upadacitinib 45/30 mg and 45/15 mg cohorts, respectively. Among subjects treated with upadacitinib, 5 adult subjects had a VTE of pulmonary embolism, and 1 of these led to discontinuation of study drug. All subjects with VTEs had underlying risk factors including prior history of thrombotic event, obesity, hormonal therapy, use of high dose steroids, hyperlipidemia, hypertension, recent surgery, prolonged severe illness with immobilization, and a history of smoking.

Crohn's Disease:

During the Phase 3 CD trials, no subjects had treatment-emergent adjudicated VTE during the placebo-controlled induction period (12 weeks) or any portion of induction or extended treatment with upadacitinib 45 mg.

During placebo-controlled maintenance treatment in the Phase 3 CD trials, for clinical responders to the induction dose, the incidence rate for treatment-emergent adjudicated VTE was 0.4 n/100 PY (1 event) in the upadacitinib 30 mg group; no event was reported in the upadacitinib 15 mg and placebo groups.

The long-term incidence rates for treatment-emergent adjudicated VTE were 0.6 n/100 PY and 0 n/100 PY in the upadacitinib 45 mg/30 mg and 45 mg/15 mg cohorts, respectively. Among the 3 subjects with VTE reported during exposure to upadacitinib during the Phase 3 studies, 2 discontinued study drug due to the event. All subjects with VTEs had at least 1 relevant risk factor for thrombosis including underlying CD, hypertension, obesity, smoking, recent surgery/hospitalization, and Factor V Leiden mutation.

Giant cell arteritis:

During Period 1 (52 weeks), TEAEs of adjudicated VTEs were reported in all treatment groups, and the EAIRs were similar across the upadacitinib 15 mg (3.9 n/100 PY), upadacitinib 7.5 mg (4.6 n/100 PY) and placebo groups (4.3 n/100 PY). Three subjects in the upadacitinib 15 mg group had concurrent DVT and PE and 1 subject had a concurrent thrombotic arterial event (right popliteal artery embolus) and a PE in the 15 mg group. The majority of events were serious and resulted in discontinuation of study drug. In addition, adjudicated arterial thromboembolic events were reported in 2 subjects (both on upadacitinib 15 mg). Both subjects had risk factors for thromboembolism.

In the long term, no adjudicated VTEs were reported in the upadacitinib 7.5 mg and placebo groups. One adjudicated VTE (0.6 n/100 PYs; pulmonary embolism) was reported in the upadacitinib 15 mg group and the subject had multiple risk factors for VTE. There were no TEAEs of arterial thromboembolic events reported in the long term.

Risk Factors and Risk Groups: Risks for VTEs in the general population also apply to patients with RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA and include prior history of VTE, contraceptive use, obesity, malignancies, smoking, hypertension, immobility, and inactivity such as bedrest following major surgeries like joint replacement. The general risk for VTE is increased in patients with AS and GCA especially in the first years after diagnosis (Aviña-Zubieta 2019). Patients with IBD have an increased risk of VTE (Papa 2020), especially during periods of disease flare (Grainge 2010). Patients with GCA have a higher underlying risk of VTE compared to matched controls and compared to patients with RA (Mohammad 2017). Risk of VTE is markedly increased within the first year after GCA diagnosis (Aviña-Zubieta 2016, Unizony 2017).
Preventability: Usual care and vigilance in patients for signs/symptoms which may be suggestive of VTEs are needed to quickly diagnose and treat patients. Physical activity, maintaining a healthy weight, smoking cessation, and blood pressure control may also be helpful to prevent this potential risk. The SmPC specifies risk factors which may put a patient at higher risk for VTE and in whom caution is needed when using upadacitinib. The SmPC advises on re-evaluation of VTE risk and states if clinical features of deep venous thrombosis/pulmonary embolism occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.
Impact on the Risk-Benefit Balance of the Product: With appropriate risk minimization measures, the risk-benefit balance remains positive.
Public Health Impact: It is anticipated that public health impact will be minimal.
Important Potential Risk 4: DILI MedDRA terms: See Annex 1
Potential Mechanisms: A potential mechanism for this important potential risk is not known.
Evidence Source and Strength of Evidence: Approved JAK inhibitors are being investigated for DILI. DILI was assessed in data from upadacitinib clinical trials described below.

Characterization of the Risk:

Rheumatoid Arthritis:

In the placebo-controlled periods of Phase 3 RA trials, transaminase or bilirubin increases were generally Grade 2 elevations, which were more frequent in the upadacitinib 15 mg group compared with the placebo group (ALT: 8.6% vs. 5.6%; AST: 5.2% vs. 4.7%; bilirubin: 0.5% vs. < 0.1%, respectively). Although infrequent, a higher percentage of subjects treated with upadacitinib 15 mg experienced ≥ 3 × upper limit of normal (ULN) or ≥ 5 × ULN increases in ALT or AST when compared to placebo. The frequency of subjects with ≥ 2 × ULN in bilirubin was comparable between upadacitinib 15 mg and placebo groups. TEAEs of hepatic disorder were comparable between the upadacitinib 15 mg (4.4%) and placebo (3.6%) groups and were mostly transaminase elevations.

In the MTX-controlled study, Study M13-545, the event rate (long-term all exposure) of hepatic disorders through the data cutoff was comparable for upadacitinib 15 mg monotherapy (17.2 E/100 PY) and MTX monotherapy (19.1 E/100 PY). In the adalimumab-controlled study (Study M14465), through the data cutoff, the long-term event rate (all study drug exposure) of hepatic disorders was 17.3 E/100 PY for upadacitinib 15 mg (plus background MTX) and 14.0 E/100 PY for adalimumab (plus background MTX).

Across the RA clinical program (Phase 2 and Phase 3 trials) as of the 31 December 2019 cutoff:

Among subjects treated with upadacitinib, TEAEs of hepatic disorders were mostly transaminase elevations. There was no trend observed regarding time to onset of the peak transaminase elevations in upadacitinib treated subjects. The majority of the transaminase elevations were mild to moderate in severity, were asymptomatic, and did not result in treatment discontinuation. There were no cases identified consistent with probable DILI attributable to upadacitinib based on medical review of the information available.

Psoriatic Arthritis:

In the placebo-controlled periods of Phase 3 PsA trials, transaminase or bilirubin increases were generally Grade 1 or 2 elevations, which were more frequent in the upadacitinib 15 mg group (ALT: 3.3%; AST: 2.2%; bilirubin: 0.3%) compared with the placebo group (ALT: 2.0%; AST: 1.4%; bilirubin: 0.2%). TEAEs of hepatic disorder were reported in a higher percentage of subjects in the upadacitinib 15 mg group (6.7%) compared with the placebo group (3.0%) and were mostly AST or ALT elevations. In the adalimumab-controlled study, Study M15-572, the event rate (long-term all exposure) of hepatic disorders through the data cutoff was lower in the upadacitinib 15 mg group (22.5 E/100 PY), compared with the adalimumab group (30.9 E/100 PY).

Across the Phase 3 PsA trials and among subjects treated with upadacitinib, TEAEs of hepatic disorders were mostly AST or ALT elevations. There was no trend observed regarding time to onset of the peak AST or ALT elevations in upadacitinib treated subjects. The majority of the ALT or AST elevations were mild to moderate in severity, were asymptomatic, and did not result in treatment discontinuation. No subjects met biochemical criteria for Hy's law.

Ankylosing Spondylitis:

In the placebo-controlled period of the Phase 2/3 bDMARD-naïve AS trial, hepatic disorders were reported more frequently in the upadacitinib 15 mg group (5.4%) compared with the placebo group (2.1%). All of these events were mild or moderate, asymptomatic ALT and/or AST elevations, and did not lead to study drug discontinuation.

During the placebo-controlled period (14 weeks) of Study 1 (bDMARD-IR AS) of the Phase 3 trial, the percentage of hepatic disorders was numerically higher in the upadacitinib 15 mg group compared with the placebo group (2.8% and 1.0%, respectively). The long-term event rate (any upadacitinib) of

hepatic disorders was 11.2 E/100 PY. The majority were ALT or AST elevations, and all ALT/AST increases were nonserious, most were mild or moderate in severity and did not result in treatment discontinuation.

Non-Radiographic Axial Spondyloarthritis:

In the placebo-controlled period of Study 2 of the Phase 3 trial, the percentage of hepatic disorders through 14 weeks was similar in the upadacitinib 15 mg and placebo groups (2.6% and 3.2%, respectively). The long-term event rate (any upadacitinib) of hepatic disorders was 6.9 E/100 PY. The majority were ALT or AST elevations, and all ALT/AST increases were nonserious and most were mild or moderate in severity and did not result in treatment discontinuation.

Atopic Dermatitis:

Placebo-controlled period:

Across all Phase 2 and 3 trials, most hepatic disorders were transaminase elevations.

Overall (adults and adolescents), in the placebo-controlled periods of the Phase 2 and 3 Phase 3 Pivotal trials, TEAEs of hepatic disorder were reported in a similar percentage across treatment groups (1.7% in both the upadacitinib 30 mg and 15 mg groups, and 1.3% in the placebo group). In adults, (Phase 2 and 3 trials), the percentage with hepatic disorders was similar across the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups (1.9% and 1.3%, and 1.5%, respectively). In the adolescent group (Phase 3 trials), the percentage of subjects with hepatic disorder was 1.7% and 3.3% in the upadacitinib 30 mg and 15 mg groups, respectively, compared with no subjects in the placebo group.

Long-term exposure:

Across all Phase 2 and 3 trials, the event rate for hepatic disorder was 5.4 E/100 PY in all upadacitinib treated subjects.

Overall, across the Phase 3 trials (adults and adolescents), the event rate of hepatic disorder was 6.1 E/100 PY and 4.5 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively. The majority of the ALT or AST elevations were mild to moderate in severity, were asymptomatic, and did not result in treatment discontinuation. In adults the event rate of hepatic disorder was 6.8 E/100 PY and 4.4 E/100 PY for upadacitinib 30 mg and 15 mg, respectively. Based on sponsor assessment, all biochemical Hy's law cases were identified to have alternate etiologies that accounted for the increased ALT/AST and total bilirubin. In adolescents the event rate of hepatic disorder was 2.7 E/100 PY and 5.0 E/100 PY in the upadacitinib 30 mg and 15 mg group, respectively. No adolescent subject met biochemical criteria for Hy's Law.

Ulcerative Colitis:

In the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials, the percentage of subjects with hepatic disorders was 3.5% in the upadacitinib 45 mg group and 2.4% the placebo group. In the extended induction period (16 weeks, upadacitinib 45 mg) for nonresponders, the percentage of subjects with hepatic disorders was 3.9%.

In the Phase 3 UC maintenance trials (up to 52 weeks) for clinical responders to the induction dose, the event rate of hepatic disorders was 9.1 E/100 PY and 17.5 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively, and 5.5 E/100 PY in the placebo group.

The long-term event rate for hepatic disorders was 12.0 E/100 PY and 14.4 E/100 PY in the upadacitinib 45/30 mg and 45/15 mg cohorts, respectively. There was no trend observed regarding time to onset of the peak AST or ALT elevations in upadacitinib-treated subjects. The majority of the ALT or AST elevations were mild to moderate in severity, were asymptomatic, and did not result in treatment discontinuation. Based on sponsor assessment, all biochemical Hy's law cases were identified to have

alternate etiologies that accounted for the increased ALT/AST and total bilirubin.

Crohn's Disease:

In the placebo-controlled induction period (12 weeks) of the Phase 3 CD trials, the percentage of subjects with treatment-emergent hepatic disorders was similar in the upadacitinib 45 mg (2.7%) and the placebo (2.9%) groups.

During placebo-controlled maintenance treatment in the Phase 3 CD trials, for clinical responders to the induction dose, the event rate of hepatic disorders was higher in the upadacitinib 30 mg and 15 mg groups (10.0 E/100 PY and 10.2 E/100 PY, respectively) compared with the placebo group (2.2 E/100 PY).

The long-term event rates for hepatic disorders were 9.7 E/100 PY and 10.1 E/100 PY in the upadacitinib 45 mg/30 mg and 45 mg/15 mg cohorts, respectively. Most hepatic disorders were mild or moderate hepatic transaminase elevations, none were serious, and few led to treatment discontinuation. No Hy's law cases attributable to upadacitinib were identified.

Giant Cell Arteritis:

During Period 1 (52 weeks), the EAERs of TEAEs of hepatic disorder were slightly higher in the upadacitinib 15 mg group (7.3 E/100 PYs), compared to the placebo group (6.4 E/100 PYs) and higher than in the upadacitinib 7.5 mg group (2.3 E/100 PYs). TEAEs of AST increased or ALT increased were mild or moderate.

For AST/ALT > 3 × ULN, AST/ALT > 5 × ULN, and AST/ALT > 10 × ULN, these criteria occurred at higher rates in the placebo group than the upadacitinib treatment groups. No AST or ALT > 20 × ULN occurred.

Two events (1 each on placebo and upadacitinib 15 mg) were identified as meeting biochemical Hy's Law criteria; however, both had alternate etiologies and were not considered true Hy's law cases.

In the long term, the EAERs of TEAEs of hepatic disorder were similar in the upadacitinib 15 mg (4.1 E/100 PY) and placebo groups (4.2 E/100 PY), both of which were higher than upadacitinib 7.5 mg (1.4 E/100 PY). For AST/ALT > 3 × ULN, AST/ALT > 5 × ULN, and AST/ALT > 10 × ULN, these criteria were infrequent and only occurring on Upadacitinib treatment. No AST or ALT > 20 × ULN occurred.

No events were identified as meeting biochemical Hy's Law criteria.

Risk Factors and Risk Groups:

Transaminase elevations can occur in the setting of RA, PsA, AS, and nr-axSpA independent of treatment (Robinson 1983, Takahashi 2010), and are commonly observed with NSAID and immunosuppressive treatment for these conditions, and with immunosuppressive treatment for AD, UC, and CD (Nygaard 2014, Restellini 2017, Takahashi 2010). Elevations have also been noted in PsA and AS patients treated with TNF inhibitors (Ghabril 2013). There is limited information on the underlying risk of hepatic disorders in patients with GCA.

Preventability: Increases in ALT and AST ≥ 5 × and ≥ 10 × ULN were observed in upadacitinib clinical trials. Most of these abnormalities occurred in studies with background DMARD (primarily MTX) therapy. The SmPC advises to evaluate liver enzymes at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of DILI. If increases in ALT or AST are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded.
Impact on the Risk-Benefit Balance of the Product: With appropriate risk minimization measures, the risk-benefit balance remains positive.
Public Health Impact: It is anticipated that public health impact will be minimal.
Important Potential Risk 5: Fetal malformation following exposure in utero MedDRA terms: See Annex 1
Potential Mechanisms: The JAK-STAT pathway is known to be involved in early embryonic development.
Evidence Source and Strength of Evidence:
Approved therapies of the JAK inhibitor class are being investigated for potential risk of fetal malformation following exposure in utero. Nonclinical studies showed that upadacitinib is teratogenic in both rats and rabbits. Pregnancy outcomes were assessed in data from upadacitinib clinical trials described below.
Characterization of the Risk: Upadacitinib administration was associated with skeletal malformations in rats at ≥ 4 mg/kg/day (exposure multiple [on an AUC basis] of 0.6 times the exposures at the clinical dose of 45 mg, 0.8 times the exposures at the clinical dose of 30 mg, and 1.6 times the exposures at the clinical dose of 15 mg) in the absence of maternal toxicity and cardiac malformations in rabbits concurrent with maternal toxicity (only at the high dose of 25 mg/kg/day; exposure multiple [on an AUC basis] of 6 times the exposures at the clinical dose of 45 mg, 7.6 times the exposures at the clinical dose of 30 mg, and 15 times the exposures at the clinical dose of 15 mg). There are limited data regarding the use of upadacitinib in pregnant women. Based on limited data in the upadacitinib development program through 15 August 2023, in 100 clinical trial pregnancies for studies which have been unblinded (RA, PsA, AS, nr-axSpA, AD, UC, CD, HS, and SLE), in which a pregnant woman had received upadacitinib within 1 month prior to conception and at least during the first trimester, the pregnancy outcomes are as follows: 1 live birth with congenital anomaly (35-week gestation premature infant with an atrial septal defect), 42 live births without congenital anomaly (including 2 infants born premature at 28 and 34 weeks gestation, neither with complications), 19 SABs, 18 elective terminations (without report of fetal defects or unknown), 1 ectopic pregnancy, 5 ongoing pregnancies, and 14 pregnancies lost to follow up. In 9 of the 19 SABs, pregnant mothers were taking concomitant MTX or used MTX within 1 month prior to conception (as background MTX was allowed in RA and PsA studies). Based on these limited data, the risk of teratogenicity in humans is not yet known.

Risk Factors and Risk Groups: Risk of fetal malformation pertains only to female patients of childbearing potential who become pregnant while receiving upadacitinib and for at least 4 weeks after treatment.
Preventability: Pregnancy is included as a contraindication in the SmPC. Female patients of childbearing potential should be advised to use effective contraception during and for 4 weeks following the final dose of upadacitinib. Upadacitinib should not be used during breastfeeding.
Impact on the Risk-Benefit Balance of the Product: With appropriate risk minimization measures, the risk-benefit balance remains positive.
Public Health Impact: The current and proposed indications for upadacitinib will be in a select subset of the adult population with moderate to severe active RA, PsA, AS, nr-axSpA, UC, CD, or GCA and in a select subset of adolescent and adult population with moderate to severe active AD. Potential risk of fetal malformation following exposure in utero pertains only to women of childbearing potential that become pregnant while receiving treatment with upadacitinib. The public health impact for fetal malformation following exposure in utero is considered very low since pregnancy is a contraindication in the SmPC and women are advised to use effective contraception in order to avoid pregnancy.
Important Potential Risk 6: Fractures MedDRA terms: See Annex 1
Potential Mechanisms: The body of available literature did not indicate a mechanism by which JAK inhibition would increase the risk of fractures; in fact, JAK inhibition is thought to prevent osteoclastogenesis and potentially promote fracture healing. Preclinical study findings with tofacitinib were supported with limited clinical data in which treatment reduced bone erosions. The upadacitinib preclinical data have not shown effects on bone growth or fractures in animals. However, dissimilar animal bone findings have been seen in the abrocitinib JAK inhibitor program, potentially due to differences in the JAK inhibitor molecules.
Evidence Source and Strength of Evidence: Results of a post hoc analyses of the post-marketing ORAL Surveillance trial involving RA patients ≥ 50 years of age with underlying CV risk factors showed numerically higher risk for fractures with tofacitinib vs. TNF inhibitors (Hansen 2022). Fracture was assessed in data from upadacitinib clinical trials described below.
Characterization of the Risk: Background incidence rates for fracture vary across indications for upadacitinib and should be referenced with caution given the variation in fracture outcome definition and study design for the datasets in which the rates are measured. In RA, a meta-analysis estimated the pooled incidence rates of overall and fragility fractures in patients with RA as 3.30 (95% CI: 1.84 – 5.92) and 1.53 (95% CI: 1.04 – 2.25) per 100 person-years, respectively (Jin 2018). In PsA, a population-based study utilizing the Health Improvement Network in the UK reported the incidence rate of fractures overall as 0.99 per 100 person-years in patients with PsA (Ogdie 2017). In AS, a study of 6,474 AS patients in a public healthcare database in Spain reported site-specific fracture incidence rates of 0.21 (95% CI: 0.16 – 0.28) per 100 person-years for clinical vertebral fractures and 0.83 (95% CI: 0.72 – 0.94) for nonvertebral fractures in AS patients (Muñoz-Ortego 2014). In AD, in a population-based study using

the Clinical Practice Research Datalink (CPRD GOLD) in the UK, comprising 526,808 patients with atopic eczema, the unadjusted incidence rate of any fracture was 1.43 (95% CI: 1.41 – 1.44) per 100 person-years (Lowe 2020). In UC, a study in the University of Manitoba IBD database with coverage of the entire Manitoba province in Canada, reported overall rate of fracture was 1.12 (95% CI: 0.98 – 1.28) per 100 person-years, with clear increase with age (Bernstein 2000). In a population-based cohort study in 83,435 patients with incident IBD in Sweden, the rate of incident hip fractures was reported as 0.20 (95% CI: 0.19 – 0.21) per 100 person-years (Ludvigsson 2019).

Rheumatoid Arthritis:

In the placebo-controlled periods of Phase 3 RA trials (12/14 weeks) fractures were reported in 1.0% of the upadacitinib 15 mg group, 1.5% of the upadacitinib 30 mg group, and 0.4% of the placebo group.

Through the data cutoff of 15 February 2022, in the MTX-controlled study, Study M13-545, the event rate (long-term all exposure) of fractures was 1.6 E/100 PY for upadacitinib 15 mg monotherapy and 2.5 E/100 PY for MTX monotherapy. In the adalimumab-controlled study (Study M14-465), through the data cutoff, the long-term event rate (all study drug exposure) of fractures was 2.9 E/100 PY for upadacitinib 15 mg (plus background MTX) and 2.3 E/100 PY for adalimumab (plus background MTX).

Through the data cutoff, across the Phase 3 RA trials, the event rate (long-term all exposure) of fracture was 2.7 E/100 PY for upadacitinib 15 mg and 4.5 events/100 PY for upadacitinib 30 mg. Note: The 15 mg dose is the approved dose for RA.

Psoriatic Arthritis:

In the placebo-controlled periods of Phase 3 PsA trials (24 weeks), events of fracture were reported in 2.2% of the upadacitinib 15 mg group, 2.0% of the upadacitinib 30 mg group, and 1.4% of the placebo group. In the adalimumab-controlled study, Study M15-572, the event rate (long-term all exposure) of fractures through the data cutoff of 15 February 2022, was 1.9 E/100 PY in the upadacitinib 15 mg group compared with 1.5 E/100 PY in the adalimumab group. Through the data cutoff, across the Phase 3 PsA trials, the event rate (long-term all exposure) of fracture was 2.0 E/100 PY for upadacitinib 15 mg and 2.4 E/100 PY for upadacitinib 30 mg. Note: The 15 mg dose is the approved dose for PsA.

Ankylosing Spondylitis:

In the placebo-controlled period of the Phase 2/3 study (14 weeks), no fractures were reported in either the upadacitinib 15 mg group or the placebo group. Through the data cutoff of 15 February 2022, across the Phase 2/3 and Phase 3 AS trials, the event rate (long-term all exposure) of fracture was 2.0 E/100 PY for upadacitinib 15 mg.

Non-Radiographic Axial Spondyloarthritis:

In the placebo-controlled period of Study 2 of the Phase 3 trial, the percentage of subjects with fractures through 14 weeks was 1.9% in the upadacitinib 15 mg group and 0% in the placebo group. Through the data cutoff of 15 February 2022, the long-term event rate (any upadacitinib) of fractures was 2.7 E/100 PY.

Atopic Dermatitis:

Placebo-controlled period:

In the placebo-controlled periods of the global Phase 2 and 3 Phase 3 Pivotal trials, events of fracture were reported in 0.6% of the upadacitinib 15 mg group and in 0.3% of the upadacitinib 30 mg group, and < 0.1% of the placebo group. In adults (Phase 3 trials), 5 events of bone fracture occurred, 1 event was serious, and none led to study drug discontinuation. In adolescents (Phase 3 trials), 3 subjects reported a bone fracture. None were considered serious, led to discontinuation of study drug, or were considered by the investigator to have a reasonable possibility of being related to study drug.

Long-term exposure:

Overall, across the Phase 3 trials (adults and adolescents), the event rate of fractures was 2.0 E/100 PY and 1.6 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively.

