TOFACITINIB RISK MANAGEMENT PLAN

RMP version to be assessed as part of this application:

RMP Version number: 32.0

Data-lock point for this RMP: 15 February 2024

Date of final sign off: 24 March 2024

Rationale for submitting an updated RMP:

The primary purpose for submitting an updated RMP is to remove study A3921329 (Corevitas [formerly Corrona] UC) as an ongoing Category 3 study.

Summary of significant changes in this RMP (version 32.0):

Part I: Pharmacotherapeutic group and ATC code for tofacitinib were updated to Janus - associated kinase inhibitor and L04AF01, respectively.

Part II, SV.1: The post-authorisation exposure estimate was updated to the 15 February 2024 data-lock point.

Part II, SVII: All post-marketing tables for all safety concerns were updated to the 15 February 2024 data-lock point.

Part II, SVII.3.2: OTIS was removed from Effects on Pregnancy and the Foetus table as an ongoing activity.

Part III.2 and Part III.3.1: A3921329 (Corevitas [formerly Corrona] UC) and A3921203 (OTIS) were removed as ongoing studies.

Part V.2: The Dear Healthcare Professional Communication (DHPC) was removed as an ongoing activity as it was implemented and completed.

Part V.3: DHPC was removed as an additional risk minimisation measure and A3921329 (Corevitas [formerly Corrona] UC) and A3921203 (OTIS) were removed additional pharmacovigilance activities.

Part VI.II.B: DHPC was removed as an additional risk minimisation measure and A3921329 (Corevitas [formerly Corrona] UC) and A3921203 (OTIS) were removed as additional pharmacovigilance activities.

Part VI.II.C: A3921329 (Corevitas [formerly Corrona] UC) and A3921203 (OTIS) were removed Category 3 studies in the post-authorisation development plan.

Part VII, Annex 2: A3921329 (Corevitas [formerly Corrona] UC) was removed as an ongoing study. A3921203 (OTIS) was recategorized as a completed study and milestone dates were updated.

The interim study report 1 for A3921321 was updated to align with the correct date in the RMP body text (Part III).

Part VII, Annex 3: A3921329 (Corevitas [formerly Corrona] UC) and A3921203 (OTIS) were removed as ongoing studies.

Studies A3921352 and A3921427 were moved from planned to ongoing to align with the information in the current approved EU RMP.

Part VII, Annex 8: Updated to reflect changes in EU RMP version 32.0.

Other RMP versions under evaluation:

None.

Details of the currently approved RMP:

Version number: 31.2

Approved with procedure: EMEA/H/C/004214/II/0054

Date of approval (opinion date): 26 October 2023

QPPV name: Barbara De Bernardi, MD

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

LIST OF ABBREVIATIONS

5-ASA	5-aminosalicylic acid
Ab	antibody
ASCVD	atherosclerotic cardiovascular disease
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aRMM	additional risk minimisation measure
ART 20	Article 20 procedure
ARTIS	Anti-rheumatic Therapies in Sweden
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AUC	area under the (concentration-time) curve
AVDOS	average daily dose
BAT	brown adipose tissue
BCC	basal cell carcinoma
BCRP	breast cancer resistance protein
bDMARD	biologic disease-modifying anti-rheumatic drug
BID	bis in die (twice daily)
BIKER	German Biologics in Pediatric Rheumatology Registry
BIOBADASER	Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas
BMI	body mass index
BSRBR	British Society for Rheumatology Biologics Register
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CHF	congestive heart failure
CI	confidence interval
Cmax	peak plasma concentration
CNS	central nervous system
CrCl	creatinine clearance
csDMARDs	conventional synthetic disease-modifying anti-rheumatic drug
CTC	Common Terminology Criteria
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
DHPC	Direct Healthcare Professional Communication
DILI	drug-induced liver injury
DLP	data lock point
DMARD	disease-modifying anti-rheumatic drug
DNA	deoxyribonucleic acid
DUS	drug utilisation study
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EEA	European Economic Area
EFD	embryo-foetal development
EHR	electronic health care records
EM	extensive metaboliser
EMA	European Medicines Agency
ENEIDA	Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales

EPAR	European Public Assessment Report
EWP	Efficacy Working Party
EU	European Union
Excl	excluding
GALT	gut-associated lymphoid tissue
GFR	glomerular filtration rate
GI	gastrointestinal
HDL	high-density lipoprotein
Hgb	haemoglobin
HZ	herpes zoster
IA	intraarticular
IBD	inflammatory bowel disease
IC50	50% inhibitory concentration
IFN	interferon
IgG	immunoglobulin g
IL	interleukin
ILD	interstitial lung disease
IM	intramuscular
IR	incidence rate
IV	intravenous
JAK	Janus Kinase
JAKi	Janus kinase inhibitor
JCV	JC polyoma virus
JIA	juvenile idiopathic arthritis
JuMBO	Juvenile Arthritis Methotrexate/Biologics long-term Observation
KCl	potassium chloride
LCV	lymphocryptovirus
LDL	low-density lipoprotein
LFT	liver function test
LLNA	local lymph node assay
LSLV	last subject last visit
LTE	long-term extension
MACE	major adverse cardiac event
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMF	mycophenolate mofetil
MN	Minnesota
mRNA	messenger ribonucleic acid
MTX	methotrexate
NK	natural killer
NMSC	non-melanoma skin cancer
NR	not reported
NSAID	non-steroidal anti-inflammatory drug
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
OI	opportunistic infection
ON	Ontario
OTIS	Organisation of Teratology Information Specialists
P2P3LTE	Phase 2, Phase 3, long-term extension
PAM	Post-Authorisation Measure
PASS	post-authorisation safety studies
pJIA	polyarticular juvenile idiopathic arthritis

PE	pulmonary embolism
P-gp	P-glycoprotein
pJIA	polyarticular course juvemile idiopathic arthritis
PM	poor metaboliser
PML	progressive multifocal leukoencephalopathy
PND	postnatal day
PR	prolonged-release
PRAC	Pharmacovigilance Risk Assessment Committee
PRL	prolactin
PsA	psoriatic arthritis
PsO	psoriasis
PT	(MedDRA) Preferred Term
PTLD	post-transplant lymphoproliferative disorder
PV	pharmacovigilance
PY	patient-year
QD	quoque die (once daily)
RA	rheumatoid arthritis
RABBIT	Rheumatoide Arthritis: Beobachtung der Biologika-Therapie
RBC	red blood cell
RCT	randomised controlled trial
REMS	Risk Evaluation and Mitigation Strategy
RF	rheumatoid factor
RMM	risk minimisation measure
RMP	risk management plan
RZV	Recombinant Zoster Vaccine
SCC	squamous cell carcinoma
SCID	severe combined immunodeficiency syndrome
SIR	standardised incidence rate
SmPC	summary of product characteristics
SMQ	Standardized MedDRA Query
SNDS	Système National des Données de Santé
SWIBREG	Swedish National Quality Registry for Inflammatory Bowel Disease
SUs	standard unit sale
TB	tuberculosis
TBD	to be determined
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
TS	targeted synthetic
TyK	tyrosine kinase
UC	ulcerative colitis
UDS	unscheduled dna synthesis
UGT	uridine-diphosphate-glucuronosyltransferase
UK	United Kingdom
ULN	upper limit normal
UM	ultra-extensive metaboliser
UR-CARE	United Registries for Clinical Assessment and Research
US	United States
UTI	urinary tract infection
VTE	venous thromboembolism
VZV	varicella zoster virus
WHO	World Health Organisation

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Tofacitinib citrate
Pharmacotherapeutic group(s) (ATC Code)	Janus-associated kinase inhibitor (L04AF01)
Marketing Authorisation Holder Applicant	Pfizer Europe MA EEIG Belgium
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	XELJANZ
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: Tofacitinib, a heterocyclic small molecule, is a selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against JAK1, JAK2, JAK3, and to a lesser extent TyK2.
	Summary of mode of action: Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signalling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signalling through the common gamma chain containing receptors for several cytokines, including interleukin (IL)-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, development, homeostasis, proliferation, and function; therefore, inhibition of their signalling may result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signalling by additional pro-inflammatory cytokines, such as IL-6 and interferon (IFN)γ. At higher exposures, inhibition of erythropoietin could occur via inhibition of JAK2 signalling.
	Important information about its composition: Each 5 mg film-coated tablet contains 59.44 mg lactose. Each 10 mg film-coated tablet contains 118.88 mg of lactose. Each 11 mg prolonged-release tablet contains 152.23 mg of sorbitol. Each mL of oral solution contains 0.9 mg of sodium benzoate.

Hyperlink to the Product Information:	Module 1.3.1
Indication(s) in the EEA	Current: Rheumatoid arthritis (RA), film-coated tablets and prolonged-release tablets: Tofacitinib, in combination with methotrexate (MTX), is indicated for treatment of moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. Psoriatic arthritis (PsA), film-coated tablets and prolonged-release tablets: Tofacitinib in combination with MTX is indicated for the treatment of active PsA in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. Ulcerative colitis (UC), film-coated tablets: Tofacitinib is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Juvenile idiopathic arthritis (JIA): Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile PsA in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs. Tofacitinib can be given in combination with MTX or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Ankylosing spondylitis (AS), film-coated tablets and prolonged-release tablets: Tofacitinib is indicated for the treatment of adult patients with active AS who have responded inadequately to conventional therapy.
Dosage in the EEA	Current: RA, film-coated tablets and prolonged-release tablets: Film-coated tablets: the recommended dose is 5 mg administered twice daily, which should not be exceeded. Prolonged-release tablets: the recommended dose is one 11 mg prolonged-release tablet administered once daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX. Switching between tofacitinib 11 mg prolonged-release tablets and tofacitinib 5 mg film-coated tablets: Patients treated with tofacitinib 5 mg film-coated tablets twice daily may be switched to tofacitinib 11 mg prolonged-release tablets once daily on the day following the last dose of tofacitinib 5 mg film-coated tablets. Patients treated with tofacitinib 11 mg prolonged-release tablets once daily may be switched to tofacitinib 5 mg film-coated tablets twice daily on the day following the last dose of tofacitinib 11 mg prolonged-release tablets. Tofacitinib 11 mg prolonged release tablets once daily has demonstrated pharmacokinetic equivalence (AUC and C_{max}) to tofacitinib 5 mg film-coated tablets twice daily.

	PsA, film-coated tablets and prolonged-release tablets: Film-coated tablets: the recommended dose is 5 mg administered twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX. Prolonged-release tablets: the recommended dose is one 11 mg prolonged-release tablet administered once daily, which should not be exceeded. Switching between tofacitinib 11 mg prolonged-release tablets and tofacitinib 5mg film-coated tablets: Treatment with tofacitinib 5 mg film coated tablets twice daily and tofacitinib 11 mg prolonged release tablets once daily may be switched between each other on the day following the last dose of either tablet. Tofacitinib 11 mg prolonged release tablets once daily have demonstrated pharmacokinetic equivalence (AUC and C_{max}) to tofacitinib 5 mg film-coated tablets twice daily. No dose adjustment is required when used in combination with MTX. Tofacitinib 11 mg prolonged release tablets once daily have demonstrated pharmacokinetic equivalence (AUC and Cmax) to tofacitinib 5 mg film coated tablets twice daily. UC, film-coated tablets: *Induction treatment* The recommended dose is 10 mg given orally twice daily for induction for 8 weeks. For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Tofacitinib induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16. *Maintenance treatment* The recommended dose for maintenance treatment is 5 mg given orally twice daily. Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known venous thromboembolism (VTE), MACE and malignancy risk factors, unless there is no suitable alternative treatment available. For patients with UC who are not at increased risk for VTE, MACE and malignancy, tofacitinib 10 mg orally twice daily may be considered if the patient experiences a decrease in response on tofacitinib 5 mg twice daily and failed to respond to alternative treatment options for ulcerative colitis such as tumour necrosis factor inhibitor (TNF inhibitor) treatment. Tofacitinib 10 mg twice daily for maintenance treatment should be used for the shortest duration possible. The lowest effective dose needed to maintain response should be used. In patients who have responded to treatment with tofacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care. *Retreatment in UC* If therapy is interrupted, restarting treatment with tofacitinib can be considered. If there has been a loss of response, reinduction with tofacitinib 10 mg twice daily may be considered. The

<table>
<tr><td></td><td>treatment interruption period in clinical studies extended up to 1 year. Efficacy may be regained by 8 weeks of 10 mg twice daily therapy.

<u>Polyarticular JIA and juvenile PsA (children between 2 and 18 years of age)</u>
Tofacitinib may be used as monotherapy or in combination with MTX.
The recommended dose in patients 2 years of age and older is based upon the following weight categories:

Table 1. Tofacitinib dose for patients with polyarticular juvenile idiopathic arthritis and juvenile PsA two years of age and older:
<table><tr><th>Body weight (kg)</th><th>Dosage regimen</th></tr><tr><td>10 - <20</td><td>3.2 mg (3.2 mL of oral solution) twice daily</td></tr><tr><td>20 - <40</td><td>4 mg (4 mL of oral solution) twice daily</td></tr><tr><td>≥40</td><td>5 mg (5 mL of oral solution or 5 mg film-coated tablet) twice daily</td></tr></table>
Patients ≥40 kg treated with tofacitinib 5 mL oral solution twice daily may be switched to tofacitinib 5 mg film-coated tablets twice daily. Patients <40 kg cannot be switched from tofacitinib oral solution.
No dose adjustment is required when used in combination with MTX.

<u>AS, film-coated tablets and prolonged-release tablets:</u>
Film-coated tablets: the recommended dose is 5 mg administered twice daily used as monotherapy or in combination with MTX or other csDMARDs.
Prolonged-release tablets: the recommended dose is 11 mg administered once daily, which should not be exceeded.</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current:
Each 5 mg film-coated tablet contains tofacitinib citrate, equivalent to 5 mg tofacitinib.
Each 10 mg film-coated tablet contains tofacitinib citrate, equivalent to 10 mg tofacitinib.
Each prolonged-release tablet contains tofacitinib citrate, equivalent to 11 mg tofacitinib.
1 mg/mL oral solution.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>Yes</td></tr>
</table>

AS = ankylosing spondylitis; bDMARD = biologic disease-modifying anti-rheumatic drug; DMARD = disease-modifying anti-rheumatic drug; EU = European Union; IFN = interferon; IL = interleukin; JAK = janus kinase; JIA = juvenile idiopathic arthritis; MTX = methotrexate; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RF = rheumatoid factor; TNF = tumour necrosis factor; TyK = tyrosine kinase; UC = ulcerative colitis

PART II. SAFETY SPECIFICATION

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

In what follows, the epidemiology of RA, PsA, UC, JIA, and AS is described with a focus on Europe and North America.

Indication: Rheumatoid Arthritis

Incidence: The majority of studies from Northern European and North American areas estimate a mean annual incidence of 0.02%-0.05%.[1] A recent model estimated an incidence of 26/100,000 in the Australasia region compared to 24/100,000 in Western Europe and 23/100,000 in high income North America.[2] Table 1 summarises estimates across Europe and North America, which range from 8.8 to 98.0 in men and women combined per 100,000 populations.

Table 1. Incidence of Rheumatoid Arthritis in European and North American Populations

Incidence (cases/100000 inhabitants)					
Author, Year	**Country (Province or State)**	**Total**	**Men**	**Women**	**Population Age**
Widdifield, 2014.[3]	Canada (ON)	62 (1996) 54 (2010)	41 (1996) 34 (2010)	81 (1996) 72 (2010)	≥15
Hanova, 2006.[4]	Czech Republic	31	18.3	43.7	≥16
Symmons, 1994.[5]	England	Not available	14.0	35.6	≥15
Savolainen, 2003.[6]	Finland	36.1	24.5	46.3	All
Kaipiainen-Seppanen, 2001.[7]	Finland	31.7	23.2	40.0	≥16
Kaipiainen-Seppanen, 2000.[8]	Finland	33.7	23.5	43.2	≥16
Guillemin, 1994.[9]	France	8.8	4.7	12.7	20-70
Drosos, 1997.[10]	Greece	24.0	12.0	36.0	≥16
Benucci, 2008.[11]	Italy	98.0	51.0	142	≥18
Riise, 2000.[12]	Norway	28.7	21.4	36.0	≥20
Uhlig, 1998.[13]	Norway	25.7	13.8	36.7	20-79
Fina Aviles, 2014.[14]	Spain	20	12	28	≥15
Soderlin, 2002.[15]	Sweden	24.0	18.0	29.0	≥16
Myasoedova, 2010.[16]	US (MN)	40.9	27.7	53.1	≥18
Doran, 2002.[17]	US (MN)	44.6	30.4	57.8	≥18
Gabriel, 1999.[18]	US (MN)	75.3	49.7	98.1	≥35

Source: Listed in table.
MN = Minnesota; ON = Ontario; US = United States

Prevalence: The majority of studies from Northern Europe and North America estimate prevalence between 0.5%-1.0%.[1] The estimated age-standardised prevalence of RA in 2010 was estimated as 0.44% in Western Europe and high income North America.[2]

Table 2 summarises RA prevalence estimates across European countries per 1000 inhabitants (based on 1987 American College of Rheumatology criteria). Differences may reflect true geographic differences in prevalence and regional variation in case ascertainment.

Table 2. Prevalence of Rheumatoid Arthritis in European and North American Populations

Author, Year	Country (Province or State)	Prevalence (Cases/1000 Inhabitants)			Population Age
		Total	Men	Women	
Widdifield, 2014.[3]	Canada (ON)	7.8 (2010) 4.7 (1996)	4.7 (2010) 2.9 (1996)	10.6 (2010) 6.4 (1996)	≥15
Symmons, 2002.[19]	England	8.1	4.4	11.6	≥16
Hakala, 1993.[20]	Finland	8.0	6.1	10.0	≥16
Guillemin, 2005.[21]	France	3.1	0.9	5.1	≥18
Saraux, 1999.[22]	France	6.2	3.2	8.6	≥18
Anagnostopoulos, 2010.[23]	Greece	5.7	NR	NR	Adult
Drosos, 1997.[10]	Greece	3.4	2.1	4.8	≥16
Kiss, 2005.[24]	Hungary	3.7	2.3	4.8	14-65
Power, 1999.[25]	Ireland	5	NR	NR	≥18
Cimmino, 1998.[26]	Italy	3.3	1.3	5.1	≥16
Riise, 2000.[12]	Norway	4.3	2.7	5.8	≥20
Kvien, 1997.[27]	Norway	4.4	1.9	6.7	20-79
Fina Aviles, 2014.[14]	Spain	4.2	2.5	5.8	≥15
Carmona, 2002.[28]	Spain	5	2	8	≥20
Simmonson, 1999.[29]	Sweden	5.1	NR	NR	20-74
Akar, 2004.[30]	Turkey	4.9	1.5	7.7	≥20
Helmick, 2008.[31]	US (MN)	~6	NR	NR	≥18
Gabriel, 1999.[18]	US (MN)	10.7	7.4	13.7	≥35

Source: Listed in table.
MN = Minnesota; NR = not reported; ON = Ontario; RA = rheumatoid arthritis; US = United States

Demographics of the population in the authorised indication–age, gender, racial and/or ethnic origin and risk factors for the disease: RA incidence increases with age and plateaus around age 60.[32] A female-to-male ratio of approximately 2.5:1 has been noted.[32] Racial and ethnic minorities have higher disability scores, worse global health assessments, greater burden of co-morbidities and delayed treatment initiation when compared with Caucasians.[33,34,35,36,37,38]

A combination of genetic, environmental, and behavioural factors may influence susceptibility to and clinical course of RA, with smoking, female gender, age, and human leukocyte antigen-shared epitope the most reproduced findings.[39]

The main existing treatment options: Currently, there is no cure for RA. The purpose of treatment is to control disease activity, alleviate signs and symptoms, maintain physical

function, optimise quality of life, reduce the rate of joint damage, and, if possible, induce complete remission.[40] There are 3 general classes of drugs commonly used in the treatment of RA: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, and DMARDs (conventional synthetic DMARDs [csDMARDs], biologic DMARDs [bDMARDs] and targeted synthetic (ts) DMARD such as tofacitinib).

Natural history of the indicated condition in the untreated population, including mortality and morbidity: RA is associated with a 1.3 to 3-fold increased risk of mortality relative to persons without RA of the same age and gender.[41,42,43,17,44] Predictors of survival are related to RA disease severity and the presence of complications and co-morbidities.[41,43,45,46] Research suggests that RA therapies may modify risk in some populations.[47,48,49]

Causes of death appear similar to those in the general population overall. Some, however, have noted more deaths attributed to Cardiovascular Disease (CVD), infections and malignancies.[41,44,50]

Bone and cartilage destruction result in functional decline and disability.[51] A recent systematic review of 31 studies of health related quality of life among RA patients found consistent reports of reduced physical function and increased pain compared with other chronic conditions such as Congestive Heart Failure (CHF) and diabetes. Mental health measures were also lower than other chronic diseases such as diabetes, CHF, hypertension and Myocardial Infarction (MI). Further, RA patients have reduced vitality, social functioning, and emotional well-being relative to the population.[52]

Important co-morbidities: The key comorbidities associated with RA are osteoporosis (including related fractures) [53,54,55,56,57,58,59,60,61,62,63,64,65] and depression. [66,67,68,69,70,71,72,73,74,75,76]

Indication: Psoriatic Arthritis

Incidence: Studies from Europe and the US report incidence rates of PsA ranging from 2.2 to 43.4 per 100,000 (Table 3). Epidemiologic estimates (eg, incidence, prevalence, mortality rates) of PsA may vary as a result of lack of a standard case definition, differences in genetics across different geographic and ethnic groups, exposure to environmental factors, and study methods.

Table 3. Incidence of Psoriatic Arthritis in Europe and North America

Author, Year	Region or Country (Province or State)	Population Age	Age-Adjusted Incidence (Cases/100,000 Inhabitants)		
			Total	Men	Women
Wilson, 2009[77]	United States	≥18	7.2[a]	9.1	5.4
Hanova, 2010[78]	Czech Republic	>16	3.6	4.5	2.8
Savolainen, 2003[6]	Finland	All	23.1	18.4	27.2
Alamanos, 2003[79]	Greece (northwest)	≥16	3.0	2.87	3.1

Table 3. Incidence of Psoriatic Arthritis in Europe and North America

Author, Year	Region or Country (Province or State)	Population Age	Age-Adjusted Incidence (Cases/100,000 Inhabitants)		
			Total	Men	Women
Hoff, 2015[80]	Norway	>20	35.9	38.7	43.4
Dönmez, 2015[81]	Turkey (Thrace)	≥16	2.8[b]	2.2	3.5

a. Age and sex-adjusted
b. Crude incidence rate

Prevalence: The prevalence of PsA was estimated in several population-based studies in Europe and the US, where age-adjusted prevalence estimates of PsA per 10,000 persons were reported as follows: Czech Republic 4.91 (95% CI 3.95-6.04),[78] Greece 5.66 (95% CI: 4.99-6.32),[79] Turkey (Thrace region; not age-adjusted) 2.79 (95% CI, 2.37-3.21),[81] Iceland (Reykjavik area; also sex-adjusted) 13.9 (11.2-16.9),[82] and US (also sex-adjusted) 6.84 (95% CI, 5.4-8.4).[83]

A population-based retrospective study conducted among 4.8 million patients in the United Kingdom (UK) reported an overall prevalence of 19 per 10,000 persons.[84] In the Nord-Trøndelag Health Study 3 in Norway, the prevalence of PsA was reported to be 67 per 10,000 persons (95% CI 59-74) in patients older than 20 years of age, with no significant difference in prevalence between men and women.[80]

Demographics of the population in the authorised indication–age, gender, racial and/or ethnic origin and risk factors for the disease: Most cases of PsA occur when subjects are in their mid-forties. Most European and US studies have identified no gender difference in the risk of developing PsA.[85] One study including US veterans of 78 PsA patients reported that twice as many Caucasians as African Americans had PsA (64.5 vs. 30.0%, respectively, $p<0.001$).[86]

Several studies have examined risk factors for PsA and have suggested that psoriasis (PsO) severity, nail dystrophy,[85] smoking,[87] excessive alcohol consumption,[88] trauma, prior glucocorticoid use,[85] acetaminophen and NSAID use,[89] the absence of a C reactive gene polymorphism,[90] vitamin D deficiency,[91] and obesity,[92,87] are all risk factors for PsA. Ogdie et al also found obesity to be a significant independent risk factor of PsA among PsO patients.[84]

The main existing treatment options: The main pharmacologic treatment options for PsA include NSAIDs, topical and intraarticular corticosteroids, csDMARDs, bDMARDs, and tsDMARDs [conventional synthetic (cs), biologic (b), and targeted synthetic (ts) DMARDs].

NSAIDs are the first line of therapy in PsA, and are effective at reducing pain and inflammation, but are rarely sufficient alone to control symptoms and have no demonstrated effect in limiting structural joint damage.[93] Intra-articular and topical corticosteroids are used as an adjunct to systemic therapy to control oligoarthritis and skin disease, respectively.

There are very few clinical study data to support the efficacy of csDMARDS in PsA (eg, methotrexate, leflunomide, sulfasalazine, cyclophosphamide, oral gold). CsDMARDs have limited evidence for efficacy in slowing or preventing progressive joint damage, enthesitis, and severe dactylitis and also may be associated with poor clinical tolerability and/or safety issues.[93,94]

Of the bDMARDS, tumour necrosis factor inhibitors (TNFi) have demonstrated in published clinical studies evidence of both clinical efficacy and retardation of joint damage and acceptable safety in the treatment for PsA.[95] Approved TNFi include infliximab, etanercept, adalimumab, certolizumab, and golimumab. However, the use of TNFi remains limited with inconvenience of the required parenteral routes of administration and apparent loss of initial efficacy with continued use in a significant proportion of patients. Ustekinumab is a parenteral interleukin (IL) 12/IL23i approved for the treatment of PsA. Secukinumab is a parenteral IL17Ai approved for the treatment of PsA. The use of these drugs is also limited by the inconvenience of parenteral administration. Abatacept, a selective T cell costimulation modulator, used alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA when the response to previous DMARD therapy including MTX has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Data are limited regarding mortality in subjects with PsA. In a population-based medical record review study in Minnesota, US, Shbeeb et al reported that survival of persons with PsA was not significantly different from that of the local general population ($p = 0.546$).[96] In a more recent retrospective cohort study conducted using the UK THIN database, Ogdie et al reported that the mortality rate of subjects with PsA was 10.37 deaths per 1000 PYs (7.80 for patients using DMARDs, and 12.46 for patients not using DMARDs).[97]

Important co-morbidities: The key comorbidities associated with PsA are hypertension,[98,99,100,101,102,103,104,105,106,107,87,97] metabolic syndrome,[108,109,104] diabetes,[110,111,101,97,98,102,103,105,107] non-alcoholic fatty liver disease (data from epidemiologic studies on the incidence, prevalence, and mortality in PsA patients were not identified in the literature), inflammatory bowel disease (includes Crohn's Disease),[101] and plaque psoriasis.[77]

Indication: Ulcerative Colitis

Incidence: A recent study evaluated data from 31 medical centers across Western and Eastern Europe (including Cyprus, Denmark, Faroe Islands, Finland, Greece, Greenland, Iceland, Ireland, Israel, Italy, Portugal, Spain, Sweden, UK, Croatia, Czech Republic, Estonia, Hungary, Lithuania, Moldova, Romania, and Russia), representing a total background population of approximately 10.1 million people, and estimated the annual incidence of UC in 2010 to be 8.2 per 100,000 European adults age $\geq$15 years. Incidence varied by Western vs. Eastern European region, and also between various regions within certain countries like Denmark, from 2.5 per 100,000 residents of Timis, Romania to 31.8 per 100,000 residents of the Faroe Islands (Denmark).[112]

Population-based estimates of UC incidence are similar across North American regions. During the period 2000-2010, UC incidence among residents of Olmsted County, Minnesota (US) was 12.2 per 100,000 PY.[113] Within that same timeframe, UC incidence in Ontario, Canada was 12.1 per 100,000 PY[114] and in Nova Scotia, Canada it was 16.7 per 100,000 PY.[115]

Prevalence: UC prevalence estimates for European populations vary widely, from 2.4 per 100,000 persons in Romania to 505 per 100,000 persons in Norway.[116] The EMA's draft Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis (Committee for Medicinal Products for Human Use [CHMP]/Efficacy Working Party [EWP]/18463/2006 Revision 1), estimates prevalence to be 70 to 500 cases per 100,000.[117] The patterns are inconsistent within individual European regions; however, data from multiple countries suggest increasing prevalence over time.[116]

In the US and Canada, depending on the region and study period the estimated prevalence of UC (per 100,000 persons) ranged from 37.5 (in Alberta, Canada) to 248.6 (in Manitoba, Canada); all but 2 studies reported prevalence estimates greater than 155 per 100,000 persons.[116]

Demographics of the population in the authorised indication–age, gender, racial and/or ethnic origin and risk factors for the disease: Although UC can occur at any age, the peak age of onset is between 15 and 25 years[117] with the majority of patients diagnosed between ages 30-40 years.[118] Some studies indicate a second peak for age at onset between 60-80 years;[118 119] however, consensus on this is lacking.[118] While most studies demonstrate either higher UC incidence among men or equal rates for men and women,[118] a recent study of approximately 10.2 million beneficiaries of US military health care (Tricare) reported a slightly greater risk for UC among women (relative risk [RR] 1.35, 95% CI 1.32-1.39).[120] For the subset of the sample with data on race (approximately 3.5 million Tricare beneficiaries), UC prevalence was higher among whites (194 cases per 100,000 persons) followed by blacks (150 cases per 100,000 persons) as compared to Asian, Hispanic, and American Indian individuals (range: 100-115 cases per 100,000 persons).[120]

There is a hereditary component to UC,[121,122] with a nationwide study in Denmark demonstrating anywhere from 1.5-4.1 times the risk of UC among first-, second-, or third-degree relatives of UC patients.[122] Jewish ancestry has also been associated with UC.[123,124] In addition, diet may contribute to UC risk, particularly high consumption of sugar and soft drinks in combination with minimal intake of vegetables[125] and/or greater intake of monounsaturated or polyunsaturated fats.[126]

The main existing treatment options: The primary goal of therapy for UC is to rapidly induce remission when the disease is in an acute flare and to maintain remission without long-term use of corticosteroids.[127] Considerations for treatment options include the severity and extent of disease, prior response to therapies and patient preference.

Current treatment options for moderately to severely active UC include corticosteroids, immunosuppressants (such as azathioprine [AZA] and 6-mercaptopurine [6-MP]), tumour

necrosis factor inhibitor (TNFi) agents (infliximab, adalimumab and golimumab), and an anti-integrin therapy (vedolizumab).

Colectomy is generally considered the last resort and is indicated only for complications such as uncontrolled gastrointestinal bleeding, dysplasia/carcinoma, disease unresponsive to medical therapies, and intolerable medication side effects.[128]

Natural history of the indicated condition in the untreated population, including mortality and morbidity: Depending on the level of disease activity, UC has the potential to cause a significant burden to both the patient and the health care system in terms of decreasing one's health-related quality of life with extensive morbidities that often require surgery and/or hospitalization.[129] Within 10 years of the UC diagnosis, approximately 10% of patients undergo colectomy surgery; in some regions, like Northern Europe, colectomy rates are even higher.[130] Compared to the general population, UC patients have approximately twice the risk of colorectal cancer (standardized incidence ratio [SIR] 2.39, 95% CI 2.10-2.73), with a cumulative colorectal cancer risk of 1.1-5.3% within 20 years of UC diagnosis.[130]

Results from mortality studies of UC patients vary depending on a broad range of factors such as the population evaluated and underlying health care system. A population-based study in Norway observed no differences in either total mortality or cause-specific mortality rates among UC patients compared to the general population.[131] However, a recent Canadian study reported statistically higher mortality due to any cause (SMR 1.21, 95% CI 1.12-1.32), digestive conditions (SMR 4.57, 95% CI 3.20-6.52), infectious diseases (SMR 2.08, 95% CI 1.29-3.35), and respiratory conditions (SMR 1.41, 95% CI 1.08-1.84) among UC patients compared to the general population.[132]

Important co-morbidities: The key comorbidities associated with UC are anaemia,[133,134,135,136,137,138] depression,[139,140] anxiety,[139] bone disease,[135] osteopenia,[135] osteoporosis,[135] epithelial dysplasia, and colorectal carcinoma.[141]

Juvenile Idiopathic Arthritis (JIA)

JIA is the newest classification system used to describe a heterogeneous group of inflammatory arthritides diagnosed in persons aged 16 or younger. This system is intended to replace the earlier classification systems used by the American College of Rheumatology and the European League Against Rheumatism (Juvenile Rheumatoid Arthritis and Juvenile Chronic Arthritis, respectively), with the intent of unifying diagnostic criteria and standardizing research definitions. Each of the 3 systems differs slightly in its approach to classifying subtypes of juvenile arthritis. Therefore, any evaluation of epidemiologic data must consider the classification system used in the study.

Incidence: A systematic literature review of juvenile idiopathic arthritis for studies published from 1972 to 2011 reported a pooled incidence rate of 8.2 per 100,000 children.[142] Observational studies specific to Europe and North America suggest incidence rates that range between 3.2 and 21.7 cases per 100,000 children per year (Table 4). The reports on incidence rates of JIA differ depending on the study design and geographic region.[143]

Incidence studies are limited in precision due to the small number of new subjects who present with juvenile arthritis each year, which results in large confidence intervals for individual studies, as well as large differences in estimates across studies.

Table 4. Incidence Rates and Prevalence of Juvenile Idiopathic Arthritis from Observational Studies in Europe and North America

Author, Year	Country/Region	Study Period	Incidence rates per 100,000 children	Prevalence per 100,000 children
EUROPE				
Kaipiainen-Seppanen, 2001[144]	Finland	1995	19.5	NR
Berntson, 2003[145]	Nordic Region	1997-1998	15	NR
Danner, 2006[146]	France	2001	3.2	19.8
Pruunsild, 2007[147]	Estonia	1998-2000	21.7	NR
Pruunsild, 2007[148]	Estonia	1995-2000	NR	83.7
Riise, 2008[149]	Norway	2004-2005	14	NR
Modesto, 2010[150]	Spain	2004-2006	6.9	39.7
Solau-Gervais, 2010[151]	France	2006	NR	15.7
Rasmussen, 2012[152]	Denmark	1980-2009	16.73	NR
Berthold, 2019[143]	Sweden	2002-2010	12.8	NR
NORTH AMERICA				
Harrold, 2013[153]	US	1996-2009	11.9	44.7
Krause 2016[154]	US	1994-2013	10.3	57.6
Shiff 2019[155]	Canada	2000-2012	8.47	52.86

NR: not reported

Prevalence: A systematic literature review of JIA for studies published from 1972 to 2011 reported a pooled prevalence of 70.2 per 100,000 children.[142] Observational studies specific to Europe and North America suggest prevalence that ranges between 15.7 (0.02%) and 83.7 (0.08%) cases per 100,000 children per year (Table 4).

A difficulty in estimating prevalence is that studies may either include children who are currently symptomatic or they may include children who have ever had a diagnosis, regardless of current symptoms. Estimates are influenced by study design, and especially setting, where clinic-based studies often suggest lower prevalence estimates than community-based studies. Although some subjects achieve complete remission post-adolescence, many children remain symptomatic throughout life and will always be considered juvenile arthritis

subjects, even as adults. Prevalence studies often do not include adult-aged subjects with JIA;[156] this should be considered when using prevalence estimates to extrapolate the total number of cases in a population.

Demographics of the population in the authorised indication–age, gender, racial and/or ethnic origin and risk factors for the disease: The age and gender distribution for JIA varies greatly by subtype; however, across all subtypes, JIA is more prevalent in females than males, with an overall female to male ratio of 1.5-2 to 1.0.[157] In a systematic review of JIA studies published from 1972 to 2011, incidence rates for JIA varied from 2.9 to 35.4 per 100,000 children for females and from 1.7 to 19.3 per 100,000 children for males. The overall pooled incidence rate was 10.0 per 100,000 children for females and 5.7 per 100,000 children for males.[142] For age, the pooled incidence was 8.7 for the age group of 0–4 years, 6.1 for the age group of 5–9 years, and 9.6 per 100,000 children for the age group of 10–15 years.[142]

A Canadian study of ethnicity in subjects with JIA found that subjects of European descent were more likely to develop any of the JIA subtypes, except RF positive polyarticular JIA, than were subjects of Indian, Asian, or African descent, and they were especially more likely to develop the extended oligoarticular and psoriatic subtypes; the ethnic distribution varied by subtype of JIA.[158] However, a US study suggested that Caucasian and African American children had similar rates of JIA.[156] Further, studies have reported geographic differences in the epidemiology of JIA, even within a single country. It is unclear whether these differences are due to environmental factors, genetic differences, or a combination of the two.

Like other autoimmune diseases, risk of developing JIA is thought to be determined by a complex combination of genetic and environmental risk factors.[159] Girls and older children are at increased risk. [150 153] There may be genetic susceptibility, and several candidate genes are under study.[159 160] Some authors have hypothesised vaccinations may trigger the disease in those genetically predisposed, but studies have not supported a link to vaccines.[160] Some infections can lead to transient post-infectious arthritis, usually lasting only a few weeks; however this can occasionally become chronic, resembling JIA.[159] Early-life risk factors include not having been breastfed and maternal smoking.[159]

The main existing treatment options: Conventional treatment options for pJIA include local glucocorticoid injections, systemic glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).[161 162]

csDMARDs are first-line therapy for the treatment of pJIA due to their proven ability to minimize joint damage and improve symptoms. Methotrexate (MTX) is the most widely used csDMARD; side effects such as gastrointestinal and hepatic toxicity are often associated with its use.[163 164]

Biological DMARDS (bDMARDs), which are directed at extracellular targets such as individual soluble cytokines, have revolutionized the treatment of pJIA, especially in those who fail to respond to csDMARDs.[165 163] Tumor necrosis factor (TNF) inhibitors were the

first bDMARD approved for the treatment of pJIA, are the most widely used class of bDMARDs, and have been shown to lead to significant improvement in the reduction of signs and symptoms of pJIA. Since their approval, several other classes of bDMARDs have also been approved for use in pJIA (IL-1 inhibitors, IL-6 inhibitors, selective T cell costimulation modulator).[166] Despite the many benefits of bDMARDs, there are still downsides to their use in children with pJIA such as route of administration (parenteral) and the potential development of anti-drug antibodies which can result in loss of efficacy over time.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: JIA is a chronic disease characterized by prolonged synovial inflammation that may cause structural joint damage.[167] Nonreversible abnormalities may also occur in extra-articular organs, such as the eye (as a complication of iridocyclitis) or the kidney (due to systemic amyloidosis), or may result from adverse effects of drug therapies.[167]

One of the most significant complications of JIA is anterior uveitis. The risk of uveitis is based on the JIA subtype, age at disease onset, and antinuclear antibody (ANA) status. The highest risk group of patients is oligoarticular JIA, especially if the patient is female, ANA-positive, and less than 4 years of age.[168] JIA may be complicated by linear or localized growth disturbance. Linear growth abnormalities are particularly observed in patients with chronic active disease and are therefore most common in children with polyarthritis or systemic JIA.[168]

Using subject hospitalization records in Scotland, findings of a study of children with JIA suggested that the overall mortality was elevated 3-5 fold over the general population.[169] The Rochester Epidemiology Project database tracked 57 subjects with a history of JIA into adulthood. Four deaths occurred among these subjects (compared to one expected death). Although this finding is statistically significant, the small sample size limits the generalizability of this finding in JIA subjects overall. Of note, all deaths were attributable to complications from other autoimmune diseases.[170] Studies of mortality among subjects with JIA have estimated that the standardized mortality rate is 3 to 14 times greater than that of the general age-matched US population.[171]

Important co-morbidities: The key comorbidities associated with JIA are growth retardation[172,173,174]; osteopenia[175,176,177]; uveitis[178,179,180] ; and diabetes[181,182]

Indication: Ankylosing Spondylitis

Incidence: The crude annual incidence of AS was reported as 7.2 per 100,000 among those 18-45 years old in Spain[183] and the age-standardised incidence as 6.4 per 100,000 in the Czech Republic.[184] A Danish study estimated incidence raging between 0.5 to 1.2 per 100,000 among men and 0.2 to 0.8 per 100,000 among women in the time period of 2000 to 2013.[185]

In a study from the US, the average age- and sex-adjusted incidence of AS in the period 1980 to 2010 was estimated at 3.1 per 100,000, with little variation over time.[186] In Canada, a higher incidence of AS between 11 and 15 per 100,000 has been reported.[187, 188]

Prevalence: The overall (pooled) prevalence of AS has been estimated at 25 per 100,000 in Europe and 20 per 100,000 in North America.[189] By country, the reported prevalence in Europe and North America ranges from 6 to 60 per 100,000 inhabitants (Table 5). The variation in prevalence may be due to difference in case definitions and study design, as well as the occurrence of risk factors in the population.

Table 5. Prevalence of Ankylosing Spondylitis in Europe and North America

Author, Year	Country	Prevalence (cases per 10,000 inhabitants)
Monjardino, 2011[190]	Portugal	6[a]
KoKo, 2014[191]	Albania	6.1[a]
Sliwczynski, 2015[192]	Poland	7.48[a]
Hanova, 2010[184]	Czech Republic	9.4[b]
Haglund, 2011[193]	Sweden	12[a]
Geiersson, 2010[194]	Iceland	12.7[a]
Munoz-Ortega, 2014[195]	Spain	13[a]
Dean, 2016[196]	Scotland	13.4[a]
Exarchou, 2015[197]	Sweden	18[a]
Quilis, 2020[198]	Spain	26[a]
Anagnosopoulos, 2010[199]	Greece	29[a]
Curtis, 2016[200]	US	10.7[c]
Barnabe, 2017[201]	Canada	First nations: 60[c], Non-First nations: 20[c]
Haroon, 2014[187]	Canada	From 7.9 in 1995 to 21.3 in 2010[c]

a. Crude estimate, b. Age-standardised, c. Sex-standardised

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

Patients with AS are relatively young with onset reported at an average age of 25.[228] The average age in population-based studies ranged from 30 to 54 years, and in most cohorts the majority (60-75%) of AS patients were male.[185, 231, 232, 202, 196, 189, 197, 195, 230, 229, 228]

Ethnicity has been studied and a US study showed that Blacks with AS have more severe disease compared to either Whites or Latinos.[203] In Canada the prevalence of AS was considerably higher among First nations (60 per 10,000) than Non-First nations (20 per 10,000). The result is considered to be linked to the higher prevalence of HLA-B27 gene among First nations.[201]

The aetiology of AS has a strong genetic component with more than 90% of AS patients being carrier of the HLA-B27 gene, compared to only 6.1% in the general population.[224] Environmental risk factors mentioned in the literature includes childhood infection[204] and smoking.[205]

The main existing treatment options: For many decades, the mainstay of treatment of AS has been NSAIDs and structured exercise programs including physical therapy with the aim of relieving clinical symptoms.[206] However, gastrointestinal and other adverse effects limit the tolerability of NSAIDs including some COX-2 selective inhibitors.[207, 208] In addition, AS patients report insufficient control with NSAIDs alone.[209] Treatment with csDMARDs that

have shown efficacy in RA have not shown similar efficacy in AS.[210, 211] Sulfasalazine may provide some benefits for peripheral arthritis but does not impact axial disease.[212, 213] Locally administered parenteral glucocorticoids are also a treatment option for patients with active enthesitis, sacroiliitis or peripheral arthritis that have not responded fully to NSAID therapy.[214, 215] However, although local corticosteroid injections are widely used in clinical practice to good effect in AS patients, no clinical trials exist to support this use. [214]

TNFα antagonists or inhibitors, also known as TNFi, have demonstrated efficacy and are approved for the reduction of clinical signs and symptoms, in patients with AS. A recent ASAS-EULAR recommendation stated that TNFi therapy is indicated for those patients with persistently high disease activity despite conventional treatment.[216] Additional bDMARDs that inhibit IL-17, secukinumab and ixekizumab, have been subsequently approved in the US. However, there is a substantial proportion of patients who have an inadequate response to each of these bDMARDs[217, 218, 219, 220] and as such therapy options are administered parenterally, this may act as an additional barrier to their use.[221] Moreover, the long-term efficacy of some TNFi and anti-IL-17 monoclonal antibody (mAb) may be limited by immunogenicity.[222, 223]

Current updates to the ACR AS treatment guidelines provide initial therapy recommendations based upon an individual's disease activity and/or risk factors.[215] Based on the current evidence and the considerations of the ACR panel, NSAIDs and TNFi remain the primary classes of medications for the treatment of AS, with sulfasalazine recommended only for persistent peripheral arthritis when TNFi are not appropriate. Secukinumab or ixekizumab are recommended for patients with active disease who have heart failure or demyelinating disease as a contraindication to TNFi, and in primary nonresponders to TNFi. Secukinumab and ixekizumab are not recommended in patients with IBD or recurrent uveitis, as TNFi monoclonal antibodies are better options.[215]

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

Progressive structural damage to the axial or peripheral skeleton resulting in irreversible physical impairment is the primary morbidity associated with AS.[224] The most common initial symptoms of AS are low back pain and sacroiliac joint syndrome (Table 6).