In adults (Phase 3 trials), the event rate of fractures was 1.7 E/100 PY and 2.1 E/100 PY in the upadacitinib 15 mg and 30 mg groups, respectively. SAEs of bone fractures occurred in both upadacitinib groups. No bone fracture event led to discontinuation of study drug.

In adolescents (Phase 3 trials), the upadacitinib 30 mg group reported a higher rate of TEAEs of bone fracture (1.9 E/100 PY) compared with upadacitinib 15 mg (1.1 E/100 PY). Three events in adolescent subjects were considered serious and none led to study drug discontinuation.

Ulcerative Colitis:

In the placebo-controlled induction period (8 weeks) of the Phase 2 and 3 UC trials, the percentage of subjects with fractures was 0.3% in the upadacitinib 45 mg, and 0 fractures were reported in the placebo group.

Through the data cutoff of 15 February 2022, in the Phase 3 UC maintenance trials (up to 52 weeks) for induction treatment clinical responders, the event rate of fractures was 0.9 E/100 PY and 0.5 E/100 PY in the upadacitinib 30 mg and 15 mg groups, respectively, and 1.5 E/100 PY in the placebo group.

The long-term event rates for fractures were 1.4 E/100 PY and 1.8 E/100 PY in the upadacitinib 45/30 mg and 45/15 mg cohorts, respectively.

Crohn's Disease:

In the placebo-controlled induction period (12 weeks) of the Phase 3 CD trials, the percentage of subjects with fractures was 0.6% in the upadacitinib 45 mg, and 0 fractures were reported in the placebo group.

During placebo-controlled maintenance treatment in the Phase 3 CD trials, for clinical responders to the induction dose, the event rates of fractures were 0.8 E/100 PY, 0.9 E/100 PY, and 0.7 E/100 PY in the upadacitinib 30 mg, upadacitinib 15 mg, and placebo groups, respectively.

With long-term treatment, the event rates of fractures were 1.2 E/100 PY and 1.4 E/100 PY in the upadacitinib 45 mg/30 mg and 45 mg/15 mg cohorts, respectively.

Across indications, the majority of subjects who experienced events of fracture had risk factors, other alternative etiology (e.g., trauma, fall), concomitant medications (e.g., steroid use), or concurrent medical conditions that pose an increased risk of fractures.

Giant Cell Arteritis:

During Period 1 (52 weeks), the EAIRs of TEAEs of bone fracture were slightly higher on upadacitinib treatment (upadacitinib 15 mg: 7.7 n/100 PYs; upadacitinib 7.5 mg: 7.1 n/100 PYs) compared to placebo (6.5 n/100 PYs).

In the long term, the EAIR of TEAEs of bone fracture was higher in the placebo group (5.8 n/100 PYs) compared to the upadacitinib treatment groups (upadacitinib 15 mg: 3.7 n/100 PYs; upadacitinib 7.5 mg: 4.3 n/100 PYs).

Risk Factors and Risk Groups: Risk factors for fractures include increasing age, female sex, previous fractures, underlying medical conditions, and use of medications such as glucocorticoids. Advanced age is common for RA, PsA, and GCA patients, patients with RA are predisposed to osteoporotic fracture (Xue 2017), patients with AS are at increased risk of vertebral fracture (Vosse 2009), patients with CD and UC have a significant risk of fractures due to osteoporosis (Bernstein 2000), background use of corticosteroids is common in RA, PsA, UC, CD, and GCA, and both systemic and topical use is common in pediatric and adult patients with AD (Ha 2022), placing these populations at increased risk.
Preventability: Standard care which can include physical activity, healthy lifestyle, good nutrition, reducing environmental hazards for falls, and prevention/monitoring for osteoporosis may be used for fracture prevention for patients at risk.
Impact on the Risk-Benefit Balance of the Product: The risk-benefit balance remains positive.
Public Health Impact: It is anticipated that public health impact will be minimal.

SVII.3.2 Presentation of the Missing Information

Missing information 1: Use in very elderly (≥ 75 years of age) MedDRA terms: See Annex 1
Population in need of further characterization: There is limited experience with upadacitinib in subjects ≥ 75 years of age; therefore, further characterization of the safety profile in this population is needed. Data from routine pharmacovigilance activities and long-term comparative cohort studies will be collected post-authorization.
Missing information 2: Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C MedDRA terms: See Annex 1
Population in need of further characterization: There is limited clinical experience with upadacitinib in subjects with evidence of untreated chronic infection with hepatitis B or hepatitis C; therefore, further characterization of the safety profile is needed. Data from routine pharmacovigilance activities and long-term comparative cohort studies will be collected post-authorization.
Missing information 3: Use in patients with moderate hepatic impairment MedDRA terms: See Annex 1

Population in need of further characterization: There are limited safety data for upadacitinib in subjects with moderate hepatic impairment and no safety data in subjects with severe hepatic impairment; therefore, further characterization of the safety profile is needed. The SmPC states that upadacitinib is contraindicated for use in patients with severe hepatic impairment; consequently, use in patients with severe hepatic impairment is not included as missing information. Data in patients with moderate hepatic impairment from routine pharmacovigilance activities and long-term comparative cohort studies will be collected post-authorization.
Missing information 4: Use in patients with severe renal impairment MedDRA terms: See Annex 1
Population in need of further characterization: Experience with upadacitinib in subjects with severe renal impairment is limited; therefore, further characterization of the safety profile is needed. Data from routine pharmacovigilance activities and long-term comparative cohort studies will be collected post-authorization.
Missing information 5: Long-term safety MedDRA terms: See Annex 1
Population in need of further characterization: Long-term upadacitinib clinical safety data are currently limited. RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA 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 and long-term comparative cohort studies will be collected post-authorization, as will data from the long-term extension portions of Phase 3 trials.
Missing information 6: Long-term safety in adolescents with AD MedDRA terms: See Annex 1
Population in need of further characterization: Long-term upadacitinib clinical safety data are currently limited in adolescents, including potential effects of upadacitinib on height in growing children. Further characterization of long-term safety in adolescents will include data from adolescent subjects who continue in the long-term extension of the Phase 3 AD clinical trials (Studies M16-045, M18-891, and M16-047), the long-term safety study of upadacitinib use in AD patients (Study P20-390), and in the additional long-term pharmacovigilance study of growth in adolescents with AD who receive upadacitinib (Study P21-824).

Module SVIII Summary of the Safety Concerns

Table 8. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Serious and opportunistic infections including TB • Herpes zoster • NMSC • GI perforation
Important potential risks	• Malignancies excluding NMSC • MACE • VTEs (deep venous thrombosis and pulmonary embolus) • DILI • Fetal malformation following exposure in utero • Fractures
Missing information	• Use in very elderly (≥ 75 years of age) • Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C • Use in patients with moderate hepatic impairment • Use in patients with severe renal impairment • Long-term safety • Long-term safety in adolescents with AD

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

III.1 Routine Pharmacovigilance Activities

Specific follow-up questionnaires for adverse reactions of serious and opportunistic infections including tuberculosis (TB), malignancies, MACE, VTEs, GI perforation, DILI, pregnancies, and fractures:

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. If the reporter is the consumer, 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 judgement or local regulations are applied to determine if further attempts (above the minimum) should be made. Data collection using the questionnaires will be done for the categories of events described in Annex 4.

Other forms of routine pharmacovigilance activities for VTE:

- Monitoring of VTE risk: Status reports to be provided within the periodic safety update report (PSUR) providing an analysis of VTE events occurring during the reporting period in order to provide an ongoing assessment of VTE risk.
- Literature review: To identify any emerging hypotheses regarding a potential association of VTE events with JAK inhibition. A status report will be provided annually within the PSUR.

III.2 Additional Pharmacovigilance Activities

Study P19-150: Long-term safety cohort studies of upadacitinib (Rinvoq®) use for the treatment of RA in Europe

Study Short Name and Title: Long-term safety studies of upadacitinib use in RA patients in Europe

Rationale and Study Objectives: Although the upadacitinib clinical trials provide valuable information on the product's efficacy and safety, assessment of safety using randomized controlled trials (RCT) data is limited by the relatively small sample sizes and short duration of follow-up. Long-term safety data are needed in patients in routine clinical practice who are exposed to upadacitinib, including patients not included in the clinical program or in populations with limited clinical trial data (e.g., the very elderly, patients with evidence of untreated chronic infection with hepatitis B or hepatitis C, patients with moderate hepatic impairment, and patients with severe renal impairment). Several disease-based prospective rheumatology registries have been established in Europe to complement clinical trial data, including providing longitudinal safety data for new therapies.

Several of these European RA registries provide nearly complete national coverage of patients in a comprehensive electronic health record with multiple registry linkages and with low attrition over time. These registries allow for the evaluation of outcomes referent to an active user comparator group, and their large size provides the ability to study rare events not well captured in RCTs. As such, these registries have been used extensively to address post-marketing safety requirements in patients with RA, including comparative analyses of rates of infections, malignancy, adverse hepatic and renal events, and MACE. There is also demonstrated feasibility to evaluate VTE risk in treated RA patient populations in these European RA registries (Davies 2011, Holmqvist 2012).

Recommended upadacitinib use in RA has been changed following the procedure under Article 20. The purpose of this study is to evaluate and characterize the important identified and potential risks of upadacitinib and missing information on the safety of upadacitinib, as described in the European Union Risk Management Plan. The primary objectives are to assess

comparability across users of upadacitinib and other select systemic treatments for RA through in-depth assessments of drug utilization and patient characteristics at baseline; to describe the incidence of the following safety outcomes in patients with RA treated with upadacitinib: malignancy excluding non-melanoma skin cancer, including malignancy by type, NMSC, MACE, VTE, serious and opportunistic infections (including herpes zoster and TB), GI perforations, liver injury (including DILI), bone fractures, and all-cause mortality; if a suitable comparator is identified, to describe and compare (when feasible) the incidence of the above safety outcomes in patients with RA treated with upadacitinib relative to those treated with other select systemic RA treatments (excluding other JAK inhibitors). Secondary objectives are to describe the incidence of the safety outcomes mentioned under the primary objective among the following patient subcohorts of upadacitinib users: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), patients with severe renal impairment (when possible using proxy measures available within a given data source), and patients with evidence of chronic infection with HBV or HCV; if a suitable comparator is identified, to describe the incidence of the safety outcomes mentioned under primary objectives in the following patient subcohorts of other select systemic RA treatments: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), patients with severe renal impairment (when possible using proxy measures available within a given data source), and patients with evidence of chronic infection with HBV or HCV.

Study Design: Prospective population-based cohort studies of patients in the real-world will be conducted utilizing European RA registries to monitor the incidence of safety outcomes among patients exposed to upadacitinib for the treatment of RA and when feasible, compared to patients exposed to selected standard of care systemic RA treatments. A new user, active comparator cohort design will be used. The study will include up to 3 – 5 years of patient accrual with up to 8 years of patient follow-up. A study period of up to 8 years will allow evaluation of longer latency outcomes, including malignancy. Initial in-depth descriptive analyses will be conducted to assess comparability across treatment cohorts and inform the design (including selection of suitable comparator/s) of subsequent analyses in response to labelling changes following the Article 20 procedure which are likely to result in substantial differences in baseline characteristics of patients initiating upadacitinib and those initiating other systemic treatments.

Study Population: Patients with RA prescribed upadacitinib and appropriate standard of care comparators will be studied in normal clinical care in 5 European RA registries including the Anti-Rheumatic Treatment in Sweden (ARTIS) registry, the Danish Registry of Biological Therapy (DANBIO), the British Society for Rheumatology Biologics Register (BSRBR), the Spanish Registry for Adverse Events of Biological Therapy in Rheumatic Diseases (BIOBADASER), and Germany's RA Biologics Register (Rheumatoide Arthritis: Beobachtung der

Biologika-Therapie [RABBIT]). The European registers initiated by national rheumatology societies vary in inclusion criteria methodology for the cohorts.

Milestones:

Milestones	Planned Dates
Upadacitinib market availability	Q1 2020[a]
Registration in the EU PASS Register	12 February 2021
Start of data collection	Q1 2020
Study progress reports	Submitted in 2022 and 2023. No longer needed per EMA advice
Interim report of study results	Approximately 5 years following market availability (estimated Q3 2025)
End of data collection	Estimated Q1 2028
Final report of study results	Estimated Q1 2030[b]

a. Dates of market availability will differ by country based on reimbursement ruling.

b. When data are available for delivery from all registries (i.e., when received from the final registry).

Study P19-141: Long-term safety study of Rinvoq™ in RA patients enrolled in the CorEvitas (formerly Corrona) RA Registry in the United States

Study Short Name and Title: Long-term safety study of upadacitinib use in RA patients in the US

Rationale and Study Objectives: Upadacitinib is a selective and reversible inhibitor of JAK with demonstrated efficacy in treatment of moderate to severe active RA. Safety has been characterized during the development program; however, additional evaluation of safety for rare events, long latency outcomes, and in the broader RA population is warranted. To provide this evidence, AbbVie plans to implement a post-approval, population-based prospective cohort study in partnership with the CorEvitas (formally Corrona) US RA Registry. The study will be designed and sufficiently powered to identify clinically meaningful increases in the risk of malignancies, VTE, MACE, and serious infections in upadacitinib patients relative to patients treated with other therapies for moderately to severely active RA. A sub-study to explore thrombosis biomarkers at baseline in upadacitinib treated and comparator biologic treated patients will be conducted. In addition, biobanking will be employed to allow for future evaluation of potential biomarkers related to VTE risk, should an increased risk be identified in upadacitinib treated patients.

The overall goal of the study is to characterize the safety of upadacitinib in RA patients in the post-approval setting. The primary objective of the study is to compare the incidence of malignancy (excluding NMSC), NMSC, MACE, VTE, serious infection events, and all-cause mortality in adults with RA who receive upadacitinib in the course of routine clinical care

relative to those who receive biologic therapy for the treatment of RA. Secondary objectives are to describe the incidence rates of herpes zoster, opportunistic infections, active TB, GI perforations, evidence of DILI, and fractures; to describe the incidence of the above outcomes in very elderly patients (aged ≥ 75 years); and to describe the incidence rates of events in primary and secondary objectives in the following subgroups of interest: patients with moderate hepatic impairment at the time of Rinvoq or biologic therapy start; patients with evidence of chronic infection with HBV or HCV at the time of Rinvoq or biologic therapy start; and patients with severe renal impairment at the time of Rinvoq or biologic therapy start. An exploratory objective is to describe the distribution of risk factors for VTE in those treated with Rinvoq and those treated with biologic therapy, and in those who do and do not experience VTE during follow-up, in a subset of participating patients providing laboratory samples.

Study Design: This study is a prospective, observational cohort study that will use the CorEvitas (formerly Corrona) RA Registry. Data from the CorEvitas RA Registry will be compiled to produce a set of drug exposure cohorts that will be used in the current study to accomplish the study objectives. The drug exposure cohorts will include an upadacitinib exposure cohort and a comparator biologic exposure cohort. A 5-year accrual period and an 8-year follow-up period are planned for the malignancy evaluation, resulting in a 13-year total study duration. The main analyses will employ propensity score methods to address confounding by indication (channeling bias), followed by estimation of incidence rates, as well as multivariable Cox proportional hazards modeling to estimate adjusted HRs and associated 95% CIs to compare the risk of an event in the upadacitinib exposure cohorts to that in the non-JAK inhibitor biologic therapy exposure cohorts. In addition to comparative analyses, the population of patients in the study will be characterized with respect to demographic, clinical, disease, and patient-reported outcomes using descriptive statistics.

Study Population: The CorEvitas US RA Registry is an established, prospective, multicenter, observational registry for adult patients with RA. Established in 2001, CorEvitas includes data from over 52,500 RA patients, 750 physicians, and 182 sites, across 42 states. Detailed data collection by participating investigators and their patients with RA enables capture of a number of clinical, behavioral, and disease severity measures as well as clinical outcomes associated with treatment for RA. Data on targeted outcomes are collected prospectively, via Targeted Adverse Event Questionnaires.

Milestones:

Milestones	Planned Dates
Start of data collection (date of Rinvoq approval in US)	16 August 2019 (ongoing registry)
Registration in the EU PASS Register	12 February 2021
Study progress reports	Submitted in 2022 and 2023. No longer needed per EMA advice[a]
Interim report of study results	Estimated Q2 2029
End of data collection	Estimated Q4 2029
Final report of study results	Estimated Q1 2030

a. After 2023, annual biomarker sub-study update to be provided in PSUR (response PSUR7). PRAC Assessment Report for the Post-Authorisation Measures EMEA/H/C/004760/MEA/003.3, 004.3 and 005.2.

Study P20-199: Drug utilisation study of upadacitinib (Rinvoq™) in Europe to evaluate the effectiveness of additional risk minimisation measures among patients with Rheumatoid Arthritis

Study Short Name and Title: Upadacitinib drug utilisation study for additional risk minimization measure (aRMM) effectiveness evaluation in RA

Rationale and Study Objectives: As with other JAK inhibitors already marketed in Europe (e.g., tofacitinib and baricitinib), important safety risks have been identified with upadacitinib that require aRMMs. Using data derived from European RA registries, AbbVie plans to implement a drug utilization study to characterize the use of upadacitinib and evaluate the effectiveness of the aRMMs (HCP educational guide and patient card) in the pre-Article 20 and post Article 20 time periods.

This study aims to evaluate the use of upadacitinib in routine clinical care through the following specific objectives: to describe the baseline characteristics of new users of, and in a similar manner, to describe new users of a selected biologic disease-modifying anti-rheumatic drug (bDMARD) for comparison; to evaluate prescribers' adherence to the upadacitinib aRMMs, specifically: compliance to recommendations for patient screening and laboratory monitoring prior to and during treatment; compliance to recommendations for limitations of use, including: Use in patients with risk factors for GI perforation; use in patients with risk factors for VTE; use in the patients aged 65 years and older; use in patients with risk factors for CVD; use in patients with risk factors for malignancy; use in patients with risk factors for serious infections; and contraindicated use (active TB and pregnancy); and to describe changes in the utilisation of upadacitinib following the updated recommendations and limitations for use implemented after the Article 20 referral procedure.

Study Design: This will be a population-based cohort study of new users of upadacitinib and selected bDMARDs marketed for the treatment of RA in Europe. The study will be conducted using data collected by a network of European RA registries, including DANBIO (Denmark), ARTIS (Sweden), BSRBR (UK), BIOBADASER (Spain), and RABBIT (Germany). Patient characteristics will be described at baseline. In addition, outcome indicators among new users of upadacitinib will be assessed during their continuous treatment to assess compliance/adherence of prescribing HCP to important safety information communicated in the additional risk minimization measures (healthcare professional educational guide and patient card). Analysis will also include assessment by pre-post Article 20 recommendations and the COVID-19 pandemic.

Study Population: The main study cohort will include new users of upadacitinib in normal clinical care. The comparator cohort will include new users of any bDMARD (i.e., a composite cohort by the drug type). The European registers initiated by national rheumatology societies vary in inclusion and exclusion criteria methodology for the cohorts. Patients will be eligible for inclusion in the study population from the date of upadacitinib market availability (based on the national reimbursement authority ruling date; expected in early 2020) to the end of the study enrolment period (anticipated to continue for 2 years after market availability). Patient characteristics will be assessed cross-sectionally at baseline. Each member of the upadacitinib-exposed cohort will be followed from the cohort entry date (i.e., upadacitinib initiation) to the earliest of the following dates: 90 days after the last prescription of the study drug, end of the study period, death, or disenrollment from the database.

Milestones:

Milestones	Planned Dates
Upadacitinib market availability	Q1 2020[a]
Draft protocol submission	16 March 2020
Date of study registration in the EU PASS Register	12 February 2021
Start of data collection	Estimated Q1 2020
Study progress reports	Submitted Q2 2022, Q1 2023; next estimated Q1 2024, Q2 2025
End of enrollment period	Estimated Q4 2024
End of data collection	Estimated Q4 2025[b]
Final report of study results	Estimated Q3 2026

a. Dates of market availability will differ by country based on reimbursement ruling.

b. When data are available for delivery from all registries (i.e., when received from the final registry).

Study P20-390: Cohort study of long-term safety of upadacitinib in the treatment of atopic dermatitis in Denmark and Sweden

Study Short Name and Title: Long-term safety study of upadacitinib use in AD patients

Rationale and Study Objectives: Upadacitinib 15 mg was approved for the treatment of adults with moderate to severe active RA in the EU on 18 December 2019. Studies to assess long-term safety of upadacitinib in the routine clinical setting for RA are currently being conducted. Upadacitinib 15 mg is approved to be used in the EU for treatment of adolescents with moderate to severe AD who weigh 30 kg or over. Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 10 March 2023), upadacitinib recommended use and doses have been changed. Upadacitinib 15 mg is approved to be used in the EU for treatment of elderly patients ≥ 65 years of age, or patients with risk factors for malignancy, MACE, or VTE. In addition, upadacitinib should only be used, if no suitable alternatives are available, in patients 65 years of age or older, in patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors and in patients with malignancy risk factors. An additional long-term safety study is proposed in order to assess the long-term safety of upadacitinib use in patients with moderate to severe AD in a real-world setting. The proposed study will be designed to evaluate and characterize the important identified and potential risks of upadacitinib and missing information as described in this RMP for the treatment of AD.

The overall goal of the study is to characterize the safety of upadacitinib in AD patients in the post-approval setting. The primary objectives of the study are to assess comparability across upadacitinib and other select systemic treatments for AD through in-depth assessments of treatment pattern and patient disposition at baseline and to describe the incidence of the following outcomes, in adolescent and adult patients treated with upadacitinib, and compare (when feasible) the incidence of the above AEs relative to those treated with other alternative systemic drug therapies for AD, in the course of routine clinical care: Malignancy (excluding NMSC), NMSC, MACE, VTE, serious infections (including opportunistic infections), herpes zoster, EH/Kaposi's varicelliform eruption, active TB, GI perforations, evidence of DILI, all-cause mortality, and fractures.

Secondary objectives are to describe the incidence of the above AEs in patients who receive upadacitinib by: dose of upadacitinib (15 mg and 30 mg); age groups (adolescents [12 – 17 years], adults aged 18 – 64 years, 65 – 74 years, and ≥ 75 years); history of moderate hepatic impairment at the time of upadacitinib initiation; history of chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) at the time of upadacitinib initiation; and history of severe renal impairment at the time of upadacitinib initiation, and, if a suitable comparator is identified, to describe the incidence of the above AEs in patients who receive other select systemic AD treatments.

Study Design: A prospective, observational cohort study will be used as the study design for the upadacitinib AD post-authorisation safety study (PASS). It will include adolescents and adults with moderate to severe AD exposed to upadacitinib or other selected systemic drug therapies for the treatment of AD. This study will be conducted using National Registers in Denmark and Sweden.

Study Population: Study population will be adolescents and adults in Denmark or Sweden who are new users of upadacitinib or a comparator agent for treatment of moderate to severe AD. Study cohorts will include upadacitinib 15 mg initiators, upadacitinib 30 mg initiators and other selected systemic drug therapy initiators. Other systemic drug therapies may include dupilumab, cyclosporine, MTX, azathioprine, and mycophenolate mofetil, and other systemic immunosuppressants that are available. A 5-year accrual period and a 5-year follow-up are planned for the malignancy evaluation, resulting in a 10-year total study duration. To make 2 cohorts comparable to address confounding by indication (channeling bias), propensity score methods will be employed before the main analyses.