Table 6. First signs and symptoms attributable to AS by year of progression[224]

First signs and symptoms	% of AS patients*	
	With disease course ≤ 2 years	With disease course > 10 years
Low back pain	72%	72%
Sacroiliac syndrome	46%	41%
Neck pain	6%	11%
Dactylitis	0%	1%
Arthritis, lower limbs	20%	16%
Arthritis, upper limbs	15%	3%
Enthesitis	13%	7%

*%s were proportions to the corresponding patient cohort, e.g. 46% of AS patients with disease course ≤2 years had low back pain, while this proportion was 41% among AS patients with disease course >10 years.

Extra-articular manifestations (i.e. IBD, Crohn's disease, ulcerative colitis, psoriasis and uveitis) are conditions associated with AS, as is GI and joint inflammation.[224] Patients with AS also have an increased risk of cardiovascular disease.[224, 225] It has been estimated that 2-10% of patients with AS have cardiac manifestations[224] and the elevated risk is only partially attributable to traditional risk factors such as comorbid hypertension, dyslipidemia, diabetes, obesity, and metabolic syndrome, even though the prevalence of these disorders is also increased in the AS population.[225]

Considering the large number and wide range of comorbidities in this patient group, a substantial increase in mortality might be expected. However, few reports on increased mortality have been published. Two studies were found that reported an increased mortality risk of about 60% among AS patients compared to non-AS groups,[226, 227] whereas another study found no difference in mortality rate between AS patients and the general population[186].

Important co-morbidities: Comorbidities associated with AS are cardiovascular disease,[228,229,230,231] hypertension,[228,229,231] diabetes,[228,229] malignancies,[228,231] asthma,[228,231] urogenital disease,[228] dyslipidaemia,[228,231] depression,[230,232,231] gastrointestinal ulcers,[231] multiple sclerosis,[231] osteoporosis,[229,231] sleep apnea,[231] extra-articular diseases,[229,231,233,234] and peripheral diseases.[233,234]

Module SII. Non-Clinical Part of the Safety Specification

Tofacitinib has undergone a comprehensive toxicological evaluation in mice, rats, rabbits, and monkeys in studies up to 2 years in duration. Safety pharmacology studies were conducted in vitro and in vivo (rats, mice, and monkeys) to assess potential effects on cardiovascular, respiratory, and neurofunctional endpoints. In vitro and in vivo genetic toxicology studies (microbial reverse mutation, mammalian cell gene mutation, in vitro cytogenetics, in vivo micronucleus, unscheduled deoxyribonucleic acid synthesis) were conducted to assess the genotoxic potential of tofacitinib. Chronic toxicity assessment was conducted in rats and monkeys. Carcinogenicity was assessed in a 6-month rasH2 transgenic mouse study and a 2-year rat carcinogenicity study. Additionally, investigative mechanistic studies, reproductive studies in rats and rabbits, in vitro and in vivo phototoxicity studies, and other local tolerance studies have been conducted. Studies in juvenile rats and monkeys were conducted to support the paediatric plan. The citrate salt (tofacitinib citrate; CP 690,550-10) was used in most nonclinical studies and was administered primarily by the oral route as this is the intended route of administration to humans. Table 7 provides a summary of key safety findings from the tofacitinib non-clinical studies.

Table 7. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
Toxicity: • Acute toxicity including important results from safety pharmacology studies (eg cardiovascular including potential for QT prolongation, CNS, etc.) • **Single-Dose Findings** In single-dose rat studies, death, decreased activity, laboured breathing, LFT increases, and decreases in eosinophils, and fibrinogen, decreases in lymphocytes in splenic white pulp, and lymphocytolysis of mesenteric lymph node and spleen were noted. The findings in rats occurred at high exposure multiples of at least ~ 933/1879-fold or ~ 466/938-fold multiple for male/female based on the human unbound AUC for the 5 or 10 mg BID dose, respectively. In an acute monkey study, emesis and decreased activity were observed.	Relevance to human usage is not expected based on the high exposure multiples at which effects occurred in the single-dose studies.
• **Repeat-dose toxicity** (by target organ for toxicity) The effects on the immune system that were observed in the rat and monkey toxicity studies were consistent with the intended pharmacologic activity, inhibition of JAK1 and JAK3. The selectivity and severity of effects observed on the immune and haematopoietic system were reflected by specificity of tofacitinib for JAK1 and JAK3 and to a lesser extent JAK2 inhibition.	The level of the pharmacologic effect (JAK inhibition) may be dependent on dose and may result in immunosuppression (potential adverse effects) versus immunomodulation (potential efficacious effects). In humans, the direct pharmacological effects of JAK inhibition may be modified by factors such as age, concomitant drugs, such as corticosteroids, or co-morbidities, such as diabetes. The effects on NK cells, T cells, and lymphocyte depletion in lymphoid tissues is not an unexpected

Table 7. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
Decreases in numbers of circulating NK cells and T cells and lymphocyte depletion in lymphoid tissues were observed in both rat (≥1 mg/kg; ~ ≥1/2- or ~ ≥0.4/1-fold multiple for male/female based on the human unbound AUC for the 5 or 10 mg BID dose, respectively) and monkey (≥0.5mg/kg; ~ ≥0.1- or ~ ≥0.2-fold multiple for the 5 or 10 mg BID dose, respectively) toxicity studies.	finding given the importance of γ-common chain cytokines (IL-2, IL-4, IL-7, IL-15, IL-21) in lymphocyte development and homeostasis.[243,244,245] Tofacitinib decreases circulating NK cell counts in patients; treatment-related decreases in total lymphocytes and circulating T cell lymphocytes may occur in some patients at therapeutic doses
Decreases in circulating B cells were observed in rats at doses ≥10 mg/kg/day (~ ≥9/21-fold or ~ ≥5/11-fold for male/female based on the human unbound AUC for the 5 or 10 mg BID dose, respectively), however, there were no tofacitinib-related decreases in B cells in monkeys or humans administered tofacitinib.	The effect on B cells in rats is consistent with findings that IL-7 and JAK3 deficient mice lack B cells whereas IL-7 and JAK3 deficient SCID humans have normal B-cell numbers.[246,247,248,249,250,251] Decreases in B cells in humans are not expected based on the differences in B-cell development between rodents and humans.
At higher exposure levels, decreases in RBC parameters (RBC, Hgb, and haematocrit), including reticulocytes, and platelets were observed in rats and monkeys. Decreases in circulating eosinophils and basophils were also reported at ≥10 mg/kg in 6-week and 6-month studies in rats (~ ≥9/21-fold or ~ ≥5/11 multiple for male/female based on the human unbound AUC for the 5 or 10 mg BID dose, respectively).	Effects on RBC parameters, reticulocytes and platelets were attributed to the inhibition of JAK2 signalling by haematopoietic growth factors[252] and cytokines critical for eosinophil (IL-5)[253] and basophil (IL-3)[254] development. Effects on these parameters are possible in humans, especially at higher exposure to tofacitinib. Thrombocytopenia has been observed in tofacitinib patients, but is not considered a treatment-related AE.
At higher exposure levels, bacterial and viral infections secondary to immunosuppression by tofacitinib were observed in rat (100 mg/kg in female rat; ~ 189- or ~ 95-fold multiple based on the human unbound AUC at 5 mg or 10 mg BID dose) and monkey (≥50 mg/kg; ~ ≥23- or ~ ≥11-fold multiple based on the human unbound AUC for the 5 or 10 mg BID dose, respectively) studies.	Immunosuppression leading to bacterial and viral infections may be observed in individual patients administered therapeutic doses of tofacitinib.
In the 39-week monkey study 3 of 8 monkeys in the high dose group (10 mg/kg/day; ~ 6- or ~ 3-fold multiple based on the human unbound AUC at the 5 or 10 mg BID dose) were observed with lymphoma. Two (2) of these cases were confirmed LCV-related B-cell lymphomas. The other lymphoma was a T cell lymphoma.	Lymphoproliferative effects and lymphoma have been observed in patients treated with tofacitinib. EBV- associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications.[255]
In the renal allograft study, 1 of 8 animals dosed with both tofacitinib and MMF had a single enlarged mesenteric lymph node, and based on microscopic evaluation was described as a lymphosarcoma.	
Chronic immunosuppression in monkeys is associated with the development of PTLD. The development of LCV (equivalent to EBV in humans)-associated B-cell lymphomas in monkeys administered tofacitinib is not unexpected since other immunomodulatory drugs produce lymphomas in	The majority of PTLD in humans are associated with EBV.[256] Although the exact mechanism for the pathogenesis of EBV-associated PTLD is not clear, there is substantial evidence that suggests that immunosuppressive therapy results in decreased

Table 7. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
rhesus or cynomolgus monkeys.[235,236,237,238,239,240,241,242] For the 39-week monkey study, all of the monkeys were infected with LCV based on the presence of anti-LCV antibodies in prestudy serum samples. Thus, the LCV-associated B-cell lymphomas were not unexpected and were similar to the LCV/EBV positive B-cell lymphomas observed with PTLD cases in nonhuman primates.[239 240 256] Therefore, the LCV-associated lymphomas observed in the 39-week monkey study were considered secondary to immunosuppression. Lymphoid (follicular) hyperplasia was observed in lymph nodes, GALT or spleen of individual animals at doses ≥0.5 mg/kg/day in the 39-week monkey study (~ ≥0.2- or ~ ≥0.1-fold multiple based on the human unbound AUC for the 5 or 10 mg BID dose, respectively). This lymphoid (follicular) hyperplasia was not associated with LCV, and based on histological characteristics is not considered a precursor to lymphoma.	numbers of EBV/LCV-specific cytotoxic T lymphocytes which are therefore unable to control the growth of EBV/LCV-transformed B cells.[257,258,259,260] The LCV-associated B-cell lymphomas were not unexpected and were similar to the LCV/EBV positive B-cell lymphomas observed with PTLD cases in humans.[239, 240, 256] Relevance to human usage is not expected because the occurrence of simple reactive follicular lymphoid hyperplasia represents a normal immune response (eg, response to an antigen or pathogen) that is reversible, not considered to be adverse, and not a precursor of lymphomas.[261,262,263]
• **Genotoxicity** In vitro, CP-690,550 did not induce microbial or mammalian gene mutations in the absence or presence of metabolic activation. Reproducible increases in chromosomal abnormalities were observed in a human lymphocyte in vitro cytogenetic assay at high cytotoxic concentrations with metabolic activation, but no effects were observed without metabolic activation. No evidence for chromosome damage was observed in an in vivo bone marrow micronucleus study. No DNA damage occurred in the in vivo/in vitro rat hepatocyte UDS assay.	Given the weight of evidence from the genetic toxicity studies, tofacitinib is not considered a genotoxicant. Reproducible increases in chromosomal abnormalities were produced in the human lymphocyte in vitro cytogenetic study only at high (≥1700 µg/mL) and cytotoxic (≥48% mitotic suppression) concentrations with metabolic activation, which is > ~ 46000- or 23000-fold the human unbound C_{max} at the 5 or 10 mg BID dose. Therefore, the positive finding in the in vitro cytogenetic assay is not considered relevant due to the high concentration that was required to induce chromosomal aberrations and the lack of chromosomal or DNA damage in vivo.
• **Carcinogenicity** In the 2-year rat carcinogenicity study tofacitinib -related neoplastic findings included: increases in benign Leydig cell tumours for males given ≥30 mg/kg/day; benign angiomas in the mesenteric lymph nodes only for males given 10 mg/kg/day, which were not dose-dependent; benign thymomas (in thymus) for females administered 100/75 mg/kg/day; and malignant hibernomas for females given ≥30 mg/kg/day. The exposure multiples for male/female rats were ~ 11/22, 35/83, and 122/187 for the low, mid and high	**Leydig Cell Tumours** The benign Leydig cell tumours observed in the rat carcinogenicity study are attributed to JAK2 inhibition of PRL signalling within the Leydig cells and creation of the same intracellular environment that is caused by dopamine agonists. This mechanism of causing Leydig cell tumours in rats is well precedented and is not associated with risk of Leydig cell tumours in humans.[264]

Table 7. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
doses, respectively, based on the human unbound AUC at the 5 mg BID dose. The exposure multiples for male/female rats were 5/11, 17/42, and 61/94 for the low, mid and high doses, respectively, based on the human unbound AUC at the 10 mg BID dose.	A thorough review of the literature and subsequent discussion of the lack of relevance of rat Leydig cell tumours to human risk is provided in a Pfizer safety assessment.[265] **Hibernoma** Malignant hibernomas observed in female rats treated with tofacitinib are not considered a significant risk for human safety at clinical exposures. This is based on a non-genotoxic proliferative effect with an adequate safety margin. Additionally, the differences in hibernoma incidence, malignancy potential, and location between rats and humans, and the association of tofacitinib with hibernoma in only a single rodent species and sex, decrease the likelihood that the hibernomas in rats are relevant to humans. Although the exact mechanism for hibernoma development is undefined, several investigative studies suggest that JAK inhibition and/or increased sympathetic stimulation might contribute to BAT proliferation induced by tofacitinib.[266] A thorough review of the literature and subsequent discussion of the relevance of rat hibernomas to human risk is provided.[267] **Thymoma** The increased incidence of benign thymomas was statistically significant only in high dose females and not considered a significant risk for humans based on the calculated safety margins. Thymomas (tumours originating from the epithelial cells of the thymus) are rarely observed in Sprague-Dawley rats.[263] [268] Thymomas can be induced in rodents by viral inoculation,[269,270] but it is not known whether immunosuppression can cause thymomas in rats due to endemic viral infection. An immunosuppressive mechanism is supported by the results from rat carcinogenicity studies on the immunosuppressant drugs mycophenolate sodium, pimecrolimus, and leflunomide. Thymoma incidence was increased in tofacitinib dosed female rats for each of these immunosuppressant drugs, although the increase reached statistical significance for both the trend and pairwise tests only for pimecrolimus.[271,272] Based on data from a large registry linkage study, thymoma risk was not elevated among 516,000 people with AIDS in the US (4 thymoma cases, SIR = 0.85). Similarly, thymoma risk does not seem elevated among immunosuppressed solid organ transplant recipients, as a literature search revealed no reported cases.[273]

Table 7. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
	In humans, the mechanism for development of thymomas is unknown.[274] Based on the high exposure margin compared to clinical exposure to tofacitinib, the risk to humans is low. **Angiomas** An increased incidence of benign angiomas was evident only in low-dose males, with no dose-related trend, no significant increase in female rats, no increase in malignant haemangiosarcomas in either male or female rats, and no increase in haemangiomas or haemangiosarcomas in male or female mice. Based on these observations, the marginally increased incidence of benign angioma in low-dose male rats is not considered biologically meaningful and not a relevant risk for humans treated with tofacitinib.[275]
• **Developmental and reproductive** (must be discussed if medicine might be used in women of child-bearing potential) • **Reproductive** In a rat EFD study, maternal toxicity was observed at doses ≥100 mg/kg/day (~ ≥203- or ~ ≥101-fold multiple based on the human unbound AUC for the 5 or 10 mg BID dose, respectively). Foetal developmental effects consisting of multiple visceral and skeletal malformations were observed at the 100 mg/kg/day dose. Multiple visceral and skeletal malformations were observed in a rabbit EFD study at doses ≥30 mg/kg/day (~ ≥13- or ~ ≥6-fold multiple based on the human total AUC for the 5 or 10 mg BID dose, respectively). However, in rabbits, no evidence of maternal toxicity was observed at doses up to 100 mg/kg/day (~ 63- or ~ 32-fold multiple based on the human total AUC for the 5 or 10 mg BID dose, respectively). In a rat fertility study, treatment-related effects on female reproduction at doses ≥10 mg/kg/day (~ ≥15- or ~ ≥8-fold multiple based on the human unbound AUC for the 5 or 10 mg BID dose, respectively) consisted of decreased pregnancy rate; decreases in the numbers of corpora lutea, implantation sites, and viable foetuses; and an increase in early resorptions. No effects on male fertility were observed in this study. Tofacitinib was secreted in milk of lactating rats. • **Developmental** At 50 mg/kg in rat (~ 102- or 51-fold multiple based on the human unbound AUC at the 5 or 10 mg BID	Results from rat and rabbit EFD toxicology studies are potentially relevant to human usage (see Table 35 for relevance on human usage). Results from a rat fertility toxicology study are potentially relevant to human usage (see Table 35 for relevance on human usage). No effects on male fertility are anticipated based on animal data results. Results from a rat study are potentially relevant to human usage (see Table 35 for relevance on human usage). Results from a rat perinatal and postnatal toxicology study are potentially relevant to human usage (see Table 35 for relevance on human usage).

Table 7. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
dose), the averages for the total number of delivered pups and the number of live born pups were reduced. All pups died between days 1-4 postpartum in litters delivered from 14 of 21 dams and 16 dams were euthanised because of no surviving pups. Tofacitinib reduced live litter weight, litter size, and individual pup weights at each weighing on days 1 and 4 postpartum. No effect occurred on sexual maturation or the ability of the F1 generation rats to learn, mate and produce viable F2 generation foetuses. In studies conducted in juvenile rats and monkeys tofacitinib-related effects on immune and hematologic parameters were consistent with those in adult animals at similar exposures. There were no tofacitinib-related changes in landmarks of sexual maturity or fertility indices, nor was there evidence of findings associated with impaired bone growth and development.	Results from juvenile animal toxicity studies are potentially relevant to human usage.
• **Safety Pharmacology as applicable:** • **Cardiovascular system** Tofacitinib (100 μM) has no significant effect on potassium channels based on results from the hERG study at concentrations ~ 890- or ~ 440-fold based on the human unbound Cmax for the 5 or 10 mg BID dose, respectively. Tofacitinib had no effect on the action potential duration, the resting membrane potential, action potential amplitude, and maximal velocity of depolarisation based on a study on dog Purkinje fibres. In isolated rat aortas, tofacitinib caused a concentration-related relaxation of KCl and norepinephrine induced contractions at 1 to 100 μM (312-31240 ng/mL). Tofacitinib has no significant effect on spontaneously beating guinea pig right atria In male rats, tofacitinib (100 mg/kg; calculated unbound C_{max} 7336 ng/mL) caused a drop in mean arterial pressure of 37 mmHg, and a heart rate increase of approximately 100 beats per minute. This dose represents exposure margins of ~ 210- or ~ 103--fold based on the human unbound C_{max} for the 5 or 10 mg BID dose, respectively. Similar effects were observed in a separate study in female rats. In a telemetry monkey study, an increase in heart rate (~ 43% over control) was seen at 2-3 hours post-dose in animals receiving 300 mg/kg (~ 61- or ~ 30-fold multiple for the human unbound C_{max} for the 5 or 10 mg BID dose, respectively). The response was transient and maximal at 3 hours post-dose. There was no effect on blood pressure or electrocardiogram.	Relevance to human usage is not expected based on the high exposure multiples at which effects occurred in the safety pharmacology studies.

Table 7. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
• **Gastrointestinal:** In rats, oral administration of tofacitinib at ≥30 mg/kg (estimated unbound AUC ≥12,070 ng•h/mL) inhibited gastric emptying and reduced the geometric centre of distribution of a radioactive marker (~≥39- or ~≥19-fold margin based on the unbound human AUC for the 5 or 10 mg BID dose, respectively).	Abdominal pain, dyspepsia, vomiting, gastritis, nausea have occurred in patients treated with tofacitinib; the relationship of these events to the effects of tofacitinib on gastric emptying and GI motility in rats is unknown.
• **Renal:** In rats dosed with tofacitinib at 100 mg/kg (~ 210- or ~ 103-fold multiple relative to the unbound human C_{max} for the 5 or 10 mg BID dose, respectively), potassium excretion was elevated by 104% with a trend of both decreased chloride (77%) and urine volume (32%).	Relevance of these clinical pathology changes to human usage is not expected based on the high exposure multiples at which effects occurred in the renal safety pharmacology study.
• **Nervous system:** In mice dosed with tofacitinib at ≥100 mg/kg (~ ≥92- or ~ ≥45-fold multiple relative to the unbound human C_{max} for the 5 or 10 mg BID dose, respectively), dose-related CNS behavioural changes were observed.	Relevance to human usage is not expected based on the high exposure multiples at which effects occurred in the CNS safety pharmacology study.
• **Nephrotoxicity and Hepatoxicity** No treatment-related nephrotoxicity or hepatotoxicity findings were observed in repeat-dose monkey studies. No nephrotoxicity findings were observed in repeat-dose rat studies. In rats dosed at ≥100 mg/kg, tofacitinib-related non-adverse hepatic findings of increased liver weight and hepatocellular hypertrophy with or without liver function transaminase elevations with no evidence of hepatocellular degeneration were observed at ~ 119/189-fold or ~ 59/95-fold multiples for male/female based on the human unbound AUC for the 5 or 10 mg BID dose, respectively) and monkey (up to 10 mg/kg; ~ 6-or ~ 3-fold multiple based on the human unbound AUC for the 5 or 10 mg BID dose, respectively) studies.	Relevance of the hepatocellular findings to human usage is not expected based on the high exposure multiples at which the effects occurred in the repeat-dose rat studies.
• **Juvenile Toxicology** At doses up to 100 mg/kg (~ 186/212-fold or ~ 93/106-fold multiple for male/female human unbound AUC at the 5 or 10 mg BID dose) in the juvenile rat fertility study, there was no evidence of developmental toxicity (sexual landmarks) or reproductive toxicity (mating and fertility) following the juvenile treatment period. In the 1-month study in juvenile rats (at PND 21-50; comparable to a 2 year-old human) and 39-week study in juvenile monkeys (at 13-14-months; comparable to ~5-year old human), tofacitinib-	No additional human risks were identified in the non-clinical juvenile toxicology studies that were not previously identified in non-clinical studies in mature animals.

Table 7. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage
related effects on immune and haematology parameters at all doses in rats (≥ 1 mg/kg/day; ~ 0.4/1-fold or ~ 0.2/0.6-fold multiple for male/female based on the human unbound AUC at the 5 or 10 mg BID dose, respectively) and monkeys (≥2 mg/kg/day; ~ ≥1.1 or ~ ≥0.6-fold multiple based on the human unbound AUC for the 5 or 10 mg BID dose, respectively), which were consistent with JAK1/3 and JAK2 inhibition; these effects were generally reversible during the recovery phase of each study. In addition, lymphoid (follicular) hyperplasia and lymphoma was not observed in the 39-week juvenile monkey study up to doses of 10 mg/kg/day (~ 6- or ~ 3-fold multiple based on the human unbound AUC for the 5 or 10 mg BID dose, respectively). In a juvenile rat toxicity study conducted to evaluate bone effects, administration of tofacitinib to juvenile rats beginning at PND 7 or 21 until PND 49 resulted in no direct tofacitinib-related bone findings at doses up to 20 mg/kg/day (≥29-fold or ≥15-fold multiple based on the human total AUC for the 5 or 10 mg BID dose, respectively).	
• **Mechanisms for Drug interactions** Tofacitinib did not significantly inhibit the major drug-metabolising CYP450 (IC50s >30μM) or UGT; (IC50s >100μM) enzymes in vitro, indicating a low potential for drug interactions with compounds metabolised by these isoforms. The in vitro potential of tofacitinib to induce CYP3A4, CYP1A2, or CYP2B6 was low based on mRNA changes in hepatocyte studies. Tofacitinib is a substrate for P-gp, but is not a substrate for the BCRP, OCT1 or OCT2, or OATP1B1 or 1B3. Tofacitinib is not an inhibitor of OATP1B3 and showed weak inhibitory properties against P-gp (IC50 311μM), OATP1B1 (IC50 55μM), and OCT2 (IC50 150μM), indicating a low risk of clinical interactions with these transporters.	The risk of tofacitinib causing a metabolism or transporter drug-drug interaction is low.
• **Other toxicity-related information or data** Tofacitinib was negative for contact sensitisation in a LLNA and was not considered an ocular or primary skin irritant in rabbits. There was no evidence of haemolysis observed in an in vitro haemolysis compatibility study conducted with an IV formulation of tofacitinib. There was no evidence that tofacitinib was phototoxic in the 3T3- NRU assay or in the in vivo phototoxicity study in pigmented rats.	None.

Table 7. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies[a]	Relevance to Human Usage

a. Exposure margins are calculated based human 5 mg BID dose (total AUC_{24} = 507 ng•h/mL and unbound AUC_{24} = 309 ng•h/mL; total C_{max} = 58 ng/mL and unbound C_{max} = 35 ng/mL) and 10 mg BID dose (total AUC_{24} = 1014 ng•h/mL and unbound AUC_{24} = 619 ng•h/mL; total C_{max} = 116 ng/mL and unbound C_{max} = 71 ng/mL).

AE = adverse event; AIDS = acquired immunodeficiency syndrome; AUC = area under the concentration-time curve; BAT = brown adipose tissue; BCRP = breast cancer resistance protein; BID = twice daily; C_{max} = peak plasma concentration; CNS = central nervous system; CYP = cytochrome P450; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; EFD = embryo-foetal development; GALT = gut-associated lymphoid tissue; GI = gastrointestinal; Hgb = haemoglobin; IC_{50} = 50% inhibitory concentration; IL = interleukin; JAK = Janus kinase; KCl = potassium chloride; LCV = lymphocryptovirus; LFT = liver function test; LLNA = local lymph node assay; MMF = mycophenolate mofetil; mRNA = messenger ribonucleic acid; NK = natural killer; NRU = Neutral Red Uptake; OATP = organic anion-transporting polypeptide; OCT = organic cation transporter; P-gp = P-glycoprotein; PND = postnatal day; PRL = prolactin; PTLD = post-transplant lymphoproliferative disorder; RBC = red blood cell; SCID = severe combined immunodeficiency syndrome; SIR = standardised incidence rate; UDS = unscheduled DNA synthesis; UGT = uridine diphosphate glucuronosyl transferase; US = United States

Module SIII. Clinical Trial Exposure

Cumulatively through 28 February 2023, it is estimated that 23,702 subjects have participated in the tofacitinib (immediate-release and prolonged-release) clinical development programme: 17,902 subjects were exposed to tofacitinib; 5431 subjects received tofacitinib in combination with other study medication with/without placebo; 78 subjects received blinded therapy; 1663 received placebo; and 3074 subjects received comparator drugs with/without placebo. Of note, some subjects may have been randomised to more than 1 treatment group.

Rheumatoid Arthritis

Prolonged-release:

The clinical trial programme to support tofacitinib 11 mg prolonged-release (PR) tablets included 7 completed Phase I studies in healthy volunteers, a completed local Japanese Phase 3 study in RA patients (A3921215), and a completed global Phase 3b/4 study in RA patients (A3921192). In the completed study A3921215, 104 subjects were treated with tofacitinib PR 11 mg once daily (QD) and 105 subjects received tofacitinib immediate-release 5 mg BID. In study A3921192, all subjects received tofacitinib PR 11 mg QD. The demographic characteristics of the subjects treated with tofacitinib PR 11 mg QD from studies A3921215 and A3921192 are provided below.

Table 8. Demographic Characteristics of Subjects Treated with Tofacitinib PR In Rheumatoid Arthritis Patients in Studies A3921215 and A3921192

	Study A3921215 (PR 11 mg QD + MTX)	Study A3921192[a] (PR 11 mg QD + MTX)
Number of subjects	104	694
Male	18	162

Table 8. Demographic Characteristics of Subjects Treated with Tofacitinib PR In Rheumatoid Arthritis Patients in Studies A3921215 and A3921192

	Study A3921215 (PR 11 mg QD + MTX)	Study A3921192[a] (PR 11 mg QD + MTX)
Female	86	532
Age (years):		
<18	0	0
18-44[b]	18	117
45-64[c]	57	391
≥65	29	186
Race:		
White	0	594
Black	0	33
Asian	104	37
Other	0	30

a. All patients received tofacitinib PR and MTX in the open-label period. In the double blind MTX withdrawal period, patients stayed on tofacitinib PR with or without MTX.
b. Age range is 18-45 for study A3921192.
c. Age range is 46-64 for study A3921192.
Source: Table 14.1.2.1 (study A3921215), Table 14.1.2.1.1 (study A3921192)
MTX=methotrexate; PR=prolonged-release; QD=once daily
Final data: 10 April 2017 (study A3921215), 14 June 2018 (study A3921192)

The following clinical trial exposure data provided below for RA is applicable for the PR and immediate-release tablets.

Prolonged-release and Immediate-release:

The tofacitinib immediate-release BID RA development programme includes 2 completed Phase 2 studies, 10 completed Phase 2 studies, 6 completed Phase 3 studies, 2 completed long-term extension (LTE) studies, and 1 completed Phase 3b/4 study. As mentioned above, the PR RA studies include A3921215, a local Japanese Phase 3 study in RA patients, and A3921192, a global Phase 3b/4 study in RA patients.

The clinical trial exposure information from the RA studies for the Phase 1, 2, 3, and LTE (P123LTE) studies (includes immediate-release and PR studies) and for the Phase 2, 3, 4 (P234) Randomised Controlled Trials (RCT) studies is presented below. There were 7964 adult patients exposed to tofacitinib PR and immediate-release totalling 23,497 patient-years of exposure to tofacitinib. Data from study A3921133 was excluded from the exposure tables presented in the P123LTE studies.

Study A3921133 was a Phase 3b/4 randomized, parallel-arm, open-label, safety endpoint study evaluating the safety of tofacitinib at 2 doses (5 mg BID and 10 mg BID) versus TNFi (adalimumab 40 mg every other week by SC injection in the US, Puerto Rico and Canada, or etanercept 50 mg once weekly by SC injection in all other countries). Subjects ≥50 years of age or older, with moderately or severely active RA who had an inadequate response to MTX and who had at least one CV risk factor (eg, current smoker, high blood pressure, high cholesterol levels, diabetes mellitus, history of heart attack, family history of coronary heart

disease, extra articular RA disease), were enrolled in this study. The co-primary endpoints of Study A3921133 were adjudicated MACE and adjudicated malignancies excluding NMSC.

In Study A3921133, 2911 adults were exposed to tofacitinib totaling 9846.9 patient-years of exposure: 1455 adults and 5073.5 patient-years in the tofacitinib 5 mg BID group; 1456 adults and 4773.4 patient-years in the tofacitinib 10 mg BID group. In the TNFi group, 1451 adults were exposed, totaling 4940.7 patient-years of exposure.

The following tables depict total exposure to tofacitinib based on clinical trial experience by duration and dose for patients treated in the Phase P123LTE studies (All RA population), either as monotherapy or on background DMARD therapy. Adalimumab was used as an active control in 3 studies, the Phase 2 Study A3921035 (as adalimumab monotherapy) the Phase 3 Study A3921064 (adalimumab with background MTX), and the Phase 3b/4 Study A3921187 (adalimumab with background MTX). MTX was used as an active control in 1 study, the Phase 3 Study A3921069, where tofacitinib was administered as monotherapy.

Clinical trial exposure to tofacitinib in the RA development programme is summarised in Table 9 to Table 13. Since subjects were allowed to switch doses between 5 mg BID and 10 mg BID during the LTE studies, the Average Daily Dose (AVDOS) was used to determine the dose group. That is, if the AVDOS is ≥15 mg daily, subjects are assigned to the 10 mg BID group, whereas if the AVDOS is less than 15 mg daily, subjects are assigned to the 5 mg BID group.

Table 9. Clinical Trial Exposure to Tofacitinib by Duration, Completed Rheumatoid Arthritis Phase 1, 2, 3 and Long-Term Extension Studies (P123LTE)

Duration of Exposure[a] (at Least)	Persons	Person Time[b] (Years)
RA **Total Exposed Population N = 7964**		
At least 1 dose	7964	23496.73
≥1 month	7792	23489.51
≥3 months	7115	23370.21
≥6 months	6622	23178.14
≥12 months	5028	21821.56
≥18 months	4504	21215.76
≥24 months	4168	20636.96
≥30 months	3816	19880.70
≥36 months	3594	19283.78
≥42 months	3318	18395.66
≥48 months	2855	16696.27
≥54 months	2462	15058.90
≥60 months	2176	13727.04
≥66 months	1779	11676.40
≥72 months	1342	9221.60
≥78 months	908	6550.72
≥84 months	435	3436.26
≥90 months	320	2625.50
≥96 months	241	2021.17

Table 9. Clinical Trial Exposure to Tofacitinib by Duration, Completed Rheumatoid Arthritis Phase 1, 2, 3 and Long-Term Extension Studies (P123LTE)

Duration of Exposure[a] (at Least)	Persons	Person Time[b] (Years)
RA **Total Exposed Population N = 7964**		
≥102 months	117	1016.41
≥108 months	27	247.18
≥114 months	4	39.62
≥120 months	2	20.66
≥126 months	1	10.42

a. Exposure is to any dose of tofacitinib

b. Patients complete exposure is included in each period if the patient contributes to N in that particular period. Patients are counted only once if they participated in both the index and LTE studies; however, their time in both the index and LTE study is included in the person time column.

Source: Table 1582.10.4

LTE=long-term extension; RA = rheumatoid arthritis

Included protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.

Final data 18 January 2019

Table 10. Clinical Trial Exposure by Dose and Duration of Treatment, Rheumatoid Arthritis Phase 2, 3, and 4 Controlled Period (P234)

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	All Tofacitinib	Placebo	Adalimumab	Methotrexate
Number of subjects	**2664**	**2024**	**6183**	**1136**	**643**	**223**
Duration Category (Month)						
≤1	58	59	168	83	12	9
>1 to ≤3	289	255	1125	604	70	15
>3 to ≤6	427	410	1370	352	38	22
> 6 to ≤ 12	1229	638	2080	97	479	44
>12 to ≤18	151	133	333	0	44	21
>18	510	529	1107	0	0	112
Total duration (PYs)	2476.7	1952.1	5097.8	297.2	518.7	293.4

Source: Table 1614.1.1

BID = twice daily; PY = patient-year

The treatments represent the initial randomised study drug. All Tofacitinib is a summary of all patients who start on any tofacitinib dose as well as patients who switch from Placebo/Adalimumab to tofacitinib. Treatment duration calculated as treatment end date minus treatment start date plus 1.

Includes protocols A3921019, A3921025, A3921032, A3921035, A3921039, A3921040, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year data), A3921073, A3921129, A3921187, and A3921237.

Table 11. Clinical Trial Exposure by Age Group and Gender, Overall (Completed Rheumatoid Arthritis Phase 1, 2, 3, and Long-Term Extension Studies) (P123LTE)

Age Group	Tofacitinib 5 mg BID and 10 mg BID and 11 mg PR (N = 6961)					
	Male		Female		Total	
	Persons	Person Time (Years)	Persons	Person Time (Years)	Persons	Person Time (Years)
18 to <65	1266	3311.38	6110	16298.27	7376	19609.65
≥65	259	578.83	995	2272.71	1254	2851.54
≥75	25	34.86	133	222.50	158	257.36
Total	1525	3890.21	7105	18570.98	8630	22461.19

Source: Table 1614.1.1
BID = twice daily; PR = prolonged-release
Any subject that changed doses from 5 mg to 10 mg or vice versa between the qualifying and LTE study is counted twice in the Person column of tofacitinib 5 mg and tofacitinib 10 mg drug group. Accordingly, their time in either the qualifying or LTE or both is included in the Person Time column.
N represents unique subjects unique subjects from Phase 2, Phase 3, and LTE studies.
Includes protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215 and A3921237.
Final data 18 January 2019

Table 12. Clinical Trial Exposure by Dose, Rheumatoid Arthritis Phase 1, 2, 3, and Long-Term Extension Studies (P123LTE)

Dose of Exposure	Persons	Person Time (Years)
RA		
Tofacitinib 5 mg BID, 11 mg PR	4256	8576.30
Tofacitinib 10 mg BID	4374	13884.89
Tofacitinib 5 mg, 11 mg PR, 10 mg BID	8630	22461.19

Source: Table 1614.1.1
BID = twice daily; PR = prolonged-release
Any subject that changed doses from 5 mg to 10 mg or vice versa between the qualifying and LTE study is counted twice in the Person column of tofacitinib 5 mg and tofacitinib 10 mg drug group. Accordingly, their time in either the qualifying or LTE or both is included in the Person Time column.
Includes protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
Final data 18 January 2019

Table 13. Clinical Trial Exposure by Ethnic or Racial Origin, Overall (Completed Rheumatoid Arthritis Phase 1, 2, 3, and Long-Term Extension Studies) (P123LTE)

Ethnicity	Tofacitinib 5 mg BID and 10 mg BID and 11 mg PR (N = 6961)	
	Persons	Person Time (Years)
White	5475	14804.19
Black	260	580.05
Asian	2070	4914.81

Table 13. Clinical Trial Exposure by Ethnic or Racial Origin, Overall (Completed Rheumatoid Arthritis Phase 1, 2, 3, and Long-Term Extension Studies) (P123LTE)

Ethnicity	Tofacitinib 5 mg BID and 10 mg BID and 11 mg PR (N = 6961)	
	Persons	Person Time (Years)
Other	779	2116.34

Source: Table 1614.1.2
BID = twice daily; PR = prolonged-release
Any subject that changed doses from 5 mg to 10 mg or vice versa between the qualifying and LTE study is counted twice in the Person column of tofacitinib 5 mg and tofacitinib 10 mg drug group. Accordingly, their time in either the qualifying or LTE or both is included in the Person Time column.
N represents unique subjects from Phase 2, Phase 3, and LTE studies.
Includes protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (- year), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215 and A3921237.
Final data 18 January 2019

Table 14. Clinical Trial Exposure to Tofacitinib by Special Population[a] (Renal Impairment) in Rheumatoid Arthritis Studies (P123LTE)

Renal Impairment	Persons	Person Time[b] (Years)
Mild impairment: CrCl >50 and ≤80 mL/min	1506	4141.13
Moderate impairment: CrCl ≥30 and ≤50 mL/min	114	218.18
Severe impairment: CrCl <30 mL/min	2	8.46

a. Exposure is to any dose of tofacitinib.
b. Patients are counted only once if they participated in both Phase 2 or Phase 3 study and also a LTE study; however, their time in both the qualifying and LTE study is included in the person time column.
CrCl = creatinine clearance; LTE = long-term extension
Studies included: A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215 and A3921237.
Final data 18 January 2019
Source: Table 1614.1.3

Psoriatic Arthritis

No studies have been conducted using the tofacitinib PR formulation in PsA patients.

The PsA database includes data from 2 completed Phase 3 studies (A3921125 and A3921091) and a completed LTE study (A3921092). For the All PsA cohort (Phase 3 randomized controlled clinical studies and LTE study [P3LTE]), the number of subjects and PY of exposure are shown in Table 15. For tofacitinib average 5 mg BID and average 10 mg BID, 458 and 325 subjects and a median duration of treatment 1176 and 1024 days, respectively, contributed to a total of 2038.0 PY of exposure for the all tofacitinib group (Table 15). Table 16 provides exposure by age > or ≤65, and by gender. Table 17 provides exposure by race. Table 18 provides exposure by mild, moderate, or severe renal function. Please note, the below source tables for PsA refer to the final data from 31 July 2019.

Table 15. Number of Subjects and Drug Exposure by Treatment Duration All Psoriatic Arthritis (P3LTE)

	Average tofacitinib 5 mg BID	Average tofacitinib 10 mg BID	All tofacitinib
Number of subjects	458	325	783
Duration			
≤1 week	2	0	2
>1 week – 1 month	7	5	12
>1 month – 2 months	6	6	12
>2 months – 3 months	6	6	12
>3 months – 6 months	14	25	39
>6 months – 12 months	44	31	75
>12 months – 18 months	34	21	55
>18 months – 24 months	19	20	39
>24 months – 30 months	17	13	30
>30 months – 36 months	26	21	47
>36 months – 42 months	56	62	118
>42 months – 48 months	97	72	169
>48 months – 54 months	46	26	72
>54 months – 60 months	61	12	73
>60 months	23	5	28
Mean (days)	1009.8	866.5	950.3
Median (days)	1176	1024	1100
Range (days)	1 – 1737	12 – 1709	1 – 1737
Patient years of exposure	1266.7	771.2	2038.0

The duration is defined as the total number of dosing days from the first day of dosing up to and including the last day of each study treatment.
Average tofacitinib 5 mg: Subjects with an average total daily dose of <15 mg from Day 1 on tofacitinib
Average tofacitinib 10 mg: Subjects with an average total daily dose of > = 15 mg from Day 1 on tofacitinib
Includes protocols A3921091, A3921125 and A3921092. Includes all Tofacitinib exposed subjects.
BID = twice daily
Final data 31 July 2019
Source: Table 00118.C3.3.12.1, Table 00118.C3.3.13.3

Table 16. Psoriatic Arthritis Clinical Trial Exposure to Tofacitinib by Age and Gender, Psoriatic Arthritis (P3LTE)

Age Group (Years)	Male		Female		Total	
	N	PY	N	PY	N	PY
<65	326	871.0	385	990.5	711	1861.5
≥65	29	71.4	43	105.1	72	176.5
Total	355	942.4	428	1095.6	783	2038.0

N = number of subjects with any exposure; PY = patient years of exposure; LTE = long-term extension
PY is calculated as the sum of duration of tofacitinib exposure of qualifying and LTE studies. Any gap between the qualifying study and the LTE is not counted. Any missed doses within the qualifying or LTE are considered dosed.
Includes protocols A3921091, A3921125 and A3921092. Includes all tofacitinib exposed subjects.
Final data 31 July 2019
Source: Table 00124.C3.13.2.1.4

Table 17. Clinical Trial Exposure to Tofacitinib by Race, Psoriatic Arthritis (P3LTE)

Race	N	PY
White	739	1926.1
Black	3	6.7
Asian	23	60.1
Other	18	45.1
Total	783	2038.0

N = number of subjects with any exposure; PY = patient years of exposure; LTE = long-term extension
PY is calculated as the sum of duration of tofacitinib exposure of qualifying and LTE studies. Any gap between the qualifying study and the LTE is not counted. Any missed doses within the qualifying or LTE are considered dosed.
Includes protocols A3921091, A3921125 and A3921092. Includes all tofacitinib exposed subjects.
Final data 31 July 2019
Source: Table 00124.C3.13.2.1.5

Table 18. Clinical Trial Exposure to Tofacitinib by Renal Function Population: Psoriatic Arthritis (P3LTE)

Renal Impairment	Persons	Person Time (Years)
Mild impairment: CrCl > 50 and ≤ 80 mL / min	75	204.3
Moderate impairment: CrCl ≥ 30 and ≤ 50 mL/min	2	3.4
Severe impairment: CrCl < 30 mL/min	0	0.0

Exposure is to any dose of tofacitinib. CrCl = creatinine clearance; LTE = long-term extension.
Patients are counted only once if they participated in both phase 3 study and also a LTE study; however, their time in both qualifying and LTE study is included in the person time column.
Includes protocols A3921091, A3921125 and A3921092. Includes all tofacitinib exposed subjects.
Final data 31 July 2019
Source: Table 00118.C3.11.4.1

Ulcerative Colitis

The UC data includes a total of 1240 subjects with moderate-to-severe UC who received at least 1 dose of placebo, tofacitinib 5 mg BID, or tofacitinib 10 mg BID. Among these subjects, 1157 subjects received at least 1 dose of tofacitinib 5 mg or 10 mg BID with 2814.4 PY of drug exposure as of 24 August 2020. A total of 83 subjects received only placebo.

Duration of tofacitinib treatment by dose from Phase 2, Phase 3, long-term extension (P2P3LTE) UC studies is shown in Table 19. Clinical trial exposures by age group and gender, by race, and by category of renal impairment are shown in Table 20, Table 21, and Table 22, respectively.

In Table 19, data are presented by predominant dose groups. Since tofacitinib was administered as either 5 mg BID or 10 mg BID, subjects categorized to the predominant dose 5 mg BID group are subjects who received tofacitinib 5 mg BID during most of their treatment duration. Similarly, subjects categorized to the predominant dose 10 mg BID group are subjects who received tofacitinib 10 mg BID during most of their treatment duration.

Table 19. Duration of Treatment of Tofacitinib in P2P3LTE Studies in Ulcerative Colitis (5 mg BID or 10 mg BID)

Duration Category (Days)	Tofacitinib 10 mg BID Predominant dose (N = 956)	Tofacitinib 5 mg BID Predominant dose (N = 201)	Tofacitinib All (N = 1157)
1-56	86	1	87
57-112	171	2	173
113-168	118	5	123
169-224	23	10	33
225-280	28	8	36
281-336	19	3	22
337-392	24	5	29
393-448	22	4	26
449-504	9	5	14
505-560	12	3	15
561-616	16	3	19
617-672	11	6	17
673-728	9	2	11
729-784	12	4	16
785-840	14	2	16
841-896	12	0	12
897-952	8	2	10
953-1008	6	3	9
1009-1064	9	3	12
1065-1120	9	4	13
1121-1176	20	1	21
1177-1232	12	6	18
1233-1288	18	1	19
1289-1344	17	2	19
1345-1400	18	5	23
1401-1456	22	3	25
1457-1512	21	3	24
>1512	210	105	315
Total Patient-Years	2038.0	776.4	2814.4
Median Duration	427	1608	623
Mean	778.6	1410.7	888.4
SD	772.4	789	811.2
Range	1-2758	52-2850	1-2850

The duration is defined as the total number of dosing days from first to and including last day of each study treatment. Any gap or withholding of study drug treatment is not counted towards Actual Duration.
Final Data: 24 Aug 2020. Source: Table 14.6.1.c3b

Table 20. Clinical Trial Exposure by Age Group and Gender in the Tofacitinib All Group in P2P3LTE Studies in Ulcerative Colitis (Combined 5 mg BID + 10 mg BID)

	Male		Female		Total	
Age group (years)	Persons	Patient-years	Persons	Patient-years	Persons	Patient-years
18-<65	626	1502.67	454	1104.79	1080	2607.46
≥65	50	134.76	19	50.48	69	185.25

Table 20. Clinical Trial Exposure by Age Group and Gender in the Tofacitinib All Group in P2P3LTE Studies in Ulcerative Colitis (Combined 5 mg BID + 10 mg BID)

	Male		Female		Total	
≥75	3	13.19	5	8.48	8	21.66
Total	679	1650.62	478	1163.75	1157	2814.36

P2P3LTE = Phase 2, Phase 3, long-term extension
Exposure is not inclusive of any gaps or withholding of tofacitinib treatment
Studies included: A3921063, A3921094, A3921095, A3921096, A3921139
Final Data: 24 Aug 2020. Source: Table 417b.1

Table 21. Clinical Trial Exposure by Race in the Tofacitinib All Group in P2P3LTE in Ulcerative Colitis (Combined 5 mg BID + 10 mg BID)

	Persons	Patient-years
Asian	144	363.81
Black	10	21.44
White	927	2244.99
Other	42	110.04
Unspecified	34	74.07

P2P3LTE = Phase 2, Phase 3, long-term extension
Exposure is not inclusive of any gaps or withholding of tofacitinib treatment.
Studies included: A3921063, A3921094, A3921095, A3921096, A3921139
Final Data: 24 Aug 2020. Source: Table 417b.2

Table 22. Clinical Trial Exposure by Renal Impairment in the Tofacitinib All Group in P2P3LTE Studies in Ulcerative Colitis (Combined 5 mg BID + 10 mg BID)

Renal impairment	Persons	Patient-years
Mild impairment: CrCl>50 and =<80 mL/min	127	364.72
Moderate impairment: CrCl>= 30 and =<50 mL/min	9	16.87
Severe impairment: CrCl<30 mL/min	0	0.00

CrCl = creatinine clearance; P2P3LTE = Phase 2, Phase 3, long-term extension
Exposure is not inclusive of any gaps or withholding of tofacitinib treatment.
Studies included: A3921063, A3921094, A3921095, A3921096, A3921139
Final Data: 24 Aug 2020. Source: Table 417b.3

A total of 71 subjects received the 15 mg BID during the Phase 2 (49 subjects) and Phase 3 (22 subjects) induction studies. Exposure to the 15 mg BID dose ranged from 4 – 65 days, with a mean of 55.5 days; the total exposure to the 15 mg BID dose was 10.8 patient-years (Table 23). Subjects did not receive 15 mg BID dose during the maintenance study or the open label LTE study.

Table 23. Duration of Treatment of Tofacitinib in P2 and P3 Induction Studies in Ulcerative Colitis (Subjects Who Received 15 mg BID)

Duration of Exposure[a]	Tofacitinib 15 mg BID (n = 71)	
	Persons	Person Time[b] (Years)
Less than 1 week	71	1.16
At least ≥ 1 week	69	1.32
At least ≥ 2 weeks	69	1.32
At least ≥ 3 weeks	68	1.29
At least ≥ 4 weeks	66	1.26
At least ≥ 5 weeks	66	1.25
At least ≥ 6 weeks	65	1.25
At least ≥ 7 weeks	65	1.24
At least ≥ 8 weeks	60	0.65
At least ≥ 9 weeks	13	0.07
Mean (SD) (days)	55.5 (12.1)	
Median (days)	57	
Range (min, max) (days)	4-65	
Total PY	10.8	

BID = twice daily; max = maximum; min = minimum; n = number; P2 = Phase 2; P3 = Phase 3; PY = patient-year; SD = standard deviation

a. Exposure is not inclusive of any gaps or withholding of tofacitinib treatment.

b. Person Time in each of the duration of exposure rows is incremental and unique; thus, does not include the duration (years) of previous time intervals.

Studies included: A3921063, A3921094, and A3921095

Final data: 24 Dec 2017. Source: Tables 237a.35.1, 237a.35

Juvenile Idiopathic Arthritis (pJIA and Juvenile PsA)

The JIA clinical development program was designed to evaluate 2 formulations of tofacitinib: oral immediate release tablet (5 mg BID) and tofacitinib oral solution (1 mg/mL, weight-based dosed, BID), for subjects with a body weight <40 kg to achieve comparable AUC for the treatment of subjects with JIA, age 2 years to <18 years. The studies included a completed Phase 1 pharmacokinetic (PK) Study A3921103 in subjects with JIA, a completed Phase 3 pivotal Study A3921104, and an on-going LTE Study A3921145 for subjects with JIA who previously participated in Studies A3921103 and A3921104. The available safety data from Study A3921145 interim data cut of 04 June 2019 are included. All subjects that received at least 1 dose of tofacitinib in any of the 3 studies (A3921103, A3921104, and A3921145) are included in the Integrated Safety Analysis Population (ISAP).

In the integrated safety dataset, a total of 251 JIA subjects (65 male and 186 female) from 2 to <18 years of age were treated with 2 to 5 mg BID doses (based on weight) of tofacitinib 5 mg BID with or without concomitant MTX. All subjects received at least 1 dose of tofacitinib in any of the 3 studies (ISAP) giving an overall exposure of 351 PY and the mean duration of exposure as 511 days (median duration 485 days).

Table 24. Number of Subjects and Drug Exposure – Integrated Safety Analysis Population

Duration of Exposure	Number of Subjects	PY (Subject-Years)
At least 1 dose	251	351.41
≥1 month	249	351.33
≥3 months	235	349.25
≥6 months	216	342.98
≥12 months	173	311.19
≥18 months	111	236.18
≥24 months	57	148.56
≥36 months	14	57.97
≥42 months	14	57.97
≥48 months	9	40.79

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Exposure is defined as the number of days the patients were on tofacitinib, does not include the days off tofacitinib. Month = 28 days.
Source: Table JIA_RMP 1 (please note, the table naming and numbering convention used for the JIA source tables differ from those used for the other indications source tables)

Table 25. Clinical Trial Exposure to Tofacitinib by Age Group and Gender - Integrated Safety Analysis Population

Treatment		Tofacitinib 5 mg BID		
Age Group		Male	Female	Total
Newborn infants (0 to 27 days)	Number of subjects	0	0	0
	Exposure PY (subject-years)	0	0	0
Infants and toddlers (28 days to 23 months)	Number of subjects	0	0	0
	Exposure PY (subject-years)	0	0	0
Children (2 to 11 years)	Number of subjects	33	71	104
	Exposure PY (subject-years)	40.79	110.42	151.21
Adolescents (12 to 17 years)	Number of subjects	32	115	147
	Exposure PY (subject-years)	42.55	157.64	200.19
Total	Number of subjects	65	186	251
	Exposure PY (subject-years)	83.34	268.06	351.4

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Exposure is defined as the number of days the patients were on tofacitinib, does not include the days off tofacitinib.
Source: Table JIA_RMP 6 (please note, the table naming and numbering convention used for the JIA source tables differ from those used for the other indications source tables)

Table 26. Clinical Trial Exposure to Tofacitinib by Formulation – Integrated Safety Analysis Population

Treatment	Tofacitinib 5 mg BID			
Formulation	Solution	Tablet	Both (Switchers)	Total
Number of subjects	73	145	33	251
Exposure PY (subject-years)	89.93	195.09	66.38	351.4

Table 26. Clinical Trial Exposure to Tofacitinib by Formulation – Integrated Safety Analysis Population

Treatment	Tofacitinib 5 mg BID			
Formulation	Solution	Tablet	Both (Switchers)	Total

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Exposure is defined as the number of days the patients were on tofacitinib, does not include the days off tofacitinib.
Source: Table JIA_RMP 2 (please note, the table naming and numbering convention used for the JIA source tables differ from those used for the other indications source tables)

Table 27. Clinical Trial Exposure to Tofacitinib by Subtype of JIA - Integrated Safety Analysis Population

Treatment	Tofacitinib 5 mg BID						
Subtype of JIA	Extended Oligoarthritis	RF+ Polyarthritis	RF- Polyarthritis	Systemic JIA	Juvenile Psoriatic Arthritis	Enthesitis Related Arthritis	Total
Number of subjects	32	39	122	13	22	23	251
Exposure PY (subject-years)	44.19	50.16	186.8	12.04	28.59	29.63	351.41

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Exposure is defined as the number of days the patients were on tofacitinib, does not include the days off tofacitinib.
Source: Table JIA_RMP 5 (please note, the table naming and numbering convention used for the JIA source tables differ from those used for the other indications source tables)

Table 28. Clinical Trial Exposure to Tofacitinib by Race – Integrated Safety Analysis Population

Treatment	Tofacitinib 5 mg BID				
Race	White	Black or African American	Asian	Other	Total
Number of subjects	221	5	0	25	251
Exposure PY (subject-years)	316.54	6.91	0.00	27.95	351.4

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Exposure is defined as the number of days the patients were on tofacitinib, does not include the days off tofacitinib.
Source: Table JIA_RMP 3 (please note, the table naming and numbering convention used for the JIA source tables differ from those used for the other indications source tables)

Table 29. Clinical Trial Exposure to Tofacitinib by Renal Impairment – Integrated Safety Analysis Population

Treatment	Tofacitinib 5 mg BID			
Renal Impairment	**Mild**	**Moderate**	**Severe**	**Total**
Number of subjects	6	0	0	6
Exposure PY (subject-years)	7.02	0.00	0.00	7.02

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
Exposure is defined as the number of days the patients were on tofacitinib, does not include the days off tofacitinib.
Source: Table JIA_RMP 4 (please note, the table naming and numbering convention used for the JIA source tables differ from those used for the other indications source tables)

Ankylosing Spondylitis

No studies have been conducted using the tofacitinib PR formulation in AS patients. What follows is the AS clinical development programme for the immediate-release tablets.

The AS clinical development programme includes a completed Phase 2 dose-ranging study (A3921119) and a completed Phase 3 study (A3921120). In the Phase 2 study (A3921119), immediate-release tofacitinib was evaluated at doses of 2, 5, and 10 mg BID. In the Phase 3 study (A3921120) immediate-release tofacitinib was evaluated at 5 mg BID. Both A3921119 and A3921120 were randomised, placebo-controlled studies; the AS clinical development programme did not include LTE studies.

Throughout the RMP, "RCTs" (placebo-controlled cohort) refers to the "Tofa 5 mg BID" group, based on the integrated pooled data in A3921119 and A3921120 for up to 16 weeks. "All AS" (All Tofa cohort) refers to the integrated pooled data (using the 48-week final data), including the separate data for the "All Tofa 5 mg BID" group and "All Tofa" group (the "All Tofa" group includes patients exposed to 5 mg BID but also patients from study A3921119 who were exposed to 2 mg BID and to 10 mg BID). Please see the following tables for the tofacitinib treatment duration by dose groups (Table 30) as well as clinical trial exposures by age group and gender (Table 31), by race (Table 32), and by category of renal impairment (Table 33) in the AS clinical development programme.

Table 30. Treatment Exposure Duration – RCTs (Placebo-Controlled Cohort) and All AS (All Tofa Cohort)

Exposure Duration	Placebo-Controlled		All Tofa			
	Tofa 5 mg BID		All Tofa 5 mg BID (N=316)		All Tofa (N=420)	
	N	PY	N1	PY	N1	PY
At least one dose	185	52.77	316	208.9	420	232.98
≥1 month	183	52.71	314	208.84	416	232.91
≥3 months	170	49.81	297	205.22	375	224.24
≥6 months	NA	NA	253	193.83	253	193.83
≥12 months	NA	NA	108	100.46	108	100.46

N: Number of subjects included in the Safety Analysis Set; N1: Number of subjects included in the analysis; NA: not applicable; PY: Patient-Year (in subject-year).
Exposure duration in days = date of last dose - date of first dose +1. Any missed doses between subject's first dose and last dose are counted as dosed. The durations of exposure are standardized to subject-years by dividing the sum of exposure times in days by 365.25. One month is equivalent to 28 days.
For subjects randomised to Placebo →Tofa 5 mg BID in All Tofa cohort, the date of first dose refers to the date of first dose of tofacitinib treatment.
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C1.4.1-E, Table C2.4.1-E

Table 31. Treatment Exposure Duration by Age and Gender – All AS (All Tofa 5 mg BID and All Tofa)

Age (Years)	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
	Male		Female		Male		Female	
	N1	PY	N1	PY	N1	PY	N1	PY
<65	255	171.56	54	32.13	322	187.23	85	39.09
≥65	6	4.83	1	0.37	11	6.07	2	0.60

Exposure of duration of subjects who received at least one dose.
N: Number of subjects included in the Safety Analysis Set; N1: Number of subjects included in the analysis; PY: Patient-Year (in subject-year). One month is equivalent to 28 days.
Exposure duration in days = date of last dose - date of first dose +1. Any missed doses between subject's first dose and last dose are counted as dosed.
The durations of exposure are standardised to subject-years by dividing the sum of exposure times in days by 365.25.
All statistics are calculated through subject-year standardisation exposure duration.
For subjects randomised to Placebo →Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment.
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C2.7.3-E

Table 32. Treatment Exposure Duration by Race – All AS (All Tofa 5 mg BID and All Tofa)

Race	All Tofa 5 mg BID (N=316)		All Tofa (N=420)	
	N1	PY	N1	PY
White	252	166.17	334	184.90
Asian	63	41.81	85	47.15
Other	1	0.92	1	0.92

Exposure of duration of subjects who received at least one dose.
N: Number of subjects included in the Safety Analysis Set; N1: Number of subjects included in the analysis; PY: Patient-Year (in subject-year).
Exposure duration in days = date of last dose - date of first dose +1. Any missed doses between subject's first dose and last dose are counted as dosed. The durations of exposure are standardized to subject-years by dividing the sum of exposure times in days by 365.25.
All statistics are calculated through subject-year standardisation exposure duration.
For subjects randomized to Placebo → Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment.
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C2.7.2-E

Table 33. Treatment Exposure Duration by Renal Impairment – All AS (All Tofa 5 mg BID and All Tofa)

Renal impairment	All Tofa 5 mg BID (N=316)		All Tofa (N=420)	
	N1	PY	N1	PY
Normal: CrCl>80 mL/min	305	200.80	402	223.21
Mild impairment: CrCl>50 to ≤80 mL/min	11	8.10	18	9.77

N: Number of subjects included in the Safety Analysis Set; N1: Number of subjects in each analysis category.
PY = Patient-Year (in subject-year) of exposure.
Exposure duration in days = date of last dose - date of first dose +1. Any missed doses between subject's first dose and last dose are counted as dosed. The durations of exposure are standardized to subject-years by dividing the sum of exposure times in days by 365.25.
All statistics are calculated through subject-year standardisation exposure duration.
For subjects randomized to Placebo → Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment.
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C2.7.1-E

Module SIV. Populations Not Studied in Clinical Trials

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

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Exclusion Criteria with Respect to Infections	1. History: infected joint prosthesis (still in situ) 2. Infection requiring hospitalization, parenteral antimicrobial therapy, or judged clinically significant by investigator within 6 months prior to 1st dose (for AS: within 3 months) 3. History: recurrent (>1 episode) or disseminated (1 episode) HZ; or disseminated (1 episode) herpes simplex	Contraindication for active TB, serious infections such as sepsis, or OIs, patients with recurrent or complicated HZ may be at increased risk for reactivation.	No	Serious infections and HZ reactivation are not considered missing information as they are considered important identified risks.
Exclusion Criteria with Respect to Hepatic Impairment	Severe, progressive, or uncontrolled hepatic diseases	Contraindication for severe hepatic impairment.	Yes	
Pregnancy and Breastfeeding	Pregnant or lactating women	Contraindication in pregnancy and lactation.	Yes, even though the use of tofacitinib during pregnancy is contraindicated, all pregnancies can't be prevented.	
Prohibited Medications (All Studies), Prohibited Medications (Protocol Specific), and Medications Requiring	Rituximab or other selective B lymphocyte depleting agents, unless discontinued >1 year prior to 1st dose and normal CD19/20 count: experimental lymphocyte depleting agents [eg, alemtuzumab (Campath®), alkylating agents (eg, cyclophosphamide or	These agents may have long-term immunosuppressive or other know or unknown effects that could put patients enrolling in clinical studies	No	Use of tofacitinib with biologic DMARDs or potent immunosuppressives is not considered missing information as it is an important potential risk.

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Specific Discontinuation Periods	chlorambucil); total lymphoid irradiation, etc. • Following to be discontinued ≥4 weeks prior to 1st dose: IA, IM, IV corticosteroids; Ciclosporin, tacrolimus, and azathioprine; Prosorba Device/Column; Experimental NSAIDS. Any investigational or marketed treatment not mentioned elsewhere (discontinued ≥4 weeks or 5 half-lives, whichever longer)	and receiving study drug (tofacitinib or active control) at higher risk for adverse effects or otherwise affect study result interpretation.		
	RA: • Discontinued 4 weeks prior to the first dose of study drug: anakinra (Kineret®) and etanercept (Enbrel®). • Discontinued for 6 weeks prior to first dose of study drug: adalimumab (Humira®). • Discontinued 8 weeks prior to the first dose of study drug: infliximab (Remicade®). • Discontinued 10 weeks prior to the first dose of study drug: certolizumab pegol (Cimizia®) (A3921045); golimumab (SIMPONI®) (A3921045, A3921044). • Discontinued 12 weeks prior to first dose of study drug: abatacept			

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	(Orencia®), tocilizumab (Actemra®). For A3921032, A3921044: certolizumab pegol (Cimzia®) and golimumab (SIMPONI®) (A3921032).			
	PsA: Any prior treatment with non-B cell-specific lymphocyte depleting agents/therapies [e.g, alemtuzumab (Campath®), efalizumab (Raptiva®)], alkylating agents (eg, cyclophosphamide or chlorambucil), or total lymphoid irradiation. Subjects who have received rituximab or other selective B-lymphocyte depleting agents (including experimental agents) are eligible if they have not received such therapy for at least 1 year prior to first dose of study drug and have normal CD19/20+ counts by FACS analysis.			

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	UC: Any of the following therapy within the designated time period: • Azathioprine, 6-mercaptopurine, or methotrexate within 2 weeks prior to baseline; • TNFi therapy (eg, infliximab, adalimumab, or certolizumab) within 8 weeks prior to baseline; • Cyclosporine, mycophenolate mofetil/mycophenolic acid, or tacrolimus within 4 weeks prior to baseline; • Interferon therapy within 8 weeks prior to baseline; • IV corticosteroids within 2 weeks prior to baseline; • Rectally administered formulation of corticosteroids or 5-ASA within 2 weeks prior to baseline; • Anti-adhesion molecule therapy taken within 1 year (eg, natalizumab or any investigational anti-adhesion molecule therapy);			

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	• Subjects with prior treatment with lymphocyte-depleting agents/therapies. Subjects who received rituximab or other selective B lymphocyte depleting agents were eligible if they had not received such therapy for at least 1 year prior to baseline; • Other marketed immunosuppressants or biologics with immunomodulatory properties within 3 months prior to baseline.			
	JIA: Subjects who have previously failed more than 3 biologic therapies (with different mechanisms of action) for JIA. Prior treatment with non B cell-specific lymphocyte depleting agents/therapies (eg, almetuzumab, alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc.). Subjects who have received rituximab or other selective B lymphocyte depleting agents (including experimental agents) are eligible if they have not received such therapy for at least 1 year prior to study baseline and have normal CD19/20+ counts by FACS analysis.			

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	Use of certain biologic and non-biologic DMARDs. For subjects with PsA, oral and topical medications and alternative treatments that could affect psoriasis are prohibited. This includes topical corticosteroids, tars, keratolytics, anthralin, vitamin D analogs, and retinoids which must be discontinued at least 2 weeks prior to first dose of study drug. Also prohibited is ultraviolet B (UVB) (narrowband or broadband) phototherapy that must be discontinued at least 2 weeks prior to first dose of study drug. Psoralens + ultraviolet A (UVA) phototherapy (PUVA) must be discontinued at least 4 weeks prior to first dose of study drug. AS: Subjects that have been exposed to or are currently receiving targeted synthetic DMARDS (including JAK inhibitors) or those currently on biological DMARDS, thalidomide (including previous use) and other prohibited concomitant medications noted in protocol. Any prior treatment with non-B cell specific lymphocyte depleting agents/therapies (eg, alemtuzamab, efalizumab), alkylating agents (eg, cyclophosphamide or chlorambucil), or total lymphoid irradiation.			

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	Drugs requiring discontinuation at least 7 days or 5 half-lives prior to first dose of study drug, whichever is longer: moderate or potent CYP3A4 inhibitors or (moderate or potent inhibitors and inducers of CYP3A for AS) potent CYP2C19 inhibitors. In pJIA studies subjects receiving potent and moderate CYP3A4 inhibitors or inducers were excluded.	Tofacitinib exposure is increased when coadministered with potent inhibitors of CYP3A4 (eg, ketoconazole) or when administration of one or more concomitant medications results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (eg, fluconazole).	No	Use of tofacitinib in combination with CYP3A4 or CYP2C19 clearly is not considered missing information as it is an important potential risk.
Renal Disorders	Estimated GFR <40 mL/min (Cockcroft-Gault calculation)	Patients with severe renal impairment have significantly higher tofacitinib exposure than patients with normal renal function or patients with mild or moderate renal impairment. Patients were randomised to tofacitinib dose without regard to their renal function; therefore, it was not appropriate to allow patients to participate when the tofacitinib dose could not be modified based on renal function.	Yes. Use in patients with moderate or severe renal impairment is missing information.	
Haematological and Biochemical Factors	1. RA: Hgb <9 g/dL or haematocrit <30%; White blood cell count $<3.0\times10^9$/L; ANC $<1.2\times10^9$/L, and Platelet count $<100\times10^9$/L, ALC $<0.5\times10^9$/L ($<500/mm^3$)	These exclusion criteria were applied to tofacitinib clinical studies to protect subject safety while the effects of tofacitinib on	No	Anaemia is not considered missing information as it is considered an important identified risk. Neutropenia and lymphopenia are not

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	PsA: Haemoglobin <10 g/dL; White blood cell count <3.0×10^9/L (<3000/mm^3); ANC ≤1.5×10^9/L(<1500/mm^3); ALC <1.0×10^9/L (<1000/mm^3); Platelet count <100×10^9/L (<100,000/mm^3). UC: Haemoglobin <9 g/dL, white blood cell count <3.0×10^9/L, ANC <1.2×10^9/L, ALC <0.5×10^9/L or platelet count <100×10^9/L JIA: Haemoglobin <10 g/dL or Hematocrit <33%; white blood cell count <3.0 × 10^9/L; neutrophil count <1.2 × 10^9/L; platelet count <100 × 10^9/L; lymphocyte count <0.75 × 10^9/L. JIA: Haemoglobin <10 g/dL or Hematocrit <33%; white blood cell count <3.0 × 10^9/L; neutrophil count <1.2 × 10^9/L; platelet count <100 × 10^9/L; lymphocyte count <0.75 × 10^9/L. AS: Haemoglobin <10 g/dL; White blood cell count <3.0×10^9/L (<3000/mm^3); ANC <1.5×10^9/L (<1500/mm^3); ALC <1.0×10^9/L (<1000/mm^3); Platelet count <100×10^9/L (<100,000/mm^3).	these haematologic parameters were further explored and understood.		considered missing information as they are listed in Section 4.2, Section 4.4, and Section 4.8 of the SmPC.

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	2. RA and PsA: AST or ALT >1.5 × upper limit for RA and PsA of the reference range at screening or uncontrolled clinically significant laboratory abnormality affecting study data or subject's participation. UC: Total bilirubin, AST or ALT >1.5 × upper limit of the reference range at screening JIA: AST or ALT ≥1.5 times the upper limit of normal or any other clinically significant laboratory abnormality. AS: Total bilirubin, AST or ALT more than 1.5 times the upper limit of normal at screening visit.	These exclusion criteria were applied to tofacitinib clinical studies to protect subject safety while the effects of tofacitinib on hepatic parameters were further explored and understood.	No	Use in patients with elevated transaminases is not considered missing information. According to the SmPC, Xeljanz is indicated in patients with mild to moderate hepatic impairment, enabling further characterisation of this concern through routine measures. Use in patients with mild, moderate, or severe hepatic impairment is also listed as missing information, and Transaminase elevation is listed as identified risk.
Other	1. Japanese subjects: findings suggestive of serious lung disease, eg, interstitial pneumonia; including serological testing with beta D glucan and KL-6	This exclusion criterion was specific for Japanese patients and addressed the higher incidence of serious lung disease in this population. This exclusion was not applied to the majority of the tofacitinib clinical study population.	No	ILD is not considered missing information as it is an important potential risk.
	2. RA and JIA: History of other rheumatic auto-immune disease other than Sjogren's syndrome is not considered missing information	This exclusion criterion was used to ensure that the study populations were specific to RA, PsA, and UC and that interpretation of study data	No	Patients with other auto-immune disease are not part of the targeted population for tofacitinib treatment.

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	because of a different safety profile is not expected in this population. PsA: any autoimmune rheumatic disease other than PsA (including systemic lupus erythematosis, mixed connective tissue disease, scleroderma, polymyositis) or known diagnosis of fibromyalgia, without approval by Sponsor. Prior history of or current rheumatic inflammatory disease other than PsA (eg, gout, reactive arthritis, chronic Lyme disease) without approval by Sponsor. UC: Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn's disease; subjects with disease limited to distal 15 cm; subjects without previous treatment for UC (ie, treatment-naïve). AS: History of any other autoimmune rheumatic disease. History of known or suspected complete ankylosis of the spine.	would not be confounded by a mixed disease population.		
	3. Vaccination with live or attenuated vaccines within 6 weeks pre-dose, during treatment, or 6 weeks post-dose.	This exclusion criterion was included due to the risk of infection associated with the use of live vaccines in patients receiving drugs	Yes. The risk of infection associated with the use of live vaccines is considered missing information.	

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	JIA: Subjects without documented evidence of having received at least one dose of the varicella vaccine in countries where the vaccine is approved and standard of care or those who do not have evidence of prior exposure to varicella zoster virus (VZV) based on serological testing (ie, VZV IgG Ab).	with immunosuppressive activity.		
	4. History: malignancy except for adequately treated or excised non-metastatic basal or squamous cell skin cancer or cervical carcinoma in situ; History: lymphoproliferative disorder or signs or symptoms suggestive of current lymphatic disease	Drugs with immunosuppressive activity may have the potential to affect host defences against malignancies, and the adequacy of previous treatment can be difficult to determine. Thus, exclusion of patients with known previous malignancy was prudent while data were generated on the incidence and type of malignancies observed in patients treated with tofacitinib.	Yes, use in patients with current or a history of malignancy is considered missing information.	
	5. PsA and AS: A subject that is considered at increased risk for GI perforation (eg, patients with history of diverticulitis) by the Investigator or Sponsor.	This exclusion criterion was applied to tofacitinib clinical studies to protect subject safety, while noting the accuracy of historical information on the risk of GI perforation is often incomplete.	No	GI perforation is considered an important potential risk.

Table 34. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

	Exclusion Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	6. JIA: Active uveitis (according to Standardized Uveitis Nomenclature criteria) within 3 months of enrollment.	A secondary objective of study A3921104 was "To evaluate the efficacy of tofacitinib versus placebo for the treatment of signs and symptoms of JIA as measured by the occurrence of active uveitis (according to Standardized Uveitis Nomenclature criteria) in the double blind phase; therefore, exclusion of patients with active uveitis within 3 months of enrollment was done in order to accurately assess this endpoint.	No	There were events of uveitis reported in the study, and in other tofacitinib clinical trials; therefore, there are data on patients with uveitis treated with tofacitinib.

5-ASA = 5-aminosalicylic acid; Ab = antibody; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AS = ankylosing spondylitis; AST = aspartate aminotransferase; CYP = cytochrome P450; DMARD = disease-modifying anti-rheumatic drug; GFR = glomerular filtration rate; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IA = intraarticular; IgG = immunoglobulin G; ILD = interstitial lung disease; IM = intramuscular; IV = intravenous; JIA = juvenile idiopathic arthritis; NSAID = non-steroidal anti-inflammatory drug; OI = opportunistic infection; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SmPC = Summary of Product Characteristics; TB = tuberculosis; TNFi = tumour necrosis factor inhibitor; UC = ulcerative colitis; VZV = varicella zoster virus

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

While some rare events may still require more clinical trial exposure than that accrued to-date for tofacitinib, the clinical trial exposure to-date is sufficient for many rare events to have been observed. The sponsor is conducting long-term safety clinical trials to study prolonged exposure. Rates of events with long latency, such as malignancy and cardiovascular events are within the ranges reported for other RA therapies. As these events are not common, continued monitoring is appropriate. The sponsor is conducting a long-term active controlled safety trial.

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

Table 35. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women. Due to very limited information, MAH is unable to calculate exposure.
Breastfeeding women	Women should not breastfeed while being treated with tofacitinib. Due to very limited information, MAH is unable to calculate exposure.
Patients with relevant co-morbidities: Patients with hepatic impairment	There is limited safety information in patients with history of hepatic impairment from clinical trials. Not included in the clinical development programme.
Patients with renal impairment	As of 18 January 2019, there were 1506 persons (4141.13 person-time [years]) with mild renal impairment; 114 persons (218.18 person-time [years]) with moderate impairment; and 2 persons (8.46 person-time [years]) with severe impairment enrolled in the P123LTE studies in the All RA population. As of 31 July 2019, there were 75 persons (204.3 person-time [years]) with mild renal impairment; 2 persons (3.4 person-time [years]) with moderate impairment; and none with severe impairment enrolled in the P3LTE studies in the All PsA population. As of 24 August 2020, there were 127 persons (364.72 person-time [years]) with mild renal impairment; 9 persons (16.87 person-time [years]) with moderate impairment; and none with severe impairment enrolled in the P2P3LTE studies in the All UC population. As of 04 June 2019, there were 6 persons (7.02 person-time [years]) with mild renal impairment in the pJIA integrated safety analysis population. As of the final 10 September 2020 data-cut, there were 18 persons (9.77 person-time [years]) with mild renal impairment in the AS immediate-release tablets clinical programme.

Table 35. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Patients with other relevant co-morbidity	There is limited clinical experience in patients with mild or moderate hepatic impairment. Not included in the clinical development programme. Patients with a history of malignancy except for adequately treated or excised non-metastatic basal or squamous cell skin cancer or cervical carcinoma in situ were excluded from the tofacitinib clinical studies. In addition, patients with a history of lymphoproliferative disorder or signs or symptoms suggestive of current lymphatic disease or patients with other rheumatic auto-immune disease other than Sjogren's syndrome were excluded from the clinical studies. Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	The indication for tofacitinib, in combination with MTX, is for moderate to severe active RA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. Patients with moderate to severe active RA were enrolled in the RA clinical trials. Tofacitinib has also been studied in healthy volunteers. The indication for PsA for tofacitinib, in combination with MTX, is the treatment of active PsA in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. Subjects enrolled in the PsA clinical trials must have had ≥3 tender/painful joints and ≥3 swollen joints and must have had active plaque psoriasis at screening. The indication for UC is the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent. Patients with moderately to severely active UC were enrolled in the UC induction studies, and patients with clinical response (including patients in remission) were enrolled in the maintenance study. There is no information on induction treatment of patients with mild to moderate UC with tofacitinib. Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (RF+ or RF- polyarthritis and extended oligoarthritis), and juvenile PsA in patients 2 years of age and older, who have responded inadequately to conventional therapy with DMARDs. In the 2 pivotal Phase 3 studies, subjects with polyarticular course JIA or PsA/enthesitis-related arthritis must have had a minimum of 5 and 3 active joints, respectively, at screening and baseline to be eligible for study entry. The indication for AS is the treatment of adult patients with active AS who have responded inadequately to conventional therapy. In clinical trials with immediate-release tablets, active AS was defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 and back pain score (BASDAI Question 2) of ≥4.
Immuno-compromised patients	Not included in the clinical development programme.

Table 35. Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Population with relevant different ethnic origin	In the tofacitinib development programme, there was evidence to suggest that there was an increased risk of HZ in Asian patients (specifically, in Japanese and Korean patients). A numerically higher IR of ILD was also observed in Asian RA patients as compared to the risk reported in RA patients of other races. There were 2070 Asian patients (4914.81 person-time [years]) enrolled in the P123LTE studies in the All RA population. As of 31 July 2019, 38 Asian patients (59.7 person-time [years]) enrolled in the P3LTE studies in the All PsA population. As of 24 August 2020, 144 Asian patients (363.81 person-time [years]) enrolled in the P2P3LTE studies in the All UC population. As of the final 10 September 2020 data-cut, 85 Asian patients (47.15 person-time [years]) participated in the AS immediate-release tablets clinical programme.
Subpopulations carrying known and relevant genetic polymorphisms	The clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal elimination of parent drug. The hepatic metabolism is primarily via CYP3A4 (approximately 53%) with a minor contribution from CYP2C19 (approximately 17%). Genotypic analysis was done for the *2, *3, *4, *5, and *17 alleles of the CYP2C19 gene based on data from a healthy volunteer study. Sixty (60) subjects were classified as either PMs: carriers of CYP2C19*2/*2, CYP2C19*2/*3 or CYP2C19*3/*3 alleles, UMs: CYP2C19*17/*17 alleles or EMs: all other alleles. The mean C_{max} and $AUC_{(0-\infty)}$ values in the PMs were approximately 15% and 17% greater, respectively, than those in the EMs indicating that genetic polymorphisms in CYP2C19 are unlikely to result in clinically relevant increases in the systemic exposure of tofacitinib.
Other Children	Children and adolescents below the age of 18 years were included in the clinical programme for JIA. As of June 2019, 251 paediatric patients with JIA were exposed to tofacitinib in the completed and on-going JIA studies in the integrated safety analysis population. The safety and benefits of tofacitinib in children or adolescents have not yet been established in patients less than 2 years of age.
Elderly	As of 18 January 2019, 1270 RA patients enrolled in the P123LTE studies in the All RA population were 65 years of age or older. In the PsA programme, as of 31 July 2019, there were 72 patients enrolled who were 65 years of age or older. As of 24 August 2020, out of 1157 subjects who received at least 1 dose of tofacitinib 5 mg BID or 10 mg BID in the UC programme, 77 subjects (6.7%) were 65 years of age or older. As of the final 10 September 2020 data-cut, 13 elderly subjects had participated in the AS immediate-release tablets clinical programme.

AS = ankylosing spondylitis; AUC = area under the concentration-time curve; BID = twice daily; C_{max} = peak plasma concentration; DMARD = disease-modifying anti-rheumatic drug; EM = extensive metaboliser; HZ = herpes zoster; ILD = interstitial lung disease; IR = incidence rate; JIA = juvenile idiopathic arthritis; LTE = long term extension; MAH = marketing authorisation holder; MTX = methotrexate; PM = poor metaboliser; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RF = rheumatoid factor; UM = ultra-extensive metaboliser

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

V.1.1. Method Used to Calculate Exposure

The cumulative worldwide exposure to tofacitinib since product approval is estimated to be 837,695 patient-years.

The worldwide estimate is based on audited standard units of tofacitinib from IQVIA Health's Database. The data were extrapolated for the fourth quarter of 2023 by taking the average of previous 4 quarters and pro-rated to the end of the current reporting period. The average dose (AVDOS) is as follows:

- the AVDOS of 2 units daily for the 5 mg and 10 mg tablets; and the 5 mg/5 mL oral solution
- the AVDOS of 1 unit daily for the 11 mg and 22 mg prolonged-release tablets

The exposure number was calculated by adding up the individual patient-years based on product formulation. The AVDOS was used to convert SUs into patient-days (days of therapy) and further divided by 365.25 (days in a year) to obtain patient-years. Allocation of the patient population by indication, gender, age, and dose is derived through prescription share calculations from IQVIA Health's Prescriber Insights database. Patient-years exposure by region is based on SU sales by country from the database.

Note that the following are important considerations:

- With the release of 1Q23 data, IQVIA was able to adapt the data from NMTA for US and Puerto Rico to reflect the paediatric population age breakdown according to the ICH E11 (R1) recommendation instead of the prior 5-year age bands presented in the prior 1-year PSUR. Consequently, separate exposure tables by age for US/Puerto Rico and the Rest of the World are no longer necessary. There was no impact on the elderly population aged >65 years.
- The patient-years metric is rounded and does not represent unique patient counts.

Cumulative estimated exposure by indication, region, dose, gender, and age group based on data provided by IQVIA Health Prescriber Insights Medical from 06 November 2012 (the international birth date) through the third quarter of 2023 and extrapolated to the end of the reporting interval (estimated region breakdown based on Pfizer internal sales data) is summarised in Table 36.

V.1.2. Exposure

Table 36. Cumulative Estimated Exposure for Tofacitinib (patient-years) from Marketing Experience (06 November 2012 through 15 February 2024) – Patient Years

Indication	Age (years)			Region				Gender		Dose				
	0-16	17-65	>65	EU	[redacted]	NA	ROW	F	M	5 mg	5 mg/ 5 mL	10 mg	11 mg	22 mg
RA[a]	18	328,143	294,526	123,166	52,683	310,191	159,698	483,771	138,916	591,278	-	15,921	15,489	-
PsA[b]	11	22,993	6938	25,722	-	37,406	13,494	12,531	17,411	22,054	-	3915	3974	-
AS	-	1356	31	1681	-	2989	314	432	955	329	-	853	205	-
UC	10	139,907	7354	29,157	17,507	30,883	4023	79,012	68,260	139,809	-	7273	104	86
Juvenile arthritis	599	893	-	1869	-	1284	361	758	734	1297	20	70	104	-
Total Other	803	27,518	6594	11,467	2361	421	11,019	27,501	7414	32,018	-	2455	442	-

a. RA indication includes a combination of patients diagnosed with both seropositive RA and Other RA

b. PsO is included in the PsA indication

Note: Patient-year data in table rounded to nearest whole number.

Module SVI. Additional EU Requirements for the Safety Specification

SVI.1. Potential for Misuse for Illegal Purposes

Given the mechanism of action of tofacitinib and the lack of reported pleasurable effects on the central nervous system, physiological or psychological dependency and resulting misuse for illegal purposes are not expected to occur with this medicinal product. Tofacitinib has no known attributes that make it attractive for intentional overdose or illegal use. Cumulatively through 28 February 2023, there were no spontaneous reports in the safety database indicative of misuse for illegal purposes with tofacitinib.

Module SVII. Identified and Potential Risks

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

Safety concerns in the initial RMP for the RA indication dated 02 February 2017 (version 1.3) are provided in Table 37 below.

Table 37. Summary of Safety Concerns in Initial RMP Submission (Immediate Release formulation)

Summary of Safety concerns	
Important identified risks	Serious and other important infections
	Herpes zoster reactivation
	Decrease in neutrophil counts and neutropenia
	Decrease in lymphocyte counts and lymphopenia
	Decrease in haemoglobin levels and anaemia
	Lipid elevations and hyperlipidaemia
	Nonmelanoma skin cancer
	Transaminase elevation and potential for drug-induced liver injury
Important potential risks	Malignancy
	Cardiovascular risk
	Gastrointestinal perforation
	Interstitial lung disease
	Progressive multifocal leukoencephalopathy
	Increased immunosuppression when used in combination with biologic DMARDs and immunosuppressants including B lymphocyte depleting agents
	Increased risk of adverse events when tofacitinib is administered in combination with MTX
	Primary viral infection following live vaccination
	Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors
	Off-label use including children with JIA
	Higher incidence and severity of adverse events in the elderly
Missing information	Effects on pregnancy and the foetus
	Use in breastfeeding
	Effect on vaccination efficacy and the use of live/attenuated vaccines
	Use in paediatric patients
	Use in RA patients with mild, moderate, or severe hepatic impairment
	Use in RA patients with moderate or severe renal impairment
	Use in patients with evidence of hepatitis B or hepatitis C infection
	Use in patients with elevated transaminases
	Use in patients with malignancy

CYP = cytochrome P450; DMARD = disease-modifying antirheumatic drug; JIA-juvenile idiopathic arthritis; MTX = methotrexate; RA = rheumatoid arthritis

VII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

VII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

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

None.

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

The important identified risks for all formulations discussed include venous thromboembolism (deep vein thrombosis [DVT]/pulmonary embolism [PE]); serious and other important infections; herpes zoster (HZ) reactivation; lung cancer; lymphoma; myocardial infarction; decrease in haemoglobin (Hgb) levels and anaemia; non-melanoma skin cancer (NMSC); transaminase elevation and potential for drug-induced liver injury (DILI); and higher incidence and severity of AEs in the elderly (please note, not applicable for JIA).

The important potential risks for all formulations include malignancy; cardiovascular risk (excl MI); gastrointestinal perforation, interstitial lung disease (ILD), progressive multifocal leukoencephalopathy (PML); all-cause mortality; fractures; increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients; and primary viral infection following live vaccination.

Missing information for all formulations include effects on pregnancy and the foetus, use in breastfeeding, effect on vaccination efficacy and the use of live/attenuated vaccines, use in patients with mild, moderate, or severe hepatic impairment, use in patients with moderate or severe renal impairment, use in patients with evidence of hepatitis B or hepatitis C infection, use in patients with malignancy. and long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances).