Milestones:

Milestones	Planned Dates
Draft protocol submission	18 March 2021
Date of study registration in the EU PASS Register	11 July 2023
Start of data collection for secondary data use (date when individual patient data extraction starts)	Q1 2024
Annual progress reports	Q3 2023-Q3 2031 (except 2028)[a]
Interim report of study results (incl. Data up to Dec 2026)	Q4 2028
End of data collection for secondary data use (date when analytical data set is available)	Q4 2032
Final report of study results (incl. data up to Dec 2031)	Q4 2033

a. First progress report in Q3 2023 will only include data from Sweden, and will be based on descriptive statistics ordered from the Swedish National Board of Health and Welfare. No individual data will be extracted for the first progress report. Data extraction is planned for Q1 2024 in both Denmark and Sweden, post EMA approval of protocol revisions following Article 20 referral procedure recommendation (10 March 2023), in due time for the second progress report.

Study P21-825: Drug utilization study evaluating additional risk minimization measures for upadacitinib in the treatment of atopic dermatitis in Europe

Study Short Name and Title: Effectiveness evaluation of aRMMs for upadacitinib in AD

Rationale and Study Objectives: Additional risk minimization is being used for upadacitinib in RA and is proposed for upadacitinib in AD. Specific risks included in upadacitinib's risk minimization program will require aRMMs. The study aims to evaluate the use of upadacitinib in

individuals with AD in routine clinical care in Denmark, Germany, Spain, and Sweden with the following specific objectives: to describe the baseline characteristics of individuals with AD who are new users of upadacitinib; to the extent measurable, evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs among individuals with AD who are new users of upadacitinib, by: quantifying the compliance to recommendations for posology (average daily dose) and by describing the duration of use; quantifying the compliance to recommendations for the use among individuals who have risk factors for GI perforation, serious infections, malignancy, MACE, and VTE; quantifying the compliance to the recommendations for the use among patients aged 65 years and older; quantifying the compliance to the recommendations for contraindicated use including pregnancy and active TB; quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark, Germany and Spain only); and to describe the changes in the utilisation of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure, specifically: describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; describe the use of upadacitinib among patients aged 65 years and older; and describe the use of upadacitinib 30 mg.

Study Design: This will be a descriptive population-based cohort study of individuals with AD newly exposed to upadacitinib marketed for the treatment of AD in Denmark, Germany, Spain, and Sweden.

Study Population: All patients with AD registered in the databases in the four countries who are treated with upadacitinib. Patients will be eligible for inclusion in the study population from the date of upadacitinib market availability for the treatment of AD in Denmark, Germany, Spain, and Sweden (22 October 2021, 27 August 2021, 04 April 2022, and 08 September 2021, respectively) to the end of the study period (i.e., 31 December 2024). Patient characteristics will be assessed cross-sectionally at baseline. Each member will be followed from the cohort entry date (i.e., upadacitinib initiation) to the earliest occurrence of: end of the study period (31 December 2024), death, or study withdrawal (emigration in Denmark and Sweden, move outside Catalonia in Spain, or withdrawn from insurance in Germany).

Milestones:

Milestones	Planned Dates
Date of study registration in the EU PASS Register	30 days post protocol approval
Start of data collection for secondary data use (date when individual patient data extraction starts)	Q2 2024
Study progress report 1	Q4 2024
Study progress report 2	Q3 2025

End of data collection for secondary data use (date when analytical data set is available)	Q1 2026
Final study report	Q3 2026

Study P21-824: A study of growth, development and maturation in adolescents with atopic dermatitis who receive upadacitinib

Study Short Name and Title: A study of growth in adolescents with AD who receive upadacitinib

Rationale and Study Objectives: Upadacitinib 15 mg and 30 mg once daily (QD) are approved for use in adults with moderate to severe AD and upadacitinib 15 mg QD is approved for use in adolescents with moderate to severe AD weighing 30 kg or over and elderly patients ≥ 65 years of age. The available nonclinical data for upadacitinib do not suggest a risk associated with bone development in patients ≥ 12 years old. However, since the long-term use of upadacitinib on growth in adolescents has not been studied, the impact of long-term use of upadacitinib on growth in adolescents is not known. Per the Pharmacovigilance Risk Assessment Committee's (PRAC's) request, this study aims to evaluate the growth, development, and maturation in North American (US and Canada)-residing adolescents with moderate to severe AD who receive upadacitinib vs. biologic and other non-biologic, non-JAKi systemic comparators in routine clinical care. Where feasible, a cohort of European-residing adolescents with moderate to severe AD will also be evaluated.

The primary objective is to compare differences in changes from baseline in height standard deviation score (SDS) and weight SDS, age at peak height velocity, age at Tanner stage progression, and incidence of bone fractures in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.

The secondary objectives of the study are to describe changes from baseline in standing height, height percentiles, height velocity, height velocity SDS, weight, weight percentiles, body mass index (BMI), BMI percentiles, and BMI SDS, as well as the frequency of delayed puberty in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.

Study Design: This will be an observational, prospective study of adolescents with AD exposed to upadacitinib or biologic or other non-biologic, non-JAKi systemic drugs for the treatment of AD.

Study Population: The study population will be drawn from patients enrolled in the CorEvitas Adolescent AD Registry which will enroll younger adolescents (12 – 15 years old) with moderate to severe AD in the US, Canada, and Europe. The primary study analyses will include cohorts of adolescents newly prescribed upadacitinib for the treatment of moderate to severe AD in routine clinical care in North American sites (US and Canada), with secondary analyses

including cohorts from Europe. The comparator cohort will include patients with moderate to severe AD newly prescribed biologic or other non-biologic, non-JAKi systemic therapies approved for the treatment of AD at the time of registry enrollment.

Milestones:

Milestones	Planned Dates
Upadacitinib market availability	Q4 2021[a]
Date of study registration in the EU PASS Register[b]	
Start of data collection	Estimated Q4 2023[c]
Annual progress reports	Annually starting in Q4 2024
Interim study report 1	Estimated Q4 2027
Interim study report 2	Estimated Q4 2030
End of data collection	Estimated Q4 2032
Final study report	Estimated Q4 2033

a. Dates of market availability will differ based on reimbursement ruling.
b. This study will be registered at the ENCePP website within a target of 30 calendar days after the protocol is approved by the agency.
c. Data collection will start after the protocol is approved by the regulatory agency and Institutional Review Board.

Study P24-343: Cohort study of long-term safety of upadacitinib for the treatment of ulcerative colitis and Crohn's disease in a real-world setting in Europe

Study Short Name and Title: Long-term safety study of upadacitinib use in UC and CD patients in Europe

Rationale and Study Objectives: Upadacitinib is approved for the treatment of adults (≥ 18 years of age) with moderate to severe UC or CD who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Upadacitinib should only be used, if no suitable alternatives are available, in patients 65 years of age or older, in patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors and in patients with malignancy risk factors. Although the upadacitinib clinical trials provide valuable information on the product's efficacy and safety, long-term safety data are needed for individuals who are exposed to upadacitinib. The study aims to evaluate the long-term safety of upadacitinib use in adults in routine clinical care for the treatment of UC and CD.

The primary objectives of the study are to: 1) describe and compare the incidence of GI perforation in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy, and 2) describe and compare, where possible, the incidence of fractures and DILI in adults with UC or CD treated with upadacitinib,

relative to those treated with select biologic IBD treatments at a similar line of therapy. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for incidence comparison of fractures and DILI.

The secondary objectives are to describe and compare, where possible, the incidence of the following secondary safety outcomes in adults with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy for UC and CD in the course of routine clinical care: malignancy excluding NMSC (stratified by type), NMSC, MACE, VTE, serious infections (defined as all infections that require hospitalization, including opportunistic infections), herpes zoster, active TB, and all-cause mortality. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for the incidence comparison of the secondary outcomes.

In addition, incidence of the primary and secondary safety outcomes will be described in patients with UC or CD who receive upadacitinib by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing). When possible, the occurrence of the safety outcomes will be described in the following subgroups of interest, with limited or missing information from the clinical development program:

- Very elderly (aged ≥ 75 years) at the time of treatment initiation;
- Patients with moderate hepatic impairment at the time of treatment initiation;
- Patients with severe renal impairment at the time of treatment initiation;
- Patients with evidence of chronic infection with HBV or HCV at the time of treatment initiation.

Study Design: A long-term, non-interventional, cohort study will be conducted using longitudinal secondary data collected from Denmark, Sweden, and Spain, from authorization date of upadacitinib for the treatment of IBD until the end of 2032. A new-user, active comparator design will be used to address the objectives of the study. Initial in-depth descriptive analyses for baseline characteristics of patients initiating upadacitinib and those initiating other systemic treatments will be conducted to assess comparability across treatment cohorts and inform the design (including selection of suitable comparator/s) of analyses subsequent to Labelling changes following Article 20 procedure.

Study Population: Study population will be adult patients with IBD as registered in the Danish National Patient Register (NPR) in Denmark, the Swedish IBD Quality Register (SWIBREG), or Swedish NPR in Sweden, and the National Study on Inflammatory Bowel Disease Genetic and

Environmental Determinants [Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales] (ENEIDA) registry in Spain, and who are new users of upadacitinib or select biologic IBD treatments. In Denmark and Sweden all individuals receiving a comparator treatment will be included, while in Spain a random sample of user matched on line of treatment, UC or CD, will be selected. Patients who used other JAK inhibitors before the index date will be excluded.

Milestones:

Milestones	Planned Dates
Start of data collection for secondary data use (date when data extraction starts)	Q1 2025[a]
Progress reports	Annual, beginning Q4 2025 (except 2029)[b]
End of interim data collection (date when interim analytical data set is available)	Q4 2028[c]
Interim report of study results (EMA)	Q4 2029[d]
End of data collection for secondary data use (date when final analytical data set is available)	Q2 2034
Final study report	Q2 2035

a. Start of data collection will be determined by approval and availability in each geographic region, with the planned date given being the date when data extraction is planned to start in Sweden. All data starting Q3 2022 will be collected and extracted at each data extraction through the entire study.

b. First progress report will only include data from Sweden, see footnote a above. No progress report will be submitted during the year of interim report.

c. Date when interim analytical data set is available will differ between the geographic regions, with the planned date given being the date when analytical data sets are available in all three regions.

d. Interim report will include description of all planned study outcomes in the population under study. The GI perforation results in the interim report will include descriptive and comparative analyses in UC and CD separately, and in IBD combined.

Study P24-344: Drug Utilization Study Evaluating Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Ulcerative Colitis in Europe

Study Short Name and Title: Effectiveness evaluation of aRMMs for upadacitinib in UC

Rationale and Study Objectives: Additional risk minimization is being used for upadacitinib in RA and is proposed for upadacitinib in UC. Specific risks included in upadacitinib's risk minimization program will require aRMMs. AbbVie plans to describe the baseline characteristics of new users of upadacitinib and evaluate the effectiveness of the aRMMs (HCP educational guide and patient card) in a drug utilisation study.

This study aims to evaluate the use of upadacitinib in routine clinical care for UC through the following specific objectives: to describe the baseline characteristics of UC patients who are

new users of upadacitinib (e.g., demographics, medical history, medical condition associated with upadacitinib use, and concomitant medication use); to the extent measurable, evaluate healthcare utilization in routine clinical care as indicator of physician adherence to the aRMMs among patients with UC who are new users of upadacitinib, by: quantifying the compliance to recommendations for posology (average daily dose) and duration of use; quantifying the compliance to recommendations for the use among patients who have risk factors for GI perforation, malignancy, MACE, VTE, and serious infections; quantifying the compliance to the recommendations for the use among patients aged 65 years and older; quantifying the compliance to the recommendations for contraindicated use including pregnancy and active TB; and quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark and Spain only); to describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure (Sweden only), specifically: describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; describe the use of upadacitinib among patients aged 65 years and older; and describe the use of higher maintenance dose of upadacitinib 30 mg.

Study Design: This will be a multi-country non-interventional descriptive drug utilization study among new users of upadacitinib for the treatment of UC. The study period ranges from the country-specific date of distribution of aRMMs for the treatment of UC in Denmark, Sweden, and Spain until 31 December 2025.

Study Population: The main study cohort will include new users of upadacitinib for the treatment of UC in routine clinical care. Study cohorts will be identified in electronic health care data from Denmark, Sweden, and Spain. In Denmark and Sweden, data will be collected from the SWIBREG registry and the Danish and Swedish nationwide registers. In Spain, data will be collected from ENEIDA registry in combination with retrospective review of electronic medical records. Each patient will be followed from the initiation of upadacitinib to the earliest occurrence of: upadacitinib discontinuation, end of the study period, study withdrawal (emigration, withdrawn from registry, or loss to follow-up), or death.

Milestones:

Milestones	Planned Dates
Date of study registration in the EU PASS Register	30 days post-protocol approval
Start of data collection for secondary data use (date when data extraction starts in Sweden)	Q1 2024[a]
Study progress report 1	Q3 2024[b]
Study progress report 2	Q3 2025
Study progress report 2	Q3 2026
End of data collection for secondary data use (date when analytical data set is available in all three countries)	Q1 2027
Final study report	Q3 2027

a. Start of data extraction will be different in the three countries due to later price and reimbursement approval for upadacitinib in Denmark and Spain (estimated end of 2023).

b. Will only include data from Sweden.

Long-term extension portion of upadacitinib clinical trials

Study M14-465:

Study Short Name and Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib to Placebo and to Adalimumab in Subjects with Moderately to Severely Active RA Who are on a Stable Background of MTX and Who Have an Inadequate Response to MTX

Rationale and Study Objectives: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.

Study Design: Subjects who completed the Week 48 visit (end of Period 1) entered the long-term extension portion of the study, Period 2 (up to 10 years). Subjects who were assigned to upadacitinib 15 mg QD at the end of Period 1 continued to receive upadacitinib 15 mg QD in a blinded manner. Subjects who were assigned to adalimumab 40 mg every other week (eow) at the end of Period 1 continued to receive adalimumab 40 mg eow in a blinded manner. When the last subject completed the last visit of Period 1 (Week 48), study drug assignment in both periods was unblinded to the Sponsor and sites, and subjects are being dispensed study drug in an open-label fashion until the completion of Period 2 and are no longer being dispensed matching placebo injections or tablets.

Study Population: Subjects with moderately to severely active RA who are on a stable background of MTX and who have an inadequate response to MTX.

Milestones:

- Final Study Report: 30 August 2028
- Targeted Final Study Report Submission to EMA: 30 November 2028.

Study M15-554:

Study Short Name and Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib to Placebo in Subjects with Active PsA Who Have a History of Inadequate Response to at Least One bDMARD

Rationale and Study Objectives: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1 (Period 1 is ongoing and all subjects have completed Week 24).

Study Design: Subjects who completed the Week 56 Visit (end of Period 1) enter the open-label long-term extension period (Period 2) of up to a total treatment duration of approximately 3 years (blinded until the last subject completes the last visit of Period 1). All subjects on upadacitinib continue study treatment to which they were assigned at baseline and subjects randomized at baseline to placebo switch to upadacitinib 15 mg or 30 mg at Week 24 (the end of the placebo-controlled part of the study).

Study Population: Subjects with moderately to severely active PsA who have an inadequate response to bDMARDs.

Milestones:

- Final Study Report: 31 December 2024
- Targeted Final Study Report Submission to EMA: 30 April 2025.

Study M15-572:

Study Short Name and Title: A Phase 3, Randomized, Double-Blind Study Comparing Upadacitinib to Placebo and to Adalimumab in Subjects with Active PsA Who Have a History of Inadequate Response to at Least One Non-Biologic DMARD

Rationale and Study Objectives: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.

Study Design: Subjects who completed the Week 56 Visit (end of Period 1) enter the open-label long-term extension period (Period 2) of up to a total treatment duration of approximately 5 years (blinded until the last subject completes the last visit of Period 1). All subjects on upadacitinib or adalimumab continue study treatment to which they were randomized at baseline, and subjects randomized at baseline to placebo switch to upadacitinib 15 mg or 30 mg at Week 24 (the end of the placebo-controlled part of the study).

Study Population: Subjects with moderately to severely active PsA who have an inadequate response to non-biologic DMARDs.

Milestones:

- Final Study Report: 30 September 2025
- Targeted Final Study Report Submission to EMA: 31 December 2025.

Study M19-944 (Study 1; biologic disease-modifying anti-rheumatic drug inadequate responder [*bDMARD-IR] AS)*

Study Short Name and Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult Subjects with axSpA Followed by a Remission-Withdrawal Period

Rationale and Study Objectives: To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active bDMARD-IR AS (Study 1), who have completed the Double-Blind Period.

Study Design: Subjects who completed the Week 14 visit (end of Double-Blind Period) enter the 90-week open-label extension (OLE) Period. Subjects in the placebo group will be switched to upadacitinib 15 mg QD at Week 52 for the OLE Period. Subjects who reach Week 104 on upadacitinib 15 mg QD will be assessed for remission; subjects in remission will be eligible for the Remission/Withdrawal Period and assessed for disease flare through Week 152.

Study Population: Adult subjects with active bDMARD-IR AS who are candidates for systemic therapy

Milestones:

- Final study report: Q2 2026
- Targeted Final Study Report Submission to EMA: Q3 2026.

Study M19-944 (Study 2; nr-axSpA)

Study Short Name and Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult Subjects with Axial Spondyloarthritis Followed by a Remission-Withdrawal Period

Rationale and Study Objectives: To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active nr-axSpA (Study 2), who have completed the Double-Blind Period.

Study Design: Subjects who completed the Week 52 visit (end of Double-Blind Period) enter the 52-week OLE Period. Subjects in the placebo group will be switched to upadacitinib 15 mg

QD at Week 52 for the OLE Period. Subjects who reach Week 104 on upadacitinib 15 mg QD will be assessed for remission; subjects in remission will be eligible for the Remission/Withdrawal Period and assessed for disease flare through Week 152.

Study Population: Adult subjects with active nr-axSpA who are candidates for systemic therapy.

Milestones:

- Final study report: Q2 2026
- Targeted Final Study Report Submission to EMA: Q3 2026.

Study M16-045:

Study Short Name and Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe AD

Rationale and Study Objectives: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with AD who have completed the double-blind Period (blinded extension [BE] period is ongoing, and all subjects have completed Week 16).

Study Design: Subjects who completed the Week 16 Visit (end of Double-Blind Period) enter the open-label long-term extension period (BE Period) of up to a total treatment duration of approximately 260 weeks (blinded until the last subject completes the last visit of the BE Period). All subjects on upadacitinib continue study treatment to which they were assigned at baseline and subjects randomized at baseline to placebo switch to upadacitinib 15 mg or 30 mg at Week 16 (the end of the placebo-controlled part of the study).

Study Population: Adolescent (age 12 to 17) and adult subjects with moderate to severe active AD who are candidates for systemic therapy

Milestones: Final Study Report: 26 February 2026

Study M16-047:

Study Short Name and Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Combination with Topical Corticosteroids in Adolescent and Adult Subjects with Moderate to Severe AD

Rationale and Study Objectives: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in combination with TCS in subjects with AD who have completed the Double-Blind Period (BE Period is ongoing, and all subjects have completed Week 16).

Study Design: Subjects who completed the Week 16 Visit (end of Double-Blind Period) enter the open-label blinded extension period (BE Period) of up to a total treatment duration of

approximately 260 weeks (blinded until the last subject completes the last visit of the BE Period). All subjects on upadacitinib continue study treatment to which they were randomized at baseline, and subjects randomized at baseline to placebo switch to upadacitinib 15 mg or 30 mg at Week 16 (the end of the placebo-controlled part of the study). Subjects who completed Week 260 of Studies M16-047, M16-045 or M18-891 without meeting any discontinuation criteria may continue their assigned treatment in Study M16-047 through Week 524 for the blinded long-term extension period (LTE Period).

Study Population: Adolescent (age 12 to 17) and adult subjects with moderate to severe active AD who are candidates for systemic therapy

Milestones: Final Study Report: Q2 2031

Study M18-891:

Study Short Name and Title: A Phase 3 Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adolescent and Adult Subjects with Moderate to Severe AD

Rationale and Study Objectives: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with AD who have completed the Double-Blind Period (BE Period is ongoing, and all subjects have completed Week 16).

Study Design: Subjects who completed the Week 16 Visit (end of Double-Blind Period) enter the open-label long-term extension period (BE Period) of up to a total treatment duration of approximately 260 weeks (blinded until the last subject completes the last visit of The BE Period). All subjects on upadacitinib continue study treatment to which they were randomized at baseline, and subjects randomized at baseline to placebo switch to upadacitinib 15 mg or 30 mg at Week 16 (the end of the placebo-controlled part of the study).

Study Population: Adolescent (age 12 to 17) and adult subjects with moderate to severe active AD who are candidates for systemic therapy

Milestones: Final Study Report: Q2 2026

Study M14-533:

Study Short Name and Title: A Phase 3 Multicenter, Long-Term Extension Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Moderate to Severe Active UC

Rationale and Study Objectives: To evaluate the long-term safety and efficacy of upadacitinib in patients with UC

Study Design: Subjects who were nonresponders in Study M14-234 Substudy 1, subjects who lost response during Study M14-234 Substudy 3, and subjects who completed Study M14-234 Substudy 3. The study consisted of 2 cohorts, with upadacitinib total treatment duration of approximately 288 weeks.

For Cohort 1, subjects received open-label upadacitinib 15 mg QD beginning at Week 0. At or after Week 2, subjects receiving upadacitinib 15 mg QD who experience inadequate response and no safety concerns identified by the investigator could be escalated to upadacitinib 30 mg QD. At least 6 weeks after dose-escalation occurred and treatment with upadacitinib 30 mg QD, subjects with persistent inadequate response while on upadacitinib 30 mg QD or who demonstrated intolerance to upadacitinib 30 mg QD discontinued from the study drug.

For Cohort 2, at Week 0, all subjects who achieved clinical remission continued to receive their original assigned double-blind treatment (placebo, upadacitinib 7.5 mg, 15 mg or 30 mg QD). Subjects who do not achieve clinical remission were eligible for dose escalation in a blinded manner and to receive upadacitinib 15 mg QD for those originally assigned to placebo or upadacitinib 7.5 mg QD; upadacitinib 30 mg QD for those originally assigned to upadacitinib 15 mg QD in Study M14-234 Substudy 3. Subjects originally assigned to upadacitinib 30 mg QD treatment were continued on the same dose. Endoscopy (if possible) was to be performed 8 weeks after the dose escalation for subjects who do not achieve clinical remission to evaluate the treatment effect.

Study Population: Adult subjects with moderately to severely active UC

Milestones: Final study report: Q3 2027.

Study M14-430 Substudy 2:

Study Short Name and Title: A Multicenter, Randomized, Double-Blind, Placebo Controlled Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Crohn's Disease Who Completed the Studies M14-431 or M14-433

Rationale and Study Objectives: To evaluate the safety and efficacy of long-term administration of upadacitinib in subjects with moderately to severely active CD who participated in the Phase 3 upadacitinib induction and maintenance studies.

Study Design: Substudy 2 (240-week long-term extension) will enroll subjects from 2 sources who will be managed as 2 separate cohorts:

- Cohort 4: Subjects who achieved clinical response in the open-label Extended Treatment Period (Part 3/Cohort 3 of Study M14-431) at Week 24 continued to receive open-label upadacitinib 30 mg QD for up to 240 weeks.
- Cohort 5: All subjects who completed Substudy 1 of Study M14-430 (52-week, randomized, double-blind, maintenance) will be eligible to enroll in this cohort. At Week 0, all subjects will continue to receive their originally assigned double-blind treatment (placebo, 15 or 30 mg QD upadacitinib). The treatment assignments will be unblinded when the last subject in Substudy 1 completes Week 52, and all subjects receiving upadacitinib will continue to receive their treatments until the

end of the study. The subjects receiving placebo will only receive the concomitant CD-related medications, if any.