For the RA clinical development programme, data from the P234 RCTs (immediate-release) and the All RA populations (P123LTE, immediate-release and PR) is final as of 18 January 2019 (this excludes study A3921133). The clinical trial information for the PR formulation (including studies A3921215 and A3921192) provides data from relatively small populations over a short time period (12 and 48 weeks, respectively). Neither study is controlled with respect to tofacitinib (i.e., neither placebo-controlled nor active comparator controlled.

Please see Annex 7 for safety information from these studies. Data from these studies is incorporated into P123LTE.

For the PsA clinical development programme, the data from the P3 (randomised controlled trials, RCTs) and All PsA populations is final as of 31 July 2019. RCTs (Phase 3 studies) included A3921125 and A3921091. All PsA (P3LTE studies) included A3921125, A3921091, and the LTE study A3921092. Data from the double-blind placebo-controlled clinical trial A3921234, conducted in China, is excluded.

For the UC clinical development programme, all P2P3 induction and P3 maintenance studies have been completed. The 24 August 2020 final data is provided for the All UC P2P3LTE population. RCTs (P2P3 induction studies) included A3921063, a Phase 2 study, and A3921094 and A3921095, Phase 3 studies. For adjudicated endpoints, incidence rates are based on data from Phase 3 studies, because data from A3921063 was not adjudicated. The P2P3 induction studies included 10 mg BID but did not include 5 mg BID. RCTs (Phase 3 maintenance study) included only A3921096. The All UC data (P2P3LTE) studies included A3921063, A3921094, A3921095, A3921096, and A3921139.

The JIA clinical development programme integrated safety dataset includes a completed Phase 1 PK study (A3921103), a completed Phase 3 study (A3921104), and an on-going LTE study (A3921145), for which the data cut-off date was 04 June 2019.

For the AS clinical development programme, RCTs (placebo-controlled cohort: “Tofa 5 mg BID” group) All AS (All Tofa cohort: “All Tofa 5 mg BID” and “All Tofa” groups) datasets are final as of 10 September 2020. RCTs (placebo-controlled cohort: “Tofa 5 mg BID” group) is based on the integrated pooled data in A3921119 and A3921120 for up to 16 weeks. All AS (“All Tofa 5 mg BID” and “All Tofa” groups) is based on the integrated pooled data using the 48-week dataset (final data), where separate data are available for the “All Tofa 5 mg BID” group and the “All Tofa” group, which includes not only the patients exposed to 5 mg BID but also the A3921119 patients exposed to 2 mg BID and to 10 mg BID.

For the clinical development programmes, for both RCT and All Tofa Cohort, incidence rate (IR) estimates and the corresponding number (%) of subjects with an event are calculated by inclusion of events occurring up to 28 days beyond the last dose. Exposure (as PY) is defined as the total follow up time calculated up to the day of the first event within the event counting period for subjects with the event or the last dose day plus a risk period of up to 28 days beyond the last dose for subjects without events. These definitions were chosen because reporting to the company safety database may occur at any time regardless of the time elapsed from the last administration of study drug or since study completion. Inclusion of all events without regard to elapsed time may inflate IR estimations as the exposure time (denominator) is not similarly increased.

The safety cut-off date for the post-marketing database update was 05 November 2021.

Following the conclusion of the US Corrona RA Registry A3921205 study, the results were incorporated under the safety concerns in the RMP that were addressed in the study: VTE

(DVT/PE), serious infections events, HZ, NMSC, malignancy, lung cancer, lymphoma, MACE, myocardial infarction, GI perforation, PML, all-cause mortality, increased risk of AEs when tofacitinib is administered in combination with MTX in RA patients, and higher incidence and severity of AEs in the elderly.

A datacut of 31 March 2018 was a priori specified as the cut point for events with risk during or very proximate to exposure (acute risk events). The study was extended to use a datacut of 31 January 2019, which was used for longer latency events (referred to throughout as "latent events") (malignancies, NMSC, and death for which risk may continue after discontinuation), to allow for a larger number of events to accrue.

In this study, the full sample cohorts included All RA patients, 18 years of age and older, who initiated tofacitinib or bDMARD. Subpopulation analyses included patients with moderate-to-severe disease severity and patients with moderate-to-severe disease, age ≥50, with at least one CV risk factor.

The final results from Study A3921133, a prospective, randomised, open-label study in adult patients with moderate to severe RA evaluating the safety of tofacitinib 5 mg BID and tofacitinib 10 mg BID compared to a TNFi, are included for safety events of interest. The IR estimates and the corresponding number (%) of subjects with an event are calculated by inclusion of events occurring up to 28 days beyond the last dose unless otherwise noted. PY exposure is defined as the total follow up time calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or to the last contact date. For MACE and its components, a risk period of 60 days beyond the last dose (the primary censoring time) was also used, where noted. For malignancies excluding NMSC and its subtypes, a risk period of total time (the primary censoring time) was also used, where noted.

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

VII.3.1.1. Important Identified Risks

VII.3.1.1.1. Venous Thromboembolism (DVT/PE)

VII.3.1.1.1.1. Potential mechanisms

Unknown.

VII.3.1.1.1.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.1.1.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA*:* In controlled studies (excluding A3921133), the rate of PE over 0-3 months in the 5 mg twice daily and 10 mg twice daily tofacitinib groups was 0.00 and 0.00 patients with events per 100 patient-years, respectively, compared to 0.40 patients with events per 100 patient-years in the placebo group. The rate for DVT over 0-3 months the 5 mg twice daily and 10

mg twice daily tofacitinib groups was 0.00 and 0.21 patients with events per 100 patient-years, respectively, compared to 0.40 patients with events per 100 patient-years in the placebo group.

In randomised studies of 6-, 12-, or 24-month duration (excluding A3921133), the rate of PE in the 5 mg twice daily and 10 mg twice daily tofacitinib groups was 0.12 and 0.15 patients with events per 100 patient-years, respectively. The rate of DVT in the 5 mg twice daily and 10 mg twice daily tofacitinib groups was 0.15 and 0.10 patients with events per 100 patient-years, respectively.

In the long-term safety all exposure population (integrated completed Phase 1, 2, 3 and LTE studies excluding A3921133), the rate of PE in the 5 mg twice daily and 10 mg twice daily tofacitinib groups was 0.12 and 0.13 patients with events per 100 patient-years, respectively. The rate of DVT in the 5 mg twice daily and 10 mg twice daily tofacitinib groups was 0.17 and 0.15 patients with events per 100 patient-years, respectively.

A3921133 final data: The IRs per 100 PY (95% CI) of adjudicated PE the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.17 (0.08, 0.33), 0.50 (0.32, 0.74), 0.33 (0.23, 0.46), 0.06 (0.01, 0.17).

The IRs per 100 PY (95% CI) of adjudicated DVT for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.21 (0.11, 0.38), 0.31 (0.17, 0.51), 0.26 (0.17, 0.38), 0.14 (0.06, 0.29).

The IRs per 100 PY (95% CI) of adjudicated venous thromboembolism for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.33 (0.19, 0.53), 0.70 (0.49, 0.99), 0.51 (0.38, 0.67), 0.20 (0.10, 0.37).

PsA: In the placebo-controlled studies (0-3 months) and randomised study period (0-12 months) there were no PE or DVT events. In the All PsA population, the IR (95% CI) per 100 PY of PE for the 5 mg and 10 mg dose groups and the combined 5 mg and 10 mg dose groups, respectively, were 0.08 (0.00, 0.43), 0.00 (0.00, 0.46), and 0.05 (0.00, 0.27). The IR (95% CI) per 100 PY of DVT for the 5 mg and 10 mg dose groups and the combined 5 mg and 10 mg dose groups, respectively, were 0.00 (0.00, 0.28), 0.13 (0.00, 0.70), and 0.05 (0.00, 0.27).

UC: In the placebo-controlled studies (0-3 months) and randomised study period (0-24 months) there were no PE or DVT events in the tofacitinib groups. In the All UC population, the IR (95% CI) per 100 PY of PE for the 5 mg and 10 mg dose groups and the combined 5 mg and 10 mg dose groups, respectively, were 0.00 (0.00, 0.46), 0.24 (0.08, 0.55), and 0.17 (0.06, 0.40). The IR (95% CI) per 100 PY of DVT for the 5 mg and 10 mg dose groups and the combined 5 mg and 10 mg dose groups, respectively, were 0.00 (0.00, 0.46), 0.05 (0.00, 0.26), and 0.03 (0.00, 0.19).

JIA: No VTE (DVT or PE) events were observed in the JIA population.

AS: No VTE (DVT or PE) events have been reported in the AS clinical development programme.

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: In the full sample (i.e., untrimmed/unmatched), crude incidence rates of DVT, PE, and DVT or PE were similar among tofacitinib and bDMARD initiators with overlapping 95% CI. Please see table below for the crude rates and 95% CI for safety events of interest (acute exposure) among eligible RA patients initiating tofacitinib or bDMARD.

Table 38. Crude Rates (per 100 PY) and 95% CI for DVT or PE, DVT, or PE Among Eligible RA Patients Initiating Tofacitinib or bDMARD (31 January 2019, Primary Analyses)

Acute Exposure	31 January 2019 Datacut									
	Tofacitinib					bDMARD				
	N	PY	Rate	95% LL	95% UL	N	PY	Rate	95% LL	95% UL
VTE (DVT or PE)	9	3145	0.29	0.13	0.54	41	12832	0.32	0.23	0.43
DVT	4	3150	0.13	0.03	0.33	20	12851	0.16	0.10	0.24
PE	6	3147	0.19	0.07	0.41	24	12849	0.19	0.12	0.28

bDMARD=biologic disease modifying antirheumatic drug; DVT=deep vein thrombosis; LL=lower limit; N=count; PE=pulmonary embolism; PY=person-years; RA=rheumatoid arthritis; UL=upper limit; VTE=venous thromboembolism
Corrona RA Registry (study A3921205) final report: Table 15, Table 24

Seriousness/outcome:

RA: In the All RA population (excluding A3921133), there were 31 pulmonary embolism cases, of which 27 were considered serious and 4 were considered non-serious. The outcomes were resolved (24), still present (2), and fatal (5). There were 37 DVT cases, of which 18 were considered serious and 19 were considered non-serious. The outcomes were resolved (34) and still present (3).

Study A3921133: The seriousness of adjudicated PE for the following treatment groups were:

- Tofacitinib 5 mg BID: serious (9), non-serious (0)
- Tofacitinib 10 mg BID: serious (22), non-serious (2)
- All Tofa: serious (31), non-serious (2)
- TNFi: serious (1), non-serious (2)

The outcomes for adjudicated PE for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (5), still present (4)
- Tofacitinib 10 mg BID: resolved (18), still present (4), death (2)

- All Tofa: resolved (23), still present (8), death (2)
- TNFi: resolved (3)

The seriousness of adjudicated DVT for the following treatment groups were:

- Tofacitinib 5 mg BID: serious (5), non-serious (6)
- Tofacitinib 10 mg BID: serious (8), non-serious (7)
- All Tofa: serious (13), non-serious (13)
- TNFi: serious (2), non-serious (5)

The outcomes for adjudicated DVT for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (9), still present (1), unknown (1)
- Tofacitinib 10 mg BID: resolved (12), still present (3)
- All Tofa: resolved (21), still present (4), unknown (1)
- TNFi: resolved (5), still present (2)

PsA: In the All PsA population, there was 1 pulmonary embolism case, which was considered serious and resolved. There was 1 DVT case, which was considered serious and resolved.

UC: In the All UC population, there were 5 pulmonary embolism cases, all considered serious. The outcomes were resolved (2) and still present (3). There was 1 DVT case, which was considered non-serious and resolved.

JIA: No VTE (DVT or PE) events were observed in the JIA population.

AS: Not applicable.

Post-Marketing:

Table 39. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Venous Thromboembolism (DVT/PE) (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Pulmonary embolism	527	527	220	24	140	4	27	332
Deep vein thrombosis	355	354	103	5	91	2	25	232
Pulmonary thrombosis	84	84	44	3	12	2	8	59
Embolism venous	32	32	2	2	4	0	1	25
Thrombophlebitis	26	12	5	0	8	0	1	17

Table 39. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Venous Thromboembolism (DVT/PE) (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Superficial vein thrombosis	19	10	2	0	3	1	0	15
Venous thrombosis limb	18	17	7	0	10	0	2	6
Retinal vein occlusion	15	15	0	0	4	1	3	7
Venous thrombosis	14	13	7	0	4	1	1	8
Portal vein thrombosis	12	12	4	0	2	0	2	8
Retinal vein thrombosis	9	6	0	0	1	0	1	7
Deep vein thrombosis postoperative	6	6	4	3	0	0	2	1
Cerebral venous sinus thrombosis	5	5	2	0	1	0	0	4
Pelvic venous thrombosis	5	5	3	0	3	0	0	2
All others	39	37	15	0	13	1	3	22
Total	1166	1135	418	37	296	12	76	745

DVT = deep vein thrombosis; H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PE = pulmonary embolism; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 40. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Venous Thromboembolism (DVT/PE) (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Pulmonary embolism	156	156	84	2	29	2	6	117
Deep vein thrombosis	106	106	47	1	21	0	3	81
Pulmonary thrombosis	58	58	34	0	11	0	9	38
Thrombophlebitis	4	2	0	0	2	0	0	2
Postoperative thrombosis	3	3	1	0	0	0	0	3
Venous occlusion	3	2	1	0	1	0	0	2
Venous thrombosis limb	3	3	1	0	1	0	1	1
All others	22	21	8	0	2	0	8	12
Total	355	351	176	3	67	2	27	256

DVT = deep vein thrombosis; H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PE = pulmonary embolism; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk:

RA: In the All RA population (excluding A3921133), 5 DVT cases were mild, 19 were moderate, and 13 were severe; 2 PE cases were mild, 11 were moderate, and 18 were severe.

Study A3921133: The severity of adjudicated PE for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (1), moderate (1), severe (7)

- Tofacitinib 10 mg BID: mild (1), moderate (7), severe (16)
- All Tofa: mild (2), moderate (8), severe (23)
- TNFi: moderate (3)

The severity of adjudicated DVT for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (2), moderate (7), severe (2)
- Tofacitinib 10 mg BID: mild (1), moderate (7), severe (7)
- All Tofa: mild (3), moderate (14), severe (9)
- TNFi: mild (1), moderate (4), severe (2)

PsA: In the All PsA population, 1 DVT case was severe; 1 PE case was severe.

UC: In the All UC population, 1 DVT case was moderate; 2 PE cases were moderate and 3 were severe.

JIA: No VTE (DVT or PE) events were observed in the JIA population.

AS: Not applicable.

VII.3.1.1.1.4. Risk factors and risk groups

Venous thromboembolism was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors in Study A3921133 (patients with RA aged 50 years and older with at least one CV risk factor). No differential risk factors were identified for the increased risk relative to TNF inhibitors.

Numerous VTE risk factors are known in the general population. These known VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (body mass index [BMI] ≥30), diabetes, hypertension, smoking status should also be considered.

Pediatric JIA patients can experience many of the risk factors seen in adults. In a review article it is noted that in children aged 2 to <18 years with JIA, cardiovascular risk factors including hypertension, dyslipidaemia and being less physically active are more frequent than in their healthy peers. JIA patients may also have other cardiovascular risk factors seen in adult RA such as obesity, diabetes, and smoking. JIA patients potentially could have other risk factors (e.g., adolescent contraceptive hormone use, major surgeries, immobilization, congenital and acquired thrombophilias),[276] which may increase their risk of such events. Published literature[277 278 279] suggest a higher prevalence of anticardiolipin antibodies positive, or elevated levels of coagulation factors in JIA patients compared with non-JIA

patients; however, these findings were not correlated with clinical features such as abnormal clotting test or anticardiolipin antibody syndrome. Data also suggest an increased risk of malignancy among JIA patients compared with non-JIA patients. In a retrospective cohort study based in the Swedish Cancer Register, the HR (95% CI) for all pediatric malignancies in JIA vs the general population was 1.43 (0.71-2.88).[280]

Summary of results from the US Corrona RA Registry A3921205: The overall number of VTE events in the tofacitinib group with moderate-to-severe disease was small and the rate [0.18 (0.04, 0.51)] was similar to the bDMARD group [0.32 (0.20, 0.47)]. The risk factors associated with VTE were generally similar between tofacitinib and bDMARD groups and were consistent with the known risk factors for VTE (e.g., advanced age). In patients with moderate-to-severe disease aged 50 years and older with at least one CV risk factor, the crude incidence rate (95% CI) was 0.22 (0.03, 0.78) in tofacitinib initiators compared with 0.51 (0.31, 0.80) for bDMARDs initiators.

VII.3.1.1.1.5. Preventability

Caution should be used in patients with risk factors for venous thromboembolism. Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known VTE, MACE and malignancy risk factors, unless there is no suitable alternative treatment available. For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥2 × ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib. Patients with signs and symptoms of venous thromboembolism should be urgently evaluated and tofacitinib should be discontinued in patients with suspected venous thromboembolism, regardless of dose or indication. Please see Section V.2 for the proposed additional risk minimisation measures for venous thromboembolism (DVT/PE).

VII.3.1.1.1.6. Impact on the risk-benefit balance of the product

Based on the established benefits of tofacitinib as described in the prescribing information where there is an approved indication and the list of routine and additional risk mitigation measures that are being proposed to manage the risk of venous thromboembolism (DVT/PE), given the determination that venous thromboembolism (DVT/PE) is an important identified risk, the benefit:risk balance for tofacitinib in treating patients with RA, PsA, UC, pJIA or juvenile PsA, and AS at the recommended doses remains favourable.

VII.3.1.1.1.7. Public health impact

Venous thromboembolism, comprised of DVT and PE, represents a global health concern. Up to 20% of patients with PE die from the event or shortly after. Other sequelae of PE can include pulmonary hypertension. With approximately 10 million cases occurring every year globally, it is the third leading vascular disease after myocardial infarction and stroke.[281] In 2007 it was reported that there were approximately 500,000 DVTs and 300,000 PEs every year across 6 European countries with a combined population of more than 300 million inhabitants.[282] Estimated incidence of pediatric VTE has ranged from 0.07 to 0.49 per 10,000 children.[283] In a UK study,[284] the incidence rates of venous thromboembolism in RA patients without DMARD and with DMARD per 10,000 person-years were 74.52 and 79.08,

respectively. In the same study, the adjusted hazard ratios (95% CI) of venous thromboembolism in RA patients without DMARD and with DMARD were 1.29 (1.18, 1.39) and 1.35 (1.27, 1.44), respectively. In a retrospective cohort study based in the German BIKER registry, 3 thrombosis events were reported in patients with nonsystemic JIA exposed to biologics (including 2 DVT and 1 thrombophlebitis event) for a frequency of 0.04 thrombosis events per 100 PY.[285] The tofacitinib post-marketing dataset contained 235 venous thromboembolism events out of a total of 67,075 cases (reporting proportion of 0.35%) with an estimated cumulative worldwide post-authorisation exposure to tofacitinib of 209,081 patient-years (estimated reporting rate of 0.11 per 100 patient-years), as of 05 May 2019. Given the background risk and the severity of most of the events, the risk of venous thromboembolism (DVT/PE) associated with tofacitinib is not expected to have a significant public health impact.

VII.3.1.1.2. Serious and Other Important Infections

VII.3.1.1.2.1. Potential mechanisms

The mechanism by which infection risk is increased in patients is likely to be multifactorial. In addition to the underlying disease, therapies used to treat the disease have effects on the immune system. For example, tumour necrosis factor (TNF) inhibitors may affect host defence against infection since TNF mediates inflammation and modulates cellular immune response. Tofacitinib inhibits cytokines that are integral to lymphocyte activation, proliferation, and function, and inhibition of their signalling may thus result in modulation of multiple aspects of the immune response.

VII.3.1.1.2.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.1.2.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: The highest number of AEs reported for patients receiving tofacitinib in the RA development programmes was from those coding to the Infections and infestations system organ class; the most common infections were respiratory tract infections.

Table 41. Serious and Other Important Infections IRs per 100 PYs (95% CI) from the RCTs and All RA Population (P123LTE)

	RCT			All RA		
	5 mg	10 mg	Overall	5 mg	10 mg	Overall
Serious infections[a]	2.61 (2.02, 3.31)	2.66 (1.99, 3.48)	2.58 (2.17, 3.06)	2.77 (2.43, 3.14)	2.30 (2.07, 2.56)	2.48 (2.28, 2.69)
Serious pneumonia	0.81 (0.50, 1.24)	0.40 (0.17, 0.79)	0.68 (0.48, 0.94)	0.88 (0.70, 1.10)	0.55 (0.44, 0.68)	0.68 (0.58, 0.79)
UTI	6.03 (5.10, 7.08)	7.81 (6.60, 9.16)	7.16 (6.44, 7.94)	5.20 (4.72, 5.72)	5.13 (4.75, 5.54)	5.16 (4.86, 5.47)

Table 41. Serious and Other Important Infections IRs per 100 PYs (95% CI) from the RCTs and All RA Population (P123LTE)

	RCT			All RA		
	5 mg	**10 mg**	**Overall**	**5 mg**	**10 mg**	**Overall**
Cellulitis	0.78 (0.47, 1.20)	0.70 (0.38, 1.18)	0.74 (0.53, 1.01)	0.57 (0.42, 0.74)	0.52 (0.41, 0.65)	0.54 (0.45, 0.64)
TB and other OI						
Overall OI[b] (excluding TB)	0.27 (0.11, 0.56)	0.30 (0.11, 0.65)	0.27 (0.14, 0.44)	0.35 (0.24, 0.50)	0.42 (0.32, 0.54)	0.39 (0.32, 0.48)
Candidiasis	0.04 (0.00, 0.22)	0.05 (0.00, 0.28)	0.06 (0.01, 0.17)	0.06 (0.02, 0.13)	0.04 (0.01, 0.09)	0.05 (0.02, 0.08)
Pneumocystis jirovecii pneumonia	0.04 (0.00, 0.22)	0.00 (0.00, 0.18)	0.02 (0.00, 0.11)	0.10 (0.05, 0.19)	0.00 (0.00, 0.02)	0.04 (0.02, 0.07)
TB	0.08 (0.01, 0.28)	0.45 (0.21, 0.86)	0.23 (0.12, 0.40)	0.12 (0.06, 0.22)	0.18 (0.12, 0.26)	0.16 (0.11, 0.22)

a. In February 2013 an external, independent committee of infectious disease experts (Opportunistic Infection Review Committee [OIRC]) began reviewing and classifying all serious infection events and all events of possible OIs occurring in the tofacitinib development programme for RA.
b. Data for OI in RA are a mixture of events identified as OI by the Sponsor (prior to establishment of the OIRC) and those assessed as OI by the committee based on the criteria defined in their charter. In addition to the committee assessment, a more detailed and extensive follow-up on individual cases has resulted in additional information available for most potential OI events since February 2013. Cases of herpes zoster that were assessed by the OIRC as involving ≤2 adjacent dermatomes are not included in analyses of OI.
Events are counted up to 28 days beyond the last dose or to the data cutoff date. Incidence rate (number of subjects with events per 100 subject-years). Exact Poisson (adjusted for patient-year) 95% confidence intervals are provided for the crude incidence rate. The treatments represent the initial randomised study drug. Overall includes all patients who start on any tofacitinib dose as well as patients who switch from placebo/adalimumab to tofacitinib.
Includes protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
CI = confidence interval; IR = incidence rate; OI = opportunistic infection; PYs = patient years; RA = rheumatoid arthritis; RCT = randomised clinical trial; TB = tuberculosis; UTI = urinary tract infection
Final data 18 January 2019
Source: Table 417a.1.3.1, Table 417a.1.2

Considering that the risk of TB varies considerably by geographic region based on endemic infection rates, the IRs of TB were evaluated by background IR in each country. The countries were grouped into 3 categories (low, intermediate, high) based on World Health Organisation (WHO) categorisation.[286] In the All RA population, the IRs (95% CI) per 100 PY of TB by these WHO categories were 0.00 (0.00, 0.04), 0.11 (0.05, 0.21), and 0.51 (0.34, 0.73) for low, intermediate, and high background incidence groups, respectively.

Study A3921133:

Table 42. Serious and Other Important Infections IRs per 100 PYs (95% CI) from Study A3921133

	Tofacitinib 5mg BID	**Tofacitinib 10mg BID**	**All Tofa**	**TNFi**
Serious infections	2.86 (2.41, 3.37)	3.64 (3.11, 4.23)	3.24 (2.89, 3.62)	2.44 (2.02, 2.92)
Serious pneumonia	1.02 (0.76, 1.34)	1.25 (0.95, 1.61)	1.13 (0.93, 1.36)	0.90 (0.66, 1.21)

Table 42. Serious and Other Important Infections IRs per 100 PYs (95% CI) from Study A3921133

	Tofacitinib 5mg BID	Tofacitinib 10mg BID	All Tofa	TNFi
UTI	4.52 (3.93, 5.17)	5.60 (4.91, 6.35)	5.04 (4.58, 5.52)	4.26 (3.69, 4.90)
Cellulitis	0.71 (0.49, 0.98)	0.69 (0.47, 0.96)	0.70 (0.54, 0.88)	1.03 (0.77, 1.36)
TB and other OI				
Adjudicated OI (excluding TB)	0.74 (0.53, 1.02)	0.81 (0.57, 1.11)	0.77 (0.61, 0.97)	0.32 (0.18, 0.52)
Adjudicated candidiasis	0.00 (0.00, 0.07)	0.00 (0.00, 0.08)	0.00 (0.00, 0.04)	0.00 (0.00, 0.07)
Adjudicated pneumocystosis	0.04 (0.00, 0.14)	0.00 (0.00, 0.08)	0.02 (0.00, 0.07)	0.02 (0.00, 0.11)
Adjudicated TB	0.02 (0.00, 0.11)	0.10 (0.03, 0.24)	0.06 (0.02, 0.13)	0.10 (0.03, 0.23)

PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or to the last contact date.
The last contact date was maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact Date). If a subject died, last contact date was the death date. First events were counted within the risk period. If a subject did not have an event or had an event but outside the risk period, the subject was censored at the end of risk period.
For subjects randomized to the TNFi group, adalimumab was administered in US, Puerto Rico, and Canada, and etanercept was administered in the rest of the world.
BID = twice daily; OI = opportunistic infection; TB = tuberculosis; TNFi = tumour necrosis factor inhibitor; UTI = urinary tract infection
Source: Table 1657.7.2.1

The IRs per 100 PY (95% CI) of adjudicated TB for patients in the low background incidence WHO category for TB for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.00 (0.00, 0.20), 0.06 (0.00, 0.31), 0.03 (0.00, 0.15), and 0.00 (0.00, 0.19).

The IRs per 100 PY (95% CI) of adjudicated TB for patients in the intermediate background incidence WHO category for TB for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.04 (0.00, 0.25), 0.05 (0.00, 0.25), 0.04 (0.01, 0.16), and 0.05 (0.00, 0.26).

The IRs per 100 PY (95% CI) of adjudicated TB for patients in the high background incidence WHO category for TB for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.00 (0.00, 0.35), 0.33 (0.07, 0.98), 0.15 (0.03, 0.45), and 0.41 (0.11, 1.05).

PsA: The highest number of AEs reported for patients receiving tofacitinib in the PsA development programme was from those coding to the Infections and infestations System Organ Class (SOC); the most common infections were respiratory tract infections.

The IRs per 100 PY (95% CI) from the RCTs for the 5 mg and 10 mg dose groups and All PsA for the 5 mg and 10 mg dose groups and combined 5 mg and 10 mg dose groups for the following infections are shown below.

Table 43. Serious and Other Important Infections IRs per 100 PYs (95% CI) from the RCTs and All PsA Populations (P3LTE)

	RCT		All PsA		
	Tofa 5 mg BID	**Tofa 10 mg BID**	**Average 5 mg BID**	**Average 10 mg BID**	**All Tofa**
Serious infections[a]	1.30 (0.16, 4.69)	2.00 (0.41, 5.83)	1.23 (0.70, 2.00)	1.01 (0.43, 1.98)	1.15 (0.74, 1.71)
Serious pneumonia	0.65 (0.02, 3.62)	0.00 (0.00, 2.44)	0.23 (0.05, 0.67)	0.25 (0.03, 0.91)	0.24 (0.08, 0.56)
UTI	3.29 (1.07, 7.67)	8.21 (4.24, 14.34)	3.50 (2.53, 4.71)	5.39 (3.85, 7.33)	4.21 (3.35, 5.22)
Cellulitis	0.00 (0.00, 2.39)	0.66 (0.02, 3.70)	0.39 (0.13, 0.90)	0.38 (0.08, 1.10)	0.38 (0.17, 0.75)
TB and other OI					
Overall OI[b] (excluding TB)	0.65 (0.02, 3.62)	0.00 (0.00, 2.44)	0.15 (0.02, 0.56)	0.63 (0.20, 1.47)	0.34 (0.13, 0.69)
Candidiasis	0.00 (0.00, 2.39)	0.00 (0.00, 2.44)	0.00 (0.00, 0.28)	0.00 (0.00, 0.46)	0.00 (0.00, 0.18)
Pneumocystis jirovecii pneumonia	0.00 (0.00, 2.39)	0.00 (0.00, 2.44)	0.00 (0.00, 0.28)	0.00 (0.00, 0.46)	0.00 (0.00, 0.18)
TB	0.00 (0.00, 2.39)	0.00 (0.00, 2.44)	0.00 (0.00, 0.28)	0.00 (0.00, 0.46)	0.00 (0.00, 0.18)

a. In February 2013 an external, independent committee of infectious disease experts (Opportunistic Infection Review Committee [OIRC]) began reviewing and classifying all serious infection events and all events of possible OIs occurring in the tofacitinib development programme for RA. All corresponding events in the development programme for PsA have been reviewed by the OIRC.
b. Data for OI in RA are a mixture of events identified as OI by the Sponsor (prior to establishment of the OIRC) and those assessed as OI by the committee based on the criteria defined in their charter. In addition to the committee assessment, a more detailed and extensive follow-up on individual cases has resulted in additional information available for most potential OI events since February 2013. Cases of herpes zoster that were assessed by the OIRC as involving ≤2 adjacent dermatomes are not included in analyses of OI. All corresponding events in the development programme for PsA have been reviewed by the OIRC.
CI = confidence interval. PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between treatment switches or between the qualifying and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data cutoff date.
IR = incidence rate (Number of subjects with events per 100 subject-years).
Exact Poisson (adjusted for Pt-yr) 95% confidence intervals are provided for the crude incidence rate.
Average Tofa 5 mg: Subjects with an average total daily dose of <15 mg from Day 1 on Tofa
Average Tofa 10mg: Subjects with an average total daily dose of ≥15 mg from Day 1 on Tofa
RCT: includes all the data from protocols A3921091 and A3921125 excluding the portion of the data from the placebo exposed period for the subjects in the placebo treatment sequences.
All PsA: includes protocols A3921091, A3921125 and A3921092.
Tofa = Tofacitinib. Includes all Tofacitinib exposed subjects.
Final data: 31 July 2019
Source tables: C2a.2.1.1, 0018.C3.2.1.1, 417a.2.2

UC: The highest number of AEs reported for patients receiving tofacitinib in the UC development programmes was from those coding to the Infections and infestations SOC; the most common infections were respiratory tract infections.

The IRs per 100 PY (95% CI) from the RCTs (10 mg dose group for induction studies and the 5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively, for maintenance study) and All UC (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) for the following infections are shown below.

Table 44. Serious and Other Important Infections IRs per 100 PYs (95% CI) from the RCTs and All UC Population

	RCTs (induction studies)	RCTs (maintenance study)			All UC		
	Tofa 10 mg BID	5 mg	10 mg	Overall	5 mg	10 mg	Overall
Serious infections[a]	4.83 (2.09, 9.52)	1.35 (0.16, 4.87)	0.64 (0.02, 3.54)	0.98 (0.20, 2.87)	1.26 (0.60, 2.31)	1.90 (1.36, 2.59)	1.72 (1.28, 2.27)
Serious Pneumonia	-	0.00 (0.00, 2.48)	0.00 (0.00, 2.35)	0.00 (0.00, 1.21)	0.13 (0.00, 0.70)	0.09 (0.01, 0.34)	0.10 (0.02, 0.30)
UTI	-	4.12 (1.51, 8.97)	6.57 (3.15, 12.08)	5.37 (3.07, 8.72)	2.88 (1.79, 4.41)	2.82 (2.13, 3.67)	2.84 (2.24, 3.55)
Cellulitis	-	0.00 (0.00, 2.48)	0.00 (0.00, 2.35)	0.00 (0.00, 1.21)	0.00 (0.00, 0.46)	0.14 (0.03, 0.41)	0.10 (0.02, 0.30)
TB and other OI							
Adjudicated OI[b] (excluding TB)	1.89 (0.39, 5.53)	1.36 (0.16, 4.92)	2.60 (0.71, 6.65)	1.99 (0.73, 4.34)	1.04 (0.45, 2.05)	1.05 (0.66, 1.60)	1.05 (0.71, 1.50)
Adjudicated Candidiasis	-	0.00 (0.00, 2.48)	0.00 (0.00, 2.35)	0.00 (0.00, 1.21)	0.00 (0.00, 0.46)	0.00 (0.00, 0.17)	0.00 (0.00, 0.13)
Adjudicated Pneumocystosis	-	0.00 (0.00, 2.48)	0.00 (0.00, 2.35)	0.00 (0.00, 1.21)	0.00 (0.00, 0.46)	0.00 (0.00, 0.17)	0.00 (0.00, 0.13)
Adjudicated TB	0.00 (0.00, 2.33)	0.00 (0.00, 2.48)	0.00 (0.00, 2.35)	0.00 (0.00, 1.21)	0.00 (0.00, 0.46)	0.00 (0.00, 0.17)	0.00 (0.00, 0.13)

a. In February 2013 an external, independent committee of infectious disease experts (Opportunistic Infection Review Committee [OIRC]) began reviewing and classifying all serious infection events and all events of possible OIs occurring in the tofacitinib development programme for RA. All corresponding events in the development programme for UC have been reviewed by the OIRC, with the exception of the Phase 2 induction study (A3921063).

b. Data for OI in RA are a mixture of events identified as OI by the Sponsor (prior to establishment of the OIRC) and those assessed as OI by the committee based on the criteria defined in their charter. In addition to the committee assessment, a more detailed and extensive follow up on individual cases has resulted in additional information available for most potential OI events since February 2013. Cases of herpes zoster that were assessed by the OIRC as involving ≤2 adjacent dermatomes are not included in analyses of OI. All corresponding events in the development programme for UC have been reviewed by the OIRC, with the exception of the Phase 2 induction study (A3921063).

Events are counted up to 28 days beyond the last dose. PY: Total follow up time calculated up to the earliest of: day of the first event, time to data cutoff or progression to next study, or time to last dose + 28 days. IR = incidence rate (Number of subjects with events per 100 subject-years). CI = confidence interval. Exact Poisson (adjusted for Pt-yr) CI are provided for the crude IR.

Table 44. Serious and Other Important Infections IRs per 100 PYs (95% CI) from the RCTs and All UC Population

	RCTs (induction studies)	RCTs (maintenance study)			All UC		
	Tofa 10 mg BID	5 mg	10 mg	Overall	5 mg	10 mg	Overall

RCTs (P2P3 induction studies) included A3921063, a Phase 2 study and A3921094 and A3921095, Phase 3 studies. For adjudicated endpoints, incidence rates are based on data from Phase 3 studies, because data from A3921063 was not adjudicated. The P2P3 induction studies included 10 mg BID, but did not include 5 mg BID. RCTs (Phase 3 maintenance study) included only A3921096. The All UC data (P2P3LTE) studies included A3921063, A3921094, A3921095, A3921096, and A3921139 (final data: 24 August 2020).
Source tables: 14.2.8.c1, 14.2.8.c2, 14.2.8.c3b, 417a.3.3.1

JIA

In the pJIA integrated safety analysis population, there were no events of adjudicated opportunistic infections, adjudicated opportunistic infections excluding TB, adjudicated opportunistic infections excluding TB and HZ, adjudicated TB, candidiasis, or pneumocystosis. The IRs per 100 PYs (95% CI) in the JIA integrated safety analysis population for the infection events reported were:

Table 45. Serious and Other Important Infections IRs per 100 PYs (95% CI) from the JIA Population – Integrated Safety Analysis Population

Tofacitinib 5 mg BID	IR (95% CI)
Serious infections	1.641 (0.602, 3.572)
Adjudicated opportunistic infection	0.000 (0.000, 1.003)
Adjudicated opportunistic infection excluding TB	0.000 (0.000, 1.003)
Adjudicated opportunistic infection excluding TB and HZ	0.000 (0.000, 1.003)
Adjudicated TB	0.000 (0.000, 1.003)
Serious pneumonia	0.272 (0.007, 1.515)
Candidiasis	0.000 (0.000, 1.003)
Cellulitis	0.821 (0.169, 2.400)
Pneumocystosis	0.000 (0.000, 1.003)
UTI	3.958 (2.164, 6.640)

Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
For subjects who also enrolled in LTE study, total risk period is the sum of index and LTE risk periods. The gap between index and LTE studies can add a maximum of 28 days to the risk period of exposure to tofacitinib. Placebo exposure may contribute a maximum of 28 days to the risk period.
BID=twice daily; CI=confidence interval; HZ=herpes zoster; IR=incidence rate; JIA = juvenile idiopathic arthritis; LTE = long-term extension; TB=tuberculosis; UTI=urinary tract infection
Source: Table JIA_RMP 14

AS

Table 46. IRs per 100 PYs (95% CI) of Serious and Other Important Infections from the RCTs and All AS Populations

	RCTs (Placebo-Controlled)	All AS (All Tofa)	
	Tofa 5 mg BID (N=185)	All Tofa 5 mg BID (N=316)	All Tofa (N=420)
Serious infections	1.77 (0.00, 5.89)	0.43 (0.01, 2.41)	0.38 (0.01, 2.12)
Serious pneumonia	0.00 (0.00, 3.28)	0.00 (0.00, 1.59)	0.00 (0.00, 1.40)
UTI	3.53 (0.00, 8.92)	3.05 (1.23, 6.28)	3.07 (1.32, 6.04)
Cellulitis	0.00 (0.00, 3.28)	0.00 (0.00, 1.59)	0.00 (0.00, 1.40)
TB and other OI			
Adjudicated OIs (excluding TB)	0.00 (0.00, 3.28)	0.00 (0.00, 1.59)	0.00 (0.00, 1.40)
Candidiasis	0.00 (0.00, 3.28)	0.00 (0.00, 1.59)	0.00 (0.00, 1.40)
Pneumocystis jirovecii pneumonia	0.00 (0.00, 3.28)	0.00 (0.00, 1.59)	0.00 (0.00, 1.40)
Adjudicated TB	0.00 (0.00, 3.28)	0.00 (0.00, 1.59)	0.00 (0.00, 1.40)

CI=confidence interval; IR=incidence rate (number of subjects with the event per 100 subject-years); N=number of subjects included in the Safety Analysis Set; PY=patient-year (in subject-year).
28-Day (While on Treatment) Risk Period is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death].
Under While on Treatment Estimand, PY (denominator for IR) is the sum of the times to the first event for subjects with an event or the risk periods for subjects without an event within the 28-Day (While on Treatment) Risk Period.
Incidence rates are estimated based on n (Number of subjects with an event within the 28-Day (While on Treatment) Risk Period) under this estimand. 95% CI for IR is based on Exact Poisson Distribution without adjustment to study.
For subjects randomized to Placebo → Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment.
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C1.5.1.2.2-E, Table C2.5.1.2.1-E

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: Results are described for the 31 March 2018 datacut, the primary analyses. Results from the larger patient population included in the 31 January 2019 datacut were similar.

In the full sample (i.e., untrimmed/unmatched), there were 288 observed serious infection events among the bDMARD group with a resulting crude incidence rate of 2.97 (95% CI=2.64-3.34) per 100 person-years. There were 64 observed serious infection events among the tofacitinib group with a resulting crude incidence rate of 3.07 (95% CI=2.36-3.92) per 100 person-years.

Crude rates of serious infection events were similar in propensity score (PS) matched and PS trimmed cohorts. In the matched cohorts, there were 145 observed serious infection events

among bDMARD initiators for a crude incidence rate of 3.43 (95% CI=2.89-4.03) per 100 person-years. There were 51 observed serious infection events (among the PS matched tofacitinib group) with a resulting crude incidence rate of 3.45 (95% CI=2.57-4.54) per 100 person-years.

Please see table below for the crude rates and 95% CI for safety events of interest (acute exposure) among eligible RA patients initiating tofacitinib, bDMARD, or csDMARD.

Table 47. Crude Rates (per 100 PY) and 95% CI for Serious and Other Important Infections Among Eligible RA Patients Initiating Tofacitinib, bDMARD, or csDMARD (Primary Analyses)

	31 March 2018 Datacut[a]								
	Tofacitinib			bDMARD			csDMARD		
	Rate	95% LL	95% UL	Rate	95% LL	95% UL	Rate	95% LL	95% UL
Serious Infections									
Full sample	3.07	2.36	3.92	2.97	2.64	3.34	2.08	1.59	2.67
PS Trimmed	3.45	2.57	4.54	3.08	2.69	3.50	NR	NR	NR
PS Matched	3.45	2.57	4.54	3.43	2.89	4.03	NR	NR	NR
Pneumonia	0.94	0.57	1.45	0.97	0.79	1.19	0.88	0.57	1.29
Cellulitis	0.42	0.19	0.8	0.53	0.39	0.69	0.2	0.07	0.44
UTI	0.47	0.23	0.86	0.42	0.3	0.56	0.3	0.14	0.57
TB	0	0	0.17	0.01	0	0.06	0.03	0	0.19

a. Primary analysis
Individual serious infections included pneumonia, cellulitis, UTI, TB
bDMARD=biologic disease modifying antirheumatic drug; csDMARD=conventional synthetic disease modifying antirheumatic drug; LL=lower limit; N=count; NR=not reported; PS=propensity score; PY=person-years; RA=rheumatoid arthritis; TB=tuberculosis; UL=upper limit; UTI=urinary tract infection
Corrona RA Registry (study A3921205) final report: Table 16

Serious infections for prolonged-release tablet and film-coated tablet from non-interventional post approval safety study: Data from a non-interventional post approval safety study that evaluated tofacitinib in RA patients from a registry (US Corrona) showed that a numerically higher IR of serious infection was observed for the PR 11 mg tablet administered once daily than the 5 mg film-coated tablet administered twice daily. Crude IRs (95% CI) (i.e., not adjusted for age or sex) from availability of both formulations at 12 months following initiation of treatment were 3.45 (1.93, 5.69) and 2.78 (1.74, 4.21) and at 36 months were 4.71 (3.08, 6.91) and 2.79 (2.01, 3.77) patients with events per 100 patient-years in the PR 11 mg tablet once daily and film-coated 5 mg tablet twice daily groups, respectively. The unadjusted HR was 1.30 (95% CI; 0.67, 2.50) at 12 months and 1.93 (95% CI; 1.15, 3.24) at 36 months for the PR 11 mg once daily dose compared to the film-coated 5 mg twice daily dose. Data is based on a small number of patients with events observed with relatively large confidence intervals and limited follow up time.

Seriousness/Outcomes

RA

Table 48. Seriousness of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from the All RA Population (P123LTE)

N = 7964	n	Serious n (%)	Not serious n (%)	Unknown n (%)
Serious infection	592	592 (100.0)	0	0
Serious pneumonia	163	163 (100.0)	0	0
UTI	1098	56 (5.1)	1042 (94.9)	0
Cellulitis	129	32 (24.8)	97 (75.2)	0
TB and other OI				
OI excluding TB	95	41 (43.2)	54 (56.8)	0
Candidiasis	11	3 (27.3)	8 (72.7)	0
Pneumocystis jirovecii pneumonia	9	9 (100.0)	0	0
TB	38	32 (84.2)	6 (15.8)	0

n = Unique number of patients with the event. For the same adverse event of interest, the most serious case was selected in this summary, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date.
Includes protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
Final data 18 January 2019
OI = opportunistic infection; TB = tuberculosis; UTI = urinary tract infection
Source: Table 1614.2.1

Table 49. Outcomes of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from the All RA Population (P123LTE)

N = 7964	n	Resolved n (%)	Still present at the time of report n (%)	Unknown n (%)	Death n (%)
Serious infection	592	528 (89.2)	32 (5.4)	1 (0.2)	31 (5.2)
Serious pneumonia	163	141 (86.5)	4 (2.5)	1 (0.6)	17 (10.4)
UTI	1098	1049 (95.5)	45 (4.1)	4 (0.4)	0
Cellulitis	129	125 (96.9)	4 (3.1)	0	0
TB and other OI					
OI excluding TB	95	84 (88.4)	7 (7.4)	0	4 (4.2)
Candidiasis	11	7 (63.6)	3 (27.3)	0	1 (9.1)
Pneumocystis jirovecii pneumonia	9	6 (66.7)	1 (11.1)	0	2 (22.2)
TB	38	19 (50.0)	18 (47.4)	1 (2.6)	0

n = Unique number of patients with the event. For the same adverse event of interest, the last case was selected in this summary, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date.
Includes protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
Final data 18 January 2019
OI = opportunistic infection; TB = tuberculosis; UTI = urinary tract infection
Source: Table 1614.3.1

Study A3921133:

Table 50. Seriousness of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from Study A3921133

		Tofacitinib 5mg BID	Tofacitinib 10mg BID	All Tofacitinib	TNFi
Serious infection	n	141	169	310	119
	Serious n (%)	141 (100)	169 (100)	310 (100)	119 (100)
	Not serious n (%)	0	0	0	0
	Unknown n (%)	0	0	0	0
Serious pneumonia	n	52	60	112	45
	Serious n (%)	52 (100)	60 (100)	112 (100)	45 (100)
	Not serious n (%)	0	0	0	0
	Unknown n (%)	0	0	0	0
UTI	n	211	241	452	196
	Serious n (%)	19 (9.0)	16 (6.6)	35 (7.7)	12 (6.1)
	Not serious n (%)	192 (91.0)	225 (93.4)	417 (92.3)	184 (93.9)
	Unknown n (%)	0	0	0	0
Cellulitis	n	36	33	69	51
	Serious n (%)	12 (33.3)	11 (33.3)	23 (33.3)	14 (27.5)
	Not serious n (%)	24 (66.7)	22 (66.7)	46 (66.7)	37 (72.5)
	Unknown n (%)	0	0	0	0
TB and other OI					
Adjudicated OI excluding TB	n	38	39	77	16
	Serious n (%)	7 (18.4)	16 (41.0)	23 (29.9)	4 (25.0)
	Not serious n (%)	31 (81.6)	23 (59.0)	54 (70.1)	12 (75.0)
	Unknown n (%)	0	0	0	0
Adjudicated candidiasis	n	0	0	0	0
	Serious n (%)	0	0	0	0
	Not serious n (%)	0	0	0	0
	Unknown n (%)	0	0	0	0
Adjudicated pneumocystosis	n	2	0	2	1
	Serious n (%)	2 (100)	0	2 (100)	1 (100)
	Not serious n (%)	0	0	0	0
	Unknown n (%)	0	0	0	0
Adjudicated TB	n	1	5	6	5
	Serious n (%)	1 (100)	4 (80.0)	5 (83.3)	2 (40.0)
	Not serious n (%)	0	1 (20.0)	1 (16.7)	3 (60.0)
	Unknown n (%)	0	0	0	0

For the same adverse event of interest, the most serious case was selected in this summary, subject to a risk period of 28 days beyond the last dose or to a risk period of up to 28 days beyond the last dose or to the last contact date.
The risk period was minimum of (last contact date, Last Study Treatment Dose date + 28 days).
The last contact date was maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact date).
If a subject died, last contact date was the death date.
For subjects randomized to the TNFi group, adalimumab was administered in US, Puerto Rico and Canada, and etanercept was administered in the rest of the world.
BID = twice daily; OI = opportunistic infection; TB = tuberculosis; TNFi = tumour necrosis factor inhibitor; UTI = urinary tract infection
Source: Table 1657.7.3.1

Table 51. Outcomes of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from Study A3921133

		Tofacitinib 5mg BID	Tofacitinib 10mg BID	All Tofacitinib	TNFi
Serious infection	n	141	169	310	119
	Resolved n (%)	127 (90.1)	148 (87.6)	275 (88.7)	110 (92.4)
	Still present n (%)	7 (5.0)	9 (5.3)	16 (5.2)	3 (2.5)
	Unknown n (%)	0	0	0	2 (1.7)
	Death n (%)	7 (5.0)	12 (7.1)	19 (6.1)	4 (3.4)
Serious pneumonia	n	52	60	112	45
	Resolved n (%)	44 (84.6)	50 (83.3)	94 (83.9)	40 (88.9)
	Still present n (%)	1 (1.9)	2 (3.3)	3 (2.7)	2 (4.4)
	Unknown n (%)	0	0	0	0
	Death n (%)	7 (13.5)	8 (13.3)	15 (13.4)	3 (6.7)
UTI	n	211	241	452	196
	Resolved n (%)	209 (99.1)	239 (99.2)	448 (99.1)	194 (99.0)
	Still present n (%)	2 (0.9)	2 (0.8)	4 (0.9)	1 (0.5)
	Unknown n (%)	0	0	0	1 (0.5)
	Death n (%)	0	0	0	0
Cellulitis	n	36	33	69	51
	Resolved n (%)	32 (88.9)	32 (97.0)	64 (92.8)	47 (92.2)
	Still present n (%)	3 (8.3)	1 (3.0)	4 (5.8)	2 (3.9)
	Unknown n (%)	1 (2.8)	0	1 (1.4)	2 (3.9)
	Death n (%)	0	0	0	0
TB and other OI					
Adjudicated OI excluding TB	n	38	39	77	16
	Resolved n (%)	35 (92.1)	36 (92.3)	71 (92.2)	14 (87.5)
	Still present n (%)	2 (5.3)	2 (5.1)	4 (5.2)	1 (6.3)
	Unknown n (%)	0	0	0	0
	Death n (%)	1 (2.6)	1 (2.6)	2 (2.6)	1 (6.3)
Adjudicated candidiasis	n	0	0	0	0
	Resolved n (%)	0	0	0	0
	Still present n (%)	0	0	0	0
	Unknown n (%)	0	0	0	0
	Death n (%)	0	0	0	0
Adjudicated pneumocystosis	n	2	0	2	1
	Resolved n (%)	1 (50.0)	0	1 (50.0)	0
	Still present n (%)	0	0	0	1 (100)
	Unknown n (%)	0	0	0	0
	Death n (%)	1 (50.0)	0	1 (50.0)	0
Adjudicated TB	n	1	5	6	5
	Resolved n (%)	1 (100)	1 (20.0)	2 (33.3)	2 (40.0)
	Still present n (%)	0	4 (80.0)	4 (66.7)	3 (60.0)
	Unknown n (%)	0	0	0	0
	Death n (%)	0	0	0	0

Table 51. Outcomes of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from Study A3921133

		Tofacitinib 5mg BID	Tofacitinib 10mg BID	All Tofacitinib	TNFi

For the same adverse event of interest, the worst case was selected in this summary, subject to a risk period of up to 28 days beyond the last dose or to the last contact date.
The risk period was minimum of (last contact date, Last Study Treatment Dose date + 28 days).
The last contact date was maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact date).
If a subject died, last contact date was the death date.
For subjects randomized to the TNFi group, adalimumab was administered in US, Puerto Rico and Canada, and etanercept was administered in the rest of the world.
BID = twice daily; OI = opportunistic infection; TB = tuberculosis; TNFi = tumour necrosis factor inhibitor; UTI = urinary tract infection
Source: Table 1657.7.3.3

PsA

Table 52. Seriousness of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from the All PsA Population (P3LTE)

N = 783	n	Serious n (%)	Not serious n (%)	Unknown n (%)
Serious infection	24	24 (100.0)	0	0
Serious pneumonia	5	5 (100.0)	0	0
Urinary tract infection	83	1 (1.2)	82 (98.8)	0
Cellulitis	8	2 (25.0)	6 (75.0)	0
OI excluding TB	7	1 (14.3)	6 (85.7)	0
Candidiasis	0	0	0	0
Pneumocystis jirovecii pneumonia	0	0	0	0
TB	0	0	0	0

n = unique patients with ≥1 event(s)
OI = opportunistic infection; PsA = psoriatic arthritis; TB = tuberculosis
Includes protocols: A3921091, A3921092 and A3921125
Final data 31 July 2019
Source: Table 00118.C3.11.6.1.1

Table 53. Outcomes of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from the All PsA Population (P3LTE)

N = 783	N	Resolved n (%)	Still present at the time of report n (%)	Unknown n (%)	Death n (%)
Serious infection	24	24 (100.0)	0	0	0
Serious pneumonia	5	5 (100.0)	0	0	0
Urinary tract infection	83	83 (100.0)	0	0	0
Cellulitis	8	8 (100.0)	0	0	0
OI excluding TB	7	6 (85.7)	1 (14.3)	0	0
Candidiasis	0	0	0	0	0
Pneumocystis jirovecii pneumonia	0	0	0	0	0
TB	0	0	0	0	0

n = unique patients with ≥1 event(s)
OI = opportunistic infection; PsA = psoriatic arthritis; TB = tuberculosis

Table 53. Outcomes of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from the All PsA Population (P3LTE)

N = 783	N	Resolved n (%)	Still present at the time of report n (%)	Unknown n (%)	Death n (%)

Includes protocols: A3921091, A3921092 and A3921125
Final data 31 July 2019
Source: Table 00118.C3.11.6.3.1

UC

Table 54. Seriousness of the Serious and Other Important Infections, TB, and OI Cases from the All UC Population (P2P3LTE)

N = 1157 (for Serious infections, serious pneumonia, urinary tract infections, cellulitis) N = 1124 (for adjudicated OI excluding TB, adjudicated candidiasis, pneumocystosis, TB)[a]	n	Serious n (%)	Not serious n (%)	Unknown n (%)
Serious infection	50	50 (100.0)	0	0
Serious pneumonia	3	3 (100.0)	0	0
Urinary tract infection	77	2 (2.6)	75 (97.4)	0
Cellulitis	3	1 (33.3)	2 (66.7)	0
Adjudicated OI (excluding TB)	30	7 (23.3)	23(76.7)	0
Adjudicated Candidiasis	0	0	0	0
Adjudicated Pneumocystosis	0	0	0	0
Adjudicated TB	0	0	0	0

a. Events confirmed by adjudication, for which data was not available for Phase 2 induction study A3921063
OI = opportunistic infection; TB = tuberculosis; UC = ulcerative colitis
n = unique number of patients with the event
Includes protocols: A3921063, A3921094, A3921095, A3921096, A3921139
Final data: 24 Aug 2020, Source: Table 417a.3.3.3

Table 55. Outcomes of the Serious and Other Important Infections, TB, and OI Cases from the All UC Population (P2P3LTE)

N = 1157 (for Serious infections, serious pneumonia, urinary tract infections, cellulitis) N = 1124 (for adjudicated OI excluding TB, adjudicated candidiasis, pneumocystosis, TB)[a]	n	Resolved n (%)	Still present at the time of report n (%)	Unknown n (%)	Death n (%)
Serious infection	50	43 (86.0)	7 (14.0)	0	0
Serious pneumonia	3	2 (66.7)	1 (33.3)	0	0
Urinary tract infection	77	69 (89.6)	7 (9.1)	1 (1.3)	0
Cellulitis	3	3 (100.0)	0	0	0
Adjudicated OI (excluding TB)	30	25 (83.3)	5 (16.7)	0	0
Adjudicated Candidiasis	0	0	0	0	0
Adjudicated Pneumocystosis	0	0	0	0	0
Adjudicated TB	0	0	0	0	0

a. Events confirmed by adjudication, for which data was not available for Phase 2 induction study A3921063
n = unique patients with ≥1 event(s)
OI = opportunistic infection; TB = tuberculosis; UC = ulcerative colitis
Includes protocols: A3921063, A3921094, A3921095, A3921096, A3921139
Final data: 24 Aug 2020, Source: Table 417a.3.3.5

JIA: In the JIA integrated safety analysis population, there were 6 serious infections (no OIs excluding TB and no TB). The outcomes were resolved (5) and still present (1).

AS

Table 56. Seriousness of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from the All AS Population

	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
	n	Serious n (%)	Not serious n (%)	Unknown n (%)	n	Serious n (%)	Not serious n (%)	Unknown n (%)
Serious infection	1	1 (100.0)	0	0	1	1 (100.0)	0	0
Serious pneumonia	0	0	0	0	0	0	0	0
Urinary tract infection	7	0	7 (100.0)	0	8	0	8 (100.0)	0
Cellulitis	0	0	0	0	0	0	0	0
Adjudicated OI excluding TB	0	0	0	0	0	0	0	0
Candidiasis	0	0	0	0	0	0	0	0
Pneumocystis jirovecii pneumonia	0	0	0	0	0	0	0	0
Adjudicated TB	0	0	0	0	0	0	0	0

AS = ankylosing spondylitis; OI = opportunistic infection; TB = tuberculosis
Based on 28-Day (While on Treatment) Risk Period, which is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death].
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C2.7.6-E

Table 57. Outcomes of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from the All AS Population

	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
	n	Resolved n (%)	Present n (%)	Unknown n (%)	n	Resolved n (%)	Present n (%)	Unknown n (%)
Serious infection	1	1 (100.0)	0	0	1	1 (100.0)	0	0
Serious pneumonia	0	0	0	0	0	0	0	0
Urinary tract infection	7	5 (71.4)	2 (28.6)	0	8	6 (75.0)	2 (25.0)	0
Cellulitis	0	0	0	0	0	0	0	0
Adjudicated OI excluding TB	0	0	0	0	0	0	0	0
Candidiasis	0	0	0	0	0	0	0	0
Pneumocystis jirovecii pneumonia	0	0	0	0	0	0	0	0
Adjudicated TB	0	0	0	0	0	0	0	0

Please note, there were no deaths in the AS clinical development programme.
AS = ankylosing spondylitis; OI = opportunistic infection; TB = tuberculosis
Based on 28-Day (While on Treatment) Risk Period, which is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death].
NOT RECOVERED/NOT RESOLVED and RECOVERING/RESOLVING are mapped as Present.
RECOVERED/RESOLVED and RECOVERED/RESOLVED WITH SEQUELAE are mapped as Resolved.
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C2.7.8-E

Post-Marketing:

Table 58. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Serious and Other Important Infections (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events[a]	Serious Events	H	F	R	RS	NR	U
Pneumonia	2261	2261	955	90	864	2	208	1112
COVID-19	538	538	250	66	129	14	34	295
Lower respiratory tract infection	533	533	46	8	155	0	93	278
Herpes zoster	526	526	317	2	273	28	55	168
Urinary tract infection	425	425	268	2	181	0	64	179
Infection	376	376	219	17	80	0	58	221
Diverticulitis	343	343	108	2	98	4	39	200
Cellulitis	327	327	114	3	140	2	40	143
Sepsis	323	323	214	49	90	3	12	169
Kidney infection	207	207	54	1	61	1	20	124
Respiratory tract infection	184	184	14	2	66	1	25	90
Influenza	161	161	123	8	62	0	20	71
Clostridium difficile infection	146	146	38	0	44	0	18	84
Bronchitis	141	141	77	2	70	0	23	46
Tuberculosis	141	141	16	3	14	0	20	104
Staphylococcal infection	136	136	36	2	42	1	18	73
Localised infection	122	122	69	0	45	0	26	51
Sinusitis	118	118	42	3	30	0	29	56
Tooth abscess	102	102	6	0	31	0	14	57
All others	4009	4009	1700	212	1450	39	537	1779
Total	11119	11119	4666	472	3925	95	1353	5300

a. Events from serious cases

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 59. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Serious and Other Important Infections (Prolonged-Release Formulation)

MedDRA PT	No. Events[a]	Serious Events	H	F	R	RS	NR	U
Pneumonia	1203	1203	442	10	323	4	94	774
COVID-19	654	654	358	30	150	6	38	430
Diverticulitis	233	233	65	0	50	0	20	164
Urinary tract infection	220	220	123	1	53	0	40	126

Table 59. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Serious and Other Important Infections (Prolonged-Release Formulation)

MedDRA PT	No. Events[a]	Serious Events	H	F	R	RS	NR	U
Cellulitis	212	212	68	2	47	1	23	139
Infection	203	203	119	1	42	0	24	136
Sepsis	160	160	113	9	31	3	6	111
Kidney infection	153	153	41	0	34	0	12	107
Tuberculosis	131	131	5	0	9	0	2	120
Respiratory tract infection	118	118	8	0	33	0	4	81
Influenza	105	105	84	0	37	3	8	57
Staphylococcal infection	102	102	31	0	18	1	8	75
All others	2100	2100	692	22	549	13	252	1264
Total	5594	5594	2149	75	1376	31	531	3584

a. Events from serious cases
F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and Nature of Risk

RA

Table 60. Severity[a] of the Serious and Other Important Infections, TB, OI (excluding TB) Cases from the All RA Population (P123LTE)

N = 7964	n	Mild n (%)	Moderate n (%)	Severe n (%)	Unknown n (%)
Serious infection	592	31 (5.2)	243 (41.1)	318 (53.7)	0
Serious pneumonia	163	3 (1.8)	71 (43.6)	89 (54.6)	0
UTI	1098	653 (59.5)	416 (37.9)	29 (2.6)	0
Cellulitis	129	53 (41.1)	62 (48.1)	14 (10.9)	0
TB and other OI					
OI excl TB	95	30 (31.6)	38 (40.0)	27 (28.4)	0
Candidiasis	11	6 (54.6)	3 (27.3)	2 (18.2)	0
Pneumocystis carinii jirovecii	9	0	1 (11.1)	8 (88.9)	0
TB	38	6 (15.8)	11 (29.0)	21 (55.3)	0

a. Severity definitions: mild = does not interfere with subject's usual function; moderate = interferes to some extent with subject's usual function; severe = interferes significantly with subject's usual function.
n = Unique number of patients with the event. For the same adverse event of interest, the most severe case was selected in this summary, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date.
Includes protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
Final data 18 January 2019
OI = opportunistic infection; TB = tuberculosis; UTI = urinary tract infection
Source: Table 1614.4.1

The most common serious infection reported in patients receiving tofacitinib was pneumonia; other commonly reported serious infections included skin and soft tissue infections. Of the 38 cases of TB above, 28 occurred in countries with high overall rates of TB. In the tofacitinib RA development programme, OIs excluding TB were infrequent. Infections classified as opportunistic that were reported in patients treated with tofacitinib in the All RA population included oesophageal candidiasis, invasive candidiasis, cytomegalovirus, cryptococcosis, pneumocystis pneumonia, multidermatomal/disseminated HZ, non-TB mycobacteria, nocardiosis, and BK virus encephalitis.

Study A3921133:

Table 61. Severity of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from Study A3921133

		Tofacitinib 5mg BID	Tofacitinib 10mg BID	All Tofacitinib	TNFi
Serious infection	n	141	169	310	119
	Mild n (%)	10 (7.1)	9 (5.3)	19 (6.1)	6 (5.0)
	Moderate n (%)	59 (41.8)	64 (37.9)	123 (39.7)	39 (32.8)
	Severe n (%)	72 (51.1)	96 (56.8)	168 (54.2)	74 (62.2)
	Unknown n (%)	0	0	0	0
Serious pneumonia	n	52	60	112	45
	Mild n (%)	0	1 (1.7)	1 (0.9)	1 (2.2)
	Moderate n (%)	21 (40.4)	21 (35.0)	42 (37.5)	14 (31.1)
	Severe n (%)	31 (59.6)	38 (63.3)	69 (61.6)	30 (66.7)
	Unknown n (%)	0	0	0	0
UTI	n	211	241	452	196
	Mild n (%)	96 (45.5)	122 (50.6)	218 (48.2)	98 (50.0)
	Moderate n (%)	102 (48.3)	109 (45.2)	211 (46.7)	94 (48.0)
	Severe n (%)	13 (6.2)	10 (4.1)	23 (5.1)	4 (2.0)
	Unknown n (%)	0	0	0	0
Cellulitis	n	36	33	69	51
	Mild n (%)	15 (41.7)	11 (33.3)	26 (37.7)	16 (31.4)
	Moderate n (%)	14 (38.9)	17 (51.5)	31 (44.9)	29 (56.9)
	Severe n (%)	7 (19.4)	5 (15.2)	12 (17.4)	6 (11.8)
	Unknown n (%)	0	0	0	0
TB and other OI					
Adjudicated OI excluding TB	n	38	39	77	16
	Mild n (%)	10 (26.3)	5 (12.8)	15 (19.5)	3 (18.8)
	Moderate n (%)	20 (52.6)	24 (61.5)	44 (57.1)	10 (62.5)
	Severe n (%)	8 (21.1)	10 (25.6)	18 (23.4)	3 (18.8)
	Unknown n (%)	0	0	0	0
Adjudicated candidiasis	n	0	0	0	0
	Mild n (%)	0	0	0	0
	Moderate n (%)	0	0	0	0
	Severe n (%)	0	0	0	0
	Unknown n (%)	0	0	0	0
Adjudicated pneumocystosis	n	2	0	2	1
	Mild n (%)	0	0	0	0
	Moderate n (%)	0	0	0	0
	Severe n (%)	2 (100)	0	2 (100)	1 (100)
	Unknown n (%)	0	0	0	0

Table 61. Severity of the Serious and Other Important Infections, TB, and OI (excluding TB) Cases from Study A3921133

		Tofacitinib 5mg BID	Tofacitinib 10mg BID	All Tofacitinib	TNFi
Adjudicated TB	n	1	5	6	5
	Mild n (%)	1 (100)	0	1 (16.7)	0
	Moderate n (%)	0	1 (20.0)	1 (16.7)	4 (80.0)
	Severe n (%)	0	4 (80.0)	4 (66.7)	1 (20.0)
	Unknown n (%)	0	0	0	0

For the same adverse event of interest, the most severe case was selected in this summary, subject to a risk period of 28 days beyond the last dose or to a risk period of up to 28 days beyond the last dose or to the last contact date.
The risk period was minimum of (last contact date, Last Study Treatment Dose date + 28 days).
The last contact date was maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact date).
If a subject died, last contact date was the death date.
For subjects randomized to the TNFi group, adalimumab was administered in US, Puerto Rico and Canada, and etanercept was administered in the rest of the world.
BID = twice daily; OI = opportunistic infection; TB = tuberculosis; TNFi = tumour necrosis factor inhibitor; UTI = urinary tract infection
Source: Table 1657.7.3.5

PsA

Table 62. Severity of the Serious and Other Important Infections, TB, OI (excluding TB) Cases from the All PsA Population (P3LTE)

N = 783	n	Mild n (%)	Moderate n (%)	Severe n (%)	Unknown n (%)
Serious infection	24	0	14 (58.3)	10 (41.7)	0
Serious pneumonia	5	0	3 (60.0)	2 (40.0)	0
Urinary tract infection	83	47 (56.6)	35 (42.2)	1 (1.2)	0
Cellulitis	8	4 (50.0)	4 (50.0)	0	0
OI excl TB	7	1 (14.3)	6 (85.7)	0	0
Candidiasis	0	0	0	0	0
Pneumocystis jirovecii pneumonia	0	0	0	0	0
TB	0	0	0	0	0

n = unique patients with ≥1 event(s)
OI = opportunistic infection; PsA = psoriatic arthritis; TB = tuberculosis
Includes protocols: A3921091, A3921092 and A3921125
Final data 31 July 2019
Source: Table 00118.C3.11.6.2.1

The most common serious infection reported in patients receiving tofacitinib was pneumonia (5 events); the only other serious infection for which there was more than a single event was gastroenteritis. In the tofacitinib PsA development programme, OIs excluding TB were infrequent. In the All PsA population, the only infections classified as opportunistic were multidermatomal/disseminated HZ.

UC

Table 63. Severity of the Serious and Other Important Infections, TB, OI Cases from the All UC Population (P2P3LTE)

N = 1157 (for Serious infections, serious pneumonia, urinary tract infections, cellulitis) N = 1124 (for adjudicated OI excluding TB, adjudicated candidiasis, pneumocystosis, TB)[a]	n	Mild n (%)	Moderate n (%)	Severe n (%)	Unknown n (%)
Serious infection	50	9 (18.0)	20 (40.0)	21 (42.0)	0
Serious pneumonia	3	2 (66.7)	0	1 (33.3)	0
Urinary tract infection	77	52 (67.5)	25 (32.5)	0	0
Cellulitis	3	2 (66.7)	1 (33.3)	0	0
Adjudicated OI (excluding TB)	30	10 (33.3)	17 (56.7)	3 (10.0)	0
Adjudicated Candidiasis	0	0	0	0	0
Adjudicated Pneumocystosis	0	0	0	0	0
Adjudicated TB	0	0	0	0	0

a. Events confirmed by adjudication, for which data was not available for Phase 2 induction study A3921063
n = unique number of patients with the event
Proportions are based on treatment group total as denominator. The proportions for event breakdown into categories are based on row total as denominator.
For the same adverse event of interest, the most severe case was selected in this summary.
OI = opportunistic infection; TB = tuberculosis; UC = ulcerative colitis
Includes protocols: A3921063, A3921094, A3921095, A3921096, A3921139
Final data 24 Aug 2020, Source: Table 417a.3.3.7

The most common serious infection reported in patients receiving tofacitinib was herpes zoster (5 events); other serious infections for which there were more than single events were anal abscess (4 events), appendicitis (3 events), *Clostridium difficile* infection, ophthalmic herpes zoster, and sinusitis (2 events each). In the tofacitinib UC development programme, OIs excluding TB were infrequent. In the All UC population, infections classified as opportunistic included multidermatomal/disseminated HZ, cryptococcosis, histoplasmosis, cytomegalovirus disease, and cytomegalovirus hepatitis.

JIA: In the JIA integrated safety analysis population, of the total 6 serious infection events, 2 were assessed as severe and 4 were assessed as moderate in severity.

AS

Table 64. Severity of the Serious and Other Important Infections, TB, OI Cases from the All AS Population

	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
	n	Mild n (%)	Moderate n (%)	Severe n (%)	n	Mild n (%)	Moderate n (%)	Severe n (%)
Serious infection	1	0	1 (100.0)	0	1	0	1 (100.0)	0
Serious pneumonia	0	0	0	0	0	0	0	0
Urinary tract infection	7	5 (71.4)	2 (28.6)	0	8	5 (62.5)	3 (37.5)	0
Cellulitis	0	0	0	0	0	0	0	0

Table 64. Severity of the Serious and Other Important Infections, TB, OI Cases from the All AS Population

	All Tofa 5 mg BID (N=316)				All Tofa (N=420)			
	n	Mild n (%)	Moderate n (%)	Severe n (%)	n	Mild n (%)	Moderate n (%)	Severe n (%)
Adjudicated OI excluding TB	0	0	0	0	0	0	0	0
Candidiasis	0	0	0	0	0	0	0	0
Pneumocystis jirovecii pneumonia	0	0	0	0	0	0	0	0
Adjudicated TB	0	0	0	0	0	0	0	0

AS = ankylosing spondylitis; OI = opportunistic infection; TB = tuberculosis
Based on 28-Day (While on Treatment) Risk Period, which is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death].
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C2.7.7-E

VII.3.1.1.2.4. Risk factors and risk groups

Risk factors/groups for serious infections include patients who are elderly or diabetic, patients that use drugs along with tofacitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts, and patients from certain Asian countries.

Summary of results from the US Corrona RA Registry A3921205: The risk factors associated with serious infection events were similar between tofacitinib and bDMARD groups in patients with moderate-to-severe disease (such as history of hypertension, history of diabetes mellitus, age 70+, age 60+). The rates of serious infection events were higher without overlapping 95% CI in patients 65 and older than in patients younger than 65 in both tofacitinib initiators [<65 years: 2.03 (1.35, 2.94); ≥65 years: 5.1 (3.57, 7.06)] and bDMARD initiators [<65 years: 2.15 (1.8, 2.54); ≥65 years: 4.54 (3.85, 5.33)]. The 95% CI overlapped between the tofacitinib group ≥65 years and bDMARD group ≥65 years.

VII.3.1.1.2.5. Preventability

In general, preventive measures may include screening for infections prior to initiation of tofacitinib treatment and monitoring lymphocytes counts during therapy.

Considering the increased risk of serious infections with tofacitinib in patients 65 years of age and older, tofacitinib should only be used in these patients if no suitable treatment alternatives are available.

It is not recommended to initiate tofacitinib treatment in adult patients with a low neutrophil count (ie, absolute neutrophil count [ANC] < 1000 cells/mm^3). It is recommended not to initiate dosing in paediatric patients with an ANC less than 1200 cells/mm^3. Tofacitinib dose should be interrupted or adjusted based on ANC. Neutrophils should be monitored at baseline, 4-8 weeks after starting tofacitinib, and every 3 months thereafter.

It is not recommended to initiate tofacitinib treatment in adult and paediatric patients with a low lymphocyte count (ie, less than 750/mm^3). In patients who develop a confirmed absolute lymphocyte count of less than 500/mm^3 treatment with tofacitinib is not recommended. Lymphocytes should be monitored at baseline and every 3 months thereafter.

Tofacitinib should not be used in combination with biologics such as TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators, IL 17 antagonists, IL 12/IL23 antagonists, and potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporin, and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

VII.3.1.1.2.6. Impact on the risk-benefit balance of the product

Infections may be mild and self-limiting or more severe and sometimes fatal.

VII.3.1.1.2.7. Public health impact

Serious infection including TB and opportunistic infection (OI) is one of the common causes of morbidity and mortality. The impact of these infections on public health is significant both in terms of lost time at work and increased burden on medical care.

VII.3.1.1.2.7.1. Risk of opportunistic infections in Asian patients

The risk of OIs was examined by geographic region and individual Asian country. As noted in VII.3.1.1.2.7.1, tofacitinib is associated with an increased risk of HZ, specifically in Japanese and Korean patients. To assess the risk of OI separately from the risk of HZ, events of HZ that are not considered OI, ie, cases other than those that were adjudicated as multidermatomal (nonadjacent or >2 adjacent dermatomes) or disseminated, were excluded from the analysis.

RA: The crude rate of OI excluding HZ and TB appears higher in the Asian region (0.41 subjects with events/100 PY) compared to the combined rate in Non-Asian regions (0.07 subjects with events/100 PY; IR point estimates ranged from 0.03-0.17 subjects with events/100 PY) (Table 65). However, the rate was not increased uniformly across the different Asian countries. No OI were reported in India, and 1 case each was reported in Thailand and China. When each individual Asian country is examined, the rate appears higher in Japan, Korea and Australia/New Zealand. The number of cases is small in Korea and Australia/New Zealand; thus, the stability of these estimates raises questions as to their accurate interpretation as well as the need to consider the influence of medical practice and geographic distribution of pathogens on reporting.

Table 65. Opportunistic Infections Excluding Herpes Zoster and Tuberculosis (Subjects with events/100 PY) by Geographic Region and Asian Country: All Rheumatoid Arthritis (P123LTE)

	Total Subjects	Subjects with Events	Exposure for Event (PY)	Incidence Rate (95% CI)
Global RA Programme	7964	38	24112.85	0.16 (0.11, 0.22)
Non-Asian[a]	6046	13	18491.59	0.07 (0.04, 0.12)
Individual Regions				

Table 65. Opportunistic Infections Excluding Herpes Zoster and Tuberculosis (Subjects with events/100 PY) by Geographic Region and Asian Country: All Rheumatoid Arthritis (P123LTE)

	Total Subjects	Subjects with Events	Exposure for Event (PY)	Incidence Rate (95% CI)
US/Canada	2021	4	5305.84	0.08 (0.02, 0.19)
Europe (European Economic Area)	2180	2	7164.49	0.03 (0.00, 0.10)
Latin America	1246	7	4005.36	0.17 (0.07, 0.36)
Asia[b]	1775	21	5107.38	0.41 (0.25, 0.63)
Individual Asian Countries				
Australia/New Zealand	143	4	513.76	0.78 (0.21, 1.99)
[redacted]	765	14	1801.91	0.78 (0.42, 1.30)
[redacted]	333	5	1059.27	0.47 (0.15, 1.10)
[redacted]	197	0	580.80	0.00 (0.00, 0.64)
Thailand/Malaysia/ Philippines	220	1	701.08	0.14 (0.00, 0.79)
China/Taiwan	260	1	964.33	0.10 (0.00, 0.58)

a. Global population excluding all subjects in Asian countries
b. Excludes Australia and New Zealand
PY (subject-year): Total follow up time calculated up the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data cutoff date. Incidence rate (number of subjects with events per 100 subject-years). Exact Poisson (adjusted for patient-year) 95% confidence intervals are provided for the crude incidence rate. Includes protocols -A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year data), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
Final data 18 January 2019
CI = confidence interval; RA = rheumatoid arthritis
Source: Tables 1571.5.2.2.3, 1571.5.2.1.7, 1614.6.1, 1614.6.2

Taken as a whole, the data do not clearly support a warning that Japanese or patients from other Asian countries are at increased risk of OI, other than the acknowledged risk for HZ. This is due to the small number of OI events and the degree of uncertainty raised by increased regional background rates of specific OI and/or differences in local medical practices such that a definitive interpretation is not possible.

Study A3921133: The IR per 100 PY (95% CI) of OI excluding HZ and TB in the All Tofa group are shown in the table below by regions and by Asian countries.

Table 66. Adjudicated Opportunistic Infections Excluding Herpes Zoster and Tuberculosis (Subjects with events/100 PY) by Geographic Region and Asian Countries in A3921133 (All Tofa)

	N	n	n1	Exposure for Event (PY)	Incidence Rate (95% CI)
Overall A3921133 All Tofa	2911	11	1	10042.31	0.11 (0.05, 0.20)
Europe	99	1	0	298.79	0.33 (0.01, 1.86)
US/Canada	811	2	0	2686.44	0.07 (0.01, 0.27)

Table 66. Adjudicated Opportunistic Infections Excluding Herpes Zoster and Tuberculosis (Subjects with events/100 PY) by Geographic Region and Asian Countries in A3921133 (All Tofa)

	N	n	n1	Exposure for Event (PY)	Incidence Rate (95% CI)
Latin America	799	1	0	2772.94	0.04 (0.00, 0.20)
Rest of the World	1202	7	1	4284.13	0.16 (0.07, 0.34)
All Non-Asian Regions Combined	2715	8	1	9405.95	0.09 (0.04, 0.17)
Asian countries (total)	196	3	0	636.35	0.47 (0.10, 1.38)
Australia/New Zealand	39	0	0	111.54	0.00 (0.00, 3.31)
China/Taiwan/Hong Kong	36	2	0	131.38	1.52 (0.18, 5.50)
Middle East (Israel, Jordan, Lebanon)	72	0	0	216.04	0.00 (0.00, 1.71)
Thailand/Malaysia	49	1	0	177.40	0.56 (0.01, 3.14)

N- The total number of subjects in the treatment group in the Safety population. n- Number of subjects with first event within the risk period. n1- Number of subjects with first event outside the risk period.
PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or to the last contact date.
The last contact date was maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact Date). If a subject died, last contact date was the death date. First events were counted within the risk period. If a subject did not have an event or had an event but outside the risk period, the subject was censored at the end of risk period.
Source: Table 1657.7.2.1, Table 1657.7.4.2, Table 1657.7.4.3, Table 1657.7.4.4

PsA: No events were reported in the PsA programme.

UC: There were 5 non-HZ, non-TB OIs in UC programme, 4 of which were reported in the predominant 10 mg BID dose group.

JIA: No events were reported in the JIA programme. No Asian subjects participated in the JIA studies A3921103, A3921104, or A3921145.

AS: No events were reported in the AS programme.

VII.3.1.1.3. Herpes Zoster (HZ) Reactivation

VII.3.1.1.3.1. Potential mechanisms

The mechanism by which infection risk is increased in patients is likely to be multifactorial. In addition to the underlying disease, therapies used to treat the disease have effects on the immune system. Tofacitinib inhibits cytokines that are integral to lymphocyte activation, proliferation, and function, and inhibition of their signalling may thus result in modulation of multiple aspects of the immune response.

VII.3.1.1.3.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.1.3.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: The IRs per 100 PY (95% CI) from the RCTs and All RA for the 5 mg dose, 10 mg dose, and overall total tofacitinib groups for HZ were:

HZ All[1]

- RCTs: 2.92 (2.29, 3.66), 4.06 (3.21, 5.06), 3.31 (2.83, 3.84)
- All RA: 3.34 (2.96, 3.75), 3.73 (3.41, 4.07), 3.58 (3.34, 3.84)

HZ serious

- RCTs: 0.31 (0.13, 0.61), 0.35 (0.14, 0.72), 0.30 (0.17, 0.49)
- All RA: 0.25 (0.16, 0.38), 0.23 (0.16, 0.32), 0.24 (0.18, 0.31)

Study A3921133: The IRs per 100 PY (95% CI) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, for HZ were:

- HZ All: 3.75 (3.22, 4.34), 3.94 (3.38, 4.57), 3.84 (3.45, 4.26), 1.18 (0.90, 1.52)
- HZ serious: 0.19 (0.09, 0.36), 0.35 (0.20, 0.56), 0.27 (0.18, 0.39), 0.04 (0.00, 0.14)

PsA: The IRs per 100 PY (95% CI) from the RCTs for the 5 mg and 10 mg dose groups and from the All PsA for the 5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively for HZ were:

HZ All

- RCTs: 1.96 (0.41, 5.74), 2.66 (0.73, 6.81)
- All PsA: 1.66 (1.03, 2.54), 1.92 (1.08, 3.17), 1.76 (1.23, 2.44)

HZ serious

- RCTs: 0.00 (0.00, 2.39), 0.00 (0.00, 2.44)
- All PsA: 0.08 (0.00, 0.43), 0.00 (0.00, 0.46), 0.05 (0.00, 0.27)

UC: The IRs per 100 PY (95% CI) from the RCTs (10 mg dose group for induction studies and the 5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively, for

[1] Herpes zoster cases include those that were assessed by the OIRC as involving ≤2 adjacent dermatomes.

maintenance study) and All UC (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) for HZ were:

HZ All

- RCTs (induction studies): 3.62 (1.33, 7.88)
- RCTs (maintenance study): 2.05 (0.42, 6.00), 6.64 (3.19, 12.22), 4.38 (2.33, 7.50)
- All UC: 3.02 (1.89, 4.58), 3.51 (2.74, 4.44), 3.38 (2.73, 4.15)

HZ serious

- RCTs (induction studies): 0.00 (0.00, 2.22)
- RCTs (maintenance study): 0.00 (0.00, 2.48), 0.00 (0.00, 2.35), 0.00 (0.00, 1.21)
- All UC: 0.13 (0.00, 0.70), 0.28 (0.10, 0.61), 0.24 (0.10, 0.49)

JIA: The IR per 100 PY (95% CI) from the integrated safety analysis population for all HZ was 0.82 (0.17, 2.40). There were no serious HZ events.

AS: The IRs per 100 PY (95% CI) from RCTs (placebo-controlled cohort) for the "Tofa 5 mg BID" group and from All AS (All Tofa cohort) for the "All Tofa 5 mg BID" and "All Tofa" groups, respectively for HZ were:

HZ All

- RCTs (Tofa 5 mg BID): 0.00 (0.00, 3.28)
- All AS (All Tofa 5 mg BID, All Tofa): 2.18 (0.71, 5.08), 2.68 (1.08, 5.53)

HZ serious

- RCTs (Tofa 5 mg BID): 0.00 (0.00, 3.28)
- All AS (All Tofa 5 mg BID, All Tofa): 0.00 (0.00, 1.59), 0.00 (0.00, 1.40)

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: Results are described for the 31 March 2018 datacut, the primary analyses. Results from the larger patient population included in the 31 January 2019 datacut were similar.

In the full sample (i.e., untrimmed/unmatched), the crude incidence rate of total HZ events was increased among the tofacitinib group with 34 events with a crude incidence rate of 1.61 (95% CI =1.11, 2.25) when compared with the bDMARD group (crude incidence rate of 0.73

[95% CI = 0.57, 0.92], CIs do not overlap). This difference was driven by non-serious HZ events (0 serious events occurred in the tofacitinib group and 4 in the bDMARD group).

When comparing crude rates of events among tofacitinib initiators with rates among csDMARD initiators, incidence rates of total HZ events were increased among the tofacitinib compared with the csDMARD group (crude incidence rate of 0.44 [95% CI = 0.23, 0.75]). CIs for total HZ did not overlap. This difference in total HZ was driven by non-serious HZ events.

The crude incidence rate of total HZ events in the trimmed cohort was increased among the tofacitinib group (crude incidence rate of 1.59 [95% CI = 1.02, 2.37]) when compared with the bDMARD group (crude incidence rate of 0.69 [95% CI = 0.52, 0.90]). This difference was driven by non-serious HZ events.

Please see table below for the crude rates and 95% CI for safety events of interest (acute exposure) among eligible RA patients initiating tofacitinib, bDMARD, or csDMARD.

Table 67. Crude Rates (per 100 PY) and 95% CI for HZ Among Eligible RA Patients Initiating Tofacitinib, bDMARD, or csDMARD (Primary Analyses)

	31 March 2018 Datacut[a]								
	Tofacitinib			bDMARD			csDMARD		
	Rate	95% LL	95% UL	Rate	95% LL	95% UL	Rate	95% LL	95% UL
HZ (all: serious and non-serious)									
Full sample	1.61	1.11	2.25	0.73	0.57	0.92	0.44	0.23	0.75
PS Trimmed	1.59	1.02	2.37	0.69	0.52	0.90	NR	NR	NR
PS Matched	1.59	1.02	2.37	0.69	0.47	0.99	NR	NR	NR
Serious HZ	0	0	0.17	0.04	0.01	0.1	0	0	0.12
Non-serious HZ	1.61	1.11	2.25	0.69	0.54	0.88	0.44	0.23	0.75

a. Primary analysis

bDMARD=biologic disease modifying antirheumatic drug; csDMARD=conventional synthetic disease modifying antirheumatic drug; HZ=herpes zoster; LL=lower limit; N=count; NR=not reported; PS=propensity score; PY=person-years; RA=rheumatoid arthritis; UL=upper limit

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Seriousness/outcomes

RA: In the All RA population, 58 HZ cases were serious and 737 were non-serious. The outcomes reported for HZ were resolved (774), still present at the time of report (20), and unknown (1).

Study A3921133: The seriousness of all HZ for the following treatment groups were:

- Tofacitinib 5 mg BID: serious (10), non-serious (170)
- Tofacitinib 10 mg BID: serious (17), non-serious (161)

- All Tofa: serious (27), non-serious (331)
- TNFi: serious (2), non-serious (56)

The outcomes for all HZ for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (176), still present (4)
- Tofacitinib 10 mg BID: resolved (174), still present (4)
- All Tofa: resolved (350), still present (8)
- TNFi: resolved (55), still present (3)

PsA: In the All PsA population, 1 HZ case was serious and 35 were non-serious. The outcomes reported for HZ were resolved (34) and still present at the time of the report (2).

UC: In the All UC population, 7 HZ cases were serious and 85 were non-serious. The outcomes reported for HZ were resolved (89) and still present at the time of the report (3).

JIA: In the JIA integrated safety analysis population, 3 HZ cases were reported and all 3 were non-serious and all 3 resolved.

AS: In the All AS population (All Tofa 5 mg BID), no HZ cases were serious and 5 were non-serious; all 5 HZ cases resolved. In the All AS population (All Tofa), no HZ cases were serious and 7 were non-serious; all 7 HZ cases resolved.