Study Population: Adult subjects with moderately to severely active CD who participated in the induction and maintenance studies

Milestones:

- Final study report: Q1 2028
- Targeted Final Study Report Submission to EMA: Q2 2028.

Study M16-852:

Study Short Name and Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects with Giant Cell Arteritis: SELECT-GCA

Rationale and Study Objectives: Period 2 (a 52-week blinded extension period): To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects with GCA who achieved remission in Period 1.

Study Design: Subjects assigned to either dose of upadacitinib who achieve sustained remission for at least 24 consecutive weeks prior to the Week 52 Visit (at the end of Period 1) will be re-randomized in a 2:1 ratio to either continue on upadacitinib or switch to PBO in Period 2. Subjects who achieved sustained remission for at least 24 weeks prior to the Week 52 visit (at the end of Period 1) who were assigned to PBO in Period 1 will continue to receive PBO in Period 2. Remission is defined as absence of GCA signs and symptoms AND adherence to the protocol-defined CS taper regimen or CS-free.

At Week 52, subjects who have absence of GCA signs and symptoms AND are CS-free at the Week 52 visit, but do not achieve sustained remission for at least 24 consecutive weeks prior to the Week 52 Visit, will continue in Period 2 on their originally randomized treatment assignment. All other subjects will be discontinued from study drug and the study at the end of Period 1.

Study Population: Adult subjects who are at least 50 years of age with a diagnosis of active GCA, either new onset or relapsing disease, within 8 weeks of Baseline.

Milestones:

- Final Study Report: March 2026
- Targeted Final Study Report Submission to EMA: June 2026

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 9. 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				
Study P19-150 Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe/Ongoing	The primary objectives are to assess comparability across users of upadacitinib and other select systemic treatments for RA through in-depth assessments of drug utilization and patient characteristics at baseline; to describe the incidence of the following safety outcomes in patients with RA treated with upadacitinib: malignancy excluding non-melanoma skin cancer, including malignancy by type, NMSC, MACE, VTE, serious and opportunistic infections (including herpes zoster and TB), GI perforations, liver injury (including DILI), bone fractures, and all-cause mortality; if a suitable comparator is identified, to describe and compare (when feasible) the incidence of the above safety outcomes in patients with RA treated with upadacitinib relative to those treated other select systemic RA treatments (excluding other JAK inhibitors). Secondary objectives are to describe the incidence of the safety outcomes mentioned under the primary objective among the following patient subcohorts of upadacitinib users: the very elderly (≥ 75 years of age), patients with	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures Missing Information: use in very elderly (≥ 75 years of age); use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C; use in patients with moderate hepatic impairment; use in patients with severe	• Draft protocol • Progress report • Interim report • Final study report	• Submitted 16 March 2020 • Submitted in 2022 and 2023. No longer needed per EMA advice. Estimated Q3 2025 • Estimated Q1 2030

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	moderate hepatic impairment (when possible using proxy measures available within a given data source), patients with severe renal impairment (when possible using proxy measures available within a given data source), and patients with evidence of chronic infection with HBV or HCV; if a suitable comparator is identified, to describe the incidence of the safety outcomes mentioned under primary objectives in the following patient subcohorts of other select systemic RA treatments: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), and patients with severe renal impairment (when possible using proxy measures available within a given data source) and patients with evidence of chronic infection with HBV or HCV.	renal impairment; long-term safety		
Study P19-141 Long-Term Safety Study of Upadacitinib Use in RA Patients in the US/Ongoing	The primary objective is to compare the incidence of malignancy (excluding NMSC), NMSC, MACE, VTE, serious infection events, and all-cause mortality in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA. Secondary objectives are to describe the incidence rates of herpes zoster, opportunistic infections, active TB, GI perforations, evidence of DILI, and fractures; to describe the incidence of the above outcomes in very elderly patients (aged ≥ 75 years); and to describe the incidence rates of events in primary and secondary objectives in the following subgroups of interest: patients with moderate	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures Missing information: use in very elderly (≥ 75 years of age); long-term safety; use in patients	• Draft protocol • Progress report • Update on prevalence of baseline biomarkers and clinical risk factors within PSUR	• Submitted 16 March 2020 • Submitted in 2022 and 2023. No longer needed per EMA advice. • Annually for the first 2 years and thereafter in accordance with the PSUR reporting schedule

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	hepatic impairment at the time of Rinvoq or biologic therapy start; patients with evidence of chronic infection with HBV or HCV at the time of Rinvoq or biologic therapy start; and patients with severe renal impairment at the time of Rinvoq or biologic therapy start. An exploratory objective is to describe the distribution of risk factors for VTE in those treated with Rinvoq and those treated with biologic therapy, and in those who do and do not experience VTE during follow-up, in a subset of participating patients providing laboratory samples.	with moderate hepatic impairment; use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C; use in patients with severe renal impairment.	• Interim report • Final study report	• Estimated Q2 2029 • Estimated Q1 2030
Study P20-199 Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA/ Ongoing	This study aims to evaluate the use of upadacitinib in routine clinical care through the following specific objectives: to describe the baseline characteristics of new users of, and in a similar manner, to describe new users of a selected bDMARD for comparison; to evaluate prescribers' adherence to the upadacitinib aRMMs, specifically: compliance to recommendations for patient screening and laboratory monitoring prior to and during treatment; compliance to recommendations for limitations of use, including: Use in patients with risk factors for GI perforation; use in patients with risk factors for VTE; use in the patients aged 65 years and older; use in patients with risk factors for CVD; use in patients with risk factors for malignancy; use in patients with risk factors for serious infections; and contraindicated use (active TB and pregnancy); and to describe changes in the utilisation of upadacitinib following the updated recommendations and limitations for use implemented after the Article 20 referral procedure.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; and fetal malformation following exposure in utero	• Draft protocol • Progress reports • Final study report	• Submitted 16 March 2020) • Submitted Q2 2022, Q1 2023; next estimated Q1 2024, Q2 2025 • Estimated Q3 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P20-390 Long-Term Safety Study of Upadacitinib Use in AD Patients/ Ongoing	To evaluate and characterise the important identified and potential risks of upadacitinib and missing information on the safety of upadacitinib. Primary objectives: To assess comparability across upadacitinib and other select systemic treatments for AD through in-depth assessments of treatment pattern and patient disposition at baseline; To describe the incidence of the following safety outcomes in adolescent and adult individuals with AD treated with upadacitinib: malignancy (excluding NMSC) including malignancy by type, NMSC, MACE, VTE, serious infections (incl. OI), HZ, EH/ KVE, active TB, GI perforation, DILI, fractures, and all-cause mortality; If a suitable comparator is identified: to describe and compare (when feasible) the incidence of the above safety outcomes in adolescent and adult individuals with AD treated with upadacitinib, relative to those treated with other selected systemic AD treatments. Secondary objectives: To describe the incidence of the outcomes above in upadacitinib users by: dose of upadacitinib (15 mg and 30 mg); age group (adolescents 12 – 17 years, 18 – 64 years, 65 – 74 years and ≥ 75 years) at the time of upadacitinib initiation; history of moderate hepatic impairment at the time of upadacitinib initiation; history of chronic infection with HBV or HCV at the time of upadacitinib initiation; history of severe renal impairment	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTE; DILI; fractures Missing information: use in very elderly (≥ 75 years of age); long-term safety; use in patients with moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies; use in patients with evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies; use in patients with severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies; long-term safety in	• Draft protocol • Progress report • Interim report • Final Study Report	• Submitted 18 March 2021 • Annually starting 2023, except 2028 • Estimated Q4 2028 • Estimated Q4 2033

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	at the time of upadacitinib initiation. • If a suitable comparator is identified, to describe the incidence of the outcomes above in adolescent and adult individuals with AD treated with other selected systemic AD treatments by: age group (adolescents 12 – 17 years, 18 – 64 years, 65 – 74 years and ≥ 75 years) at the time of treatment initiation; history of moderate hepatic impairment at the time of treatment initiation; history of chronic infection with HBV or HCV at the time of treatment initiation; history of severe renal impairment at the time of treatment initiation.	adolescents with AD		
Study P21-825 Drug Utilization Study Evaluating Additional Risk Minimization Measures for Upadacitinib in the Treatment of Atopic Dermatitis in Europe/ Planned	To evaluate the use of upadacitinib in individuals with AD through the following objectives: To describe the baseline characteristics of individuals with AD who are new users of upadacitinib; To the extent measurable, evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs among individuals with AD who are new users of upadacitinib, by: a) Quantifying the compliance to recommendations for posology (average daily dose) and by describing the duration of use; b) Quantifying the compliance to recommendations for the use among individuals who have risk factors for GI perforation, serious infections, malignancy, MACE, and VTE; c) Quantifying the compliance to the recommendations	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC, GI perforation Important potential risks: MACE; VTEs; malignancies excluding NMSC; and fetal malformation following exposure in utero	• Draft protocol • Progress Report 1 • Progress Report 2 • Final Study Report	• Submitted 27 May 2021 • Q4 2024 • Q3 2025 • Q3 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	for the use among patients aged 65 years and older; d) Quantifying the compliance to the recommendations for contraindicated use including pregnancy, and active TB; e) Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark, Germany, and Spain only). To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure, specifically: a) Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; b) Describe the use of upadacitinib among patients aged 65 years and older; c) Describe the use of upadacitinib 30 mg.			
Study P21-824 A Study of Growth in Adolescents with AD Who Receive Upadacitinib/Ongoing	To evaluate the growth, development, and maturation in North American (US and Canada)-residing adolescents with moderate to severe AD who receive upadacitinib vs. biologic and other non-biologic, non-JAKi systemic comparators in routine clinical care. Where feasible, a cohort of European-residing adolescents with moderate to severe AD will also be evaluated. The primary objective is to compare differences in changes from baseline in height SDS and weight SDS, age at peak height velocity, age at Tanner stage progression, and incidence of bone fractures in adolescents with	Important potential risk: fractures Missing information: long-term safety in adolescents with AD	• Draft Protocol • Annual reports • Interim report 1 • Interim report 2 • Final study report	• Submitted 27 May 2021 • Annually starting Q4 2024 • Estimated Q4 2027 • Estimated Q4 2030 • Estimated Q4 2033

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD. The secondary objectives of the study are to describe changes from baseline in standing height, height percentiles, height velocity, height velocity SDS, weight, weight percentiles, BMI, BMI percentiles, and BMI SDS, as well as the frequency of delayed puberty in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.			

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P24-343 Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe /Planned	Primary Objectives: To describe and compare the incidence of GI perforation in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy; To describe and compare, where possible, the incidence of fractures and DILI in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for incidence comparison of fractures and DILI. Secondary objectives: To describe and compare, where possible, the incidence of the following secondary safety outcomes in adults with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy for UC and CD in the course of routine clinical care: malignancy excluding NMSC (stratified by type), NMSC, MACE, VTE, serious infections (defined as all infections that require hospitalization, including opportunistic infections), herpes zoster, active TB, and all-cause mortality. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures Missing Information: use in very elderly (≥ 75 years of age); long-term safety; use in patients with: moderate hepatic impairment at the time of initiation of upadacitinib or other systemic drug therapies; evidence of chronic infection with HBV or HCV at the time of initiation of upadacitinib or other systemic drug therapies; severe renal impairment at the time of initiation of upadacitinib or other systemic drug therapies.	• Draft protocol • Progress report • Interim study report • Final study report	• Submitted 09 August 2023 • Annually starting Q4 2025, except 2029 • Estimated Q4 2029 • Estimated Q2 2035

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for the incidence comparison of the secondary outcomes. In addition, incidence of the primary and secondary safety outcomes will be described in patients with UC or CD who receive upadacitinib by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing). When possible, the occurrence of the safety outcomes will be described in the following subgroups of interest, with limited or missing information from the clinical development program: very elderly (aged ≥ 75 years) at the time of treatment initiation; patients with moderate hepatic impairment at the time of treatment initiation; patients with severe renal impairment at the time of treatment initiation; patients with evidence of chronic infection with HBV or HCV at the time of treatment initiation.			

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study P24-344 Effectiveness Evaluation of aRMMs for Upadacitinib in UC/Planned	To evaluate the use of upadacitinib in routine clinical care for UC through the following specific objectives: To describe the baseline characteristics of UC patients who are new users of upadacitinib; To the extent measurable, evaluate healthcare utilization in routine clinical care as indicator of physician adherence to the aRMMs among patients with UC who are new users of upadacitinib, by: a) Quantifying the compliance to recommendations for posology (average daily dose) and duration of use; b) Quantifying the compliance to recommendations for the use among patients who have risk factors for GI perforation, malignancy, MACE, VTE, and serious infections; c) Quantifying the compliance to the recommendations for the use among patients aged 65 years and older; d) Quantifying the compliance to the recommendations for contraindicated use including pregnancy and active TB; e) Quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark and Spain only).	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: MACE; VTEs; malignancies excluding NMSC; and fetal malformation following exposure in utero	• Draft protocol • Progress report • Final study report	• Submitted 21 October 2022 • Annually starting 2024 • Estimated Q3 2027

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	To describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure (Sweden only), specifically: a) Describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; b) Describe the use of upadacitinib among patients aged 65 years and older; Describe the use of higher maintenance dose of upadacitinib 30 mg.			
Long-Term Extension Portion of Study M14-465/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 30 August 2028 • 30 November 2028

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M15-554/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 31 December 2024 • 30 April 2025
Long-Term Extension Portion of Study M15-572/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• 30 September 2025 • 31 December 2025

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M19-944 (Study 1)/ Ongoing	To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active bDMARD-IR AS (Study 1), who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI, fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• Q2 2026 • Q3 2026
Long-Term Extension Portion of Study M19-944 (Study 2)/ Ongoing	To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active nr-axSpA (Study 2), who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI, fractures, fetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• Q2 2026 • Q3 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-045/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Targeted submission of final study report to EMA	• Q2 2026

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M16-047/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in combination with TCS in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Interim report • Targeted submission of final study report to EMA	• Q3 2026 • Q2 2031

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M18-891/ Ongoing	To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in adolescent and adult subjects with AD who have completed the Double-Blind Period.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety; long-term safety in adolescents with AD	• Targeted submission of final study report to EMA	• Q2 2026
Long-Term Extension Study M14-533/ Ongoing	To evaluate the long-term safety and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with UC who were nonresponders in Study M14-234 Substudy 1, subjects who lost response during Study M14-234 Substudy 3, and subjects who completed Study M14-234 Substudy 3	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final study report	• Q3 2027

Study Name/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Long-Term Extension Portion of Study M14-430/ Ongoing	To evaluate safety and efficacy of long-term administration of upadacitinib in subjects with moderately to severely active CD who participated in the Phase 3 upadacitinib induction and maintenance studies.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: long-term safety	• Final study report • Targeted submission of final study report to EMA	• Q1 2028 • Q2 2028
Long-Term Extension Portion of Study M16-852/ Ongoing	To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects with GCA who achieved remission in Period 1.	Important identified risks: serious and opportunistic infections including TB; herpes zoster; NMSC; GI perforation Important potential risks: malignancies excluding NMSC; MACE; VTEs; DILI; fractures; fetal malformation following exposure in utero Missing Information: use in very elderly (≥ 75 years of age), long-term safety	• Final CSR • Target submission of final CSR to EMA	• Q1 2026 • Q2 2026

Part IV: Plans for Post-Authorization Efficacy Studies

No post-authorization efficacy studies are currently planned.

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

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 10. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Serious and opportunistic infections including TB	Routine risk communication: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. • SmPC Section 4.4 includes a statement on dose dependency of upadacitinib on reports of serious infection. • SmPC Section 4.4 specifies a higher incidence of infections in the elderly and diabetic populations. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. • SmPC Section 4.2 outlines interruption guidelines based on ALC and ANC. • SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections. • SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. • SmPC Section 4.4 advises to consider the risks and benefits of

	initiating upadacitinib in patients with chronic or recurrent infections. • A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. • Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection. • SmPC Section 4.4 specifies patient populations for which upadacitinib should be used with caution. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. <u>Other routine risk minimization measures:</u> Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Herpes zoster	<u>Routine risk communication:</u> • SmPC Section 4.4 describes the risk of viral reactivation such as herpes zoster. • SmPC Section 4.8 describes findings from upadacitinib clinical trials. • The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL warns that patients who have had a herpes zoster infection (shingles) should tell their doctor if they get a painful skin rash with blisters as these can be signs of shingles. <u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u> • SmPC Section 4.4 advises that prior to initiating upadacitinib patients be brought up to date with all immunizations including herpes zoster according to current immunization guidelines. • SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. <u>Other routine risk minimization measures:</u> Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
NMSC	Routine risk communication: • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 indicates that NMSCs have been reported in patients treated with upadacitinib and includes a statement on dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 advises on periodic skin examination. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
GI perforation	Routine risk communication: • SmPC Section 4.4 informs on reports of diverticulitis and GI perforation in clinical trials and from post-marketing sources. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 advises to use with caution in patients who may be at risk for GI perforation and prompt evaluation if specific signs/symptoms occur. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Malignancies excluding NMSC	Routine risk communication: • SmPC Section 4.4 indicates that malignancies have been reported in patients receiving JAK inhibitors, including upadacitinib, and includes a statement on upadacitinib dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid

	arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
MACE	Routine risk communication: • SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 indicates that events of MACE were observed in clinical trials for upadacitinib. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk communication: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in clinical trials for upadacitinib. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get certain symptoms.

	• SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies in patients with VTE risk factors other than cardiovascular or malignancy risk factors, use upadacitinib with caution. Examples of the risk factors which may put a patient at higher risk for VTE are provided. • SmPC Section 4.4 on re-evaluation of VTE risk and to promptly evaluate patients with signs and symptoms of VTE and discontinue upadacitinib in patients with suspected VTE, regardless of dose. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
DILI	Routine risk communication: SmPC Section 4.4 describes the effect of upadacitinib on transaminases. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 recommends prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI. • SmPC Section 4.4 advises that if increases in ALT or AST are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded. Other routine risk minimization measures: Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
Fetal malformation following exposure in utero	Routine risk communication: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and state that there are no or limited data from use of upadacitinib in pregnant women. • The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy, and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy. • SmPC Section 4.6 and PL advise on use of effective contraception. • SmPC Section 4.6 advises that female pediatric patients and/or their caregivers should be informed about the need to contact the treating physician once the patient experiences menarche. • The PL informs caregivers to let their doctor know if their child has their first menstrual period while using Rinvoq. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Fractures	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

Safety Concern	Routine Risk Minimization Activities
Use in very elderly (≥ 75 years of age)	Routine risk communication: • SmPC Section 4.2 states that there are limited data in patients 75 years of age and older. • SmPC Section 4.4 indicates that there is an increased risk of adverse reactions with upadacitinib 30 mg in patients 65 years of age and older. • SmPC Section 4.4 specifies increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomized study of tofacitinib (another JAK inhibitor). Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 specifies that upadacitinib 15 mg is recommended in patients 65 years of age and older. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Other routine risk minimization measures: Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	Routine risk communication: • SmPC Section 4.4 describes the risk of viral reactivation. • The PL warns that patients who have ever had hepatitis B or hepatitis C should consult their doctor or pharmacist before and during treatment with Rinvoq. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if HBV DNA is detected. Other routine risk minimization measures: Prescription only medicine

Safety Concern	Routine Risk Minimization Activities
Use in patients with moderate hepatic impairment	Routine risk communication: • SmPC Section 4.2 describes use in patients with hepatic impairment. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Other routine risk minimization measures: Prescription only medicine
Safety Concern	**Routine Risk Minimization Activities**
Use in patients with severe renal impairment	Routine risk communication: • SmPC Section 4.2 describes use in patients with renal impairment. Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC Section 4.2 states that upadacitinib should be used with caution in patients with severe renal impairment. • SmPC Section 4.2 specifies that for RA, PsA, AS, nr-axSpA, AD, and GCA, the recommended dose is 15 mg QD for patients with severe renal impairment and that for UC and CD, the recommended dose is 30 mg QD for induction treatment and 15 mg QD for maintenance treatment for patients with severe renal impairment. Other routine risk minimization measures: Prescription only medicine.
Safety Concern	**Routine Risk Minimization Activities**
Long-term safety	Routine risk communication: • SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures: Prescription only medicine.

Long-term safety in adolescents with AD	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

Additional Risk Minimization:

Although the risks for upadacitinib are familiar to prescribers, consistent with marketed JAK inhibitor products, additional risk minimization will consist of an educational program targeted to both HCPs and patients.

Health Care Professional-Directed Measure – Health Care Professional Educational Guide

Objectives:

Overall objective for the HCP measure: To increase awareness of HCPs on the following upadacitinib risks: serious and opportunistic infections including TB, herpes zoster, fetal malformation (pregnancy risk), MACE, VTEs, malignancy, and GI perforation and ways to manage these risks.

- The HCP measure will also serve to remind HCPs on clinical measures which are relevant in reducing each risk.
- The HCP measure will also remind HCPs on key points to discuss with their patients and importance of the patient card.

Patient-Directed Measure – Patient Card

Objectives:

Overall objective for the patient card:

- To increase awareness of patients and caregivers on the following upadacitinib risks: serious and opportunistic infections including TB, herpes zoster, fetal malformation (pregnancy risk), MACE, VTEs, malignancy, and GI perforation and signs/symptoms to be aware of in order to alert their doctor.
- To communicate these risks to other treating HCPs (i.e., non upadacitinib prescribing HCPs in emergency or other settings)

Rationale for the Additional Risk Minimization Activity (Health Care Professional Educational Guide and Patient Card):

Consistent with already marketed JAK inhibitor products in the EU, additional risk minimization will be used. The targeted risks are serious and opportunistic infections including TB, herpes zoster, fetal malformation, MACE, VTEs, malignancy, and GI perforation. Reinforcement of awareness for these risks is deemed important, especially since all of these risks have specific clinical measures which may be used to help reduce the risk. In addition, awareness of the patient of these risks is important in order for the patient to know when to seek medical attention and why particular laboratory parameters are being following during treatment with upadacitinib.

Implementation Plan (Including Target Audience and Planned Distribution Path):

Health Care Professional Measure

Depending on local regulatory regulations, the HCP measure will be distributed to HCPs who prescribe upadacitinib for RA, PsA, AS, nr-axSpA, AD, UC, CD, or GCA (i.e., rheumatologists, dermatologists, gastroenterologists, and others, depending on the local area) via multiple methods (i.e., delivery via the sales force, mail, email). If applicable, the measure will have information on how to access the same information but in digital format.

Depending on local regulatory regulations, the HCP measure is available on the local health authority website and/or the specific upadacitinib website, or other websites, if available in local countries.

Patient Card

Depending on local regulatory regulations, the patient measure will be distributed to HCPs who would then distribute the patient card to patients who are prescribed upadacitinib. Patient support programs or inclusion in medication packs may be used. If applicable, the patient measure will have information on how to access the same information but in digital format.

Depending on local regulatory regulations, the patient card is available on the local health authority website, AbbVie Care website, and/or the specific upadacitinib website, or other websites, if available in local countries.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success (Health Care Professional Educational Guide and Patient Card):

Effectiveness of the additional risk minimization program will be performed using Category 3 PASS – Drug utilization patterns and evaluation of the extent to which recommendations for patient screening and laboratory monitoring targeted by the additional risk minimization program are followed in RA, AD, and UC populations (see Part III.2 for additional details).