Post-Marketing:

Table 68. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – HZ Reactivation (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Herpes zoster	3718	526	317	2	1245	48	314	2110
Ophthalmic herpes zoster	79	79	13	0	32	1	9	37
Herpes zoster disseminated	21	21	11	0	6	3	0	12
Herpes zoster reactivation	16	2	1	0	6	0	1	9
Herpes zoster cutaneous disseminated	10	10	2	0	3	1	0	6
Herpes zoster oticus	10	10	4	0	6	2	1	1
Genital herpes zoster	9	1		0	3	0	0	6
Herpes zoster infection neurological	6	6	1	0	4	0	1	1
Herpes zoster meningitis	6	6	3	0	5	0	0	1
Herpes zoster meningoencephalitis	6	6	3	1	3	1	0	1
Herpes zoster meningomyelitis	2	2	0	0	0	0	0	2

Table 68. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – HZ Reactivation (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Herpes zoster meningoradiculitis	1	1	1	0	0	0	1	0
Total	3884	670	356	3	1313	56	327	2186

F = fatal; H = hospitalisation; HZ = herpes zoster; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 69. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – HZ Reactivation (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Herpes zoster	1315	79	45	0	360	7	135	814
Ophthalmic herpes zoster	29	29	3	0	4	1	5	19
Herpes zoster reactivation	4	0	0	0	0	0	1	3
Herpes zoster disseminated	3	3	2	0	2	0	0	1
Herpes zoster oticus	2	2	0	0	0	0	0	2
Herpes zoster infection neurological	1	1	0	0	0	0	1	0
Total	1354	114	50	0	366	8	142	839

H = hospitalisation; F = fatal; HZ = herpes zoster; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk

RA: In the All RA population 327 HZ cases were mild, 434 were moderate, and 34 were severe.

Study A3921133: The severity of all HZ for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (61), moderate (110), severe (9)
- Tofacitinib 10 mg BID: mild (49), moderate (116), severe (13)
- All Tofa: mild (110), moderate (226), severe (22)
- TNFi: mild (16), moderate (40), severe (2)

PsA: In the All PsA population, 15 HZ cases were mild, 20 were moderate, and 1 was severe.

UC: In the All UC population, 34 HZ cases were mild, 53 were moderate, and 5 were severe.

JIA: In the JIA integrated safety analysis population, 2 HZ cases were mild and 1 was moderate.

AS: In the All AS population (All Tofa 5 mg BID), 3 HZ cases were mild and 2 were moderate. None were severe. In the All AS population (All Tofa), 4 HZ cases were mild and 3 were moderate. None were severe.

VII.3.1.1.3.4. Risk factors and risk groups

There is a higher rate of HZ in Japanese and Korean patients. Patients who have had RA for many years, were elderly, or have previously used two or more medicines that depress the immune system, including so called targeted biologic (antibody) therapies, such as those that inhibit tumour necrosis factor, and corticosteroids also have an increased risk. Patients with a low white blood cell (lymphocyte) count may have an increased risk of HZ. Patients treated with 10 mg twice daily also have an increased risk.

VII.3.1.1.3.5. Preventability

In general, preventive measures may include screening for infections prior to initiation of tofacitinib treatment and monitoring lymphocytes counts during therapy.

Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding RA who have received 2 or more prior bDMARDs.

VII.3.1.1.3.6. Impact on the risk-benefit balance of the product

HZ may be mild, moderate, or severe and sometimes life-threatening.

VII.3.1.1.3.7. Public health impact

HZ infections, in particular severe types of HZ infection (eg, disseminated HZ), can lead to morbidity and mortality. The impact of these infections on public health is significant both in terms of lost time at work and increased burden on medical care.

VII.3.1.1.3.7.1. Risk of herpes zoster infections in Asian patients

RA: In tofacitinib RA clinical studies, the large majority of subjects who self-identified as of Asian race were from Japan, Korea, China, Taiwan, or the south Asian countries (Thailand, Malaysia, Philippines, and India). The self-identified racial category of Asian had a higher proportion of subjects reporting HZ infections than did the other race categories in the All RA population (Table 70).

To determine whether this increased rate is a broad regional effect versus a country level effect, the rate of HZ was assessed by individual Asian country. As shown in Table 71, only the HZ rates in Japan and Korea were clearly higher than in non-Asian regions based on non-overlapping confidence intervals and also compared to rates in other Asian countries (range 2.9-5.4/100 PY). The increased risk of HZ in Japanese and Korean patients treated with tofacitinib is communicated in the Summary of Product Characteristics (SmPC).

Table 70. Rheumatoid Arthritis Exposure Estimates and Incidence Rates for All Herpes Zoster by Race, in the All Rheumatoid Arthritis Population (P123LTE)

	White	Black	Asian	Other
Total pts exposure (n)	5170	252	1812	730
Unique pts with events (n)	454	17	259	65
Total PY of exposure for event	14865.73	597.00	4624.01	2112.14
Incidence rate per 100 PY (95% CI)–Crude	3.05 (2.78, 3.35)	2.85 (1.66, 4.56)	5.60 (4.94, 6.33)	3.08 (2.38, 3.92)

PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data cutoff date. Incidence rate (number of subjects with events per 100 subject-years). Exact Poisson (adjusted for Pt-yr) 95% confidence intervals are provided for the crude incidence rate.
Includes protocols: A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215 and A3921237.
Final data 18 January 2019
CI = confidence interval; Pt = patient; PY = patient year
Source: Table 1614.6.3

Table 71. Rheumatoid Arthritis Exposure Estimates and Incidence Rates for All Herpes Zoster by Regions/Countries in the All Rheumatoid Arthritis Population (P123LTE)

	Total Subjects	Subjects with Events	Exposure for Event (PY)	Incidence Rate (95% CI)
Global RA programme	7964	795	22198.96	3.58(3.34, 3.84)
Non-Asian[a]	6046	515	17189.18	3.00 (2.74, 3.27)
Individual Regions				
US/Canada	2021	195	4849.95	4.02(3.48, 4.63)
Europe (European economic Area)	2180	184	6673.64	2.76 (2.37, 3.19)
Latin America	1246	123	3688.58	3.33 (2.77, 3.98)
Asia[b]	1775	255	4546.92	5.61(4.94, 6.34)
Individual Asian Countries				
Australia/New Zealand	143	25	462.78	5.40 (3.50, 7.97)
[redacted]	765	122	1595.73	7.65 (6.35, 9.13)
[redacted]	333	64	869.51	7.36 (5.67, 9.40)
[redacted]	197	16	546.38	2.93 (1.67, 4.76)
Thailand/Malaysia/ Philippines	220	27	638.17	4.23 (2.79, 6.16)
China/Taiwan	260	26	897.14	2.90 (1.89, 4.25)

a. Global population excluding all subjects in Asian countries
b. Excludes Australia and New Zealand
CI = confidence interval. PY (subject-year): Total follow up time calculated up the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data cutoff date. Incidence rate (number of subjects with events per 100 subject-years). Exact Poisson (adjusted for patient-year) 95% confidence intervals are provided for the crude incidence rate. Includes protocols -A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year data), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215 and A3921237.

Table 71. Rheumatoid Arthritis Exposure Estimates and Incidence Rates for All Herpes Zoster by Regions/Countries in the All Rheumatoid Arthritis Population (P123LTE)

	Total Subjects	Subjects with Events	Exposure for Event (PY)	Incidence Rate (95% CI)

Final data 18 January 2019.
Source: Table 1614.6.4, Table 1614.6.5, Table 1571.2.2.3, Table 1571.5.2.1.1

Study A3921133: The IR per 100 PY (95% CI) of all HZ in the All Tofa group are shown in the table below by race and by geographic region.

Table 72. Exposure Estimates and Incidence Rates for All Herpes Zoster by Race, in A3921133 (All Tofa)

	White	Black	Asian	Other
N	2254	128	121	408
n	265	7	26	60
n1	7	0	2	0
Total PY of exposure for event	7173.45	415.92	382.03	1345.96
Incidence rate per 100 PY (95% CI)	3.69 (3.26, 4.17)	1.68 (0.68, 3.47)	6.81 (4.45, 9.97)	4.46 (3.40, 5.74)

N- The total number of subjects in the treatment group in the Safety population.
n- Number of subjects with first event within the risk period. n1- Number of subjects with first event outside the risk period.
PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of up to 28 days beyond the last dose or to the last contact date.
The last contact date was maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact Date). If a subject died, last contact date was the death date. First events were counted within the risk period. If a subject did not have an event or had an event but outside the risk period, the subject was censored at the end of risk period.
Source: Table 1657.7.4.5

PsA

Table 73. PsA Exposure Estimates and Incidence Rates for All Herpes Zoster by Race, in the All PsA Population (P3LTE)

	White	Black	Asian	Other
Total pts exposure (n)	739	3	23	18
Unique pts with events (n)	34	0	1	1
Total PY of exposure for event	1934.54	6.90	58.79	45.76
Incidence rate per 100 pt-yr (95% CI) – Crude	1.76 (1.22, 2.46)	0.00 (0.00, 53.47)	1.70 (0.04, 9.48)	2.19 (0.06, 12.18)

CI = confidence interval; n = number; PY = patient-year; PsA = psoriatic arthritis
Each patient is counted once per treatment cohort administered, ie, a patient may contribute to more than one treatment cohort.
Includes protocols: A3921125, A3921091, A3921092.
Final data 31 July 2019
Source: Table 00118.C3.2.1.4

Table 74. PsA Exposure Estimates and Incidence Rates for All Herpes Zoster by Regions in the All PsA Population (P3LTE)

	Total Subjects	Subjects with Events	Exposure for Event	Incidence Rate (95% CI)
Global PsA Programme	783	26	1532.72	1.70 (1.11, 2.49)
Non-Asian[a]	768	35	2007.61	1.74 (1.21, 2.42)
Individual Regions				
US/Canada	158	10	356.80	2.80 (1.34, 5.15)
Latin America	68	1	184.12	0.54 (0.01, 3.03)
Asia[b]	15	1	38.37	2.61 (0.07, 14.52)
Australia and Western Europe	173	12	378.83	3.17 (1.64, 5.53)
Russia and Eastern Europe	369	12	1087.86	1.10 (0.57, 1.93)

a. Global population excluding all subjects in Asian countries.
b. Asian countries include only Taiwan
PsA = psoriatic arthritis, CI = confidence interval; US = United States
Includes protocols: A3921091, A3921092 and A3921125
Final data 31 July 2019
Source: Tables 00118.C3.2.1.1, 00118.C3.2.1.15, 00118.C3.11.7.1

UC

Table 75. UC Exposure Estimates and Incidence Rates for All Herpes Zoster by Race, in the All UC Population (P2P3LTE)

	White	Black	Asian	Other	Not reported
Total pts exposure (n)	927	10	144	42	34
Unique pts with events (n)	64	0	20	5	3
Total PY of exposure for event	2182.17	22.21	343.91	101.46	70.56
Incidence rate per 100 PY (95% CI) – Crude	2.93 (2.26, 3.75)	0.00 (0.00, 16.61)	5.82 (3.55, 8.98)	4.93 (1.60, 11.50)	4.25 (0.88, 12.42)

PY = patient-year, CI = confidence interval; UC = ulcerative colitis
n: Number of subjects with the event. Events are counted up to 28 days beyond the last dose.
PY: Total follow up time calculated up to the earliest of: day of the first event, progression to next study, or time to last dose + 28 days.
IR: Incidence Rate (Number of subjects with events per 100 subject-years). CI = Confidence Interval. Exact Poisson (adjusted for Pt-yr) CI are provided for the crude IR.
Includes protocols: A3921063, A3921094, A3921095, A3921096, A3921139.
Final data 24 August 2020Source: Table 417b.4

Table 76. UC Exposure Estimates and Incidence Rates for All Herpes Zoster by Regions/Countries in the All UC Population (P2P3LTE)

	Total Subjects	Subjects with Events	Exposure for Event	Incidence Rate (95% CI)
Global UC Programme	1157	92	2720.32	3.38 (2.73, 4.15)
Individual Regions/Countries				
Eastern Europe	342	10	934.67	1.07 (0.51, 1.97)
Western Europe	344	30	730.69	4.11 (2.77, 5.86)
[redacted]	32	3	61.33	4.89 (1.01, 14.30)
[redacted]	35	1	90.82	1.10 (0.03, 6.14)
Individual Asian Countries				
[redacted]	65	10	146.86	6.81 (3.27, 12.52)
[redacted]	57	6	153.78	3.90 (1.43, 8.49)

CI = confidence interval, Exact Poisson (adjusted for Pt-yr) CI are provided for the crude IR; IR = incidence rate (Number of subjects with events per 100 subject-years); UC = ulcerative colitis
Events are counted up to 28 days beyond the last dose.
Patient years: Total follow up time calculated up to the earliest of: day of the first event, time to progression to next study, or time to last dose + 28 days.Includes protocols: A3921063, A3921094, A3921095, A3921096, A3921139
Final data 24 August 2020
Source: Table 14.2.9.1.c3b

JIA: No Asian subjects participated in the JIA studies A3921103, A3921104, or A3921145.

AS

Table 77. AS Exposure Estimates and Incidence Rates for All Herpes Zoster by Race, in the All AS Population

	All Tofa 5 mg BID			All Tofa		
	White	Asian	Other	White	Asian	Other
N	252	63	1	334	85	1
n	5	0	0	6	1	0
PY	182.64	46.09	1.00	207.05	52.84	1.00
Incidence rate per 100 PY (95% CI)	2.74 (0.89, 6.39)	0.00 (0.00, 8.00)	0.00 (0.00, 369.14)	2.90 (1.06, 6.31)	1.89 (0.05, 10.54)	0.00 (0.00, 369.14)

AS = ankylosing spondylitis; CI = confidence interval; PY = patient-year
Based on 28-Day (While on Treatment) Risk Period, which is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death]. Under While on Treatment Estimand, PY (denominator for IR) is the sum of the times to the first event for subjects with an event or the risk periods for subjects without an event within the 28-Day (While on Treatment) Risk Period.
N: Number of subjects included in the Safety Analysis Set; n: Number of subjects with an event within the 28-Day (While on Treatment) Risk Period; IRs are estimated based on n under this estimand. 95% CI for IR is based on Exact Poisson Distribution without adjustment to study. For subjects randomized to Placebo à Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment.
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C2.3.3.4.4-E

Table 78. AS Exposure Estimates and Incidence Rates for All Herpes Zoster by Regions in the All AS Population

	All Tofa 5 mg BID				All Tofa			
	N	n	PY	IR (95% CI)	N	n	PY	IR (95% CI)
Global	316	5	229.74	2.18 (0.71, 5.08)	420	7	260.89	2.68 (1.08, 5.53)
Individual Regions/Countries								
US/Canada	38	2	23.53	8.50 (1.03, 30.71)	51	2	27.11	7.38 (0.89, 26.65)
European Union	136	3	96.33	3.11 (0.64, 9.10)	200	4	115.61	3.46 (0.94, 8.86)
Asia	61	0	44.05	0.00 (0.00, 8.37)	83	1	50.80	1.97 (0.05, 10.97)
Rest of World	81	0	65.82	0.00 (0.00, 5.60)	86	0	67.37	0.00 (0.00, 5.48)

AS = ankylosing spondylitis, CI = confidence interval; IR = incidence rate; PY = patient-year; US = United States
Based on 28-Day (While on Treatment) Risk Period, which is defined as the smallest of [time (in days) to last dose + 28 days], [time to discontinuation from study], [time to last observation], and [time to death]. Under While on Treatment Estimand, PY (denominator for IR) is the sum of the times to the first event for subjects with an event or the risk periods for subjects without an event within the 28-Day (While on Treatment) Risk Period.
N: Number of subjects included in the Safety Analysis Set; n: Number of subjects with an event within the 28-Day (While on Treatment) Risk Period; IRs are estimated based on n under this estimand. 95% CI for IR is based on Exact Poisson Distribution without adjustment to study. For subjects randomized to Placebo à Tofa 5 mg BID, the date of first dose refers to the date of first dose of tofacitinib treatment.
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C2.5.1.2.1-E, Table C2.3.3.4.3-E

VII.3.1.1.4. Lung Cancer

VII.3.1.1.4.1. Potential mechanisms

The potential mechanism of tofacitinib, as a risk for lung cancer, is unclear. It is possible that tofacitinib may affect tumour immunosurveillance as a result of its immunosuppressive effects; this may manifest particularly in patients whose immune system is compromised due to biologic considerations (such as older age) or extrinsic factors (such as smoking).

VII.3.1.1.4.2. Evidence source and strength of evidence

Clinical trial data (A3921133).

VII.3.1.1.4.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: In the RCTs the IRs (95% CI) per 100 PY of lung cancer for the 5 mg BID, 10 mg BID dose groups and overall tofacitinib, respectively, were 0.12 (0.02, 0.34), 0.05 (0.00, 0.28), 0.08 (0.02, 0.19). In the All RA population, the IRs (95% CI) per 100 PY of lung cancer for the 5 mg BID, 10 mg BID dose groups and overall tofacitinib, respectively, were 0.13 (0.07, 0.23), 0.12 (0.07, 0.19), 0.12 (0.08, 0.18).

Study A3921133: The IRs per 100 PY (95% CI) for adjudicated lung cancer for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.21 (0.11, 0.38), 0.21 (0.10, 0.38), 0.21 (0.13, 0.32), 0.12 (0.04, 0.26).

PsA: In the RCTs the IRs (95% CI) per 100 PY of lung cancer for the 5 mg BID and 10 mg BID dose groups, respectively, were 0.00 (0.00, 2.39), 0.00 (0.00, 2.44). In the All PsA population, the IRs (95% CI) per 100 PY of lung cancer for the 5 mg BID, 10 mg BID, and combined 5 mg and 10 mg dose groups, respectively, were 0.00 (0.00, 0.28), 0.00 (0.00, 0.46), 0.00 (0.00, 0.18).

UC: In RCTs no lung cancer cases were reported. The IRs per 100 PY (95% CI) of lung cancer from the All UC (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 0.00 (0.00, 0.46), 0.05 (0.00, 0.26), 0.03 (0.00, 0.19).

JIA: There were no cases of lung cancer from the JIA integrated safety analysis population.

AS: There were no cases of lung cancer in the AS clinical development programme.

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: The crude rates and 95% CI for lung cancer among eligible RA patients initiating tofacitinib, bDMARD, or csDMARD, respectively, were 0.13 (95% CI 0.05, 0.29), 0.11 (95% CI 0.06, 0.17), 0.26 (95% CI 0.14, 0.43).

Seriousness/outcomes

RA: In the All RA population, the outcomes for lung cancer were resolved (3), still present (8), death (16), and unknown (3).

Study A3921133: The outcomes for adjudicated lung cancer (all assessed as serious) for the following treatment groups were:

- Tofacitinib 5 mg BID: still present (10), death (1)
- Tofacitinib 10 mg BID: resolved (3), still present (7)
- All Tofa: resolved (3), still present (17), death (1)
- TNFi: resolved (1), still present (5)

PsA: In the All PsA population, no lung cancer cases were reported.

UC: In the All UC population, there was 1 lung cancer case, which was serious and still present.

JIA: There were no cases of lung cancer from the JIA integrated safety analysis population.

AS: There were no cases of lung cancer in the AS clinical development programme.

Post-Marketing:

Table 79. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Lung Cancer (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Lung neoplasm malignant	181	181	32	28	10	1	41	101
Lung adenocarcinoma	17	17	10	0	5	2	7	3
Lung carcinoma cell type unspecified stage IV	11	11	2	1	1	0	4	5
Throat cancer	10	10	0	0	0	0	2	8
Lung cancer metastatic	9	9	2	4	1	0	2	2
Squamous cell carcinoma of lung	7	7	4	1	4	0	0	2
Lung adenocarcinoma stage III	3	3	2	0	0	0	2	1
Lung carcinoma cell type unspecified recurrent	3	3	0	0	0	0	0	3
Lung carcinoma cell type unspecified stage I	3	3	2	0	0	0	0	3
Non-small cell lung cancer	3	3	1	1	2	0	0	0
All others	12	12	5	1	0	0	7	4
Total	259	259	60	36	23	3	65	132

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 80. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Lung Cancer (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Lung neoplasm malignant	101	101	13	4	8	0	10	79
Lung carcinoma cell type unspecified stage IV	11	11	1	0	0	0	2	9
Lung cancer metastatic	4	4	2	1	0	0	1	2
Lung carcinoma cell type unspecified stage I	4	4	2	0	2	0	0	2
Lung adenocarcinoma	3	3	1	1	0	0	0	2
All others	7	7	1	1	0	0	2	4
Total	130	130	20	7	10	0	15	98

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk

RA: In the All RA population 1 case of lung cancer was mild, 7 were moderate, and 22 were severe.

Study A3921133: The severity of adjudicated lung cancer for the following treatment groups were:

- Tofacitinib 5 mg BID: moderate (1), severe (10)
- Tofacitinib 10 mg BID: severe (10)
- All Tofa: moderate (1), severe (20)
- TNFi: moderate (3), severe (3)

PsA: In the All PsA population, no lung cancer cases were reported.

UC: In the All UC population, there was 1 lung cancer case, which was severe.

JIA: There were no cases of lung cancer from the JIA integrated safety analysis population.

AS: There were no cases of lung cancer in the AS clinical development programme.

VII.3.1.1.4.4. Risk factors and risk groups

Patients with RA may be at higher risk than the general population for the development of lung cancer. In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer, lymphoma, and an increase in NMSC was observed with tofacitinib compared to TNF inhibitors.

Summary of Study A3921133 results: an increase in malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with tofacitinib compared to TNF inhibitor. The IRs of lung cancer per 100 PY (95% CI) (based on total time) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All tofacitinib, and TNFi groups, respectively, were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), 0.28 (0.19, 0.39), 0.13 (0.05, 0.26).

VII.3.1.1.4.5. Preventability

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.

VII.3.1.1.4.6. Impact on the risk-benefit of the product

Based on the established benefits of tofacitinib for the approved indications and the routine and additional risk mitigation measures that are being proposed to manage the risk of lung cancer, the benefit:risk balance for tofacitinib at the recommended doses remains favourable.

VII.3.1.1.4.7. Public health impact

Lung cancer is a major public health burden and is the leading cause of cancer-related death among men and women globally.[287]

VII.3.1.1.5. Lymphoma

VII.3.1.1.5.1. Potential mechanisms

The potential mechanism of tofacitinib, as a risk for lymphoma, is unclear. It is possible that tofacitinib may affect tumour immunosurveillance as a result of its immunosuppressive effects; this may manifest particularly in patients whose immune system is compromised due to biologic considerations (such as older age) or extrinsic factors (such as smoking).

VII.3.1.1.5.2. Evidence source and strength of evidence

Clinical trial data (A3921133).

VII.3.1.1.5.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: In the RCTs the IRs (95% CI) per 100 PY of lymphoma for the 5 mg BID, 10 mg BID dose groups and overall tofacitinib, respectively, were 0.00 (0.00, 0.14), 0.15 (0.03, 0.44), 0.06 (0.01, 0.17). In the All RA population, the IRs (95% CI) per 100 PY of lymphoma for the 5 mg BID, 10 mg BID dose groups and overall tofacitinib, respectively, were 0.01 (0.00, 0.06), 0.07 (0.04, 0.13), 0.05 (0.03, 0.09).

Study A3921133: The IRs per 100 PY (95% CI) for adjudicated lymphoma for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.08 (0.02, 0.20), 0.10 (0.03, 0.24), 0.09 (0.04, 0.17), 0.02 (0.00, 0.11).

PsA: In the RCTs the IRs (95% CI) per 100 PY of lymphoma for the 5 mg BID and 10 mg BID dose groups, respectively, were 0.00 (0.00, 2.39), 0.00 (0.00, 2.44). In the All PsA population, the IRs (95% CI) per 100 PY of lymphoma for the 5 mg BID, 10 mg BID, and combined 5 mg and 10 mg dose groups, respectively, were 0.08 (0.00, 0.43), 0.00 (0.00, 0.46), 0.05 (0.00, 0.27).

UC: In RCTs no lymphoma cases were reported. The IRs per 100 PY (95% CI) of lymphoma from the All UC (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 0.13 (0.00, 0.70), 0.05 (0.00, 0.26), 0.07 (0.01, 0.25).

JIA: There were no cases of lymphoma from the JIA integrated safety analysis population.

AS: There were no cases of lymphoma in the AS clinical development programme.

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: The crude rates and 95% CI for lymphoma among eligible RA patients initiating tofacitinib, bDMARD, or csDMARD, respectively, were 0.09 (95% CI 0.02, 0.23), 0.09 (95% CI 0.05, 0.15), 0.02 (95% CI 0.00, 0.10).

Seriousness/outcomes

RA: In the All RA population, the outcomes for lymphoma were resolved (7) and still present (5).

Study A3921133: The outcomes for adjudicated lymphoma (all assessed as serious) for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (1), still present (3)
- Tofacitinib 10 mg BID: resolved (2), still present (3)
- All Tofa: resolved (3), still present (6)
- TNFi: still present (1)

PsA: In the All PsA population, the outcome for the lymphoma case was resolved.

UC: In the All UC population, the outcomes for lymphoma were resolved (1) and still present (1).

JIA: There were no cases of lymphoma from the JIA integrated safety analysis population.

AS: There were no cases of lymphoma in the AS clinical development programme.

Post-Marketing:

Table 81. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Lymphoma (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Lymphoma	110	110	22	5	16	3	21	65
Hodgkin's disease	19	19	6	1	9	0	4	5
B-cell lymphoma	18	18	8	2	2	0	4	10
Diffuse large B-cell lymphoma	17	17	13	1	8	1	3	4
Non-Hodgkin's lymphoma	17	17	3	1	1	0	2	13
Epstein-Barr virus associated lymphoproliferative disorder	4	4	2	0	2	1	0	1

Table 81. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Lymphoma (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Mantle cell lymphoma	4	4	2	0	0	0	2	2
Cutaneous lymphoma	3	3	1	0	2	0	1	0
T-cell lymphoma	3	3	0	0	0	0	0	3
All others	20	20	5	0	4	0	3	13
Total	215	215	62	10	44	5	40	116

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 82. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Lymphoma (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Lymphoma	28	28	3	0	4	0	6	18
B-cell lymphoma	7	7	3	0	2	0	2	3
Non-Hodgkin's lymphoma	6	6	1	0	1	0	2	3
Hodgkin's disease	3	3	0	0	1	0	0	2
Follicle centre lymphoma, follicular grade I, II, III	2	2	0	0	0	0	2	0
All others	7	7	4	1	0	0	3	3
Total	53	53	11	1	8	0	15	29

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk

RA: In the All RA population 6 cases of lymphoma were moderate and 6 were severe.

Study A3921133: The severity of adjudicated lymphoma for the following treatment groups were:

- Tofacitinib 5 mg BID: moderate (1), severe (3)
- Tofacitinib 10 mg BID: mild (1), severe (4)
- All Tofa: mild (1), moderate (1), severe (7)
- TNFi: severe (1)

PsA: In the All PsA population, no lung cancer cases were reported.

UC: In the All UC population, there were 2 lymphoma cases, which were severe.

JIA: There were no cases of lymphoma from the JIA integrated safety analysis population.

AS: There were no cases of lymphoma in the AS clinical development programme.

VII.3.1.1.5.4. Risk factors and risk groups

Patients with RA, particularly those with highly active disease, may be at higher risk (up to several fold) than general population for the development of lymphoma. In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer, lymphoma, and an increase in NMSC was observed with tofacitinib compared to TNF inhibitors.

Summary of Study A3921133 results: an increase in malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with tofacitinib compared to TNF inhibitor. The IRs of lymphoma per 100 PY (95% CI) (based on total time) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All tofacitinib, and TNFi groups, respectively, were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), 0.09 (0.04, 0.17), 0.02 (0.00, 0.10).

VII.3.1.1.5.5. Preventability

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.

VII.3.1.1.5.6. Impact on the risk-benefit of the product

Based on the established benefits of tofacitinib for the approved indications and the routine and additional risk mitigation measures that are being proposed to manage the risk of lymphoma, the benefit:risk balance for tofacitinib at the recommended doses remains favourable.

VII.3.1.1.5.7. Public health impact

Lymphoma is the seventh most frequent cancer diagnosis in the world[288] and thus may pose a major public health burden.

VII.3.1.1.6. Myocardial Infarction

VII.3.1.1.6.1. Potential mechanisms

The potential mechanism of tofacitinib, as a risk for MI, is unknown. Assessments of clinical and molecular/biomarker data (such as D-Dimer, lipids, and platelet) from the tofacitinib program have been conducted to better understand the potential mechanism. Whilst an increase in MI was observed in Study A3921133 in tofacitinib treatment arms relative to the TNF inhibitor treatment arm, a conclusive mechanistic basis for this finding has not been identified.

VII.3.1.1.6.2. Evidence source and strength of evidence

Clinical trial data (A3921133)

VII.3.1.1.6.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: In the All RA population the IR (95% CI) per 100 PY of adjudicated events of total MI for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.18 (0.10,0.30), 0.15 (0.09,0.22), 0.16 (0.11,0.22).

Study A3921133: The IRs of adjudicated MI (total) per 100 PY (95% CI) for the tofacitinib 5 mg, tofacitinib 10 mg, All Tofa, and TNFi groups, respectively, were 0.35 (0.21, 0.55), 0.39 (0.24, 0.61), 0.37 (0.26, 0.51), 0.20 (0.10, 0.37). The IRs of adjudicated MI (non-fatal) per 100 PY (95% CI) (60-Day On-Treatment Time) for the tofacitinib 5 mg, tofacitinib 10 mg, All Tofa, and TNFi groups, respectively, were 0.35 (0.21, 0.55), 0.33 (0.19, 0.54), 0.34 (0.24, 0.48), 0.16 (0.07, 0.31).

PsA: In the All PsA population, the IRs (95% CI) of MI (total) for the 5 mg and 10 mg dose groups and the combined 5 mg and 10 mg dose groups, respectively, were 0.11 (0.00, 0.60), 0.16 (0.00, 0.87), 0.13 (0.02, 0.46).

UC: The IRs per 100 PY (95% CI) of adjudicated MI from the All UC (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 0.38 (0.08, 1.11), 0.00 (0.00, 0.17), 0.10 (0.02, 0.30).

JIA: There were no cases of MI from the JIA integrated safety analysis population.

AS: There were no cases of MI in the AS clinical development programme.

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: The crude rates and 95% CI for MI among eligible RA patients initiating tofacitinib, bDMARD, or csDMARD, respectively, were 0.28 (95% CI 0.1, 0.61), 0.3 (95% CI 0.21, 0.43), 0.3 (95% CI 0.14, 0.58).

Seriousness/outcomes:

RA: In the All RA population, there were 37 adjudicated MI, of which 34 were serious and 3 were non-serious. The outcomes were resolved (33), still present (2), and fatal (2).

Study A3921133: The outcomes for adjudicated myocardial infarction (all assessed as serious) for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (15), still present (3)
- Tofacitinib 10 mg BID: resolved (13), still present (3), death (3)
- All Tofa: resolved (28), still present (6), death (3)

TNFi: resolved (7), still present (1), death (2)

PsA: In the All PsA population there were 2 adjudicated MI, which were all serious. The outcomes were resolved (2).

UC: In the All UC population, there were 3 adjudicated MI cases, all assessed as serious. The outcomes were resolved (3).

JIA: There were no cases of MI from the JIA integrated safety analysis population.

AS: There were no cases of MI in the AS clinical development programme.

Post-Marketing:

Table 83. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Myocardial Infarction (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Myocardial infarction	393	393	130	46	74	2	17	254
Acute myocardial infarction	67	67	36	11	17	4	3	32
Coronary artery occlusion	28	28	15	0	6	0	6	16
Angina unstable	10	10	5	0	2	0	3	5
Coronary artery thrombosis	7	7	0	0	1	0	3	3
Acute coronary syndrome	6	6	4	0	0	2	0	4
Troponin increased	4	1	0	0	1	0	0	3
Acute cardiac event	2	2	1	1	0	0	0	1
Blood creatine phosphokinase MB increased	2	0	0	0	0	0	1	1
Silent myocardial infarction	1	1	0	0	0	0	0	1
Total	520	515	191	58	101	8	33	320

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 84. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Myocardial Infarction (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Myocardial infarction	250	250	94	11	39	0	11	189
Acute myocardial infarction	20	20	13	3	1	0	0	16
Coronary artery occlusion	11	11	4	0	3	0	0	8
Coronary artery thrombosis	6	6	1	0	1	0	1	4
Troponin increased	4	3	3	0	1	0	1	2
Acute coronary syndrome	3	3	3	0	1	1	0	1
Angina unstable	3	3	2	0	0	0	0	3
Total	297	296	120	14	46	1	13	223

H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk:

RA: In the All RA population 28 adjudicated MI were severe and 9 were moderate.

Study A3921133: The severity of adjudicated myocardial infarction for the following treatment groups were:

- Tofacitinib 5 mg BID: moderate (4), severe (14)
- Tofacitinib 10 mg BID: moderate (2), severe (17)
- All Tofa: moderate (6), severe (31)
- TNFi: moderate (3), severe (7)

PsA: In the All PsA population, adjudicated 1 MI was moderate and 1 was severe.

UC: In the All UC population, 1 adjudicated MI was mild, 2 were severe.

JIA: There were no cases of MI from the JIA integrated safety analysis population.

AS: There were no cases of MI in the AS clinical development programme.

VII.3.1.1.6.4. Risk factors and risk groups

In Study A3921133, a large, randomised active-controlled post authorisation safety surveillance study of RA patients who were 50 years of age and older and had at least one additional cardiovascular risk factor, the following predictive factors for development of MI (fatal and non-fatal) were identified using a multivariate Cox model with backward selection: age ≥65 years, male, current or past smoking, history of diabetes, and history of coronary artery disease (which includes myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures).

Summary of Study A3921133 results: an increase in incidence of non-fatal MI was observed with tofacitinib compared to TNFi. The IRs of adjudicated non-fatal MI per 100 PY (95% CI) (based on 60 days risk period) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All tofacitinib, and TNFi groups, respectively, were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), 0.35 (0.24, 0.48), 0.16 (0.07, 0.31). The IRs of adjudicated fatal MI per 100 PY (95% CI) (based on 60 days risk period) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All tofacitinib, and TNFi groups, respectively, were 0.00 (0.00, 0.07), 0.06 (0.01, 0.18), 0.03 (0.01, 0.09), 0.06 (0.01, 0.17).

VII.3.1.1.6.5. Preventability

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of MI was observed with tofacitinib compared to TNF inhibitors. In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of

atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

VII.3.1.1.6.6. Impact on the risk-benefit balance of the product

Based on the established benefits of tofacitinib for the approved indications and the routine and additional risk mitigation measures that are being proposed to manage the risk of MI, the benefit:risk balance for tofacitinib at the recommended doses remains favourable.

VII.3.1.1.6.7. Public health impact

MI is a key component of the burden of cardiovascular disease, which is among the leading causes of morbidity and mortality worldwide.[289] People with MI have a risk of recurrence and/or development of coronary heart disease-related conditions 6 times higher than those with no history of MI.[290]

VII.3.1.1.7. Decrease in Haemoglobin (Hgb) Levels and Anaemia

VII.3.1.1.7.1. Potential mechanisms

The mechanism of action of tofacitinib in the development of anaemia is not known. In RA patients, tofacitinib-mediated inhibition of erythropoietin signalling may occur via inhibition of JAK2 signalling; however, this mechanism likely requires higher doses than those recommended for use in RA patients.

VII.3.1.1.7.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.1.7.3. Characterisation of the risk

Frequency

RA: The IRs of anaemia AEs per 100 PY (95% CI) from RCTs for the 5 mg and 10 mg dose groups, and overall, respectively, were 2.95 (2.32, 3.70), 3.11 (2.38, 3.99), 3.10 (2.64, 3.62). In the All RA population, the IR of anaemia AEs for the combined tofacitinib treatment group was 2.13 per 100 PY (95% CI: 1.95, 2.33).

Study A3921133: The IRs per 100 PY (95% CI) for anaemia for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 1.90 (1.54, 2.33), 2.70 (2.25, 3.21), 2.28 (1.99, 2.61), 1.48 (1.16, 1.86).

PsA: The IRs of anaemia AEs per 100 PY (95% CI) from the RCTs for the 5 mg and 10 mg dose groups, respectively, were 1.95 (0.40, 5.70) and 1.33 (0.16, 4.81). In the All PsA population, the IR per 100 PY (95% CI) of the anaemia AEs for the combined 5 mg and 10 mg dose groups was 1.07 (0.67, 1.61).

UC: The IR of anaemia AEs per 100 PY (95% CI) from the RCT induction studies for the 10 mg dose group was 14.70 (9.42, 21.88). The IRs of anaemia AEs per 100 PY (95% CI) from the RCT maintenance study for the 5 mg and 10 mg dose groups, and combined 5 mg and 10 mg dose groups, respectively, were 5.51 (2.38, 10.85), 2.55 (0.70, 6.54), and 3.97 (2.05,

6.94). In the All UC population, the IR for anaemia AEs per 100 PY (95% CI) for the combined 5 mg and 10 mg dose groups was 2.81 (2.22, 3.51).

JIA: The IR per 100 PY (95% CI) from the integrated safety analysis population for anaemia was 4.03 (2.20, 6.77).

AS: The IR of anaemia AEs per 100 PY (95% CI) from the RCTs (Tofa 5 mg BID) was 1.76 (0.00, 5.89). In the All AS population, the IRs per 100 PY (95% CI) of the anaemia AEs for All Tofa 5 mg BID and All Tofa, respectively, were 1.30 (0.27, 3.81) and 1.15 (0.24, 3.35).

Seriousness/outcomes

RA: In the All RA population, there were 21 serious anaemia cases (473 were non-serious). The outcomes reported for anaemia were resolved (325), still present at the time of report (166), and unknown (3).

Study A3921133: The seriousness of anaemia for the following treatment groups were:

- Tofacitinib 5 mg BID: serious (7), non-serious (88)
- Tofacitinib 10 mg BID: serious (3), non-serious (122)
- All Tofa: serious (10), non-serious (210)
- TNFi: serious (1), non-serious (72)

The outcomes for anaemia for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (73), still present (21), unknown (1)
- Tofacitinib 10 mg BID: resolved (90), still present (34), unknown (1)
- All Tofa: resolved (163), still present (55), unknown (2)
- TNFi: resolved (45), still present (27), unknown (1)

PsA: In the All PsA population, there were no serious anaemia cases (22 were non-serious). The outcomes reported for anaemia were resolved (18), still present at the time of report (3), and unknown (1).

UC: In the All UC population, there were 2 serious anaemia cases (76 were non-serious). The outcomes reported for anaemia were resolved (49) and still present at the time of report (29).

JIA: In the pJIA integrated safety analysis population, there were 14 non-serious anaemia cases. The outcomes reported for anaemia were resolved (10) and still present at the time of report (4).

AS: In the All AS population (All Tofa 5 mg BID), 3 anaemia cases were reported, which were all assessed as non-serious; the outcomes were resolved (2) and still present at the time of report (1). In the All AS population (All Tofa), 3 anaemia cases were reported, which were all assessed as non-serious; the outcomes were resolved (2) and still present at the time of report (1).

Post-Marketing:

Table 85. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Decrease in Hgb Levels and Anaemia (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Anaemia	637	164	75	3	131	1	137	365
Haemoglobin decreased	363	98	40	2	61	0	60	240
Red blood cell count decreased	150	24	12	0	20	0	27	104
Haematocrit decreased	67	11	2	0	2	0	7	58
Haemoglobin abnormal	13	4	0	0	0	0	2	11
Red blood cell count abnormal	7	3	0	0	1	0	1	5
Anaemia macrocytic	4	2	0	0	1	0	2	1
Haematocrit abnormal	4	1	1	0	0	0	0	4
Microcytic anaemia	4	1	0	0	0	0	1	3
Normocytic anaemia	3	0	0	0	0	0	0	3
Aplastic anaemia	2	2	0	0	0	0	0	2
Normochromic anaemia	2	1	1	0	0	0	1	1
Aplasia pure red cell	1	1	1	0	0	0	1	
Normochromic normocytic anaemia	1	0	0	0	0	0	0	1
Total	1258	312	132	5	216	1	239	798

F = fatal; H = hospitalisation; Hgb = haemoglobin; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 86. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Decrease in Hgb Levels and Anaemia (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Anaemia	346	75	24	2	35	0	57	252
Haemoglobin decreased	109	31	9	0	6	0	11	92
Red blood cell count decreased	86	8	1	0	7	0	17	62
Haematocrit decreased	31	6	1	0	0	0	4	27
Haemoglobin abnormal	11	1	1	0	0	0	1	10
Red blood cell count abnormal	11	1	1	0	0	0	0	11
Normocytic anaemia	5	1	0	0	1	0	1	3
Haematocrit abnormal	2	0	0	0	0	0	1	1
Anaemia macrocytic	1	0	0	0	0	0	0	1

Table 86. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Decrease in Hgb Levels and Anaemia (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Microcytic anaemia	1	0	0	0	0	0	0	1
Normochromic normocytic anaemia	1	0	0	0	0	0	0	1
Total	604	123	37	2	49	0	92	461

F = fatal; H = hospitalisation; Hgb = haemoglobin; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of the risk

RA: In RCTs, severity based on the assessment of lab values[2] for the overall total tofacitinib group included: mild – 26.3%; moderate – 4.7%, severe-<1.0%; life – threatening-<1.0%.

Table 87. Number and Proportion of Patients with Decreased Hgb Levels (All RA Population, Post-baseline Hgb Levels Assessed using CTC Grades) (P123LTE)

Treatment Group	N	Grade 1[a] (Mild)	Grade 2[b] (Moderate)	Grade 3[c] (Severe)	Grade 4[d] (Life-Threatening)
Tofacitinib 5 mg BID	3928	1160 (29.5%)	270 (6.9%)	20 (<1.0%)	2 (<1.0%)
Tofacitinib 10 mg BID	3961	1337 (33.8%)	332 (8.4%)	18 (<1.0%)	0
All tofacitinib	7889	2497(31.7%)	602 (7.6%)	38 (<1.0%)	2 (<1.0%)

a. < lower limit of normal to 10 g/dL
b. <10.0 to 8.0 g/dL
c. <8.0 to 6.5 g/dL
d. <6.5 g/dL
The CTC grades are based on post-baseline lab values.
Includes protocols -A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year data), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215 and A3921237.
Final data 18 January 2019.
BID = twice daily; Hgb = haemoglobin; CTC = Common Terminology Criteria
Source: Table 1614.7.11

Severity based on the assessment of the clinical events[3] in the All RA population included: mild – 326 cases; moderate – 148 cases; severe – 20 cases.

[2] RA: The CTC grades are based on post-baseline lab values. CTC Grade Categories: Grade 1 (Mild) < lower limit of normal to 10 g/dL; Grade 2 (Moderate) < 10.0 to 8.0 g/dL; Grade 3 (Severe) <8.0 to 6.5 g/dL; Grade 4 (Life-Threatening) <6.5 g/dL

[3] Severity definitions: mild = does not interfere with subject's usual function; moderate = interferes to some extent with subject's usual function; severe = interferes significantly with subject's usual function.

Study A3921133: The severity of anaemia for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (50), moderate (39), severe (6)
- Tofacitinib 10 mg BID: mild (73), moderate (45), severe (7)
- All Tofa: mild (123), moderate (84), severe (13)
- TNFi: mild (38), moderate (32), severe (3)

PsA: In the All PsA population, post-baseline Hgb values were assessed using CTC grades.

Table 88. Number and Proportion of Patients with Decreased Hgb Levels (All PsA Population, Post-baseline Hgb Levels Assessed Using CTC Grades) (P3LTE)

Treatment Group	N	Grade 1[a] (Mild)	Grade 2[b] (Moderate)	Grade 3[c] (Severe)	Grade 4[d] (Life Threatening)
Tofacitinib 5 mg BID	457	47 (10.3%)	4 (0.9%)	0 (0.0%)	0 (0.0%)
Tofacitinib 10 mg BID	325	40 (12.3%)	4 (1.2%)	1 (0.3%)	0 (0.0%)
Combined 5 mg and 10 mg	782	87 (11.1%)	8 (1.0%)	1 (0.1%)	0 (0.0%)

a. < lower limit of normal to 10 g/dL
b. <10.0 to 8.0 g/dL
c. <8.0 to 6.5 g/dL
d. <6.5 g/dL
Each subject will be counted once based on the worst severity (right most identified category) from all post-dose values.
At least 2 consecutive measurements can confirm itself within the subject.
Includes protocols A3921091, A3921125 and A3921092 (main and substudy).
Final data 31 July 2019
BID = twice daily; Hgb = haemoglobin; CTC = Common Terminology Criteria
Source: Table 00118.C3.6.7.1.3

Severity based on the assessment of the clinical events[3] in the All PsA population included: mild – 19 cases and moderate – 3 cases.

UC: In the RCT maintenance study, severity based on the assessment of lab values[4] (unconfirmed nadir values) for the combined 5 mg and 10 mg dose groups included: mild – 21.1%; moderate – 4.1%; severe – 2.5%.

Severity based on the assessment of lab values (confirmed by second test)[4] for the All UC population combined 5 mg and 10 mg dose included: mild – 18.7%; moderate – 4.5%; severe – 1.9%.

[4] UC and AS: The grades are based on post-baseline lab values. Category 1 (mild): decrease by 2 ≤ change from baseline in haemoglobin ≤ decrease by 1; Category 2 (moderate): decrease by 3 < change from baseline in haemoglobin < decrease by 2) or (7 < haemoglobin < 8); Category 3 (severe): change from baseline in haemoglobin ≤ decrease by 3 or haemoglobin ≤ 7.

Severity based on the assessment of clinical events[3] in the All UC population included: mild – 40 cases; moderate – 35 cases; severe – 3 cases.

JIA: In the CISAP, severity based on the assessment of lab values[5] for the 5 mg BID dose group were mild – 28.4%; moderate – 2.8%; severe – 1.6%. Severity based on the assessment of clinical events in the integrated safety analysis population were mild (12) and moderate (2).

AS: Severity based on the assessment of lab values[4] (based on 2 conseutive post dose values) for RCTs (Tofa 5 mg BID) were mild – 1.6%; moderate – 0%; severe – 0%.

Severity based on the assessment of lab values[4] (based on 2 consecutive post dose values) for the All AS population (All Tofa 5 mg BID) were mild – 8.0%; moderate – 1.6%; severe – 0.6%. Severity based on the assessment of lab values for the All AS population (All Tofa) were mild – 7.5%; moderate – 1.2%; severe – 0.5%.

Severity based on the assessment of the clinical events in the All AS population was mild (2 in All Tofa 5 mg BID, 2 in All Tofa) and moderate (1 in All Tofa 5 mg BID, 1 in All Tofa).

VII.3.1.1.7.4. Risk factors and risk groups

No risk groups have been identified.

VII.3.1.1.7.5. Preventability

It is recommended that tofacitinib not be initiated in patients with Hgb < 9 g/dL. It is recommended not to initiate dosing in paediatric patients with haemoglobin less than 10 g/dL. No data are available to identify specific measures that can be used to prevent the occurrence of anaemia; however, the Phase 3 data have demonstrated that instances of clinically important anaemia are infrequent and can be adequately managed by routine monitoring.

VII.3.1.1.7.6. Impact on the risk-benefit balance of the product

The risk of clinically important anaemia is generally manageable with appropriate screening and monitoring.

VII.3.1.1.7.7. Public health impact

Anaemia can pose a significant impact on public health. Untreated anaemia can lead to morbidity and mortality and increase the burden on healthcare.

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[5] pJIA: Severity based on post-baseline lab values Hgb (g/dL). Mild: decrease by 2 ≤ change from baseline in haemoglobin ≤ decrease by 1; moderate: (decrease by 3 < change from baseline in haemoglobin < decrease by 2) or (7 < haemoglobin < 8); severe: change from baseline in haemoglobin ≤ decrease by 3 or haemoglobin ≤ 7.

VII.3.1.1.8. Non-melanoma Skin Cancer (NMSC)

VII.3.1.1.8.1. Potential mechanisms

Given tofacitinib is an immunomodulator, the risk of NMSC might be due to the impact of tofacitinib treatment on the immune system.

VII.3.1.1.8.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.1.8.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: The IRs of NMSC AEs per 100 PY (95% CI) from the RCTs for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.43 (0.21, 0.76), 0.45 (0.21, 0.86), 0.40 (0.25, 0.61). In the All RA population, 133 subjects with NMSC AEs were observed in the tofacitinib RA development programme. The overall IR (95% CI) for NMSC for the All RA population for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.45 (0.32, 0.61), 0.63 (0.50, 0.77), 0.56 (0.47, 0.66).

The overall IRs per 100 PY (95% CI) for basal cell carcinoma (BCC) from the RCTs for the 5 mg, 10 mg, and overall dose groups were 0.31 (0.13, 0.61), 0.25 (.0.08, 0.59), and 0.27 (0.15, 0.45), respectively. The overall IRs per 100 PY (95% CI) for squamous cell carcinoma (SCC) from the RCTs for the 5 mg, 10 mg, and overall dose groups were 0.12 (0.02, 0.34), 0.25 (.0.08, 0.58), and 0.15 (0.07, 0.30), respectively. The overall IRs per 100 PY (95% CI) for BCC and SCC for the overall All RA population were 0.31 (0.25, 0.39) and 0.35 (0.28, 0.43), respectively.

Study A3921133: The IRs per 100 PY (95% CI) for adjudicated NMSC for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.61 (0.41, 0.86), 0.69 (0.47, 0.96), 0.64 (0.50, 0.82), 0.32 (0.18, 0.52).

The IRs per 100 PY (95% CI) for adjudicated BCC for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.37 (0.22, 0.58), 0.33 (0.19, 0.54), 0.35 (0.24, 0.49), 0.26 (0.14, 0.44).

The IRs per 100 PY (95% CI) for adjudicated SCC for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.29 (0.16, 0.48), 0.45 (0.29, 0.69), 0.37 (0.26, 0.51), 0.16 (0.07, 0.31).

PsA: The IRs of NMSC AEs per 100 PY (95% CI) from the RCTs for the 5 mg and 10 mg dose groups, respectively, were 0.00 (0.00, 2.39) and 0.66 (0.02, 3.69). In the All PsA population, the IR per 100 PY (95% CI) of the NMSC AEs for the 5 mg and 10 mg dose groups and the combined 5 mg and 10 mg dose groups, respectively, were 0.86 (0.43, 1.53), 0.63 (0.21, 1.48), and 0.77 (0.44, 1.25).

The IRs per 100 PY (95% CI) for BCC from the RCTs for the 5 mg and 10 mg dose groups, respectively, were 0.00 (0.00, 2.39) and 0.66 (0.02, 3.69). The BCC IRs per 100 PY (95% CI) in the All PsA population for 5 mg, 10 mg, and combined 5 mg and 10 mg dose groups respectively, were 0.54 (0.22, 1.12), 0.51 (0.14, 1.29), and 0.53 (0.26, 0.95). The IRs per 100 PY (95% CI) for SCC from the RCT studies for the 5 mg and 10 mg dose groups were 0.00 (0.00, 2.39) and 0.00 (0.00, 2.44). The SCC IRs per 100 PY (95% CI) in the All PsA population for 5 mg, 10 mg, and combined 5 mg and 10 mg dose groups respectively, were 0.31 (0.08, 0.79), 0.13 (0.00, 0.70), and 0.24 (0.08, 0.56).

UC: The IR of NMSC AEs per 100 PY (95% CI) from the RCTs (induction studies, 10 mg dose group) was 1.26 (0.15, 4.56). The IRs per 100 PY (95% CI) from the RCT (maintenance study, 5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were: 0.00 (0.00, 2.48), 1.91 (0.39, 5.59), and 0.98 (0.20, 2.87). The IRs per 100 PY (95% CI) of NMSC AEs in the All UC population (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were: 0.63 (0.21, 1.48), 0.77 (0.44, 1.25), and 0.73 (0.45, 1.12).

The IR per 100 PY (95% CI) for BCC from the RCT (induction studies, 10 mg dose group) was 0.63 (0.02, 3.52). The IRs per 100 PY (95% CI) for BCC from the RCT (maintenance study, 5 mg, 10 mg, and combined 5 mg and 10 mg dose group, respectively) were 0.00 (0.00, 2.48), 0.64 (0.02, 3.54), and 0.33 (0.01, 1.82). The IRs per 100 PY (95% CI) for BCC in the All UC population (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 0.51 (0.14, 1.30), 0.53 (0.26, 0.94), and 0.52 (0.29, 0.86).

The IR per 100 PY (95% CI) for SCC from the RCT (induction studies, 10 mg dose group) was 0.63 (0.02, 3.51). The IRs for SCC from the RCT (maintenance study, 5 mg, 10 mg, and combined 5 mg and 10 mg dose group, respectively) were 0.00 (0.00, 2.48), 1.27 (0.15, 4.61), and 0.65 (0.08, 2.36). The IRs per 100 PY (95% CI) for SCC in the All UC population (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 0.25 (0.03, 0.91), 0.43 (0.20, 0.82), and 0.38 (0.19, 0.68).

JIA: There were no cases of NMSC from the JIA integrated safety analysis population.

AS: The IRs of NMSC AEs per 100 PY (95% CI) from RCTs (Tofa 5 mg BID) was 0.00 (0.00, 3.28). In the All AS population, the IR (95% CI) of the NMSC AEs for All Tofa 5 mg BID and All Tofa, respectively, were 0.00 (0.00, 1.59) and 0.00 (0.00, 1.40).

The IRs per 100 PY (95% CI) for BCC and SCC from the RCTs (Tofa 5 mg BID) was 0.00 (0.00, 3.28). In the All AS population, the IR (95% CI) of BCC and SCC for All Tofa 5 mg BID and All Tofa, respectively, were 0.00 (0.00, 1.59) and 0.00 (0.00, 1.40).

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: The table below presents crude incidence rates (i.e., number of events per 100 person-years) and associated 95% CIs for NMSC in the full sample, trimmed, and matched tofacitinib, bDMARD, and csDMARD (full sample only) initiators.

In the full sample, crude and age- and sex- adjusted incidence rates of NMSC were similar among the tofacitinib group when compared with the bDMARD group and the CIs overlapped. Across trimmed and matched populations, incidence rates of NMSC were similar among the tofacitinib and bDMARD treated patients with overlapping CIs.

Table 89. Crude Rates (per 100 PY) and 95% CI for NMSC Among Eligible RA Patients Initiating Tofacitinib, bDMARD, or csDMARD (31 January 2019, Primary Analyses)

Latent Exposure	31 January 2019 Datacut								
	Tofacitinib			bDMARD			csDMARD		
	Rate	95% LL	95% UL	Rate	95% LL	95% UL	Rate	95% LL	95% UL
NMSC									
Full sample	1.13	0.84	1.49	1.03	0.88	1.2	1.07	0.82	1.39
PS Trimmed	1.08	0.75	1.51	1.10	0.92	1.30	NR	NR	NR
PS Matched	1.09	0.76	1.53	1.11	0.89	1.36	NR	NR	NR

bDMARD=biologic disease modifying antirheumatic drug; csDMARD=conventional synthetic disease modifying antirheumatic drug; LL=lower limit; NMSC=non-melanoma skin cancer; NR=not reported; PS=propensity score; PY=person-years; RA=rheumatoid arthritis; UL=upper limit
Corrona RA Registry (study A3921205) final report: Table 24

Seriousness/outcomes

RA: In the All RA population, of 133 NMSC cases, 29 were serious and 102 were non-serious (seriousness was unknown in 2). The outcomes reported were resolved (128), still present at the time of report (3), and unknown (2).

In the All RA population, of 75 BCC cases, 17 were serious and 56 were non-serious (seriousness was unknown in 2). The outcomes reported were resolved (73), still present at the time of report (1), and unknown (1).

In the All RA population, of 83 SCC cases, 16 were serious and 67 were non-serious. The outcomes reported were resolved (79), still present at the time of report (3), and unknown (1).

Study A3921133: The seriousness of adjudicated NMSC for the following treatment groups were:

- Tofacitinib 5 mg BID: serious (2), non-serious (29)
- Tofacitinib 10 mg BID: serious (4), non-serious (29)
- All Tofa: serious (6), non-serious (58)
- TNFi: serious (3), non-serious (13)

The outcomes for adjudicated NMSC for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (27), still present (3), unknown (1)

- Tofacitinib 10 mg BID: resolved (29), still present (3), unknown (1)
- All Tofa: resolved (56), still present (6), unknown (2)
- TNFi: resolved (14), still present (2)

The seriousness of adjudicated BCC for the following treatment groups were:

- Tofacitinib 5 mg BID: serious (0), non-serious (19)
- Tofacitinib 10 mg BID: serious (1), non-serious (15)
- All Tofa: serious (1), non-serious (34)
- TNFi: serious (2), non-serious (11)

The outcomes for adjudicated BCC for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (17), still present (2)
- Tofacitinib 10 mg BID: resolved (15), unknown (1)
- All Tofa: resolved (32), still present (2), unknown (1)
- TNFi: resolved (11), still present (2)

The seriousness of adjudicated SCC for the following treatment groups were:

- Tofacitinib 5 mg BID: serious (1), non-serious (14)
- Tofacitinib 10 mg BID: serious (3), non-serious (19)
- All Tofa: serious (4), non-serious (33)
- TNFi: serious (1), non-serious (7)

The outcomes for adjudicated SCC for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (13), still present (1), unknown (1)
- Tofacitinib 10 mg BID: resolved (19), still present (2), unknown (1)
- All Tofa: resolved (32), still present (3), unknown (2)
- TNFi: resolved (7), still present (1)

PsA: In the All PsA population, of 16 NMSC cases, 4 were serious and 12 were non-serious. The outcomes reported were resolved (16).

In the All PsA population, of 11 BCC cases, 2 were serious and 9 were non-serious. The outcomes reported were resolved (11).

In the All PsA population, of 5 SCC cases, 2 were serious and 3 were non-serious. The outcomes reported were resolved (5).

UC: In the All UC population, of NMSC cases, 5 were serious and 16 were non-serious. The outcomes reported were resolved (20) and still present at the time of report (1).

In the All UC population, of BCC cases, 3 was serious and 12 were non-serious. The outcomes reported were resolved (13) and still present at the time of report (2).

In the All UC population, of SCC cases, 2 were serious and 9 were non-serious. The outcomes reported were resolved (11).

JIA: There were no cases of NMSC from the JIA integrated safety analysis population.

AS: There were no NMSC cases in the AS clinical development programme.

Post-Marketing:

Table 90. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – NMSC (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Skin cancer	206	206	11	0	34	0	38	134
Basal cell carcinoma	101	101	11	0	28	1	17	55
Squamous cell carcinoma	57	57	4	2	10	0	8	37
Squamous cell carcinoma of skin	42	42	7	0	10	0	5	27
Neuroendocrine carcinoma of the skin	15	15	6	0	2	1	7	5
Bowen's disease	8	8	2	0	6	0	1	1
Neoplasm skin	6	4	1	0	2	0	1	3
Sebaceous carcinoma	2	2	0	0	1	0	1	0
Skin cancer metastatic	2	2	1	0	0	0	2	0
Basosquamous carcinoma of skin	1	1	0	0	1	0	0	0
Keratoacanthoma	1	1	0	0	1	0	0	0
Total	441	439	43	2	95	2	80	262

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; NMSC = non-melanoma skin cancer; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 91. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – NMSC (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Skin cancer	158	158	4	0	21	0	28	109
Basal cell carcinoma	37	37	0	0	2	0	6	29
Squamous cell carcinoma	25	25	1	0	2	0	3	20
Squamous cell carcinoma of skin	21	21	0	0	2	0	4	15
Neoplasm skin	4	1	0	0	1	1	0	2
Neuroendocrine carcinoma of the skin	2	2	1	0	0	0	1	1
Total	247	244	6	0	28	1	42	176

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; NMSC = non-melanoma skin cancer; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity[6] and nature of risk

RA: In the All RA population 64 NMSC cases were mild, 57 were moderate, and 10 were severe (severity was unknown in 2).

In the All RA population, 45 BCC cases were mild, 25 were moderate, and 3 were severe (severity was unknown in 2).

In the All RA population, 39 SCC cases were mild, 37 were moderate, and 7 were severe.

Study A3921133: The severity for adjudicated NMSC for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (13), moderate (16), severe (2)
- Tofacitinib 10 mg BID: mild (12), moderate (19), severe (2)
- All Tofa: mild (25), moderate (35), severe (4)
- TNFi: mild (4), moderate (12)

The severity of adjudicated BCC for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (7), moderate (12)
- Tofacitinib 10 mg BID: mild (8), moderate (8)

[6] Severity definitions: mild = does not interfere with subject's usual function; moderate = interferes to some extent with subject's usual function; severe = interferes significantly with subject's usual function.

- All Tofa: mild (15), moderate (20)
- TNFi: mild (3), moderate (10)

The severity of adjudicated SCC for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (9), moderate (5), severe (1)
- Tofacitinib 10 mg BID: mild (9), moderate (11), severe (2)
- All Tofa: mild (18), moderate (16), severe (3)
- TNFi: mild (2), moderate (6)

PsA: In the All PsA population, 8 NMSC cases were mild, 5 were moderate, and 3 were severe. In the All PsA population, 6 BCC cases were mild, 4 were moderate, and 1 was severe. In the All PsA population, 2 SCC cases were mild, 1 was moderate, and 2 were severe.

UC: In the All UC population 11 NMSC cases were mild, 9 were moderate, and 1 was severe. In the All UC population, 7 BCC cases were mild and 8 were moderate. In the All UC population, 6 SCC cases were mild, 4 was moderate, and 1 was severe.

JIA: There were no cases of NMSC from the JIA integrated safety analysis population.

AS: There were no NMSC cases in the AS clinical development programme.

VII.3.1.1.8.4. Risk factors and risk groups

In the RA programme, NMSC primarily occurred in sun-exposed areas of the body including the face/head and hands. The commonly reported risk factors of NMSC include sun exposure (ie, ultraviolet), medications that suppress the immune system, light therapy, virus infections (eg, Human papilloma virus), age, and certain types of radiation.

In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer, lymphoma, and an increase in NMSC was observed with tofacitinib compared to TNF inhibitors.

VII.3.1.1.8.5. Preventability

Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer. As there is a higher incidence of NMSC in the elderly and in patients with a prior history of NMSC, caution should be used when treating these types of patients. In general, avoidance of risk factors like excessive exposure to sun is recommended.

VII.3.1.1.8.6. Impact on the risk-benefit balance of the product

NMSCs that are detected at an early stage and removed promptly are almost always curable and cause minimal damage. Advanced-stage skin cancers that are located in the head and neck region may require surgery that can be disfiguring.[291]

VII.3.1.1.8.7. Public health impact

Skin cancer is the most common type of cancer in fair-skinned individuals around the world. Although NMSC is rarely fatal, it can cause significant morbidity.

VII.3.1.1.8.7.1. Ratio of squamous cell carcinoma vs. basal cell carcinoma

RA: BCC is more common than SCC in the general population, whereas among immunocompromised subjects (such as transplant recipients) the ratio is reversed.[292] In the tofacitinib RA clinical programme, the ratio for SCC to BCC based on the combined dataset from the Phase 1, 2, 3 and LTE studies was approximately 1:1. Although there appears to be a shift in relative proportions of SCC and BCC as compared to those reported in general population, that change is generally expected in RA patients who are often treated with immunomodulatory drugs. The ratio of SCC to BCC observed in RA patients treated with tofacitinib (ie, 1:1) appears to be comparable to what have been reported in RA patients treated with bDMARDs.[293,294] In study A3921133, a randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, an increase in overall NMSC, including cutaneous squamous cell carcinomas, was observed with tofacitinib compared to TNF inhibitors. When examining the ratio of SCC to BCC across the dose groups (5 mg vs. 10 mg BID), no significant differences were noted. Additionally, there appears to be no difference in the absolute risk of SCC when comparing the IR of SCC between patients treated with tofacitinib vs. other bDMARDs. For example, the IR of SCC in RA patients treated with tofacitinib 5 mg BID was 0.21 per 100 PYs, which is similar to 0.26 per 100 PYs reported in RA patients treated with TNFi.

In summary, based on review of the tofacitinib clinical data, a shift in relative proportions of SCC and BCC as compared to those reported in general population was noted. That change is expected in RA patients considering the underlying disease and concomitant use of immunomodulatory drugs. The ratio of SCC to BCC in RA patients treated with tofacitinib appears to be comparable to those reported in RA patients treated with bDMARDs. The risk of NMSC and the ratio of SCC to BCC will continue to be monitored and evaluated through on-going and future Pharmacovigilance (PV) activities.

PsA: The SCC to BCC ratio for the All PsA population (combined 5 mg and 10 mg dose groups) is 5:11.

The risk of NMSC and the ratio of SCC to BCC will continue to be monitored and evaluated through on-going and future pharmacovigilance activities.

UC: The SCC to BCC ratio for the All UC population (combined 5 mg and 10 mg dose groups) is 11:15.

The risk of NMSC and the ratio of SCC to BCC will continue to be monitored and evaluated through on-going and future pharmacovigilance activities.

JIA: There were no cases of NMSC from the JIA integrated safety analysis population.

AS: There were no NMSC cases in the AS clinical development programme.

VII.3.1.1.9. Transaminase Elevation and Potential for Drug-induced Liver Injury (DILI)

VII.3.1.1.9.1. Potential mechanisms

Unknown.

VII.3.1.1.9.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.1.9.3. Characterisation of the risk

Frequency

RA: In the All RA population, Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) elevation of >3 × Upper Limit Normal (ULN) were reported for 1.6% and <1.0% of patients who had normal baseline values, respectively. ALT and AST elevations of >3 × ULN were reported for 7.7% and 2.7% of patients who had abnormal baseline values, respectively. Confirmed increases in liver enzymes >3 × ULN were uncommonly observed.

Table 92. Incidence of Confirmed Measures of ALT and AST Elevations by Baseline Abnormality Status in the All RA Population (P123LTE)

	ALT Tofacitinib All Doses	AST Tofacitinib All Doses
Normal Baseline[a]	**N = 7136 n (%)**	**N = 7359 n (%)**
>1 × ULN	1489 (20.9%)	1356 (18.4%)
>3 × ULN	116 (1.6%)	56 (<1.0%)
>5 × ULN	31 (<1.0%)	16 (<1.0%)
>10 × ULN	9 (<1.0%)	4 (<1.0%)
Abnormal Baseline[a]	**N = 598 n (%)**	**N = 371 n (%)**
>1 × ULN	392 (65.6%)	233 (62,8%)
>3 × ULN	46 (7.7%)	10 (2.7%)
>5× ULN	5 (<1.0%)	2 (<1.0%)
>10 × ULN	0	0

a. Normal = Baseline value ≤ ULN, Abnormal = Baseline value > ULN
Includes protocols -A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year data), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215 and A3921237.
Final data 18 January 2019
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit normal
Source: Table 1614.8.1, Table 1614.8.2

In the RA programme, there was 1 atypical case of a probable drug-induced liver injury (DILI) in a patient on tofacitinib 10 mg BID with background MTX. Since the inception of the Tofacitinib Hepatic Event Review Committee, no definite DILI cases have been identified in the RA LTE studies.

Study A3921133: The number of patients (and percentage) of ALT and AST elevation of >1 × ULN, ≥3 × ULN, and ≥5 × ULN in A3921133 by dose groups are shown below.

Table 93. Elevations of Transaminase Levels >1×ULN, ≥3×ULN, ≥5×ULN in Study A3921133

	ALT				AST			
	Tofacitinib 5mg BID (N=1455) (N2=1431)	**Tofacitinib 10mg BID (N=1456) (N2=1423)**	**All Tofa (N=2911) (N2=2854)**	**TNFi (N=1451) (N2=1431)**	**Tofacitinib 5mg BID (N=1455) (N2=1431)**	**Tofacitinib 10mg BID (N=1456) (N2=1423)**	**All Tofa (N=2911) (N2=2854)**	**TNFi (N=1451) (N2=1431)**
>1×ULN n (%)	756 (52.83)	775 (54.46)	1531 (53.64)	620 (43.33)	656 (45.84)	734 (51.58)	1390 (48.70)	532 (37.18)
≥3× ULN n (%)	86 (6.01)	93 (6.54)	179 (6.27)	54 (3.77)	46 (3.21)	65 (4.57)	111 (3.89)	34 (2.38)
≥5× ULN n (%)	24 (1.68)	28 (1.97)	52 (1.82)	16 (1.12)	14 (0.98)	23 (1.62)	37 (1.30)	10 (0.70)

Table 93. Elevations of Transaminase Levels >1×ULN, ≥3×ULN, ≥5×ULN in Study A3921133

	ALT				AST			
	Tofacitinib 5mg BID (N=1455) (N2=1431)	Tofacitinib 10mg BID (N=1456) (N2=1423)	All Tofa (N=2911) (N2=2854)	TNFi (N=1451) (N2=1431)	Tofacitinib 5mg BID (N=1455) (N2=1431)	Tofacitinib 10mg BID (N=1456) (N2=1423)	All Tofa (N=2911) (N2=2854)	TNFi (N=1451) (N2=1431)

N2 – Number of subjects with at least one post-baseline visit with non-missing value. Subjects are counted in more than one category.
Includes data within 28-Day on-treatment period. The 28-Day on-treatment period is minimum of (Last contact date, Last Study Treatment Dose date + 28 days).
The last contact date is maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact Date). If a subject died, last contact date is the death date.
For subjects randomized to the TNFi group, adalimumab was administered in US, Puerto Rico and Canada, and etanercept was administered in the rest of the world.
Source: Table 14.3.4.3.31

There were no definite DILI cases identified in Study A3921133.

PsA: Subjects with ALT or AST ≤1.5× ULN at screening were eligible to enter the PsA clinical programme studies. In P3LTE studies, the following confirmed ALT and AST values were reported. At least 2 consecutive measurements can confirm itself within the subject; subjects in their worse categories were also counted in their less severe categories:

Table 94. Incidence (%) of Peak (Unconfirmed) Measures of ALT and AST (IU/L) Elevations (without regard to baseline status in the All PsA population) (P3LTE)

	ALT Tofacitinib 5 mg and 10 mg combined dose groups	AST Tofacitinib 5 mg and 10 mg combined dose groups
	N = 782 n (%)	N = 782 n (%)
>1 × ULN	260 (33.2)	173 (22.1)
≥2 × ULN	48 (6.1)	16 (2.0)
≥3 × ULN	11 (1.4)	2 (0.3)
≥5 × ULN	4 (0.5)	2 (0.3)
≥10 × ULN	1 (0.1)	0 (0.0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PsA = psoriatic arthritis; ULN = upper limit normal
At least 2 consecutive measurements can confirm itself within the subject. Subjects in their worse categories were also counted in their less severe categories.
Includes protocols A3921091, A3921125 and A3921092 (main and substudy)
Final data 31 July 2019
Source: Tables 00118.C3.6.7.11.1, 00118.C3.6.7.10.1

In the All PsA population, 4 cases were adjudicated by the HERC. Of these, 2 were assessed as unrelated, 1 was assessed as unlikely DILI, and 1 was assessed as possible DILI. There were no cases adjudicated as probable, highly likely, or definite DILI.

UC: In the All UC population, peak values in the combined 5 mg and 10 mg dose groups of ALT and AST > 3 × ULN regardless of baseline status were 2.9% and 2.2%, respectively.

In the All UC population, there were 7 cases adjudicated by the HERC as possible DILI in the combined 5 mg and 10 mg dose groups. There were no cases adjudicated as probable, highly likely, or definite DILI.

Table 95. Incidence (%) of Peak Measures of ALT and AST (IU/L) Elevations (without regard to baseline status[a] in the All UC population)

	ALT Tofacitinib All Doses	AST Tofacitinib All Doses
	N = 1157 n (%)	N = 1157 n (%)
>1 × ULN	370 (32.0)	309 (26.7)
>2 × ULN	97 (8.4)	70 (6.1)
>3 × ULN	38 (3.3)	28 (2.4)
>5 × ULN	10 (0.9)	14 (1.2)

a. In the UC Phase 3 induction studies, subjects with screening ALT, AST, or total bilirubin >1.5 × the ULN were excluded from enrollment.
A subject can contribute to multiple rows per lab result.
Only post-baseline data are summarised in the table.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; UC = ulcerative colitis; ULN = upper limit normal
Final Data 24 Aug 2020
Source: Table 14.3.4.c3b

JIA: The table below presents the number (%) of subjects with confirmed ALT (u/L) values as multiples of ULN, by baseline abnormality status in the CISAP, which includes subjects who received at least 1 dose of tofacitinib in either of the index studies, without any interruption in tofacitinib treatment exceeding 14 days.

Table 96. Number (%) of Subjects with Confirmed ALT and AST (U/L) Values as Multiples of ULN, by Baseline Abnormality Status – CISAP

Treatment Baseline Status[a]	Tofacitinib 5 mg BID	
Confirmed ALT	Normal at Baseline (N=240) n (%)	Abnormal at Baseline (N=11) n (%)
>1 × ULN	13 (5.4)	4 (36.4)
≥3 × ULN	1 (0.4)	1 (9.1)
≥5 × ULN	1 (0.4)	0 (0.0)
≥10 × ULN	1 (0.4)	0 (0.0)
Confirmed AST	Normal at Baseline (N=250) n (%)	Abnormal at Baseline (N=1) n (%)
>1 × ULN	7 (2.8)	0 (0.0)
≥3 × ULN	0 (0.0)	0 (0.0)
≥5 × ULN	0 (0.0)	0 (0.0)
≥10 × ULN	0 (0.0)	0 (0.0)

a. Normal = Baseline value ≤ ULN, Abnormal = Baseline value > ULN
Includes Studies: A3921103, A3921104, A3921145 (Cutoff date: 04JUN2019)
N=number of subjects who had a post-baseline visit. ULN=upper limit of normal; Confirmed=at least 2 measurements with the subject.
Source: Table JIA_RMP 39, Table JIA_RMP 40

AS: Confirmed elevated liver test values ≥3 × ULN and higher multiples of ULN were rare for both the RCTs (placebo-controlled) and All AS (All Tofa) populations.

Table 97. Incidence (%) of Liver Parameter Results as Indicative of Potential Drug-Induced Liver Injury (DILI) Categories – Subjects with Baseline AST or ALT or Total Bilirubin Values Above Normal Range

Post Dose Visit[a]	RCTs	All AS	
	Tofa 5 mg BID (N=18) n (%)	All Tofa 5 mg BID (N=24) n (%)	All Tofa (N=33) n (%)
No Abnormal Criteria	14 (77.8)	20 (83.3)	29 (87.9)
Gilbert's Syndrome or Cholestasis (ALT ≤3×ULN and AST ≤3×ULN) and TBili >2×ULN)	0	0	0
Isolated Transaminase Elevation (ALT >3×ULN or AST >3×ULN) and TBili ≤2×ULN	4 (22.2)	4 (16.7)	4 (12.1)
Potential Hy's Law ({{[AST >2 times the baseline values and AST >3×ULN] or AST >8×ULN} or {[ALT >2 times the baseline values and ALT >3×ULN] or ALT >8×ULN}} and [TBili level increased from baseline value by an amount of at least 1xULN or TBili >3×ULN].)	0	0	0

a. The most elevated post-baseline values across multiple visits/observations, which do not necessarily occur at the same visit, are used

N refers to the sample size with baseline AST or ALT or Total Bilirubin values above normal range.
n is the number of subjects who meet the criteria.
Each participant is counted only once in the severest category.
Included Protocols: A3921119, A3921120 (Final Data)
Final Data: 10Sep2020
Source: Table C1.5.5.4.2-E, Table C2.5.5.4.2-E

Seriousness/outcomes

RA: In the All RA population, 1023 patients experienced AEs that coded to the Drug related hepatic disorders Standardized MedDRA Query (SMQ) and 144 of these patients discontinued study drug due to events in this SMQ.

Study A3921133: There were 172 AES (5 serious) in the tofacitinib 5mg BID, 175 (6 serious) in the tofacitinib 10mg BID, 347 (11 serious) in the All tofa, and 135 (6 serious) in the TNFi groups that coded to the Drug related hepatic disorders SMQ. There were 2, 10, 12, and 4 discontinuations due to hepatobiliary disorders AEs in the tofacitinib 5mg BID tofacitinib 10mg BID, All tofa, and TNFi groups, respectively.

PsA: In the RCTs, 1 subject was discontinued due to an AE of transaminases increased. In the All PsA population, an additional subject was discontinued due to an AE of significant elevation of liver enzymes.

UC: In the RCTs (induction studies), 1 subject in the 10 mg dose group with elevated liver transaminases was discontinued (adjudicated as possible DILI). In the RCT (maintenance study), 1 subject in the 10 mg dose group with elevated liver transaminases was discontinued (adjudicated as possible DILI).

JIA: In the ISAP population, 1 case of adjudicated possible DILI and 2 cases of adjudicated probable DILI were reported in subjects on background MTX. All 3 cases resolved after discontinuation of MTX therapy and after interruption, or permanent discontinuation, of tofacitinib.

AS: In the RCTs (Tofa 5 mg BID), 1 subject was discontinued with increased AST, ALT, and GGT, but was not adjudicated as possible DILI.

Post-Marketing:

Table 98. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Transaminase Elevation and Potential for DILI (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Hepatic enzyme increased	705	109	25	2	102	1	112	488
Liver disorder	410	70	22	6	73	0	83	248
Alanine aminotransferase increased	228	41	9	1	61	0	36	130
Aspartate aminotransferase increased	151	31	9	1	45	0	18	87
Hepatic steatosis	124	21	7	0	11	0	22	91
Transaminases increased	106	24	3	1	33	0	13	59
Liver injury	61	61	9	3	10	0	11	37
Hepatitis	51	51	5	4	8	0	10	29
Hepatic cirrhosis	43	43	4	3	1	0	12	27
Drug-induced liver injury	40	40	13	1	14	1	9	15
Hepatotoxicity	35	34	4	1	7	1	6	20
Hepatic cancer	25	25	3	2	0	0	8	15
Hepatic failure	25	25	8	7	4	0	2	12
All others	123	108	34	7	22	0	21	73
Total	2127	683	155	39	391	3	363	1331

DILI = drug-induced liver injury; F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 99. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Transaminase Elevation and Potential for DILI (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Hepatic enzyme increased	594	27	12	0	73	0	69	452
Liver disorder	171	16	5	1	13	0	22	135
Hepatic steatosis	103	9	3	0	5	0	20	78
Alanine aminotransferase increased	81	7	0	0	5	0	10	66
Aspartate aminotransferase increased	42	5	0	0	4	0	4	34

Table 99. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Transaminase Elevation and Potential for DILI (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Hepatitis	32	32	2	0	5	0	4	23
Liver injury	32	32	1	0		0	2	30
Hepatic cirrhosis	18	18	3	0	1	0	7	10
Transaminases increased	15	3	1	0	2	0	1	12
All others	85	70	12	1	6	2	15	61
Total	1173	219	39	2	114	2	154	901

DILI = drug-induced liver injury; F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity[7] and nature of risk

RA: Transaminase increases were relatively common in RA patients treated with tofacitinib but were mostly mild to moderate (<3 × ULN) and most of these abnormalities occurred in patients with background DMARDs (primarily MTX). Transaminase elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency.

Study A3921133: A slight median increase from baseline over time in transaminase levels (ALT, AST) was observed for subjects in both tofacitinib arms, which was numerically higher than in the TNFi arm. Overall, a greater proportion of subjects in the tofacitinib arms experienced elevated transaminase levels >1 × ULN. A higher proportion of subjects in the tofacitinib 10 mg BID arm had elevations of ALT and AST ≥3 × ULN, and ALT, AST ≥5 × ULN.

PsA: Transaminase increases were relatively common in PsA patients treated with tofacitinib, but most were mild (<2 × ULN), and all patients were on background DMARDs (primarily MTX).

UC: Unconfirmed transaminase increases were relatively common in UC patients treated with tofacitinib, but most were mild to moderate (< 3 × ULN).

JIA: In the ISAP population, 1 case of adjudicated possible DILI and 2 cases of adjudicated probable DILI were reported in subjects on background MTX. All 3 cases resolved after discontinuation of MTX therapy and after interruption, or permanent discontinuation, of tofacitinib.

[7] Severity definitions (AST and ALT): mild = 1.2-1.5 × ULN; moderate = 1.6-3.0 × ULN; severe = 3.0-8.0 × ULN; includes life-threatening = >8.0 ULN.

AS: Confirmed elevated liver test values ≥3 × ULN and higher multiples of ULN were rare for both the RCTs and All AS populations. No patients in the AS programme had confirmed elevations of AST ≥5 × ULN or ALT ≥10 × ULN or increases in bilirubin ≥2 or 3 × ULN.

VII.3.1.1.9.4. Risk factors and risk groups

Use of other medications (called DMARDs) to treat RA or to treat PsA at the same time as tofacitinib.

VII.3.1.1.9.5. Preventability

In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of tofacitinib, or reduction in tofacitinib dose, resulted in decrease or normalisation of liver enzymes.

VII.3.1.1.9.6. Impact on the risk-benefit balance of the product

Most patients experiencing hepatic enzyme elevation are asymptomatic; however, patients may experience nausea, vomiting, decreased appetite, abdominal pain, and jaundice because of severe hepatotoxicity.

VII.3.1.1.9.7. Public health impact

Transaminase increase is not expected to have a significant impact on public health. DILI is an important public health problem, contributing to more than 50% of acute liver failure cases, a fraction of which require urgent liver transplantation because of the irreversible damage to the liver.[295]

VII.3.1.1.10. Higher Incidence and Severity of Adverse Events (AEs) in the Elderly

VII.3.1.1.10.1. Potential mechanisms

Aging is one of known factors that are associated with an increased risk of many medical events, such as cardiac disorders and malignancy. Additionally, elderly patients often have other concurrent medical conditions and take many concomitant medications, which may put them at higher risk of developing AEs.

VII.3.1.1.10.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.1.10.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: The IRs (95% CI) per 100 PY of special events of interest in the All RA population by age group are shown below.

Table 100. The IRs (95% CI) per 100 PY of Special Events of Interest in the All RA Population (P123LTE) by Age

Event	Age Group (Years)	Incidence Rate/100 PY (95% CI)
Serious infections	<65	2.17 (1.98, 2.38)
	≥65	4.57 (3.84, 5.39)
HZ	<65	3.34 (3.09, 3.61)
	≥65	5.26 (4.44, 6.17)
OIs (excl TB)	<65	0.33 (0.26, 0.42)
	≥65	0.80 (0.52, 1.19)
NMSC	<65	0.40 (0.32, 0.50)
	≥65	1.62 (1.20, 2.14)
Malignancy (excl NMSC)	<65	0.65 (0.54, 0.77)
	≥65	1.38 (1.00, 1.86)
MACE	<65	0.31 (0.24, 0.40)
	≥65	0.75 (0.47 1.14)
GI perforation	<65	0.10 (0.07, 0.16)
	≥65	0.16 (0.05, 0.37)
ILD	<65	0.16 (0.11, 0.23)
	≥65	0.35 (0.18, 0.63)
DVT	<65	0.13 (0.09, 0.19)
	≥65	0.29 (0.13, 0.55)
Mortality	<65	0.39 (0.31, 0.48)
	≥65	1.28 (0.91, 1.74)

CI = Confidence Interval. PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data cutoff date. Incidence rate (number of subjects with events per 100 subject-years). Exact Poisson (adjusted for Pt-yr) 95% confidence intervals are provided for the crude incidence rate.
Includes Protocols-A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
Final data 18 January 2019
Excl = excluding; CI = confidence interval; DVT = deep vein thrombosis, GI = gastrointestinal; HZ = herpes zoster; ILD = interstitial lung disease; IR = incidence rate; MACE = major adverse cardiac event; NMSC = non-melanoma skin cancer; OI = opportunistic infections; PY = patient-year; TB = tuberculosis; RA = rheumatoid arthritis
Source: Tables 1571.5.2.2.1, 1614.11, 1614.11.1, 1614.11.2, 353a.1.1

Study A3921133, a large, randomised active-controlled post authorisation safety surveillance study of RA patients who were 50 years of age and older and had at least one additional cardiovascular risk factor, an increase in non-fatal MI and malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with tofacitinib compared to TNF inhibitor.

Study A3921133: The IRs (95% CI) per 100 PY of special events of interest from Study A3921133 age group are shown below.

Table 101. The IRs (95% CI) per 100 PY of Special Events of Interest from Study A3921133 by Age

Event	Age Group (Years)	Incidence Rate/100 PY (95% CI)			
		Tofacitinib 5mg BID	Tofacitinib 10mg BID	All Tofa	TNFi
Serious infections	<65	2.43 (1.95, 3.00)	2.73 (2.20, 3.36)	2.58 (2.21, 2.98)	1.88 (1.45, 2.40)
	≥65	4.03 (3.02, 5.27)	5.85 (4.64, 7.30)	4.95 (4.15, 5.88)	3.73 (2.81, 4.85)
HZ	<65	3.72 (3.11, 4.42)	3.56 (2.94, 4.28)	3.65 (3.20, 4.13)	1.02 (0.71, 1.42)
	≥65	3.82 (2.82, 5.05)	4.87 (3.75, 6.21)	4.35 (3.58, 5.23)	1.54 (0.97, 2.31)
Adjudicated OIs (excl TB)	<65	0.64 (0.41, 0.95)	0.68 (0.43, 1.02)	0.66 (0.48, 0.87)	0.23 (0.10, 0.45)
	≥65	1.02 (0.56, 1.72)	1.12 (0.64, 1.82)	1.07 (0.72, 1.53)	0.52 (0.23, 1.03)
Adjudicated NMSC	<65	0.35 (0.18, 0.59)	0.47 (0.27, 0.76)	0.40 (0.27, 0.58)	0.20 (0.08, 0.41)
	≥65	1.33 (0.79, 2.10)	1.21 (0.70, 1.93)	1.27 (0.88, 1.76)	0.59 (0.27, 1.12)
Adjudicated malignancy (excl NMSC)	<65	0.77 (0.51, 1.10)	0.73 (0.47, 1.08)	0.75 (0.56, 0.98)	0.63 (0.40, 0.95)
	≥65	1.89 (1.24, 2.78)	1.39 (0.85, 2.15)	1.64 (1.20, 2.18)	1.11 (0.64, 1.77)
Adjudicated MACE	<65	0.72 (0.47, 1.05)	0.70 (0.45, 1.05)	0.71 (0.53, 0.94)	0.63 (0.40, 0.96)
	≥65	1.32 (0.78, 2.08)	1.76 (1.14, 2.60)	1.54 (1.12, 2.08)	0.85 (0.45, 1.46)
Adjudicated GI perforation	<65	0.16 (0.06, 0.35)	0.09 (0.02, 0.26)	0.12 (0.06, 0.24)	0.06 (0.01, 0.21)
	≥65	0.22 (0.04, 0.63)	0.14 (0.02, 0.50)	0.18 (0.06, 0.41)	0.13 (0.02, 0.47)
Adjudicated ILD	<65	0.24 (0.11, 0.45)	0.26 (0.12, 0.50)	0.25 (0.15, 0.40)	0.29 (0.14, 0.53)
	≥65	0.43 (0.16, 0.95)	0.56 (0.24, 1.10)	0.50 (0.27, 0.84)	0.46 (0.18, 0.94)
Adjudicated VTE	<65	0.19 (0.07, 0.38)	0.59 (0.36, 0.91)	0.38 (0.25, 0.55)	0.20 (0.08, 0.41)
	≥65	0.73 (0.35, 1.34)	0.99 (0.54, 1.66)	0.86 (0.55, 1.28)	0.20 (0.04, 0.57)
All-cause deaths	<65	0.26 (0.13, 0.49)	0.58 (0.36, 0.90)	0.42 (0.28, 0.59)	0.23 (0.10, 0.45)
	≥65	1.16 (0.66, 1.88)	1.32 (0.79, 2.06)	1.24 (0.86, 1.72)	0.58 (0.27, 1.11)

BID = twice daily; CI = confidence interval; Excl = excluding; GI = gastrointestinal; HZ = herpes zoster; ILD = interstitial lung disease; IR = incidence rate; MACE = major adverse cardiac event; NMSC = non-melanoma skin cancer; OI = opportunistic infections; PY = patient-year; TB = tuberculosis; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism

The risk period was minimum of (last contact date, Last Study Treatment Dose date + 28 days).