To assess the effectiveness of messaging contained in the HCP educational guide, outcome indicators will be described for patients who are treated with upadacitinib, including the following:

- Drug utilization of upadacitinib in populations of special interest which are targeted by messaging in the HCP educational guide:
  - Patients who are currently being treated for active TB;
  - Patients who are at high risk for VTEs (deep venous thrombosis and/or pulmonary embolus);
  - Patients who are pregnant at the time of initiation or become pregnant while taking upadacitinib;
  - Additional objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.
- The extent to which recommendations for patient screening and laboratory monitoring are followed, including the following recommendations:
  - Assess lipid levels 12 weeks after starting upadacitinib; monitor and manage lipid levels during treatment: Occurrence of lipid testing;
  - Screen for viral hepatitis and monitor for reactivation in accordance with clinical guidelines: Occurrence of viral hepatitis screening;
  - Monitor patients for herpes zoster infections;
  - Check absolute lymphocyte count (ALC) and absolute neutrophil count (ANC) before and during upadacitinib treatment: Occurrence of lymphocyte and neutrophil screening;
  - No use of live, attenuated vaccines during, or immediately prior to starting upadacitinib treatment: Occurrence of live vaccination receipt;
  - Discontinue upadacitinib treatment in the event a patient experiences a deep venous thrombosis and/or pulmonary embolus;
  - Additional objectives to evaluate changes to aRMM (EMA procedure under Article 20 of Regulation (EC) 726/2004 [EMEA/H-A20/1517/C/004760/0017]) will be added based on feasibility.

Direct Healthcare Professional Communication (DHPC)

In accordance with a request by the EMA during the Article 20 referral procedure (EMEA/H-A20/1517/C/004760/0017), a DHPC will be developed and distributed to communicate The Summary of Product Characteristics (SmPC) information updates occurring as an outcome of the procedure.

Objectives

The objective will be to inform prescribers on the risks in scope of the Article 20 procedure.

Implementation Plan (Including Target Audience and Planned Distribution Path):

Depending on local regulations, the DHPC will be distributed to HCPs in the EU who prescribe upadacitinib for RA, PsA, AS, nr-axSpA, AD, or UC (i.e., rheumatologists, dermatologists, gastroenterologists, allergologists and general medicine, depending on the local area) via multiple methods (i.e., delivery via the sales force, mail, email). This distribution will occur one-time following conclusion of the Article 20 referral procedure.

Plans to Evaluate Effectiveness: Routine pharmacovigilance.

Removal of Additional Risk Minimization Activity:

Not applicable.

V.3 Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table 11. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious and opportunistic infections including TB	Routine risk minimization measures: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. • SmPC Section 4.4 includes a statement on dose-dependency of upadacitinib on reports of serious infection. • SmPC Section 4.4 specifies a higher incidence of infections in the elderly and diabetic populations. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. • SmPC Section 4.2 outlines interruption guidelines based on ALC and ANC. • SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections. • SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for serious and opportunistic infections including TB Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials

	of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. • SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with chronic or recurrent infections. • A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. • Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in patients with risk factors for TB infection. • SmPC Section 4.4 specifies patient populations for which upadacitinib should be used with caution. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU • Other routine risk minimization measures: • Prescription only medicine.	(Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19 944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
Herpes zoster	Routine risk minimization measures: • SmPC Section 4.4 describes the risk	Pharmacovigilance activities beyond adverse reaction

	of viral reactivation such as herpes zoster. • SmPC Section 4.8 describes findings from upadacitinib clinical trials. • The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL warns that patients who have had a herpes zoster infection (shingles) should tell their doctor if they get a painful skin rash with blisters as these can be signs of shingles. • SmPC Section 4.4 advises that prior to initiating upadacitinib patients be brought up to date with all immunizations including herpes zoster according to current immunization guidelines. • SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: • HCP educational guide • Patient card Other routine risk minimization measures: Prescription only medicine.	reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for serious infections Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr axSpA) of Phase 3 trial (Study M19 944)

		• Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
NMSC	Routine risk minimization measures: • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 indicates that NMSCs have been reported in patients treated with upadacitinib and includes a statement on dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 advises on periodic skin examination. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. aRMMs: • HCP educational guide • Patient card • One-time distribution of DHPC in EU	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC

	Other routine risk minimization measures: Prescription only medicine	• Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
GI perforation	Routine risk minimization measures: • SmPC Section 4.4 informs on reports of diverticulitis and GI perforation in clinical trials and from post-marketing sources. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 advises to use with caution in patients who may be at risk for GI perforation and prompt evaluation if specific signs/symptoms occur. Additional risk minimization measures: • HCP educational guide	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for GI perforation Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM

	• Patient card Other routine risk minimization measures: Prescription only medicine.	Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19 944) • Long-term extension portion of Study 2 (nr axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16 047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)

Malignancies excluding NMSC	Routine risk minimization measures: • SmPC Section 4.4 indicates that malignancies have been reported in patients receiving JAK inhibitors, including upadacitinib, and includes a statement on upadacitinib dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. aRMMs: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-

		axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16 047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
MACE	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 indicates that events of MACE were observed in clinical trials for upadacitinib. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for MACE Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness

	Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine.	Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trials (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19 944) • Long-term extension portion of Study 2 (nr axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
VTEs (deep venous thrombosis and pulmonary embolus)	Routine risk minimization measures: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in clinical trials for upadacitinib. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get certain symptoms. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including: • Follow-up questionnaire for VTEs • Monitoring of VTE risk and literature review provided within the PSUR Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use

	from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies in patients with VTE risk factors other than cardiovascular or malignancy risk factors, use upadacitinib with caution. Examples of the risk factors which may put a patient at higher risk for VTE are provided. • SmPC Section 4.4 on re-evaluation of VTE risk and to promptly evaluate patients with signs and symptoms of VTE and discontinue upadacitinib in patients with suspected VTE, regardless of dose. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU Other routine risk minimization measures: Prescription only medicine.	in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19 944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16 047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial

		(Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
DILI	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on transaminases. • SmPC Section 4.4 recommends prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI. • SmPC Section 4.4 advises that if increases in ALT or AST are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for DILI Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19 944) • Long-term extension portion of Study 2 (nr axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16 047, and M18-891)

		• Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
Fetal malformation following exposure in utero	Routine risk minimization measures: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and states that there are no or limited data from use of upadacitinib in pregnant women. • The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy, and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. • SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy. • SmPC Section 4.6 and PL advise on use of effective contraception. • SmPC Section 4.6 advises that female pediatric patients and/or their caregivers should be informed about the need to contact the treating physician once the patient experiences menarche. • The PL informs caregivers to let their doctor know if their child has their first menstrual period while using Rinvoq. Additional risk minimization measures: • HCP educational guide • Patient card Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaires for pregnancies Additional pharmacovigilance activities (see Part III.2): • P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19 944) • Long-term extension portion of Study 2 (nr axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials

		(Studies M16-045, M16 047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
Fractures	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Follow-up questionnaire for fractures Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-824: A Study of Growth in Adolescents with AD Who Receive Upadacitinib • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial

		(Study M19 944) • Long-term extension portion of Study 2 (nr axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16 047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
Use in very elderly (≥ 75 years of age)	Routine risk minimization measures: • SmPC Section 4.2 states that there are limited data in patients 75 years of age and older. • SmPC Section 4.4 indicates that there is an increased risk of adverse reactions with upadacitinib 30 mg in patients 65 years of age and older. • SmPC Section 4.4 specifies increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomised study of tofacitinib (another JAK inhibitor). • SmPC Section 4.2 specifies that upadacitinib 15 mg is recommended in patients 65 years of age and older. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 GCA trial (Study M16-852)

Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation. • The PL warns that patients who have ever had hepatitis B or hepatitis C should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if HBV DNA is detected. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe
Use in patients with moderate hepatic impairment	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with hepatic impairment. • SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe

Use in patients with severe renal impairment	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with renal impairment. • SmPC Section 4.2 states that upadacitinib should be used with caution in patients with severe renal impairment. • SmPC Section 4.2 specifies that for RA, PsA, AS, nr-axSpA, AD and GCA, the recommended dose is 15 mg QD for patients with severe renal impairment and that for UC and CD, the recommended dose is 30 mg QD for induction treatment and 15 mg QD for maintenance treatment for patients with severe renal impairment. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe
Long-term safety	Routine risk minimization measures: SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Routine pharmacovigilance activities including follow-up questionnaire for malignancies Additional pharmacovigilance activities (see Part III.2): • P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial

		(Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19 944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16 047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)
Long-term safety in adolescents with AD	Routine risk minimization measures: None Additional risk minimization measures: None Other routine risk minimization measures: Prescription only medicine.	Pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities (see Part III.2): • P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • P21-824: A Study of Growth in Adolescents with AD Who Receive Upadacitinib • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16 047, and M18-891)

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Rinvoq™ (upadacitinib)

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

Rinvoq's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how Rinvoq should be used.

This summary of the RMP for Rinvoq 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 Rinvoq's RMP.

I The Medicine and What it Is Used For

Rinvoq is authorized for the treatment of:

- Rheumatoid arthritis (RA)
- Psoriatic arthritis (PsA)
- Ankylosing spondylitis (AS)
- Non-radiographic axial spondyloarthritis (nr-axSpA)
- Atopic dermatitis (AD)
- Ulcerative colitis (UC)
- Crohn's disease (CD)
- Giant cell arteritis (GCA)

See the SmPC for full indication statements. Rinvoq contains upadacitinib as the active substance and it is given orally.

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

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

Important risks of Rinvoq, together with measures to minimize such risks and the proposed studies for learning more about Rinvoq'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 HCPs;
- 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 the case of Rinvoq, these measures are supplemented with additional risk minimization measures (aRMMs) mentioned under relevant important risks, below.

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 Rinvoq is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of Rinvoq 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 Rinvoq. 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 and opportunistic infections including tuberculosis (TB) • Herpes zoster • Non-melanoma skin cancer (NMSC) • Gastrointestinal (GI) perforation
Important potential risks	• Malignancies excluding NMSC • Major adverse cardiovascular event (MACE) • Venous thromboembolic events (VTEs) (deep venous thrombosis and pulmonary embolus) • Drug-induced liver injury (DILI) • Fetal malformation following exposure in utero • Fractures
Missing information	• Use in very elderly (≥ 75 years of age) • Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C • Use in patients with moderate hepatic impairment • Use in patients with severe renal impairment • Long-term safety • Long-term safety in adolescents with AD

II.B Summary of Important Risks

Important identified risk 1: Serious and opportunistic infections including TB	
Evidence for linking the risk to the medicine	Approved therapies of the Janus kinase (JAK) inhibitor class are associated with or are being investigated for risk of serious infections and opportunistic infections. Serious and opportunistic infections including TB were assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS nr-axSpA, and GCA clinical trial data.
Risk factors and risk groups	Advanced age and background immunosuppressive medications such as concomitant conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and prednisone are common in the moderate to severe active RA, PsA, and GCA populations and can also be found in the AS, and nr-axSpA, populations, although to a lesser extent, and systemic corticosteroids such as prednisone are common in the moderate to severe active AD, UC, CD, and GCA populations, placing these populations at increased risk. Corticosteroids and csDMARDs are not recommended for axial symptoms in AS and nr-axSpA; therefore, immunosuppressive medication burden is smaller than in RA, PsA or GCA. Eczema herpeticum (EH) is an infection that has been associated with AD

	and is the most commonly recognized viral complication in patients with AD (Beck 2009).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 summarizes the risk and provides guidance on ways to reduce the risk. • SmPC Section 4.4 includes a statement on dose-dependency of upadacitinib on reports of serious infection. • SmPC Section 4.4 specifies a higher incidence of infections in the elderly and diabetic populations. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL advises that patients do not take Rinvoq if they have active TB and warns that patients with a history of TB, or who have been in close contact with someone with TB should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 outlines lymphocyte and neutrophil counts and when not to initiate upadacitinib dosing. • SmPC Section 4.2 outlines interruption guidelines based on absolute lymphocyte count and absolute neutrophil count. • SmPC Section 4.3 indicates that upadacitinib is contraindicated in patients with active TB or active serious infections. • SmPC Section 4.4 states that patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and that upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. • SmPC Section 4.4 advises to consider the risks and benefits of initiating upadacitinib in patients with chronic or recurrent infections. • A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib should be interrupted if the patient is not responding to therapy. • Screening for TB prior to initiation is advised, and upadacitinib should not be given if active TB is diagnosed. Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with untreated latent TB or in

	patients with risk factors for TB infection. • SmPC Section 4.4 specifies patient populations for which upadacitinib should be used with caution. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of direct healthcare professional communication (DHPC) in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • Study P20-390: Long-Term safety study of upadacitinib use in AD patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (biologic disease-modifying anti-rheumatic drug inadequate responder [bDMARD-IR] AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852)

	See Section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk 2: Herpes zoster	
Evidence for linking the risk to the medicine	Approved therapies of the JAK inhibitor class show increased risk of herpes zoster in patients with RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA. Herpes zoster was assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and in AS, nr-axSpA, and GCA clinical trial data.
Risk factors and risk groups	Herpes zoster is caused by reactivation of latent varicella zoster virus; therefore, it can only occur in patients who have previously been infected with varicella zoster virus. Herpes zoster can also occur in people who have received the varicella vaccine. Herpes zoster occurs most frequently among older adults and immunocompromised persons such as patients using immunomodulatory products or immunosuppressive products. Advanced age and background immunosuppressive medications such as concomitant csDMARDs and prednisone are common in the moderate to severe active RA, PsA, and GCA populations, and can also be found in the AS and nr-axSpA populations, and systemic corticosteroids such as prednisone are common in the moderate to severe active AD, UC, CD, and GCA populations, placing these populations at increased risk. As anticipated based on published literature regarding herpes zoster in these conditions, prior herpes zoster and advanced age were risk factors for the development of herpes zoster while receiving upadacitinib. Additionally, a higher rate of herpes zoster was seen in the Asian region, as reported with other JAK inhibitors (Winthrop 2014).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation such as herpes zoster. • SmPC Section 4.8 describes findings from upadacitinib clinical trials. • The PL warns that patients who have an infection or who have a recurring infection should consult their doctor or pharmacist before and during treatment with Rinvoq and describes the risk of viral reactivation. • The PL warns that patients who have had a herpes zoster infection (shingles) should tell their doctor if they get a painful skin rash with blisters as these can be signs of shingles. • SmPC Section 4.4 advises that prior to initiating upadacitinib patients be brought up to date with all immunizations including herpes zoster according to current

	immunization guidelines. • SmPC Section 4.4 advises that if a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves. Additional risk minimization measures: • HCP educational guide • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • Study P20-390: Long-Term safety study of upadacitinib use in AD patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.

Important identified risk 3: NMSC	
Evidence for linking the risk to the medicine	NMSC was assessed in data from upadacitinib clinical trials described below and from the company post-marketing database. An analysis of NMSC was performed to evaluate NMSC using the pooled data from all unblinded and open label extension upadacitinib studies as of 15 August 2021. The data analysis showed that the crude overall rate of NMSC was higher with upadacitinib 30 mg (0.62 events per 100 PY) compared with upadacitinib 15 mg (0.38 events per 100 PY), with a hazard ratio of 1.76 (95% CI, 1.20 to 2.58; stratified by indication, p = 0.004). The higher incidence of NMSC with upadacitinib 30 mg emerged after approximately 1 year of upadacitinib treatment as compared to the 15 mg dose and continued to increase beyond 1 year. Additionally, the proportion of subjects with recurrent NMSC was higher with upadacitinib 30 mg as compared to upadacitinib 15 mg. These observations further suggest a potential higher risk of NMSC over long-term exposure with upadacitinib 30 mg compared with upadacitinib 15 mg.
Risk factors and risk groups	Inflammation is considered a key process in skin tumorigenesis (Neagu 2019). Patients with inflammatory diseases such as RA and inflammatory bowel disease (IBD) have higher risks of NMSC than the general population (Raaschou 2016, Singh 2011). Immunosuppressive medications, such as methotrexate (MTX) and tumor necrosis factor (TNF) inhibitors, have been found to be associated with a higher risk of NMSC (Assassi 2016). Basal cell carcinoma (BCC) (a type of NMSC) develops primarily on sun-exposed skin; thus, ultraviolet (UV) radiation plays a critical role in the pathogenesis of BCC. The occurrence of BCC increases as the population ages and approximately 80% of all BCC's are diagnosed above age 55 years (Ciążyńska 2021). The most critical risk factor for squamous cell carcinoma (a type of NMSC) is UV radiation from sunlight exposure (Fagan 2023). Traditional risk factors of NMSC such as cumulative UV exposure, radiation therapy, prolonged immunosuppression, human papillomavirus infection, smoking, lower Fitzpatrick skin types, and other genetic risk factors also apply in patients with RA, PsA, AS, nr axSpA, AD, UC, CD, and GCA.
Risk minimization measures	Routine risk minimization measures: • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 indicates that NMSCs have been reported in patients treated with upadacitinib and includes a statement on dose-dependency. • SmPC Section 4.4 provides information on this risk for

	another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 advises on periodic skin examination. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. <u>Additional risk minimization measures:</u> • HCP educational guide • Patient card • One-time distribution of DHPC in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430)

	• Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk 4: GI perforation	
Evidence for linking the risk to the medicine	Approved JAK inhibitors are being investigated for risk of GI perforation. GI perforation was assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS, nr-axSpA, and GCA clinical trial data.
Risk factors and risk groups	Risk factors for GI perforations include history of diverticulitis, use of glucocorticoids, exposure to nonsteroidal anti-inflammatory drugs (NSAIDs), increasing age, and higher levels of co-morbidity (Curtis 2012). Advanced age is common for RA, PsA, and GCA patients, background immunosuppressive medications and NSAIDs are common in the moderate to severe active RA, PsA, AS, nr-axSpA, and GCA populations, and background immunosuppressive medications, i.e., glucocorticoids are common in the moderate to severe AD, UC, CD, and GCA populations placing these populations at increased risk. Use of tocilizumab, an interleukin-6 inhibitor, has been associated with increased risk for GI perforation (Monemi 2016, Strangfeld 2017). Patients with moderate to severe inflammatory bowel diseases (UC and CD) have an increased risk of GI perforation compared to the general population (McAuliffe 2015). In CD, patients with moderate to severe disease have a higher risk of intestinal/gastric perforations compared to those with mild disease (McAuliffe 2015).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 informs on reports of diverticulitis and GI perforation in clinical trials and from post-marketing sources. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 advises to use with caution in patients who may be at risk for GI perforation and prompt evaluation if specific signs/symptoms occur. Additional risk minimization measures: • HCP educational guide • Patient card

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risk 1: Malignancies excluding NMSC	
Evidence for linking the risk to the medicine	Malignancies were assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS, nr-axSpA, and GCA clinical trial data.
Risk factors and risk groups	There is evidence that RA PsA, AD, UC, CD, and GCA patients have a higher occurrence of certain malignancies compared to the general population. The etiology of this finding may include immune dysregulation and/or chronic immune activation as seen in RA patients (Shah 2015) AD patients (Wang 2019), and UC and CD patients (Ullman and Itzkowitz 2011). Lymphoproliferative disorders

	occur with increased frequency in patients with RA and PsA (Smitten 2008), and patients with UC or CD exposed to specific therapies are at increased risk of lymphoproliferative disease (Beaugerie 2009, Kandiel 2005). The lymphoma incidence increases as active RA and PsA persists and correlates with the severity of disease activity (Baecklund 2006, Naschitz and Rosner 2008). In addition to lymphoma, RA patients are at increased risk for lung cancer, and patients with CD are at increased risk of colorectal cancer (Olen 2020). Patients with AS and nr-axSpA have not been reported to have an increased risk of malignancy, with the exception of those exposed to spinal radiation treatment, with is no longer used (Exarchou 2016). There is mixed evidence on the risk of malignancy among patients with GCA. Chronic inflammation associated with GCA may be a potential driver of malignancy pathogenesis and progression, while an increased risk of hematologic malignancies in GCA may be attributed to shared environmental triggers (e.g., viral infections) (Dar 2021).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 indicates that malignancies have been reported in patients receiving JAK inhibitors, including upadacitinib, and includes a statement on upadacitinib dose-dependency. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA

	• Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 2: MACE	
Evidence for linking the risk to the medicine	Adjudicated MACE was assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS, nr-axSpA, and GCA clinical trial data.
Risk factors and risk groups	Traditional cardiovascular (CV) risk factors such as prior CV events, smoking, dyslipidaemia, obesity, hypertension, diabetes mellitus, and age also apply to patients with RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA. The potential for MACE in these patients as a result of elevations of lipid levels while on a JAK inhibitor or other therapies for these conditions remains unclear.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on lipids and describes that impact on CV morbidity and mortality has not been determined. • SmPC Section 4.4 indicates that events of MACE were observed in clinical trials for upadacitinib. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral

	Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.2 describes monitoring of lipid parameters following initiation of upadacitinib. • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533)

	• Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 3: VTEs (deep venous thrombosis and pulmonary embolus)	
Evidence for linking the risk to the medicine	Baricitinib, an approved JAK inhibitor with similar selectivity for JAK1 and JAK2, is being investigated for potential risk of thromboembolic events. It is not yet known if there is a role of JAK inhibition in the potential for developing VTEs. Adjudicated VTEs (deep venous thrombosis and pulmonary embolus) were assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS, nr-axSpA, and GCA clinical trial data.
Risk factors and risk groups	Risks for VTEs in the general population also apply to patients with RA, PsA, AS, nr-axSpA, AD, UC, CD, and GCA and include prior history of VTE, contraceptive use, obesity, malignancies, smoking, and inactivity such as bedrest following major surgeries like joint replacement. The general risk for VTE is increased in patients with AS especially in the first years after diagnosis (Aviña-Zubieta 2019). Patients with inflammatory bowel disease have an increased risk of VTE (Papa 2020), especially during periods of disease flare (Grainge 2010). Patients with GCA have a higher underlying risk of VTE compared to matched controls and compared to patients with RA (Mohammad 2017). Risk of VTE is markedly increased within the first year after GCA diagnosis (Aviña-Zubieta 2016, Unizony 2017).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 indicates that events of deep vein thrombosis and pulmonary embolism have been reported in clinical trials for upadacitinib. • The PL warns when patients should consult their doctor or pharmacist before and during treatment with Rinvoq and advises that patients tell their doctor if they get certain symptoms. • SmPC Section 4.4 provides information on this risk for another JAK inhibitor (tofacitinib) with results from Oral Surveillance (A randomized active-controlled study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor). • SmPC Section 4.2 specifies when the 15 mg dose is recommended. • SmPC Section 4.4 specifies in patients with VTE risk factors

	other than cardiovascular or malignancy risk factors, use upadacitinib with caution. Examples of the risk factors which may put a patient at higher risk for VTE are provided. • SmPC Section 4.4 on re-evaluation of VTE risk and to promptly evaluate patients with signs and symptoms of VTE and discontinue upadacitinib in patients with suspected VTE, regardless of dose. Additional risk minimization measures: • HCP educational guide • Patient card • One-time distribution of DHPC in EU
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Study P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the

	post-authorization development plan.
Important potential risk 4: DILI	
Evidence for linking the risk to the medicine	Approved JAK inhibitors are being investigated for DILI. DILI was assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS, nr-axSpA, and GCA clinical trial data.
Risk factors and risk groups	Transaminase elevations can occur in the setting of RA, PsA, AS, and nr-axSpA independent of treatment (Robinson 1983, Takahashi 2010), and are commonly observed with NSAID and immunosuppressive treatment for these conditions, and with immunosuppressive treatment for AD, UC, and CD (Nygaard 2014, Restellini 2017, Takahashi 2010). Elevations have also been noted in AS patients treated with TNF inhibitors (Ghabril 2013). There is limited information on the underlying risk of hepatic disorders in patients with GCA.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 describes the effect of upadacitinib on transaminases. • SmPC Section 4.4 recommends prompt investigation of the cause of liver enzyme elevation to identify potential cases of DILI. • SmPC Section 4.4 advises that if increases in alanine transaminase or aspartate transaminase are observed during routine patient management and DILI is suspected, upadacitinib should be interrupted until this diagnosis is excluded. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944)

	• Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 5: Fetal malformation following exposure in utero	
Evidence for linking the risk to the medicine	Approved therapies of the JAK inhibitor class are being investigated for potential risk of fetal malformation following exposure in utero. Nonclinical studies showed that upadacitinib is teratogenic in both rats and rabbits.
Risk factors and risk groups	Risk of fetal malformation pertains only to female patients of childbearing potential who become pregnant while receiving upadacitinib or and for at least 4 weeks after treatment.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 describes the teratogenic effects observed in animals receiving upadacitinib and states that there are no or limited data from use of upadacitinib in pregnant women. • The PL advises that patients do not take Rinvoq if they are pregnant, that Rinvoq must not be used during pregnancy, and that patients who become pregnant while taking Rinvoq must consult their doctor straight away. • SmPC Section 4.3 and Section 4.6 indicate that upadacitinib is contraindicated during pregnancy. • SmPC Section 4.6 and PL advise on use of effective contraception. • SmPC Section 4.6 advises that female pediatric patients and/or their caregivers should be informed about the need to contact the treating physician once the patient experiences menarche. • The PL informs caregivers to let their doctor know if their child has their first menstrual period while using Rinvoq. Additional risk minimization measures: • HCP educational guide • Patient card

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P20-199: Upadacitinib Drug Utilisation Study for aRMM Effectiveness Evaluation in RA • Study P21-825: Effectiveness Evaluation of aRMMs for Upadacitinib in AD • Study P24-344: Effectiveness Evaluation of aRMMs for Upadacitinib in UC • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk 6: Fractures	
Evidence for linking the risk to the medicine	Results of a post hoc analyses of the post-marketing ORAL Surveillance trial involving RA patients ≥ 50 years of age with underlying CV risk factors showed numerically higher risk for fractures with tofacitinib versus (vs.) TNF inhibitors (Hansen 2022). Events of fracture were assessed in integrated upadacitinib RA, integrated PsA, integrated AD, integrated UC, and integrated CD clinical trial data, and AS, nr-axSpA, and GCA clinical trial data.
Risk factors and risk groups	Risk factors for fractures include increasing age, female sex, previous fractures, underlying medical conditions, and use of medications such as glucocorticoids. Advanced age is common for RA, PsA, and GCA patients, patients with RA are predisposed to osteoporotic fracture (Xue 2017), patients with AS are at increased risk of vertebral fracture (Vosse 2009), patients with CD and UC have a significant risk of fractures due to osteoporosis (Bernstein 2000), background use of corticosteroids is common in RA, PsA, UC, CD, and GCA and both systemic and topical use is common in child and adult patients with AD (Ha 2022), placing these populations at increased risk.

Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P21-824: A Study of Growth in Adolescents with AD Who Receive Upadacitinib • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information 1: Use in very elderly (≥ 75 years of age)	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 states that there are limited data in patients 75 years of age and older. • SmPC Section 4.4 indicates that there is an increased risk of adverse reactions with upadacitinib 30 mg in patients 65 years of age and older. • SmPC Section 4.4 specifies increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomized study of tofacitinib (another JAK inhibitor). • SmPC Section 4.2 specifies that upadacitinib 15 mg is recommended in patients 65 years of age and older. • SmPC Section 4.4 specifies patient populations for which upadacitinib should only be used if no suitable treatment alternatives are available. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information 2: Use in patients with evidence of untreated chronic infection with hepatitis B or hepatitis C	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 describes the risk of viral reactivation. • The PL warns that patients who have ever had hepatitis B or hepatitis C should consult their doctor or pharmacist before and during treatment with Rinvoq. • SmPC Section 4.4 describes the need for screening and consultation with a hepatologist if hepatitis B DNA is detected. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 3: Use in patients with moderate hepatic impairment	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with hepatic impairment. • SmPC Section 4.2 states that upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment. • SmPC Section 4.3 indicates that upadacitinib is contraindicated for use in patients with severe hepatic impairment. • The PL advises that patients do not take Rinvoq if they have severe liver problems and warns that patients should consult their doctor or pharmacist before and during treatment with Rinvoq if their liver does not work as well as it should. Additional risk minimization measures: None

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe See Section II.C of this summary for an overview of the post-authorization development plan.
Missing Information 4: Use in patients with severe renal impairment	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 describes use in patients with renal impairment. • SmPC Section 4.2 states that upadacitinib should be used with caution in patients with severe renal impairment. • SmPC Section 4.2 specifies that for RA, PsA, AS, nr-axSpA, AD, and GCA, the recommended dose is 15 mg once daily (QD) for patients with severe renal impairment and that for UC and CD, the recommended dose is 30 mg QD for induction treatment and 15 mg QD for maintenance treatment for patients with severe renal impairment. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information 5: Long-term safety	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.4 indicates that upadacitinib clinical data on malignancies are currently limited and long-term studies are ongoing. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P19-150: Long-Term Safety Studies of Upadacitinib Use in RA Patients in Europe • Study P19-141: Long-Term Safety Study of Upadacitinib Use in RA Patients in the US • Study P20-390: Long-Term Safety Study of Upadacitinib Use in AD Patients • Study P24-343: Long-Term Safety Study of Upadacitinib Use in UC and CD Patients in Europe • Long-term extension portion of Phase 3 RA trial (Study M14-465) • Long-term extension portion of Phase 3 PsA trials (Studies M15-554 and M15-572) • Long-term extension portion of Study 1 (bDMARD-IR AS) of Phase 3 trial (Study M19-944) • Long-term extension portion of Study 2 (nr-axSpA) of Phase 3 trial (Study M19-944) • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891) • Long-term extension Phase 3 UC trial (Study M14-533) • Long-term extension portion of Phase 3 CD trial (Study M14-430) • Long-term extension portion of Phase 3 GCA trial (Study M16-852) See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information 6: Long-term safety in adolescents with AD	
Risk minimization measures	Routine risk minimization measures: None Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study P20-390: Long-term safety study of upadacitinib use in AD patients • Study P21-824: A Study of Growth in Adolescents with AD Who Receive Upadacitinib • Long-term extension portion of Phase 3 AD trials (Studies M16-045, M16-047, and M18-891)

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 Rinvoq.

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

Additional pharmacovigilance pharmacoepidemiology studies: Study P19-150: Long-term safety cohort studies of upadacitinib (Rinvoq®) use for the treatment of RA in Europe

Purpose of the studies: Although the upadacitinib clinical trials provide valuable information on the product's efficacy and safety, assessment of safety using randomized controlled trial (RCT) data is limited by the relatively small sample sizes and short duration of follow-up. Long-term safety data are needed in patients in routine clinical practice who are exposed to upadacitinib, including patients not included in the clinical program or in populations with limited clinical trial data (e.g., the very elderly, patients with evidence of untreated chronic infection with hepatitis B or hepatitis C, patients with moderate hepatic impairment, and patients with severe renal impairment). Several disease-based prospective rheumatology registries have been established in Europe to complement clinical trial data, including providing longitudinal safety data for new therapies.

Several of these European RA registries provide nearly complete national coverage of patients in a comprehensive electronic health record with multiple registry linkages and with low attrition over time. These registries allow for the evaluation of outcomes referent to an active user comparator group, and their large size provides the ability to study rare events not well captured in RCTs. As such, these registries have been used extensively to address

post-marketing safety requirements in patients with RA, including comparative analyses of rates of infections, malignancy, adverse hepatic and renal events, and major adverse cardiovascular event (MACE). There is also demonstrated feasibility to evaluate venous thromboembolic event (VTE) risk in treated RA patient populations in these European RA registries (Davies 2011, Holmqvist 2012).

Recommended upadacitinib use in RA has been changed following the procedure under Article 20. The purpose of this study is to evaluate and characterize the important identified and potential risks of upadacitinib and missing information on the safety of upadacitinib, as described in the European Union Risk Management Plan. The primary objectives are to assess comparability across users of upadacitinib and other select systemic treatments for RA through in-depth assessments of drug utilization and patient characteristics at baseline; to describe the incidence of the following safety outcomes in patients with RA treated with upadacitinib: malignancy excluding non-melanoma skin cancer, including malignancy by type, NMSC, MACE, VTE, serious and opportunistic infections (including herpes zoster and TB), GI perforations, liver injury (including DILI), bone fractures, and all-cause mortality; if a suitable comparator is identified, to describe and compare (when feasible) the incidence of the above safety outcomes in patients with RA treated with upadacitinib relative to those treated other select systemic RA treatments (excluding other JAK inhibitors). Secondary objectives are to describe the incidence of the safety outcomes mentioned under the primary objective among the following patient subcohorts of upadacitinib users: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), patients with severe renal impairment (when possible using proxy measures available within a given data source), and patients with evidence of chronic infection with HBV or HCV; if a suitable comparator is identified, to describe the incidence of the safety outcomes mentioned under primary objectives in the following patient subcohorts of other select systemic RA treatments: the very elderly (≥ 75 years of age), patients with moderate hepatic impairment (when possible using proxy measures available within a given data source), patients with severe renal impairment (when possible using proxy measures available within a given data source), and patients with evidence of chronic infection with HBV or HCV.

Additional pharmacovigilance pharmacoepidemiology study: Study P19-141: Long-term safety study of Rinvoq™ in RA patients enrolled in the CorEvitas (formerly Corrona) RA Registry in the United States

Purpose of the study: Upadacitinib is a selective and reversible inhibitor of Janus kinase (JAK) with demonstrated efficacy in treatment of moderate to severe active RA. Safety has been characterized during the development program; however, additional evaluation of safety for rare events, long latency outcomes, and in the broader RA population is warranted. To provide this evidence, AbbVie plans to implement a post-approval, population-based prospective cohort study in partnership with the CorEvitas (formally Corrona) United States (US) RA Registry. The study will be designed and sufficiently powered to identify clinically meaningful increases in the

risk of malignancies, VTE, MACE, and serious infections in upadacitinib patients relative to patients treated with other therapies for moderately to severely active RA. A sub-study to explore thrombosis biomarkers at baseline in upadacitinib treated and comparator biologic treated patients will be conducted. In addition, biobanking will be employed to allow for future evaluation of potential biomarkers related to VTE risk, should an increased risk be identified in upadacitinib treated patients.

The CorEvitas US RA Registry is an established, prospective, multicenter, observational registry for adult patients with RA. Established in 2001, CorEvitas includes data from over 52,500 RA patients, 750 physicians, and 182 sites, across 42 states. Detailed data collection by participating investigators and their patients with RA enables capture of a number of clinical, behavioral, and disease severity measures as well as clinical outcomes associated with treatment for RA. Data on targeted outcomes are collected prospectively, via Targeted Adverse Event Questionnaires. The overall goal of the study is to characterize the safety of upadacitinib in RA patients in the post-approval setting. The primary objective of the study is to compare the incidence of malignancy (excluding NMSC), NMSC, MACE, VTE, serious infection events, and all-cause mortality in adults with RA who receive upadacitinib in the course of routine clinical care relative to those who receive biologic therapy for the treatment of RA. Secondary objectives are to describe the incidence rates of herpes zoster, opportunistic infections, active TB, GI perforations, evidence of DILI, and fractures; to describe the incidence of the above outcomes in very elderly patients (aged ≥ 75 years); and to describe the incidence rates of events in primary and secondary objectives in the following subgroups of interest: patients with moderate hepatic impairment at the time of Rinvoq or biologic therapy start; patients with evidence of chronic infection with HBV or HCV at the time of Rinvoq or biologic therapy start; and patients with severe renal impairment at the time of Rinvoq or biologic therapy start. An exploratory objective is to describe the distribution of risk factors for VTE in those treated with Rinvoq and those treated with biologic therapy, and in those who do and do not experience VTE during follow-up, in a subset of participating patients providing laboratory samples.

Additional pharmacovigilance pharmacoepidemiology study: Study P20-199: Drug utilisation study of upadacitinib (Rinvoq™) in Europe to evaluate the effectiveness of additional risk minimisation measures among patients with Rheumatoid Arthritis

Purpose of the study: As with other JAK inhibitors already marketed in Europe (e.g., tofacitinib and baricitinib), important safety risks have been identified with upadacitinib that require aRMMs. Using data derived from European RA registries, AbbVie plans to implement a drug utilization study to characterise the use of upadacitinib and evaluate the effectiveness of the aRMMs (HCP educational guide and patient card) in the pre-Article 20 and post Article 20 time periods.

This study aims to evaluate the use of upadacitinib in routine clinical care through the following specific objectives: to describe the baseline characteristics of new users of, and in a similar

manner, to describe new users of a selected bDMARD for comparison; to evaluate prescribers' adherence to the upadacitinib aRMMs, specifically: compliance to recommendations for patient screening and laboratory monitoring prior to and during treatment; compliance to recommendations for limitations of use, including: Use in patients with risk factors for GI perforation; use in patients with risk factors for VTE; use in the patients aged 65 years and older; use in patients with risk factors for CVD; use in patients with risk factors for malignancy; use in patients with risk factors for serious infections; and contraindicated use (active TB and pregnancy); and to describe changes in the utilisation of upadacitinib following the updated recommendations and limitations for use implemented after the Article 20 referral procedure.

Additional pharmacovigilance pharmacoepidemiology study: Study P20-390: Cohort study of long-term safety of upadacitinib in the treatment of atopic dermatitis in Denmark and Sweden

Purpose of the study: Upadacitinib 15 mg was approved for the treatment of adults with moderate to severely active RA in the European Union on 18 December 2019. Studies to assess long-term safety of upadacitinib in the routine clinical setting for RA are currently being conducted. Upadacitinib 15 mg is approved to be used in the EU for treatment of adolescents with moderate to severe AD weighing at least 30 kg. Following the procedure under Article 20 of Regulation (EC) No 726/2004 (concluded 10 March 2023), upadacitinib recommended use and doses have been changed. Upadacitinib 15 mg is approved to be used in the EU for treatment of elderly patients (≥ 65 years of age) or patients with risk factors for malignancy, MACE, or VTE. In addition, upadacitinib should only be used, if no suitable alternatives are available, in patients 65 years of age or older, in patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors and in patients with malignancy risk factors. An additional long-term safety study is proposed in order to assess the long-term safety of upadacitinib use in patients with moderate to severe AD in a real-world setting. The proposed study will be designed to evaluate and characterize the important identified and potential risks and missing information as described in this RMP.

The overall goal of the study is to characterize the safety of upadacitinib in AD patients in the post-approval setting. The primary objectives of the study are to assess comparability across upadacitinib and other select systemic treatments for AD through in-depth assessments of treatment pattern and patient disposition at baseline and to describe the incidence of the following outcomes, in adolescent and adult patients treated with upadacitinib, and compare (when feasible) the incidence of the above AEs relative to those treated with other alternative systemic drug therapies for AD, in the course of routine clinical care: Malignancy (excluding NMSC), NMSC, MACE, VTE, serious infections (including opportunistic infections), herpes zoster, eczema herpeticum (EH)/Kaposi's varicelliform eruption, active TB, GI perforations, evidence of DILI, all-cause mortality, and fractures.

Secondary objectives are to describe the incidence of the above AEs in patients who receive upadacitinib by: dose of upadacitinib (15 mg and 30 mg); age groups (adolescents [12 – 17 years], adults aged 18 – 64 years, 65 – 74 years, and ≥ 75 years); history of moderate hepatic impairment at the time of upadacitinib initiation; history of chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) at the time of upadacitinib initiation; and history of severe renal impairment at the time of upadacitinib initiation, and, if a suitable comparator is identified, to describe the incidence of the above AEs in patients who receive other select systemic AD treatments.

Additional pharmacovigilance pharmacoepidemiology study: Study P21-825: Drug utilization study evaluating additional risk minimization measures for Upadacitinib in the treatment of atopic dermatitis in Europe

Purpose of the study: Additional risk minimization is being used for upadacitinib in RA and is proposed for upadacitinib in AD. Specific risks included in upadacitinib's risk minimization program will require aRMMs.

The study aims to evaluate the use of upadacitinib in individuals with AD in routine clinical care in Denmark, Germany, Spain, and Sweden with the following specific objectives:

- to describe the baseline characteristics of individuals with AD who are new users of upadacitinib;
- to the extent measurable, evaluate healthcare utilization in routine clinical care as an indicator of physician adherence to the aRMMs among individuals with AD who are new users of upadacitinib, by: quantifying the compliance to recommendations for posology (average daily dose) and by describing the duration of use; quantifying the compliance to recommendations for the use among individuals who have risk factors for GI perforation, serious infections, malignancy, MACE, and VTE; quantifying the compliance to the recommendations for the use among patients aged 65 years and older; quantifying the compliance to the recommendations for contraindicated use including pregnancy and active TB; and quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark, Germany and Spain only); and to describe the changes in the utilisation of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure, specifically: describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; describe the use of upadacitinib among patients aged 65 years and older; and describe the use of upadacitinib 30 mg.

Additional pharmacovigilance pharmacoepidemiology study: Study P21-824: A study of growth, development and maturation in adolescents with atopic dermatitis who receive upadacitinib

Purpose of the study: Upadacitinib 15 mg and 30 mg once daily (QD) are approved for use in adults with moderate to severe AD and upadacitinib 15 mg QD is approved for use in adolescents with moderate to severe AD weighing 30 kg or over and elderly patients ≥ 65 years of age. The available nonclinical data for upadacitinib do not suggest a risk associated with bone development in patients ≥ 12 years old. However, since the long-term use of upadacitinib on growth in adolescents has not been studied, the impact of long-term use of upadacitinib on growth in adolescents is not known.

Per Pharmacovigilance Risk Assessment Committee's (PRAC's) request, this study aims to evaluate the growth, development, and maturation in North American (US and Canada)-residing adolescents with moderate to severe AD who receive upadacitinib vs. biologic and other non-biologic, non-JAKi systemic comparators in routine clinical care. Where feasible, a cohort of European-residing adolescents with moderate to severe AD will also be evaluated. The primary objective is to compare differences in changes from baseline in height standard deviation score (SDS) and weight SDS, age at peak height velocity, age at Tanner stage progression, and incidence of bone fractures in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.

The secondary objectives of the study are to describe changes from baseline in standing height, height percentiles, height velocity, height velocity SDS, weight, weight percentiles, body mass index (BMI), BMI percentiles, and BMI SDS, as well as the frequency of delayed puberty in adolescents with moderate to severe AD being treated with upadacitinib and those treated with comparator medications for AD.

Additional pharmacovigilance pharmacoepidemiology study: Study P24-343: Cohort study of long-term safety of upadacitinib for the treatment of ulcerative colitis and Crohn's disease in a real-world setting in Europe

Purpose of the study: Upadacitinib is approved for the treatment of adults (≥ 18 years of age) with moderate to severe UC or CD who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Upadacitinib should only be used, if no suitable alternatives are available, in patients 65 years of age or older, in patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors and in patients with malignancy risk factors. This study aims to evaluate the long-term safety of upadacitinib use in adults in routine clinical care for the treatment of UC and CD.

The primary objectives of the study are to: 1) describe and compare the incidence of GI perforation in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy, and 2) describe and compare, where

possible, the incidence of fractures and DILI in adults with UC or CD treated with upadacitinib, relative to those treated with select biologic IBD treatments at a similar line of therapy. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for incidence comparison of fractures and DILI.

The secondary objectives are to describe and compare, where possible, the incidence of the following secondary safety outcomes in adults with UC or CD treated with upadacitinib, relative to those treated with biological drug therapies at a similar line of therapy for UC and CD in the course of routine clinical care: malignancy excluding NMSC (stratified by type), NMSC, MACE, VTE, serious infections (defined as all infections that require hospitalization, including opportunistic infections), herpes zoster, active TB, and all-cause mortality. Comparability across upadacitinib and biological IBD treatments will be evaluated through in-depth assessments of number of users, treatment patterns and patient disposition at baseline to determine whether suitable comparators are identified and number of users allow for the incidence comparison of the secondary outcomes.

In addition, incidence of the primary and secondary safety outcomes will be described in patients with UC or CD who receive upadacitinib by dosing pattern (45 mg induction followed by 15 mg and/or 30 mg maintenance dosing). When possible, the occurrence of the safety outcomes will be described in the following subgroups of interest, with limited or missing information from the clinical development program: very elderly (aged ≥ 75 years) at the time of treatment initiation; patients with moderate hepatic impairment at the time of treatment initiation; patients with severe renal impairment at the time of treatment initiation; patients with evidence of chronic infection with HBV or HCV at the time of treatment initiation.

Additional pharmacovigilance pharmacoepidemiology study: Study P24-344: Drug Utilization Study Evaluating Additional Risk Minimisation Measures for Upadacitinib in the Treatment of Ulcerative Colitis in Europe

Purpose of the study: Additional risk minimization is being used for upadacitinib in RA and is proposed for upadacitinib in UC. Specific risks included in upadacitinib's risk minimization program will require aRMMs. AbbVie plans to describe the baseline characteristics of new users of upadacitinib and evaluate the effectiveness of the aRMMs (HCP educational guide and patient card) in a drug utilisation study. This study aims to evaluate the use of upadacitinib in routine clinical care for UC through the following specific objectives: to describe the baseline characteristics of UC patients who are new users of upadacitinib; to the extent measurable, evaluate healthcare utilization in routine clinical care as indicator of physician adherence to the aRMMs among patients with UC who are new users of upadacitinib, by: quantifying the compliance to recommendations for posology (average daily dose) and duration of use; quantifying the compliance to recommendations for the use among patients who have risk

factors for GI perforation, malignancy, MACE, VTE, and serious infections; quantifying the compliance to the recommendations for the use among patients aged 65 years and older; quantifying the compliance to the recommendations for contraindicated use including pregnancy and active TB; and quantifying the compliance to recommendations for patient screening and laboratory monitoring prior to and during upadacitinib treatment (Denmark and Spain only); to describe the changes in the utilization of upadacitinib following the implementation of revised aRMMs from the Article 20 referral procedure (Sweden only), specifically: describe the use of upadacitinib among patients with risk factors for VTE, MACE, malignancy, and serious infections; describe the use of upadacitinib among patients aged 65 years and older; and describe the use of higher maintenance dose of upadacitinib 30 mg.

Long-term extension portion of upadacitinib clinical trials

Study M14-465:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD in subjects with RA who have completed Period 1.

Study M15-554:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.

Study M15-572:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with PsA who have completed Period 1.

Study M19-944 (Study 1):

Purpose of the study: To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active biologic disease-modifying anti-rheumatic drug inadequate responder (bDMARD-IR) AS (Study 1), who have completed the Double-Blind Period.

Study M19-944 (Study 2):

Purpose of the study: To evaluate the safety and tolerability of upadacitinib 15 mg QD in extended treatment in adult subjects with active nr-axSpA (Study 2), who have completed the Double-Blind Period.

Study M16-045:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with AD who have completed the Double-Blind Period.

Study M16-047:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg and 30 mg QD in combination with topical corticosteroids in subjects with AD who have completed the Double-Blind Period.

Study M18-891:

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy of upadacitinib 15 mg QD and 30 mg QD in subjects with AD who have completed the Double-Blind Period.

Study M14-533:

Purpose of the study: To evaluate the long-term safety and efficacy of upadacitinib in subjects with UC.

Study M14-430 Substudy 2:

Purpose of the study: To evaluate the safety and efficacy of long-term administration of upadacitinib in subjects with moderately to severely active CD who participated in the Phase 3 upadacitinib induction and maintenance studies.

Study M16-852

Purpose of the study: To evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in subjects with GCA who achieved remission in Period 1.

Part VII: Annexes

Annex 4. Specific Adverse Drug Reaction Follow-Up Forms

Follow-up forms included:

Upadacitinib AESI Serious Infections Letter Ver 1

Rinvoq_Upadacitinib_Drug exposure during pregnancy

Rinvoq_Upadacitinib_Pregnancy letter for the infant outcomes

Upadacitinib AESI Malignancies Letter Ver 1

Upadacitinib AESI Major Adverse Cardiac Event (MACE) Letter Ver 1

Upadacitinib AESI Thromboembolic Events Letter Ver 1

Rinvoq AESI GI Perf Letter FINAL Ver1

Rinvoq AESI DILI Letter Final Ver1

Targeted Event - Upadacitinib Bone Fracture Medical Concept Questionnaire

Patient information:
Name:
Street address:
City: State: Zip code:

Reference Numbers:
AER#:
Affiliate#:
Other reference#:

Initials:	Patient ID:	Sex: Male ☐ Female ☐	Date of Birth:	Age at time of event:

Please provide detailed event information including symptoms the patient experienced leading up to the events:

Please provide risk factors that could have triggered the event (including sick contacts, recent hospitalization, recent antibiotic therapy, etc):

Adverse Event	Event Onset (d/m/y)	Event End (d/m/y)	Event Criteria+	Was this caused by suspect? ++	Outcome **

+ Event Criteria codes: Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability) or Non-serious
++ Causality Code: Reasonable Possibility, No Reasonable Possibility, Non-Assessable
**Outcome codes: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Suspect Product:

Name	Dose	Form	Frequency	Route	Start Date (d/m/y)	End Date (d/m/y)	Indication	If stopped, did event abate? If so, provide date

Please provide Lot number for time of event: **Expiration date:**
If unable to provide Lot number, provide rationale: discarded ☐ not accessible to physician ☐ not on patient's file ☐ did not receive in original package ☐ not legible on package ☐
If AbbVie product was discontinued, date restarted: Dose: Did the event(s) return? Yes ☐ No ☐ Please describe:

Patient Medical History:

Immunosuppressive disorders Yes ☐ No ☐ Specify:	Diabetes Mellitus Yes ☐ No ☐ Specify:	Latent TB Yes ☐ No ☐	
Please also include patient history of pregnancy, risk factors, HIV,…)			

Concomitant (Other medications at time of event) (C), Past (P), Treatment (T) information (Please include herbal, recreational, OTC medication and supplements):

Name	C, P or T	Form	Dose	Frequency	Route	Start date	End Date	Indication

Please provide what treatment or interventions the patient underwent for the events:

Please provide Laboratory and Diagnostic Test results:

Laboratory test	Date (d/m/y)	Result (include units of measure)	Reference Range
Blood culture			
Urine culture			
Tissue/fluid culture			
Blood White blood cell count			
Blood Neutrophil Count			
Blood Lymphocyte Count			
Antigen titres			
Serologic titres			

Diagnostic test	Date (d/m/y)	Results (key findings) (If desired attach results) *Include reference ranges:*

Patient information:

Height: cm ☐ in ☐	Weight: kg ☐ lbs ☐	Race/Ethnicity:
Tobacco use: Yes ☐ No ☐ (amount/start/stop dates)		Alcohol use: Yes ☐ No ☐ (amount/type/start and stop dates)
Allergies: Yes ☐ No ☐ (type and manifestation)		Illicit drug use: Yes ☐ No ☐ (amount/type/start and stop dates)

If the patient died, Date of Death (d/m/y):	Autopsy: Yes ☐ No ☐ Unknown ☐	Autopsy Date (d/m/y):
Autopsy results:	Cause of Death:	

Does reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐

Physician/HCP Name/Specialty:		
Street Address:		
City:	State:	Zip:
Phone Number:		

Person completing form:

Name:		
Street address:		
City:	State:	Zip:
Phone Number:		

Initial Pregnancy Report

AER # _____ **AbbVie Awareness Date** ____/____/____

INITIAL REPORT SOURCE INFORMATION

Patient ☐ **Primary Reporter**

Name: _____

Address: _____

_____

Phone: _____ Fax: _____

☐ M ☐ F DOB ____/____/____ Age ____

Race: _____ Occupation: _____

Does patient agree to have MD contacted?
[☐] Yes [☐] No [☐] Not Applicable

Health Care Provider ☐ **Primary Reporter**

Name: _____

Address: _____

_____

Phone: _____ Fax: _____

Specialty: _____

ABBVIE PRODUCT INFORMATION

Product Name	Form	Unit Dose & Frequency	Route	Start Date/ Duration	End Date	Indication(s)	Lot & Expiration date*

***If unable to provide Lot number, provide rationale: discarded [ ], not accessible to physician [ ], not on patient's file [ ], did not receive in original package [ ], not legible on package [ ]**

CURRENT PREGNANCY

Is pregnancy ongoing? ☐ Yes ☐ No ***If no, was the termination:*** ☐ Spontaneous abortion ____/____ (date/EGA)

☐ Elective abortion ____/____ (date/EGA) Were any fetal abnormalities diagnosed? ☐ Yes ☐ No

If yes, please provide further details including dates and pathology results (if available): _____

Date of last menstrual period (LMP): ____/____/____ Estimated date of delivery (EDC): ____/____/____

Date of pregnancy confirmation: ____/____/____ Confirmed by: ☐ Serum ☐ Dipstick ☐ Ultrasound

Confirmed by: ☐ Consumer ☐ Healthcare Provider Any medical problems or complications during this pregnancy? ☐ Yes ☐ No

If *yes*, please provide further details: _____

Diagnostic tests performed during pregnancy? ☐ Yes ☐ No

If *yes, provide further details including dates and results*: _____

PREGNANCY HISTORY

Total:

Pregnancies _____ Full term deliveries _____ Premature deliveries _____ Ectopic pregnancies _____

Stillbirths _____ Spontaneous abortions _____ Elective abortions _____

Any family history of birth defects, genetic disorders, multiple births, fetal abnormalities, or pregnancy complications?

If yes, circle and provide further details: _____

MATERNAL PAST MEDICAL HISTORY

☐ Hypertension ☐ Seizures ☐ Thyroid disorder ☐ Allergies ☐ Heart disease ☐ Rheumatologic disease

☐ Autoimmune disease ☐ Diabetes ☐ Infectious disease (hepatitis, rubella, Epstein-Barr virus, cytomegalovirus, HIV, etc.) ☐ Recreational drug use

☐ Environmental/ occupational exposure ☐ Hospitalization ☐ Surgery ☐ Tobacco ☐ Alcohol ☐ Other _____

Please provide further details and onset dates for checked items: _____

Initial Pregnancy Report

AER # _____ **AbbVie Awareness Date** ____/____/____

CONCOMITANT MEDICATION INFORMATION

List prescribed drugs and over-the-counter drugs, including dietary/herbal supplements, vaccines, inhalers and insertable or implantable medical devices.

Product Name	Total Daily Dose	Unit Dose & Frequency	Route	Start/ Duration	End	Indication(s)

Name: _____ Date: _____ Signature and Date: _____

Note: A signature/date is not required on the form, if it is documented in an electronic system.

Pregnancy Follow-Up Report

AER # _____ **AbbVie Awareness Date** ____/____/____

FOLLOW-UP REPORT SOURCE INFORMATION

Patient ☐ **Primary Reporter**	**Health Care Provider** ☐ **Primary Reporter**
Name: _____	Name: _____
Address: _____	Address: _____
Phone: _____	Phone: _____
Fax: _____	Fax: _____
☐ M ☐ [redacted] DOB ____/____/____ Age ____	Specialty: _____
Race: _____ Occupation: _____	
Does patient agree to have MD contacted? [☐] Yes [☐] No [☐] Not Applicable	

PREGNANCY OUTCOME

PREGNANCY STATUS

Is pregnancy ongoing? ☐ Yes ☐ No ***If no, was the termination:***

☐ Spontaneous abortion: ____/____ (date/EGA) ☐ Elective abortion: ____/____ (date/EGA)

Were any abnormalities diagnosed? ☐ Yes ☐ N[redacted]

If yes, please provide further details including dates and pathology results (if available): _____

MATERNAL STATUS

Actual date of delivery: ____/____/____ ☐ Vaginal delivery ☐ C-Section

Maternal age at the time of delivery: ____

Total maternal weight gain: ____ (lb/kg)

Any medical problems or complications during delivery or postpartum period such as pre-eclampsia, DIC, hemorrhage, hypertension, premature labor, premature delivery, etc.? ☐ Yes ☐ No

Did the mother receive sedation or an anesthetic? ☐ Yes ☐ No

If yes to either question, please provide further details: _____

MEDICATIONS

*List any **new** medications, over-the-counter drugs, including dietary/herbal supplements, vaccines, inhalers and insertable or implantable medical devices taken during the pregnancy.*

Product Name	Form	Unit Dose & Frequency	Route	Start/ Duration	End	Indication(s)	Lot & Expiration*

***If unable to provide Lot number, provide rationale: discarded [ ], not accessible to physician [ ], not on patient's file [ ], did not receive in original package [ ], not legible on package [ ]**

Pregnancy Follow-Up Report

AER # _____ **AbbVie Awareness Date** ____/____/____

INFANT STATUS

Fetal death/stillborn? ☐ Yes ☐ No Live birth? ☐ Yes ☐ [redacted]o Gestational age at delivery ____ weeks

Birth weight: ____ (lb/kg) Length: ____ (cm/inches) ☐ [redacted]ale ☐ [redacted]emale

Apgar scores: ____ 1 min. ____ 5 min. Any complications? ☐ Yes ☐ No Any congenital anomalies? ☐ Yes ☐ No

If ***yes,*** please provide further detail including, lab/blood gas results, need for resuscitation, admission to intensive care nursery, developmental assessment, neonatal illnesses, hospitalizations, drug therapies, etc.: _____

ADDITIONAL INFORMATION NOT INCLUDED ABOVE

[redacted]

Name: _____ Date: _____ Signature and Date: _____

Note: A signature/date is not required on the form, if it is documented in an electronic system.

Patient information:
Name:
Street address:
City: State: Zip code:

Reference Numbers:
AER#:
Affiliate#:
Other reference#:

Initials:	Patient ID:	Sex: Male ☐ Female ☐	Date of Birth:	Age at time of event:

Please provide detailed event information including symptoms the patient experienced leading up to the events and clinical staging:

If treatment for malignancy was performed, please specify, including dates:

Adverse Event Primary site of malignancy and cell type	Event Onset (d/m/y)	Event End (d/m/y)	Event Criteria+	Was this caused by suspect product? ++	Outcome **

+ Event Criteria codes: Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability) or Non-serious

++ Causality Code: Reasonable Possibility, No Reasonable Possibility, Non-Assessable

**Outcome codes: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Patient Medical History:

Solid organ transplantation Yes☐ No ☐ Specify:	Exposure to radiation, environmental chemicals/sun, occupational exposure: Yes ☐ No ☐ Specify:	Family history of malignancy/ies Yes ☐ No ☐ Specify:	Prior history malignancies (same or other site Yes ☐ No ☐ Specify:
Tobacco Use Yes ☐ No ☐ (form/amount/start/stop-year(s)):	History of use of immunosuppression/antineoplastic drugs Yes ☐ No ☐ Specify:	Secondary tobacco exposure Yes ☐ No ☐	Alcohol use Yes ☐ No ☐ (amount/start/stop-year(s)):

Suspect Product:

Name	Dose	Form	Frequency	Route	Start Date (d/m/y)	End Date (d/m/y)	Indication	If stopped, did event abate? If so, provide date

Please provide Lot number for time of event: **Expiration date:**

If unable to provide Lot number, provide rationale: discarded ☐ not accessible to physician ☐ not on patient's file ☐ did not receive in original package ☐ not legible on package ☐

If Suspect product(s) were discontinued, date restarted: Dose: Did the event(s) return? Yes ☐ No ☐ Please describe:

Concomitant (Other medications at time of event) (C), Past (P), Treatment (T) information (Please include herbal, recreational, OTC medication and supplements):

Name	C, P or T	Form	Dose	Frequency	Route	Start date	End Date	Indication

Please provide what treatment or interventions the patient underwent for the events:

Please provide Laboratory and Diagnostic Test results:

Laboratory test	Date (d/m/y)	Result (include units of measure)	Reference Range
CBC			
Genetic testing/ Immunophenotyping			
Relevant tumor markers			

Diagnostic test	Date (d/m/y)	Results (key findings) (If desired attach results)
Biopsy		*Indicate tumor (cell) type, grade, staging classification and tissue source:*
MRI		
CT		
Ultrasound		
Endoscopy		
Mammogram		*If Breast Cancer, please include date and results of prior screening mammogram:*
Bone scan		

Patient information:

Height: cm ☐ in ☐	Weight: kg ☐ lbs ☐	Race/Ethnicity:
Allergies: Yes ☐ No ☐ (type and manifestation)		Illicit drug use: Yes ☐ No ☐ (amount/type/start and stop dates)

If the patient died, Date of Death (d/m/y):	Autopsy: Yes ☐ No ☐ Unknown ☐	Autopsy Date (d/m/y):
Autopsy results:	Cause of Death:	

Does reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐

Physician/HCP Name/Specialty:		
Street Address:		
City:	State:	Zip:
Phone Number:		

Person completing form:

Name:		
Street address:		
City:	State:	Zip:
Phone Number:		

Upadacitinib AESI Major Adverse Cardiac Event (MACE) Letter

Patient information:
Name:
Street address:
City: State: Zip code:

Reference Numbers:
AER#:
Affiliate#:
Other reference#:

Initials:	Patient ID:	Sex: Male ☐ Female ☐	Date of Birth:	Age at time of event:

Is this a cardiovascular event, cerebral vascular accident or transient ischemic attack? If yes, please specify and include symptoms (please see table below):

Adverse Event	Symptoms Associated with Adverse Event	Event Onset (d/m/y)	Outcome (d/m/y)	Event Criteria+	Was this caused by suspect? ++	Outcome **

+ Event Criteria codes: Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability) or Non-serious

++ Causality Code: Reasonable Possibility, No Reasonable Possibility, Non-Assessable

**Outcome codes: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Please provide detailed event information including symptoms the patient experienced leading up to the events:

Patient Medical History (include patient history of pregnancy, risk factors **(please see section below for specific risk factors)**, HIV,…):

Hyperlipidemia Yes ☐ No ☐	Obesity Yes ☐ No ☐	Sleep apnea Yes ☐ No ☐ Specify:	Stroke: Yes ☐ No ☐ Specify:
Congestive heart failure Yes ☐ No ☐	Hypertension Yes ☐ No ☐ Specify:	Diabetes mellitus Yes ☐ No ☐ Specify:	Atrial fibrillation Yes ☐ No ☐ Specify:
Any previous heart disease such as myocardial infarction, arrhythmia, heart murmur, syncope, stent placement, etc.) Yes ☐ No ☐ Specify:	**Family** history of coronary heart disease or sudden death of young/middle aged relatives Yes ☐ No ☐ Specify:	Other Yes ☐ No ☐ Specify:	

Please provide what treatment or interventions the patient underwent for the events:

Suspect Product:

Name	Dose	Form	Frequency	Route	Start Date (d/m/y)	End Date (d/m/y)	Indication	If stopped, did event abate? If so, provide date

Please provide Lot number for time of event: **Expiration date:**

If unable to provide Lot number, provide rationale: discarded ☐ not accessible to physician ☐ not on patient's file ☐ did not receive in original package ☐ not legible on package ☐

If AbbVie product was discontinued, date restarted: Dose: Did the event(s) return? Yes ☐ No ☐ Please describe:

Concomitant (Other medications at time of event) (C), Past (P), Treatment (T) information (Please include **anticoagulants,** recreational, OTC medication and supplements):

Name	C, P or T	Form	Dose	Frequency	Route	Start date	End Date	Indication

Please provide Laboratory and Diagnostic Test results:

Laboratory test	Date (d/m/y)	Result (include units of measure)	Reference range (units of measure)
CPK-MB			
Troponins			
Lipid panel (HDL/LDL)			
Complete metabolic panel			

Diagnostic test	Date (d/m/y)	Results (key findings) (If desired attach results)
Echo		
MUGA scan		
Stress test		
Cardiac interventions (catheterization, PTCA procedures, etc.) *Specify*		
EKG		
Carotid doppler		

Patient information:

Height: cm ☐ in ☐	Weight: kg ☐ lbs ☐	Race/Ethnicity:
Tobacco use: Yes ☐ No ☐ (amount/start/stop dates)		Alcohol use: Yes ☐ No ☐ (amount/type/start and stop dates)
Allergies: Yes ☐ No ☐ (type and manifestation)		Illicit drug use: Yes ☐ No ☐ (amount/type/start and stop dates)

If the patient died, Date of Death (d/m/y):	Autopsy: Yes ☐ No ☐ Unknown ☐	Autopsy Date (d/m/y):
Autopsy results:	Cause of Death:	

Does reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐

Physician/HCP Name/Specialty:		
Street Address:		
City:	State:	Zip:
Phone Number:		

Person completing form:

Name:		
Street address:		
City:	State:	Zip:
Phone Number:		

Follow-Up Questionnaire for Thromboembolic Adverse Events with Upadacitinib

Patient information:
Name:
Street address:
City: State: Zip code:

Reference Numbers:
AER#:
Affiliate#:
Other reference#:

Initials:	Patient ID:	Sex: Male ☐ Female ☐	Date of Birth:	Age at time of event:

Is this a non-cardiac, non-CNS embolic or thrombotic event (e.g. deep vein thrombosis, pulmonary embolism, peripheral arterial thromboembolism)? If yes, please specify and include location/symptoms:

Adverse Event Please specify location	Symptoms Associated with Adverse Event	Event Onset (d/m/y)	Outcome (d/m/y)	Event Criteria+	Was this caused by suspect? ++	Outcome **

+ Event Criteria codes: Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability) or Non-serious

++ Causality Code: Reasonable Possibility, No Reasonable Possibility, Non-Assessable

**Outcome codes: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Please provide detailed event information including symptoms the patient experienced leading up to the events:

Leg tenderness/pain Yes ☐ No ☐	Leg swelling Yes ☐ No ☐	Palpable cord Yes ☐ No ☐	Skin warmth Yes ☐ No ☐
Skin erythema/discoloration Yes ☐ No ☐	Hypotension Yes ☐ No ☐	Shortness of breath Yes ☐ No ☐	Hemoptysis Yes ☐ No ☐
Syncope (loss of consciousness) Yes ☐ No ☐	Pleuritic chest pain Yes ☐ No ☐	Tachycardia (heart rate >100 bpm) Yes ☐ No ☐	Ischemic resting pain Yes ☐ No ☐
Ischemic ulcers Yes ☐ No ☐	Nocturnal resting pain Yes ☐ No ☐	Pulselessness Yes ☐ No ☐	Pallor Yes ☐ No ☐
Paresthesia Yes ☐ No ☐	Paralysis Yes ☐ No ☐	Dry/wet gangrene Yes ☐ No ☐ Specify:	Claudication w/ ambulation Yes ☐ No ☐

Patient Medical History (include patient history of pregnancy, risk factors **(please see section below for specific risk factors)**, HIV,…):

Patient history of venous thromboembolism Yes ☐ No ☐ Specify:	**Patient** history of thrombosis Yes ☐ No ☐ Specify:	**Family** history of venous thromboembolism Yes ☐ No ☐ Specify:	**Family** history of thrombosis Yes ☐ No ☐ Specify:
History of DVT/PE/pulmonary infarction Yes ☐ No ☐ Specify:	History of recent or current malignancy Yes ☐ No ☐ Specify:	Recent trauma to lower extremities Yes ☐ No ☐ Specify:	Recent surgical procedure (e.g. lower extremity fracture/surgery.) Yes ☐ No ☐ Specify:
Use of estrogen preparation (e.g. hormonal contraceptives, hormone replacement therapy, etc.) Yes ☐ No ☐ Specify:	Diabetes mellitus Yes ☐ No ☐ Specify:	Hypertension Yes ☐ No ☐ Specify:	Atrial fibrillation Yes ☐ No ☐ Specify:
Prolonged immobilization (e.g. prolonged bed rest, prolonged travel with protracted sitting, hospitalization, etc.) Yes ☐ No ☐ Specify:	Inflammatory bowel disease Yes ☐ No ☐ Specify:	Genetic blood conditions that affect clotting, Yes ☐ No ☐ Specify:	Lower extremity varicose veins Yes ☐ No ☐ Specify:
Congestive heart failure Yes ☐ No ☐	Other Yes ☐ No ☐ Specify:		

Please provide what treatment or interventions the patient underwent for the events:

Follow-Up Questionnaire for Thromboembolic Adverse Events with Upadacitinib

Suspect Product:

Name	Dose	Form	Frequency	Route	Start Date (d/m/y)	End Date (d/m/y)	Indication	If stopped, did event abate? If so, provide date

Please provide Lot number for time of event: **Expiration date:**

If unable to provide Lot number, provide rationale: discarded ☐ not accessible to physician ☐ not on patient's file ☐ did not receive in original package ☐ not legible on package ☐

If AbbVie product was discontinued, date restarted: Dose: Did the event(s) return? Yes ☐ No ☐ Please describe:

Concomitant (Other medications at time of event) (C), Past (P), Treatment (T) information (Please include **anticoagulants,** recreational, OTC medication and supplements):

Name	C, P or T	Form	Dose	Frequency	Route	Start date	End Date	Indication

Please provide Laboratory and Diagnostic Test results:

Laboratory test	Date (d/m/y)	Result (include units of measure)	Reference range (units of measure)
D-Dimer			
Platelet count			
PT/INR			

Diagnostic test	Date (d/m/y)	Results (key findings) (If desired attach results)
Angiography		
CT Scan		
Impedance plethysmography		
Ultrasound - Doppler		
Venography		
Ventilation-Perfusion Scan		
MRI		

Patient information:

Height: cm ☐ in ☐	Weight: kg ☐ lbs ☐	Race/Ethnicity:
Tobacco use: Yes ☐ No ☐ (amount/start/stop dates)		Alcohol use: Yes ☐ No ☐ (amount/type/start and stop dates)
Allergies: Yes ☐ No ☐ (type and manifestation)		Illicit drug use: Yes ☐ No ☐ (amount/type/start and stop dates)

If the patient died, Date of Death (d/m/y):	Autopsy: Yes ☐ No ☐ Unknown ☐	Autopsy Date (d/m/y):
Autopsy results:	Cause of Death:	

Does reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐

Physician/HCP Name/Specialty:		
Street Address:		
City:	State:	Zip:
Phone Number:		

Person completing form:

Name:		
Street address:		
City:	State:	Zip:
Phone Number:		

We are requesting more information regarding the adverse event that your patient experienced *to help us ensure the safety and effectiveness of our medications for all individuals using them.*

Patient Information

Reference Numbers

Name: Initials: Patient ID: AER #

Address: City, State: Zip: Affiliate Ref #

Height: _____ cm ☐ in ☐ Weight: _____ kg ☐ lb ☐ Race/Ethnicity: Other reference #:

Sex: M ☐ F ☐ Date of Birth:_____/_____/_____ (dd/mm/yyyy) Age at Time of Event: Age group^:

^ Age group codes: Neonate (Day 0 to Day 27), Infant (28 days to 23 months), Child (2 years to 11 years), Adolescent (12 years to 17 years), Adult (18 years to 64 years), Elderly (65 years and over)

Medical History

Abdominal/Pelvic Surgery	Yes ☐	No ☐	Unknown ☐	Type(s):
Recent procedure (*e.g. colonoscopy*)	Yes ☐	No ☐	Unknown ☐	
Laxative Use	Yes ☐	No ☐	Unknown ☐	
Abd/Pelvic Injury/Trauma	Yes ☐	No ☐	Unknown ☐	Type(s):
Steroid Use	Yes ☐	No ☐	Unknown ☐	Dates of Use:
NSAID Use	Yes ☐	No ☐	Unknown ☐	Dates of Use:
Aspirin use	Yes ☐	No ☐	Unknown ☐	Dates of Use:
Opioid use	Yes ☐	No ☐	Unknown ☐	Dates of Use:
Pancreatitis	Yes ☐	No ☐	Unknown ☐	
Diverticular disease	Yes ☐	No ☐	Unknown ☐	Details (*e.g.diverticulitis*):
Cholecystitis	Yes ☐	No ☐	Unknown ☐	
Appendicitis	Yes ☐	No ☐	Unknown ☐	
Hernia/volvulus	Yes ☐	No ☐	Unknown ☐	
Inflammatory Bowel disease	Yes ☐	No ☐	Unknown ☐	Details:
Peptic Ulcer disease	Yes ☐	No ☐	Unknown ☐	
Malignancy	Yes ☐	No ☐	Unknown ☐	Type(s):
Connective Tissue disease	Yes ☐	No ☐	Unknown ☐	Type(s):

Other pertinent medical history (including pregnancy, HIV, etc.):

Medication List, Laboratory Tests & Diagnostic Test Results

For convenience you may print this information from your electronic medical record (EMR) and include with this form or hand write in tables on page 4.

Instructions to print from EMR

- Include active medication list at time of patient event. Write the start/end date or indication of patient medications if not included in EMR print out.
- Include laboratory tests and diagnostic tests for the 3-day period surrounding the event or most currently available.

Suspect Medication(s)

Name	Dose	Form	Frequency	Route	Start Date (d/m/y)	End Date (d/m/y)	Indication	If medication stopped, did event abate? *If yes, provide date*
					___/___/_____	___/___/_____		
					___/___/_____	___/___/_____		
					___/___/_____	___/___/_____		

AbbVie Medication Lot Number(s) Expiration Date: ____/_____/_____(d/m/y) *If unable to provide lot number,* indicate reason below:

Discarded ☐ Not Accessible to Physician ☐ Not on Patient's File ☐ Didn't Receive in Original Package ☐ Not Legible on Package ☐

Adverse Event Details

Select one of the following codes to answer the questions designated with numbers 1-3.

1. Event Criteria Codes: Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability) or Non-serious
2. Causality Code: Reasonable Possibility, No Reasonable Possibility, Non-Assessable
3. Outcome Codes: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Adverse Event	Event Onset (d/m/y)	Event End (d/m/y)	Event Criteria[1]	Was this caused by suspect?[2]	Outcome[3]
	___/___/_____	___/___/_____			
	___/___/_____	___/___/_____			
	___/___/_____	___/___/_____			
	___/___/_____	___/___/_____			
	___/___/_____	___/___/_____			

AbbVie medication was restarted after being discontinued? Yes ☐ No ☐ Unknown ☐

Date Restarted: ___/___/_____(d/m/y)

Did the event(s) return when restarted? Yes ☐ No ☐ Unknown

Did the Patient Die? Yes ☐ No ☐ Unknown ☐

Date of Death: _____/_____/_____ (d/m/y)

Autopsy Date: _____/_____/_____ (d/m/y)

Autopsy Results:

GI perforation resolved at time of death: Yes ☐ No ☐ Unknown ☐

If Yes, answer the following questions

Dose:

Describe:

If Yes, answer the following questions

Autopsy: Yes ☐ No ☐ Unknown ☐

Cause of Death:

Provide detailed event information including symptoms the patient experienced leading up to the events (including location of GI perforation):

Provide what treatment or interventions the patient underwent for the events, including surgical interventions and operative findings:

Provide risk factors that could have triggered the event (gastrointestinal illness, recent invasive medical procedures):

Contact Information

Does reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐

Physician/HCP Name/Specialty:	
Address:	
City, State:	Zip:
Phone Number:	

Person completing form *if different from Physician/HCP*

Name:	
Address:	
City, State:	Zip:
Phone Number:	

Supplemental Tables *(if needed)*

Medications *Indicate Concomitant (active at time of event) (C), Past (P), and Treatment information (T). Include herbal, OTC medications, and supplements*

Name	C, P or T	Dose	Form	Frequency	Route	Start date	End Date	Indication
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	

Laboratory Test and Diagnostic Test Results *Include laboratory tests and diagnostic tests for the 3 day period surrounding the event or most currently available*

Laboratory test	Date (d/m/y)	Result (include units of measure)	Reference Range
Albumin	___/___/_____		
Alk Phos	___/___/_____		
AST/ALT	___/___/_____		
Amylase/Lipase	___/___/_____		
Direct bilirubin	___/___/_____		
Total bilirubin	___/___/_____		
Lactic Acid	___/___/_____		
CRP	___/___/_____		
PT/INR	___/___/_____		
Stool PCR	___/___/_____		
Stool culture			
C. difficile toxin			
Include others deemed important to report			
	___/___/_____		
	___/___/_____		
	___/___/_____		

Diagnostic test	Date (d/m/y)	Results (key findings). *If desired attach results.* *Include reference ranges:*
Abdominal X-ray	___/___/_____	
Ultrasound	___/___/_____	
CT Scan	___/___/_____	
MRI	___/___/_____	
Barium studies	___/___/_____	
Endoscopy	___/___/_____	
Colonoscopy	___/___/_____	
Biopsy	___/___/_____	
Surg Path	___/___/_____	

We are requesting more information regarding the adverse event that your patient experienced *to help us ensure the safety and effectiveness of our medications for all individuals using them.*

Patient Information

Reference Numbers

Name: Initials: Patient ID: AER #

Address: City, State: Zip: Affiliate Ref #

Height: _____ cm ☐ in ☐ Weight: _____ kg ☐ lb ☐ Race/Ethnicity: Other reference #:

Sex: M ☐ F ☐ Date of Birth:_____/_____/_____ (dd/mm/yyyy) Age at Time of Event: Age group^:

^ Age group codes: Neonate (Day 0 to Day 27), Infant (28 days to 23 months), Child (2 years to 11 years), Adolescent (12 years to 17 years), Adult (18 years to 64 years), Elderly (65 years and over)

Medical History

Alcohol Use	Yes ☐ No ☐ Unknown ☐	Amount/Start/Stop Dates:
Illicit Drug Use	Yes ☐ No ☐ Unknown ☐	Type/Amount/Start/Stop Dates:
Liver Disease (e.g. Gilbert's, NAFLD, autoimmune, non viral hepatitis)	Yes ☐ No ☐ Unknown ☐	Types(s):
Viral Hepatitis	Yes ☐ No ☐ Unknown ☐	Type: A ☐ B ☐ C ☐ E ☐
Transplant	Yes ☐ No ☐ Unknown ☐	Type/Date:
Blood Transfusion	Yes ☐ No ☐ Unknown ☐	
Recent Travel	Yes ☐ No ☐ Unknown ☐	If YES, provide details
Cirrhosis	Yes ☐ No ☐ Unknown ☐	Baseline cirrhosis status/Child-Pugh Score/History of complications:
Family Liver Disease	Yes ☐ No ☐ Unknown ☐	
Family Autoimmune Disease	Yes ☐ No ☐ Unknown ☐	
Recent Acetaminophen use	Yes ☐ No ☐ Unknown ☐	If YES, provide details in Suspect Product Table below
Recent strenuous exercise	Yes ☐ No ☐ Unknown ☐	
Herbal/OTC/alternative med	Yes ☐ No ☐ Unknown ☐	If YES, provide details in Suspect Product Table below
Other pertinent medical history (including pregnancy, HIV, CV disease etc.):		If YES, provide details

Medication List, Laboratory Tests & Diagnostic Test Results

For convenience you may print this information from your electronic medical record (EMR) and include with this form or hand write in tables on pages 4 and 5.

Instructions to print from EMR

- Include active medication list at time of patient event. Write the start/end date or indication of patient medications if not included in EMR print out.
- Include laboratory tests and diagnostic tests for the 3-day period surrounding the event or most currently available.

Suspect Medication(s)

Name	Dose	Form	Frequency	Route	Start Date (d/m/y)	End Date (d/m/y)	Indication	If medication stopped, did event abate? *If yes, provide date*
					___/___/_____	___/___/_____		
					___/___/_____	___/___/_____		
					___/___/_____	___/___/_____		

AbbVie Medication Lot Number (s): Expiration Date: ____/_____/_____(d/m/y) *If unable to provide lot number,* indicate reason below:

Discarded ☐ Not Accessible to Physician ☐ Not on Patient's File ☐ Didn't Receive in Original Package ☐ Not Legible on Package ☐

Adverse Event Details

Select one of the following codes to answer the questions designated with numbers 1-3.

1. Event Criteria Codes: Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability) or Non-serious
2. Causality Code: Reasonable Possibility, No Reasonable Possibility, Non-Assessable
3. Outcome Codes: Death, Recovered, Not recovered, Recovering, Worsened, Unknown, or Recovered with Sequela (provide Sequela if available)

Adverse Event	Event Onset (d/m/y)	Event End (d/m/y)	Event Criteria[1]	Was this caused by suspect?[2]	Outcome[3]
	___/___/_____	___/___/_____			
	___/___/_____	___/___/_____			
	___/___/_____	___/___/_____			
	___/___/_____	___/___/_____			
	___/___/_____	___/___/_____			

AbbVie medication was restarted after being discontinued? Yes ☐ No ☐ Unknown ☐

Date Restarted: ___/___/_____(d/m/y)

Did the event(s) return when restarted? Yes ☐ No ☐ Unknown

If Yes, answer the following questions

Dose:

Describe:

Did the Patient Die? Yes ☐ No ☐ Unknown ☐

Date of Death: _____/_____/_____ (d/m/y)

Autopsy Date: _____/_____/_____ (d/m/y)

Autopsy Results:

DILI event resolved at time of death: Yes ☐ No ☐ Unknown

If Yes, answer the following questions

Autopsy: Yes ☐ No ☐ Unknown ☐

Cause of Death:

Provide detailed event information including symptoms the patient experienced leading up to the events:

Provide what treatment or interventions the patient underwent for the events:

Were there any prodromal or associated signs or symptoms, including fever, fatigue, nausea, malaise, rash, eosinophilia, abdominal pain, dark urine, jaundice, etc? Specify:

Did the event result in a liver transplant or placement on a waiting list? Yes ☐ No ☐ If yes, provide date:

Contact Information

Does reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐

Physician/HCP Name/Specialty:	
Address:	
City, State:	Zip:
Phone Number:	

Person completing form *if different from Physician/HCP*

Name:	
Address:	
City, State:	Zip:
Phone Number:	

Supplemental Tables *(if needed)*

Medications *Indicate Concomitant (active at time of event) (C), Past (P), and Treatment information (T). Include herbal, OTC medications, and supplements*

Name	C, P or T	Dose	Form	Frequency	Route	Start date	End Date	Indication
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	
						___/___/_____	___/___/_____	

Laboratory Test and Diagnostic Test Results *Include laboratory tests and diagnostic tests for the 3 day period surrounding the event or most currently available*

Laboratory test	Date (d/m/y)	Result (include units of measure)	Reference Range
Albumin	___/___/_____		
Alkaline Phosphatase	___/___/_____		
ALT	___/___/_____		
AST	___/___/_____		
Ammonia	___/___/_____		
Direct Bilirubin	___/___/_____		
Total Bilirubin	___/___/_____		
Sodium	___/___/_____		
Creatinine	___/___/_____		
GGT	___/___/_____		
LDH	___/___/_____		
CPK	___/___/_____		
PT/INR	___/___/_____		
ANA	___/___/_____		
CMV IgM/IgG	___/___/_____		
EBV panel	___/___/_____		
Hepatitis A/B/ C/E serologies	___/___/_____		
Anti-smooth muscle Ab	___/___/_____		

Diagnostic test	Date (d/m/y)	Results (key findings). *If desired attach results.* *Include reference ranges:*
Liver biopsy (with histology)	___/___/_____	
Ultrasound	___/___/_____	
CT Scan	___/___/_____	
ERCP	___/___/_____	
MRI	___/___/_____	
	___/___/_____	
	___/___/_____	
	___/___/_____	
	___/___/_____	

Anti-mitochondrial Ab	___/___/_____					
IgG	___/___/_____					
Anti-LKM-1, 2, 3	___/___/_____					
ANCA	___/___/_____					
DS DNA	___/___/_____					
Anti-SLA/LP	___/___/_____					
CBC with differential						
WBC	___/___/_____					
Hgb	___/___/_____					
Platelets	___/___/_____					
Ferritin	___/___/_____					
Iron	___/___/_____					
TIBC	___/___/_____					
Acetaminophen level	___/___/_____					
Include others deemed important to report					___/___/_____	
	___/___/_____				___/___/_____	
	___/___/_____				___/___/_____	
	___/___/_____				___/___/_____	

Document Approval

Risk Management Plan - Rinvoq AESI DILI Letter FINAL Ver 1_09Aug2021 - 06-Feb-2022

Version: 1.0 **Date:** 06-Feb-2022 **Company ID:** 20220206-0900f9f6853437da-1.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	06-Feb-2022 02:25 UTC	Approver

Follow-up Questionnaire for Bone Fracture Adverse Events Reported with Rinvoq

Patient Information:
Name:
Street Address:
City: State: Zip code:

Reference Numbers:
AER#:
Affiliate#:
Other Reference#:

PATIENT INFORMATION:

Initials:	Patient ID:	Sex: Male ☐ Female ☐	Date of Birth:	Age at time of event:	Age group^:
Height: cm ☐ in ☐	Weight: kg ☐ lbs ☐		Illicit drug use: Yes ☐ No ☐ (amount/type/start and stop dates):		
Tobacco use: Yes ☐ No ☐ (amount/start/stop dates)			**Alcohol use: Yes ☐ No ☐ (amount/type/start and stop dates):**		
Allergies: Yes ☐ No☐ (type and manifestation)			Race/Ethnicity:		

^ Age group codes: Neonate (Day 0 to Day 27), Infant (28 days to 23 months), Child (2 years to 11 years), Adolescent (12 years to 17 years), Adult (18 years to 64 years), Elderly (65 years and over)

PATIENT MEDICAL HISTORY

Osteoporosis	Yes ☐ No ☐ Date of diagnosis: _____
History of known low bone mineral density	Yes ☐ No ☐
Diabetes	Yes ☐ No ☐
Onset of puberty/pubertal changes (for pediatric studies only) (Breast development in females and testicular changes in males)	Yes ☐ No ☐ N/A* ☐
For adult females are they postmenopausal (for adult studies only)	Yes ☐ No ☐ N/A* ☐
Is the adult female on hormonal replacement therapy	Yes ☐ No ☐
Is the patient immobile, wheelchair bound or bedridden	Yes ☐ No ☐
Prior history of fracture due to trauma	Yes ☐ No ☐
Prior history of fracture with no known trauma	Yes ☐ No ☐
History of parent fractured hip	Yes ☐ No ☐
Low body weight (BMI < 18.5)	Yes ☐ No ☐
Poor visual capacity	Yes ☐ No ☐
Neuromuscular disorder If yes, indicate type _____	Yes ☐ No ☐
Chronic liver disease	Yes ☐ No ☐

*Not applicable

Corticosteroid use within the preceding 3 months of the fracture event	Yes ☐ No ☐ Unknown ☐
Equivalent to ≥ 7.5 mg/day of Prednisone	Yes ☐ No ☐ Unknown ☐
Equivalent to ≥ 2.5 to 7.5 mg/day	Yes ☐ No ☐ Unknown ☐

OTHER MEDICAL HISTORY text (include family history, pregnancy, risk factors, HIV…):

Follow-up Questionnaire for Bone Fracture Adverse Events Reported with Rinvoq

ADVERSE EVENT DETAILS

Please provide the location of fracture(s) in the Adverse event section below. (eg wrist, hand, forearm, shoulder spine, elbow, pelvis, hip, rib, arm, leg, foot, other (specify))

Adverse Event (undesirable reaction)	Event Onset (d/m/y)	Event End(d/m/y)	Event Criteria+	Causality++	Outcome Status**

Event Criteria Codes: 1. Serious (Death, Hospitalization, Prolonged Hospitalization, Congenital anomaly, Life-threatening, Medically Important, Persistent or Significant Disability), 2. Non-serious
Causality Code: 1. Reasonable Possibility, 2. No Reasonable Possibility, 3. Non-Assessable
Outcome Codes: 1. Death, 2. Recovered, 3. Not recovered, 4. Recovering, 5 Worsened, 6. Unknown, 7. Recovered with Sequela (provide Sequela if available)

Did the patient undergo a surgery due to the facture? Yes ☐ No ☐ Unknown ☐
Was the fracture spontaneous with no known trauma? Yes ☐ No ☐ Unknown ☐
Was the fracture a result due to trauma (e.g., injury or a fall?) Yes ☐ No ☐ Unknown ☐
Was the fracture due to playing contact sports or sports activity? Yes ☐ No ☐ Unknown ☐

MEDICATION LIST

SUSPECT PRODUCT (S)

Name	Dose	Form	Frequency	Route	Start Date (d/m/y)	End Date (d/m/y)	Indication	If stopped, did event abate? If so, provide date

Please provide Lot number for Abbvie product at time of event: **Expiration date:**
If unable to provide Lot number, provide rationale: discarded ☐ not accessible to physician ☐ not on patient's file ☐ did not receive in original package ☐ not legible on package ☐

Concomitant (medication at time of event) **(C), Past (P), Treatment (T) medication information** (Please include herbal, recreational, over the counter and supplements):

Name	C, P or T	Form	Dose	Frequency	Route	Start date	End Date	Indication

Please provide Laboratory and Diagnostic Test results:

Laboratory test	Prior to starting Abbvie product		Test Peak during treatment		When event improved/resolved		Reference Range (Including units of measure)
	Test date (d/m/y)	Test result	Test date (d/m/y)	Test result	Test date (d/m/y)	Test result	

Diagnostic Test	Date (d/m/y)	Results (key findings) (If desired attach results)
MRI/CT Scan		
Bone Density scan		
X-Ray		
Any additional test		

If the patient died, Date of Death (d/m/y):	Autopsy: Yes ☐ No ☐ Unknown ☐	Autopsy Date (d/m/y):
Autopsy results:	Cause of Death:	

Does reporter agree to have HCP/MD contacted? Yes ☐ No ☐ Not Applicable ☐

Physician/HCP Name:		
Street Address:		
City:	State:	Zip:
Phone Number:		

Person completing form:

Name:		
Street Address:		
City:	State:	Zip:
Phone Number:		

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

The additional risk minimization program will be an educational program targeted to both HCP and patients.

Key messages of the additional risk minimization measures

HCP Material

HCP Educational Guide:

- General introductory language that the HCP measure contains important information to assist the discussion with patients when prescribing upadacitinib. The guide also informs on steps which can be taken to reduce a patient's risk for key safety aspects of upadacitinib.
- Indication and posology statements provided to reinforce in whom upadacitinib should be used

Use in patients 65 years of age and older

- Language to reinforce risks in these patients and use of the 15 mg dose

Language for HCPs to inform patients of the importance of the patient card

Risk of serious and opportunistic infections including TB

- Language on the risk of infections during treatment with upadacitinib
- Language on increased risk of serious infections in patients 65 years of age and older
- Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate upadacitinib, screening for TB, and getting patients immunised as per local guidelines, and interruption of upadacitinib if an infection develops)
- Language on contraindication in patients with active TB and on consideration of anti-TB therapy in patients with latent TB
- Language on avoidance of live vaccines (i.e., Zostavax) prior to and during upadacitinib treatment
- Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.

Risk of herpes zoster

- Language on the risk of herpes zoster during treatment with upadacitinib
- Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.

Risk of fetal malformation

- Language on teratogenicity of upadacitinib in animals
- Details on how to reduce the risk of exposure during pregnancy for female patients of childbearing potential based on the following: upadacitinib is contraindicated during pregnancy, female patients of childbearing potential should be advised to use effective contraception both during treatment and for 4 weeks after the final dose of upadacitinib treatment, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.

Risk of MACE

- Reminder that in patients at high risk for MACE upadacitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk
- Language on the risk of hyperlipidaemia during upadacitinib therapy
- Details on monitoring of lipid levels and management of elevated lipid levels per clinical guidelines

Risk of VTE

- Examples of the risk factors which may put a patient at higher risk for VTE and in whom caution is needed when using upadacitinib
- Use of caution in patients at high risk during treatment with upadacitinib
- Language that patients should be periodically re-evaluated for changes in VTE risk
- Language on need for discontinuation of upadacitinib, evaluation, and appropriate treatment for VTE if clinical features of deep venous thrombosis or pulmonary embolism develop

Risk of malignancy

- In patients at high risk for malignancy upadacitinib should only be used if no suitable treatment alternatives are available, with examples of who may be at high risk
- Reminder about the need for periodic skin examination for patients

Risk of GI perforation

- Upadacitinib should be used with caution in patients at risk for GI perforation with examples of those who may be at risk
- Reminder that patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or GI perforation

Information for upadacitinib use in moderate to severe AD

The 30 mg upadacitinib dose in AD

- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib
- Language on dose-dependent increase in NMSC and malignancy
- Language on dose-dependent increase in plasma lipids with upadacitinib
- Language that the 30 mg dose is not recommended in certain populations (patients with severe renal impairment and patients taking strong CYP3A4 inhibitors)
- Language to reinforce that the lowest effective dose of upadacitinib should be used for treatment

Upadacitinib use in adolescents 12 years and older

- Reminder that live, attenuated vaccines (i.e., varicella; measles, mumps, and rubella [MMR]; bacilli Calmette-Guérin) which depending on local guidelines may be considered in adolescents. Language not to administer these vaccines immediately prior to or during upadacitinib treatment
- Language to remind adolescents of the potential pregnancy risks and on the appropriate use of effective contraception
- Language that if their adolescent patient has not experienced menarche, to inform their adolescent patient or caregiver to let them know when they do

Information for upadacitinib use in moderate to severe UC or CD

- Reminder to review induction and maintenance dosing in product labeling
- Language on dose-dependent increase in serious infections and herpes zoster with upadacitinib
- Language on dose-dependent increase in NMSC and malignancy
- Reminder about induction and maintenance dose in certain populations (patients taking strong CYP3A4 inhibitors and severe renal impairment)

- Language to reinforce that the lowest effective dose of upadacitinib should be used for maintenance treatment

Instructions on where to report AEs will be included.

Instructions for how to access digital HCP information will be included, if applicable.

Patient Card:

- Contact details of the upadacitinib prescriber
- Language that the patient card should be carried by the patient at any time and to share it with HCPs involved in their care (i.e., non-upadacitinib prescribers, emergency room HCPs, etc.)
- Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:
  - Language to advise patients and their HCPs about the risk of live vaccinations when given during upadacitinib therapy. Examples of live vaccines are provided.
  - Language to advise patients to tell their HCP if they have history of TB or have been in contact with TB.
- Description of targeted risks for awareness by the patient and for HCPs involved in their care including:
  - Risk of heart disease - Description of signs/symptoms of heart disease that the patient needs to be aware of, so that they can seek attention from their HCP
  - Reminder to use contraception, that upadacitinib is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking upadacitinib
  - Description of signs/symptoms of deep venous thrombosis or pulmonary embolism which the patient needs to be aware of, so that they can seek attention from an HCP
  - Reminder of the risk of cancer. Regarding skin cancer reminder to let their doctor know if they notice any new growth on the skin.
  - Risk of a hole in the bowel – description of signs/symptoms which the patient needs to be aware of, so that they can seek attention from an HCP