The last contact date was maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact Date). If a subject died, last contact date was the death date.

First events were counted within the risk period. If a subject did not have an event or had an event but outside the risk period, the subject was censored at the end of risk period.

For subjects randomized to the TNFi group, adalimumab was administered in US, Puerto Rico and Canada, and etanercept was administered in the rest of the world.

Source: Table 1657.7.2.2

PsA: The IRs (95% CI) per 100 PY of special events of interest in the All PsA population by age group are shown below.

Table 102. The IRs (95% CI) per 100 PY of Special Events of Interest in the All PsA Population (P3LTE) by Age

Event	Age Group (Years)	Incidence Rate/100 PY (95% CI)
Serious infections	<65	1.10 (0.68, 1.68)
	≥65	1.65 (0.34, 4.82)
Herpes zoster	<65	1.77 (1.22, 2.48)
	≥65	1.67 (0.34, 4.88)
Opportunistic infections (excl TB)	<65	0.31 (0.12, 0.68)
	≥65	0.55 (0.01, 3.09)
Nonmelanoma skin cancer	<65	0.53 (0.25, 0.97)
	≥65	3.48 (1.28, 7.58)
Malignancy (excl NMSC)	<65	0.63 (0.32, 1.09)
	≥65	1.65 (0.34, 4.82)
MACE	<65	0.16 (0.03, 0.46)
	≥65	1.66 (0.34, 4.84)
GI perforation	<65	0.05 (0.00, 0.29)
	≥65	0.00 (0.00, 2.03)
Interstitial lung disease	<65	0.05 (0.00, 0.29)
	≥65	0.00 (0.00, 2.03)

CI = Confidence Interval. PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data cutoff date. Incidence rate (number of subjects with events per 100 subject-years). Exact Poisson (adjusted for Pt-yr) 95% confidence intervals are provided for the crude incidence rate.
Included protocols A3921091, A3921125 and A3921092 (main and substudy).
CI = confidence interval; excl = excluding; GI = gastrointestinal; MACE = major adverse cardiac event; NMSC = nonmelanoma skin cancer; PsA = psoriatic arthritis; PY = patient years; TB = tuberculosis
Final data 31 July 2019
Source: Tables 00118.C3.2.1.2, 00118.C3.2.2.2, 00118.C3.2.5.2, 00118.C3.2.8.2, 00118.C3.2.10.2

UC: The IRs (95% CI) per 100 PY of special events of interest in the All UC population by age group is shown below.

Table 103. The IRs (95% CI) per 100 PY of Special Events of Interest in the All UC Population by (P2P3LTE) Age

Event	Age Group (Years)	Incidence Rate/100 PY (95% CI)
Serious infections	<65	1.71 (1.25, 2.28)
	≥65	1.87 (0.51, 4.80)
Herpes zoster	<65	3.08 (2.43, 3.84)
	≥65	7.48 (4.09, 12.56)
Opportunistic infections (excl TB)	<65	1.02 (0.67, 1.49)
	≥65	1.41 (0.29, 4.12)
Nonmelanoma skin cancer	<65	0.45 (0.23, 0.78)
	≥65	4.74 (2.17, 8.99)
Malignancy (excl NMSC)	<65	0.59 (0.34, 0.96)
	≥65	1.89 (0.51, 4.84)
MACE	<65	0.19 (0.06, 0.43)
	≥65	1.45 (0.30, 4.23)
GI perforation (revised definition)[a]	<65	0.11 (0.02, 0.32)
	≥65	0.00 (0.00, 1.72)
Interstitial lung disease	<65	No ILD events in UC programme

Table 103. The IRs (95% CI) per 100 PY of Special Events of Interest in the All UC Population by (P2P3LTE) Age

Event	Age Group (Years)	Incidence Rate/100 PY (95% CI)
	≥65	No ILD events in UC programme

a. Revised definition of GI perforation: Events that were confirmed by adjudication, excluding MedDRA PTs of Perirectal abscess, Rectal abscess, Anal abscess, Perineal abscess, Pilonidal cyst, and any PTs containing the term fistula regardless of the location of the fistula.
CI = Confidence Interval. PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data cutoff date. Incidence rate (number of subjects with events per 100 subject-years). Exact Poisson (adjusted for Pt-yr) 95% confidence intervals are provided for the crude incidence rate.
Includes protocols A3921063, A3921094, A3921095, A3921096 and A3921139.
CI = confidence interval; excl = excluding; GI = gastrointestinal; ILD = interstitial lung disease; MACE = major adverse cardiac event; NMSC = nonmelanoma skin cancer; PY = patient years; TB = tuberculosis; UC = ulcerative colitis
Final data: 24 Aug 2020, Source: Table 417a.3.3.2

JIA: Not applicable.

AS: The IRs (95% CI) per 100 PY of special events of interest in the All AS population by age group is shown below. In the AS programme, there were no cases of VTE, OIs (excluding TB), NMSC, malignancy (excluding NMSC), MACE, GI perforation, or ILD.

Table 104. The IRs (95% CI) per 100 PY of Special Events of Interest in the All AS Population by Age

Event	Age Group (Years)	All Tofa 5 mg BID	All Tofa
		IR/100 PY (95% CI)	IR/100 PY (95% CI)
Serious infections	<65	0.44 (0.01, 2.47)	0.39 (0.01, 2.18)
	≥65	0.00 (0.00, 65.18)	0.00 (0.00, 48.80)
Herpes zoster	<65	2.23 (0.72, 5.21)	2.76 (1.11, 5.69)
	≥65	0.00 (0.00, 65.18)	0.00 (0.00, 48.80)

CI = confidence interval; IR = incidence rate; PY = person-year
Included Protocols: A3921119, A3921120 (Final Data).
Final Data: 10Sep2020
Source: Table C2.3.3.4.1-E

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: Crude rates (per 100 PY) and 95% CI for safety events of interest among eligible RA patients <65 years and ≥65 years of age initiating tofacitinib and bDMARD are found in the table below.

Table 105. Crude Rates (per 100 PY) and 95% CI for Safety Events of Interest Among Eligible RA Patients Initiating Tofacitinib or bDMARD (31 March 2018 Primary Analyses) Subgroup Analysis: Age Group

Event of interest	Age	Tofacitinib Initiators					bDMARD Initiators				
		N	PY	Rate	95% CI LL	95% CI UL	N	PY	Rate	95% CI LL	95% CI UL
Malignancy excluding NMSC	<65 years	18	2936.43	0.61	0.36	0.97	54	10753.3	0.5	0.38	0.66
	≥65 years	27	1526.65	1.77	1.17	2.57	70	5719.19	1.22	0.95	1.55
Death	<65 years	11	2957.27	0.37	0.19	0.67	36	10831.11	0.33	0.23	0.46
	≥65 years	25	1548.18	1.61	1.05	2.38	76	5833.64	1.3	1.03	1.63
NMSC	<65 years	19	2924.59	0.65	0.39	1.01	63	10708.23	0.59	0.45	0.75
	≥65 years	31	1501.91	2.06	1.4	2.93	106	5653.46	1.87	1.54	2.27
MACE	<65 years	6	1397.92	0.43	0.16	0.93	41	6405.67	0.64	0.46	0.87
	≥65 years	9	731.08	1.23	0.56	2.34	49	3425	1.43	1.06	1.89
Serious infection events	<65 years	28	1378.67	2.03	1.35	2.94	136	6338.83	2.15	1.8	2.54
	≥65 years	36	706.33	5.1	3.57	7.06	152	3345.08	4.54	3.85	5.33
TB	<65 years	0	1402.58	0	0	0.26	0	6438.5	0	0	0.06
	≥65 years	0	735.58	0	0	0.5	1	3466.42	0.03	0	0.16
Total HZ	<65 years	22	1384.92	1.59	1	2.41	36	6410.08	0.56	0.39	0.78
	≥65 years	12	727.58	1.65	0.85	2.88	36	3432.5	1.05	0.73	1.45
Serious HZ	<65 years	0	1402.58	0	0	0.26	0	6438.5	0	0	0.06
	≥65 years	0	735.58	0	0	0.5	4	3464.25	0.12	0.03	0.3
Non-serious HZ	<65 years	22	1384.92	1.59	1	2.41	36	6410.08	0.56	0.39	0.78
	≥65 years	12	727.58	1.65	0.85	2.88	32	3434.67	0.93	0.64	1.32
DVT or PE	<65 years	2	1401.33	0.14	0.02	0.52	17	6422	0.26	0.15	0.42
	≥65 years	2	735.08	0.27	0.03	0.98	13	3457.25	0.38	0.2	0.64
GI perforation	<65 years	1	1402.5	0.07	0	0.4	2	6438.25	0.03	0	0.11
	≥65 years	0	735.58	0	0	0.5	3	3465.67	0.09	0.02	0.25

bDMARD=biologic disease modifying antirheumatic drug; CI=confidence interval; DVT=deep vein thrombosis; HZ=herpes zoster; LL=lower limit; MACE=major adverse cardiovascular event; N=count; NMSC=nonmelanoma skin cancer; PE=pulmonary embolism; PY=person years; RA=rheumatoid arthritis; UL=upper limit
Corrona RA Registry (study A3921205) final report: Table 17, Table 22, Table 23, Table 25

Seriousness/outcome

RA: The seriousness and outcomes of the events of interest in the elderly population (≥65 years) are presented below.

Table 106. Seriousness and Outcomes of the Events of Interest in the All RA Elderly Population (P123LTE, ≥65 years)

Event	Total	Serious	Resolved	Still Present	Unknown	Fatal
Serious infections	140	140	116	11	0	13
TB	4	3	2	2	0	0
OIs (excl TB)	25	15	21	2	0	2
HZ	148	15	141	7	0	0
Neutropenia	19	0	18	1	0	0
Lymphopenia	55	0	35	20	0	0
Anaemia	100	8	70	29	1	0
Hyperlipidaemia	32	0	9	23	0	0
NMSC	49	15	47	2	0	0
Malignancy (excl NMSC)	43	43	20	12	2	9
MACE	22	20	18	0	0	4
GI perforation	5	4	5	0	0	0
ILD	11	7	6	5	0	0

Source: Tables 417a.1.3.4, 417a.1.3.6
Excl = excluding; GI = gastrointestinal; ILD = interstitial lung disease; MACE = major adverse cardiac event; NMSC = nonmelanoma skin cancer; OI = opportunistic infection; TB = tuberculosis
Includes protocols: A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237
Final data 18 January 2019

Study A3921133: The seriousness and outcomes of the events of interest by treatment group in the elderly population (≥65 years) are presented below.

Table 107. Seriousness and Outcomes of the Events of Interest in the Elderly Population from Study A3921133 by Treatment Group (≥65 years)

Event	Treatment Group	Total	Serious	Resolved	Still Present	Unknown	Fatal
Serious infections	Tofacitinib 5mg BID	53	53	43	4	0	6
	Tofacitinib 10mg BID	79	79	67	6	0	6
	All Tofa	132	132	110	10	0	12
	TNFi	55	55	52	0	1	2
HZ	Tofacitinib 5mg BID	49	7	48	1	0	0
	Tofacitinib 10mg BID	64	8	63	1	0	0
	All Tofa	113	15	111	2	0	0
	TNFi	23	2	20	3	0	0
Adjudicated OIs (excl TB)	Tofacitinib 5mg BID	14	5	13	1	0	0
	Tofacitinib 10mg BID	16	7	13	2	0	1
	All Tofa	30	12	26	3	0	1
	TNFi	8	2	7	0	0	1
	Tofacitinib 5mg BID	18	2	14	3	1	0

Table 107. Seriousness and Outcomes of the Events of Interest in the Elderly Population from Study A3921133 by Treatment Group (≥65 years)

Event	Treatment Group	Total	Serious	Resolved	Still Present	Unknown	Fatal
Adjudicated NMSC	Tofacitinib 10mg BID	17	2	15	2	0	0
	All Tofa	35	4	29	5	1	0
	TNFi	9	2	9	0	0	0
Adjudicated malignancy (excl NMSC)	Tofacitinib 5mg BID	26	26	4	17	1	4
	Tofacitinib 10mg BID	20	20	6	13	0	1
	All Tofa	46	46	10	30	1	5
	TNFi	17	16	2	14	0	1
Adjudicated MACE	Tofacitinib 5mg BID	18	18	11	2	0	5
	Tofacitinib 10mg BID	25	25	9	7	0	9
	All Tofa	43	43	20	9	0	14
	TNFi	13	13	6	2	0	5
Adjudicated GI perforation	Tofacitinib 5mg BID	3	3	3	0	0	0
	Tofacitinib 10mg BID	2	2	1	1	0	0
	All Tofa	5	5	4	1	0	0
	TNFi	2	2	2	0	0	0
Adjudicated ILD	Tofacitinib 5mg BID	6	1	4	1	0	1
	Tofacitinib 10mg BID	8	4	3	4	1	0
	All Tofa	14	5	7	5	1	1
	TNFi	7	3	1	4	2	0
Adjudicated VTE	Tofacitinib 5mg BID	10	6	5	4	1	0
	Tofacitinib 10mg BID	14	11	12	2	0	0
	All Tofa	24	17	17	6	1	0
	TNFi	3	1	3	0	0	0

BID = twice daily; Excl = excluding; GI = gastrointestinal; HZ = herpes zoster; ILD = interstitial lung disease; MACE = major adverse cardiac event; NMSC = non-melanoma skin cancer; OI = opportunistic infections; TB = tuberculosis; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism
For the same adverse event of interest, the most serious case was selected in this summary, subject to a risk period of 28 days beyond the last dose or to a risk period of up to 28 days beyond the last dose or to the last contact date.
For the same adverse event of interest, the worst case outcome was selected in this summary, subject to a risk period of up to 28 days beyond the last dose or to the last contact date.
The risk period was minimum of (last contact date, Last Study Treatment Dose date + 28 days)
The last contact date was maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact date).
If a subject died, last contact date was the death date.
For subjects randomized to the TNFi group, adalimumab was administered in US, Puerto Rico and Canada, and etanercept was administered in the rest of the world.
Source: Table 1657.7.3.2, Table 1657.7.3.4

PsA: In the All PsA population, the seriousness and outcomes of the events of interest in the elderly population (≥65 years) are presented below.

Table 108. Seriousness and Outcomes of the Events of Interest in the All PsA Elderly Population (P3LTE, ≥65 years)

Event	Total	Serious	Resolved	Still Present	Unknown	Fatal
Serious infections	3	3	3	0	0	0
TB	0	0	0	0	0	0
OIs (excl TB)	1	0	1	0	0	0
HZ	3	1	3	0	0	0
Neutropenia	1	0	1	0	0	0
Lymphopenia	0	0	0	0	0	0
Anaemia	4	0	3	0	1	0
Hyperlipidaemia	5	0	1	4	0	0
NMSC	6	2	6	0	0	0
Malignancy	3	3	2	1	0	0
MACE	3	3	2	0	0	1
GI perforation	0	0	0	0	0	0
ILD	0	0	0	0	0	0

Excl = excluding; GI = gastrointestinal; ILD = interstitial lung disease; MACE = major adverse cardiac event; NMSC = nonmelanoma skin cancer; OI = opportunistic infection; TB = tuberculosis
Includes protocols: A3921091, A3921092 and A3921125
Final data 31 July 2019
Source: Tables 00118.C3.11.6.1.2, 00118.C3.11.6.3.2

UC: The seriousness and outcomes of the events of interest in the elderly population (≥65 years) are presented below.

Table 109. The Seriousness and Outcomes of the Events of Interest in the All UC Elderly Population (P2P3LTE, ≥65 years)

Event	Total	Serious	Resolved	Still Present	Unknown	Fatal
Serious infections	4	4	3	1	0	0
Adjudicated TB	0	0	0	0	0	0
Adjudicated OIs (excl TB)	3	2	2	1	0	0
HZ	14	1	13	1	0	0
Neutropenia	1	0	1	0	0	0
Lymphopenia	5	0	3	1	1	0
Anaemia	4	0	1	3	0	0
Hyperlipidaemia	1	0	0	1	0	0
Adjudicated NMSC	9	2	9	0	0	0
Adjudicated Malignancy (excl NMSC)	4	3	2	1	0	1
Adjudicated MACE	3	3	2	0	0	1
GI perforation [revised definition][a]	0	0	0	0	0	0
ILD	0	0	0	0	0	0

a. Revised definition of GI perforation: Events that were confirmed by adjudication, excluding MedDRA PTs of Perirectal abscess, Rectal abscess, Anal abscess, Perineal abscess, Pilonidal cyst, and any PTs containing the term fistula regardless of the location of the fistula.
Please note that death was not included as an outcome option in Table 417a.3.3.6 due to a programming decision. Deaths are listed as an outcome in Table 14.2.6.c3b. Two of the 5 deaths in the UC programme

Table 109. The Seriousness and Outcomes of the Events of Interest in the All UC Elderly Population (P2P3LTE, ≥65 years)

Event	Total	Serious	Resolved	Still Present	Unknown	Fatal

were in subjects ≥65 (pulmonary embolism, associated with cholangiocarcinoma and malignant melanoma with multi organ dysfunction syndrome as a result of the cancer – the outcome for these subjects was coded as "still present" and "resolved" in Table 417a.3.3.6 when in fact the event was fatal, as documented in Table 14.2.6.c3b.
Excl = excluding; GI = gastrointestinal; ILD = interstitial lung disease; MACE = major adverse cardiac event; NMSC = nonmelanoma skin cancer; OI = opportunistic infection; TB = tuberculosis
Includes protocols: A3921063, A3921094, A3921095, A3921096, A3921139
Final data: 24 August 2020
Source: Tables 417a.3.3.4, 417a.3.3.6, 14.2.6.c3b, 16.2.8.3.1.c3b

JIA: Not applicable.

AS: In the All AS population, no events of interest were reported in the elderly population (age ≥65 years).

Post-Marketing:

Table 110. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Higher Incidence and Severity of AEs in the Elderly (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Drug ineffective	3672	136	34	2	200	0	480	2991
Off label use	3082	38	9	9	17	0	58	2998
Pain	2655	185	80	1	342	3	718	1591
Condition aggravated	2225	406	107	13	417	3	630	1193
Arthralgia	1854	125	51	1	269	0	605	1001
Pain in extremity	1456	99	43	0	199	0	494	774
Therapeutic product effect incomplete	1415	18	2	1	115	0	151	1148
Headache	1346	61	32		409	2	283	653
Malaise	1333	85	56	1	173	0	306	855
Fatigue	1301	70	35	1	186	0	356	758
Diarrhoea	1223	96	47	0	433	1	203	588
Herpes zoster	1221	235	169	1	498	28	150	544
Death	1142	1142	15	1142	0	0	0	0
Pneumonia	1061	1061	540	61	445	2	108	451
Illness	1005	87	70	0	146	0	92	768
All others	70239	19519	7029	821	12450	135	13676	43215
Total	96230	23363	8319	2054	16299	174	18310	59528

AE = adverse event; H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 111. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Higher Incidence and Severity of AEs in the Elderly (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Pain	2904	128	58	0	223	2	542	2139
Drug ineffective	2576	24	10	1	56	1	253	2266
Condition aggravated	1662	145	44	1	202	3	362	1111
Arthralgia	1501	85	30	0	157	0	307	1058
Off label use	1237	3	2	0	9	0	13	1215
Pain in extremity	1205	59	28	0	115	1	279	817
Product dose omission issue	1204	11	4	0	16	0	26	1162
Illness	1165	120	95	1	102	0	78	986
Malaise	1037	46	32	0	83	0	139	817
Headache	867	30	17	0	168	0	113	586
Fatigue	855	19	14	0	109	0	154	594
COVID-19	820	250	171	17	158	2	48	596
Peripheral swelling	810	48	22	0	113	0	170	534
All others	51833	13589	3760	963	6026	72	6556	38262
Total	69676	14557	4287	983	7537	81	9040	52143

AE = adverse event; H = hospitalisation; F = fatal; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk

RA: The severity of the events of interest in the elderly population (≥65 years) is presented below.

Table 112. Severity of Events of Interest in the All RA Elderly Population (P123LTE, ≥65 Years)

Event	Mild	Moderate	Severe	Unknown
Serious infections	11	57	72	0
TB	1	1	2	0
OIs (excl TB)	6	11	8	0
HZ	51	86	11	0
Neutropenia	15	3	1	0
Lymphopenia	34	18	3	0
Anaemia	63	33	4	0
Hyperlipidaemia	23	9	0	0
NMSC	23	22	4	0
Malignancy (excl NMSC)[a]	5	13	25	0
MACE	1	5	16	0
GI perforation	0	2	3	0
ILD	4	4	3	0

a. There were 43 cases of malignancies (excluding NMSC) in the elderly dataset. Of these cases, there were 3 cases of lymphoma, 9 cases of lung cancer, 2 cases of melanoma, and 4 cases of breast cancer (female subjects only).

Table 112. Severity of Events of Interest in the All RA Elderly Population (P123LTE, ≥65 Years)

Event	Mild	Moderate	Severe	Unknown

For the same adverse event of interest, the most severe case was selected in this summary, subject to a risk period of 28 days beyond the last dose or the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date.
Includes protocols A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2-year), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
Final data 18 January 2019
Excl = excluding; GI = gastrointestinal; ILD = interstitial lung disease; MACE = major adverse cardiac event; NMSC = nonmelanoma skin cancer; OI = opportunistic infection; TB = tuberculosis
Source: Table 417a.1.3.8

Study A3921133: The severity of the events of interest by treatment group in the elderly population (≥65 years) are presented below.

Table 113. Severity of the Events of Interest in the Elderly Population from Study A3921133 by Treatment Group (≥65 years)

Event	Treatment Group	Mild	Moderate	Severe	Unknown
Serious infections	Tofacitinib 5mg BID	3	21	29	0
	Tofacitinib 10mg BID	6	30	43	0
	All Tofa	9	51	72	0
	TNFi	1	21	33	0
HZ	Tofacitinib 5mg BID	13	32	4	0
	Tofacitinib 10mg BID	17	41	6	0
	All Tofa	30	73	10	0
	TNFi	8	13	2	0
Adjudicated OIs (excl TB)	Tofacitinib 5mg BID	3	8	3	0
	Tofacitinib 10mg BID	1	11	4	0
	All Tofa	4	19	7	0
	TNFi	1	5	2	0
Adjudicated NMSC	Tofacitinib 5mg BID	7	9	2	0
	Tofacitinib 10mg BID	7	10	0	0
	All Tofa	14	19	2	0
	TNFi	1	8	0	0
Adjudicated malignancy (excl NMSC)	Tofacitinib 5mg BID	1	6	19	0
	Tofacitinib 10mg BID	1	3	16	0
	All Tofa	2	9	35	0
	TNFi	1	4	12	0
Adjudicated MACE	Tofacitinib 5mg BID	1	3	14	0
	Tofacitinib 10mg BID	0	6	19	0
	All Tofa	1	9	33	0
	TNFi	1	3	9	0
Adjudicated GI perforation	Tofacitinib 5mg BID	0	0	3	0
	Tofacitinib 10mg BID	0	0	2	0
	All Tofa	0	0	5	0
	TNFi	0	1	1	0

Table 113. Severity of the Events of Interest in the Elderly Population from Study A3921133 by Treatment Group (≥65 years)

Event	Treatment Group	Mild	Moderate	Severe	Unknown
Adjudicated ILD	Tofacitinib 5mg BID	2	3	1	0
	Tofacitinib 10mg BID	3	1	3	1
	All Tofa	5	4	4	1
	TNFi	2	2	1	2
Adjudicated VTE	Tofacitinib 5mg BID	3	4	3	0
	Tofacitinib 10mg BID	2	3	9	0
	All Tofa	5	7	12	0
	TNFi	0	2	1	0

BID = twice daily; CI = confidence interval; Excl = excluding; GI = gastrointestinal; HZ = herpes zoster; ILD = interstitial lung disease; IR = incidence rate; MACE = major adverse cardiac event; NMSC = non-melanoma skin cancer; OI = opportunistic infections; PY = patient-year; TB = tuberculosis; TNFi = tumour necrosis factor inhibitor; VTE = venous thromboembolism
For the same adverse event of interest, the most severe case was selected in this summary, subject to a risk period of 28 days beyond the last dose or to a risk period of up to 28 days beyond the last dose or to the last contact date.
The risk period was minimum of (last contact date, Last Study Treatment Dose date + 28 days)
The last contact date was maximum of (AE start date, AE stop date, last study visit date, withdrawal date, Telephone Contact date).
If a subject died, last contact date was the death date.
For subjects randomized to the TNFi group, adalimumab was administered in US, Puerto Rico and Canada, and etanercept was administered in the rest of the world.
Source: Table 1657.7.3.6

PsA: In the All PsA population, the severity of the events of interest in the elderly population (≥65 years) is presented below.

Table 114. Severity of Events of Interest in All PsA Elderly Population (P3LTE, ≥65 years)

Event	Mild	Moderate	Severe	Unknown
Serious infections	0	1	2	0
TB	0	0	0	0
OIs (excl TB)	0	1	0	0
HZ	0	3	0	0
Neutropenia	1	0	0	0
Lymphopenia	0	0	0	0
Anaemia	3	1	0	0
Hyperlipidaemia	3	2	0	0
NMSC	4	0	2	0
Malignancy (excl NMSC)[a]	0	0	3	0
MACE	0	1	2	0
GI perforation	0	0	0	0
ILD	0	0	0	0

Table 114. Severity of Events of Interest in All PsA Elderly Population (P3LTE, ≥65 years)

Event	Mild	Moderate	Severe	Unknown

a. There were 0 cases of lymphoma, 0 cases of lung cancer, 0 cases of melanoma, and 1 case of breast cancer.
Excl = excluding; GI = gastrointestinal; ILD = interstitial lung disease; MACE = major adverse cardiac event; NMSC = nonmelanoma skin cancer; OI = opportunistic infection; TB = tuberculosis
Includes protocols: A3921091, A3921092 and A3921125
Final data 31 July 2019
Source: Table 00118.C3.11.6.2.2

UC: The severity of the events of interest in the elderly population (≥65 years) is presented below.

Table 115. Severity of the Events of Interest in the All UC Elderly Population (P2P3LTE, ≥65 years)

Event	Mild	Moderate	Severe	Unknown
Serious infections	2	1	1	0
Adjudicated TB	0	0	0	0
Adjudicated OIs (excl TB)	2	0	1	0
HZ	5	7	2	0
Neutropenia	0	1	0	0
Lymphopenia	4	1	0	0
Anaemia	3	1	0	0
Hyperlipidaemia	0	1	0	0
Adjudicated NMSC	5	3	1	0
Adjudicated Malignancy (excl NMSC)[a]	1	1	2	0
Adjudicated MACE	1	0	2	0
GI perforation [revised definition][b]	0	0	0	0
Adjudicated ILD	0	0	0	0

a. There were 0 cases of lymphoma, 0 case of lung cancer, 0 cases of melanoma, and 0 cases of breast cancer.
b. Revised definition of GI perforation: Events that were confirmed by adjudication, excluding MedDRA PTs of Perirectal abscess, Rectal abscess, Anal abscess, Perineal abscess, Pilonidal cyst, and any PTs containing the term fistula regardless of the location of the fistula.
Excl = excluding; GI = gastrointestinal; ILD = interstitial lung disease; MACE = major adverse cardiac event; NMSC = nonmelanoma skin cancer; OI = opportunistic infection; TB = tuberculosis
Includes protocols: A3921063, A3921094, A3921095, A3921096, A3921139
Final data 24 Aug 2020Source: Table 417a.3.3.8

JIA: Not applicable.

AS: In the All AS population, no events of interest were reported in the elderly population (age ≥65 years).

VII.3.1.1.10.4. Risk factors and risk groups

In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, patients 65 years of age and older had an increased risk of serious infections, MI, malignancies, and all-cause mortality with tofacitinib.

VII.3.1.1.10.5. Preventability

Considering the increased risk of serious infections, MI, malignancies, and all-cause mortality with tofacitinib in patients 65 years of age and older, tofacitinib should only be used in these patients if no suitable treatment alternatives are available.

VII.3.1.1.10.6. Impact on the risk-benefit balance of the product

As compared to younger patients, AEs reported in elderly patients may be more severe and sometimes life-threatening.

VII.3.1.1.10.7. Public health impact

The higher risk of AEs may have some significant impacts on public health both in terms of lost time at work and increased burden on medical care.

VII.3.1.2. Important Potential Risks

VII.3.1.2.1. Malignancy

VII.3.1.2.1.1. Potential mechanisms

The potential role of Janus kinase inhibition in malignancies (excluding NMSC) is not known.

VII.3.1.2.1.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.2.1.3. Characterisation of the risk

Frequency

Interventional Clinical Trials: Please see Section VII.3.1.1.4.3 for risk characterisation of lung cancer and Section VII.3.1.1.5.3 for lymphoma.

RA: In the RCTs the IRs (95% CI) per 100 PY for the 5 mg BID, 10 mg BID dose groups and overall tofacitinib, respectively, were:

- Malignancies (excluding NMSC): 0.35 (0.16, 0.66), 0.65 (0.35, 1.11), 0.47 (0.31, 0.70)
- Breast cancer (female subject only): 0.09 (0.01, 0.34), 0.12 (0.01, 0.43), 0.09 (0.02, 0.23)

- Prostate cancer (male subjects only): 0.21 (0.01, 1.19), 0.30 (0.01, 1.70), 0.33 (0.07, 0.96)

- Pancreatic cancer: No cases reported

In the All RA population, the IRs (95% CI) per 100 PY for the 5 mg BID, 10 mg BID dose groups and overall tofacitinib, respectively, were:

- Malignancies (excluding NMSC): 0.74 (0.57, 0.94), 0.74 (0.61, 0.90), 0.74 (0.64, 0.86)

- Breast cancer (female subjects only): 0.16 (0.08, 0.28), 0.14 (0.09, 0.23), 0.15 (0.10, 0.22)

- Prostate cancer (male subjects only): 0.19 (0.04, 0.55), 0.27 (0.11, 0.55), 0.24 (0.11, 0.44)

- Melanoma: 0.03 (0.01, 0.10), 0.07 (0.04, 0.13), 0.06 (0.03, 0.10)

- No cases of pancreatic cancer were reported in the All RA population.

Study A3921133: The IRs per 100 PY (95% CI) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, for the adjudicated events below were:

- Malignancy (excluding NMSC): 1.07 (0.80, 1.39), 0.93 (0.67, 1.24), 1.00 (0.81, 1.21), 0.78 (0.55, 1.06)

- Breast cancer (female subjects only): 0.17 (0.07, 0.35), 0.16 (0.06, 0.35), 0.16 (0.09, 0.28), 0.25 (0.12, 0.47)

- Prostate cancer (male subjects only): 0.10 (0.00, 0.56), 0.64 (0.26, 1.33), 0.39 (0.17, 0.76), 0.27 (0.06, 0.79)

- Melanoma: 0.02 (0.00, 0.11), 0.02 (0.00, 0.11), 0.02 (0.00, 0.07), 0.10 (0.03, 0.23)

- Pancreatic cancer: 0.06 (0.01, 0.17), 0.02 (0.00, 0.11), 0.04 (0.01, 0.10), 0.02 (0.00, 0.11)

PsA: In the RCTs the IRs (95% CI) per 100 PY for the 5 mg BID and 10 mg BID dose groups, respectively, were:

- Malignancies (excluding NMSC): 1.95 (0.40, 5.70), 0.00 (0.00, 2.44)

- Breast cancer (female subjects only): 1.27 (0.03, 7.09), 0.00 (0.00, 4.24)

- Prostate cancer (male subjects only): 0.00 (0.00, 4.88), 0.00 (0.00, 5.76)

- Pancreatic cancer: 0.00 (0.00, 2.39), 0.00 (0.00, 2.44)

In the All PsA population, the IRs (95% CI) per 100 PY for the 5 mg BID, 10 mg BID, and combined 5 mg and 10 mg dose groups, respectively, were:

- Malignancies (excluding NMSC): 1.00 (0.53, 1.71), 0.25 (0.03, 0.91), 0.71 (0.40, 1.18)
- Breast cancer (female subjects only): 0.28 (0.03, 1.01), 0.00 (0.00, 0.89), 0.18 (0.02, 0.64)
- Prostate cancer (male subjects only): 0.17 (0.00, 0.95), 0.26 (0.01, 1.45), 0.21 (0.02, 0.74)
- Pancreatic cancer: 0.08 (0.00, 0.43), 0.00 (0.00, 0.46), 0.05 (0.00, 0.27)

UC: The IRs per 100 PY (95% CI) from the RCTs (10 mg dose group for induction studies and the 5 mg, 10 mg, and combined 5 mg and 10 mg dose groups respectively for maintenance study) for the following malignancies were:

- Malignancies (excluding NMSC): No cases reported
- Breast cancer (female subjects only): No cases reported
- Prostate cancer (male subjects only): No cases reported

The IRs per 100 PY (95% CI) from the All UC (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) for the following malignancies were:

- Malignancies (excluding NMSC): 0.38 (0.08, 1.10), 0.81 (0.47, 1.29), 0.69 (0.42, 1.06)
- Breast cancer (female subjects only): 0.31 (0.01, 1.71), 0.11 (0.00, 0.63), 0.17 (0.02, 0.60)
- Prostate cancer (male subjects only): No cases reported
- Melanoma: 0.00 (0.00, 0.46), 0.09 (0.01, 0.34), 0.07 (0.01, 0.25)
- Pancreatic cancer: No cases reported

JIA: There were no cases of malignancy from the JIA integrated safety analysis population.

AS: In RCTs (Tofa 5 mg BID) no malignancy cases were reported. The IRs (95% CI) per 100 PY for RCTs (Tofa 5 mg BID) were:

- Malignancies (excluding NMSC): 0.00 (0.00, 3.28)
- Lymphoma: 0.00 (0.00, 3.28)

- Lung cancer: 0.00 (0.00, 3.28)
- Breast cancer (female subject only): 0.00 (0.00, 17.20)
- Prostate cancer: 0.00 (0.00, 3.85)
- Pancreatic cancer: 0.00 (0.00, 3.28)

In the All AS population (All Tofa 5 mg BID, All Tofa) no malignancy cases were reported. The IRs (95% CI) per 100 PY for All Tofa 5 mg BID and All Tofa, respectively, were:

- Malignancies (excluding NMSC): 0.00 (0.00, 1.59), 0.00 (0.00, 1.40)
- Lymphoma: 0.00 (0.00, 1.59), 0.00 (0.00, 1.40)
- Lung cancer: 0.00 (0.00, 1.59), 0.00 (0.00, 1.40)
- Breast cancer (female subject only): 0.00 (0.00, 10.18), 0.00 (0.00, 8.06)
- Prostate cancer: 0.00 (0.00, 1.89), 0.00 (0.00, 1.70)
- Pancreatic cancer: 0.00 (0.00, 1.59), 0.00 (0.00, 1.40)

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: In the full sample, crude and age- and sex- adjusted incidence rates of malignancy excluding NMSC were slightly increased among the tofacitinib group when compared with the bDMARD group, although the CIs overlapped. Across trimmed and matched populations, incidence rates of malignancy excluding NMSC were similar among the tofacitinib and bDMARD treated patients with overlapping CIs.

Please see table below for the crude rates and 95% CI for safety events of interest (latent exposure) among eligible RA patients initiating tofacitinib, bDMARD, or csDMARD.

Table 116. Crude Rates (per 100 PY) and 95% CI for Malignancy Among Eligible RA Patients Initiating Tofacitinib, bDMARD, or csDMARD (31 January 2019, Primary Analyses)

Latent Exposure	31 January 2019 Datacut								
	Tofacitinib			bDMARD			csDMARD		
	Rate	95% LL	95% UL	Rate	95% LL	95% UL	Rate	95% LL	95% UL
Malignancy excluding NMSC									
Full Sample	1.01	0.74	1.35	0.75	0.63	0.9	0.94	0.7	1.24
PS Trimmed	0.88	0.58	1.27	0.81	0.66	0.98	NR	NR	NR
PS Matched	0.89	0.59	1.29	0.88	0.69	1.11	NR	NR	NR
Lymphoma	0.09	0.02	0.23	0.09	0.05	0.15	0.02	0.00	0.10
Lung cancer	0.13	0.05	0.29	0.11	0.06	0.17	0.26	0.14	0.43
Breast cancer	0.18	0.08	0.35	0.17	0.12	0.25	0.2	0.10	0.36
Other cancer	0.53	0.34	0.8	0.29	0.21	0.38	0.38	0.24	0.59

Table 116. Crude Rates (per 100 PY) and 95% CI for Malignancy Among Eligible RA Patients Initiating Tofacitinib, bDMARD, or csDMARD (31 January 2019, Primary Analyses)

Latent Exposure	31 January 2019 Datacut								
	Tofacitinib			bDMARD			csDMARD		
	Rate	95% LL	95% UL	Rate	95% LL	95% UL	Rate	95% LL	95% UL
Melanoma	0.09	0.02	0.23	0.11	0.07	0.18	0.16	0.08	0.31

bDMARD=biologic disease modifying antirheumatic drug; csDMARD=conventional synthetic disease modifying antirheumatic drug; LL=lower limit; NMSC=non-melanoma skin cancer; NR=not reported; PS=propensity score; PY=person-years; RA=rheumatoid arthritis; UL=upper limit
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Seriousness/outcomes

RA: In the All RA population, of the 179 malignancies (excluding NMSC), 175 were reported as serious and 4 as non-serious. The outcomes reported for malignancy (excluding NMSC) cases were resolved (92), still present (53), death (27), and unknown (7). In the All RA population, 30 cases of breast cancer were serious. The outcomes for breast cancer were resolved (17), still present (11), death (1), and unknown (1). In the All RA population, 13 cases of melanoma were serious and 1 was non-serious. The outcomes for melanoma were resolved (12), still present (1), and unknown (1).

Study A3921133: The outcomes for adjudicated malignancy excluding NMSC (all assessed as serious except for 2 assessed as non-serious in the TNFi group) for the following treatment groups were:

- Tofacitinib 5 mg BID: still present (38), resolved (11), unknown (1), death (5)
- Tofacitinib 10 mg BID: still present (35), resolved (9), death (1)
- All Tofa: still present (73), resolved (20), unknown (1), death (6)
- TNFi: still present (30), resolved (8), death (1)

PsA: In the All PsA population, all 13 malignancies (excluding NMSC) were reported as serious. The outcomes for malignancy (excluding NMSC) cases were resolved (8), still present (4), and death (1). In the All PsA population, 2 cases of breast cancer were serious. The outcome for the 2 breast cancer cases was resolved. There were no melanoma cases reported.

UC: In the All UC population, 16 malignancies (excluding NMSC) were reported as serious and 4 were reported as non-serious. The outcomes reported for malignancy (excluding NMSC) cases were resolved (10), still present (6), and death (4). In the All UC population 2 cases of breast cancer were serious. The outcomes for breast cancer were resolved (1) and still present (1). In the All UC population, 2 cases of melanoma were serious. The outcomes for melanoma were resolved (1) and still present (1).

JIA: There were no cases of malignancy from the JIA integrated safety analysis population.

AS: There were no malignancies in the AS programme.

Post-Marketing:

Table 117. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Malignancy (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Neoplasm malignant	345	345	29	13	19	1	45	267
Lung neoplasm malignant	180	180	32	28	10	1	41	100
Breast cancer	159	159	24	4	24	0	28	103
Lymphoma	109	109	22	5	16	3	21	64
Colon cancer	93	93	30	15	21	2	13	42
Breast cancer female	81	81	9	0	8	1	22	50
Colectomy	77	77	17	0	8	1	9	59
Malignant melanoma	73	73	5	1	15	0	4	53
Prostate cancer	67	67	10	0	8	0	18	41
Neoplasm	53	30	4	0	5	0	9	39
Gastric cancer	48	48	25	4	16	2	7	19
Bladder cancer	36	36	9	2	5	0	1	28
Pancreatic carcinoma	36	36	10	14	1	0	6	15
Leukaemia	29	29	2	1	0	0	4	24
Lymphoproliferative disorder	28	28	12	2	14	0	1	11
Hepatic cancer	24	24	3	2	0	0	8	14
Uterine cancer	24	24	6	1	4	0	7	12
Metastases to liver	22	22	8	6	1	0	6	9
Ovarian cancer	22	22	5	2	3	0	4	13
Brain neoplasm	21	21	4	1	1	0	7	12
All others	1035	968	239	75	148	12	229	571
Total	2562	2472	505	176	327	23	490	1546

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 118. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Malignancy (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Neoplasm malignant	236	236	15	1	10	0	24	201
Lung neoplasm malignant	97	97	11	4	8	0	9	76
Breast cancer	77	77	4	2	2	0	9	64
Breast cancer female	70	70	5	0	6	0	9	55
Prostate cancer	45	45	4	0	5	0	11	29
Malignant melanoma	39	39	3	0	5	0	6	28
Hysterectomy	30	29	6	0	5	0	1	24
Lymphoma	28	28	3	0	4	0	6	18

Table 118. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Malignancy (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Colon cancer	27	27	9	0	4	0	2	21
Leukaemia	25	25	2	0	1	0	2	22
Neoplasm	23	13	2	0	2	0	0	21
Renal cancer	21	21	5	0	2	0	6	13
Brain neoplasm	17	17	4	1	3	0	2	11
Pancreatic carcinoma	15	15	5	3	1	0	2	9
All others	459	436	95	16	43	3	81	316
Total	1209	1175	173	27	101	3	170	908

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity[8] and nature of the risk

RA: In the All RA population, there were 179 cases of malignancies (excluding NMSC). Of these cases, there were 14 cases of melanoma and 30 cases of breast cancer. Of the 179 cases of malignancies (excluding NMSC), the severity was assessed as mild (24), moderate (58), severe (95), and unknown (2).

Study A3921133: The severity of adjudicated malignancy excluding NMSC for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (6), moderate (14), severe (35)
- Tofacitinib 10 mg BID: mild (2), moderate (8), severe (35)
- All Tofa: mild (8), moderate (22), severe (70)
- TNFi: mild (3), moderate (14), severe (22)

PsA: In the All PsA population, there were 15 cases of malignancies (excluding NMSC). Of these cases, there were 2 cases of breast cancer. All of the malignancies (excluding NMSC) were assessed as serious. Of the 15 cases of malignancies (excluding NMSC), the severity was assessed as mild (1), moderate (6), and severe (8).

UC: In the All UC population, there were 20 cases of malignancies (excluding NMSC). Of these cases, there were 2 cases of breast cancer and 2 cases of melanoma.

JIA: There were no cases of malignancy from the JIA integrated safety analysis population.

[8] Severity definitions: mild = does not interfere with subject's usual function; moderate = interferes to some extent with subject's usual function; severe = interferes significantly with subject's usual function.

AS: There were no malignancies in the AS programme.

VII.3.1.2.1.4. Risk factors and risk groups

The risk of malignancy (cancer) in general is increased in the elderly population. In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies, particularly NMSC, lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors. The following predictive factors for development of malignancies excluding NMSC were identified using a Multivariate Cox model with backward selection: age ≥65 years and current or past smoking.

Summary of results from the US Corrona RA Registry A3921205: The rates of malignancy excluding NMSC were higher without overlapping 95% CI in patients 65 and older than in patients younger than 65 in both tofacitinib and bDMARD initiator groups. The rate of malignancy excluding NMSC in patients 65 and older in tofacitinib initiators was 1.77 (95% CI=1.17, 2.57) and the rate in bDMARD initiators was 1.22 (95% CI=0.95, 1.55); the 95% CI overlapped.

Summary of Study A3921133 results: an increase in malignancies (excluding NMSC), particularly lymphoma and lung cancer, was observed with tofacitinib compared to TNFi. This increased risk was predominantly observed in older patients and in patients who are current or past smokers.

The IR per 100 PY (95% CI) (based on total time) of adjudicated malignancies (excluding NMSC) in adults aged ≥65 years or who had ever smoked for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 1.38 (1.01, 1.82), 1.59 (1.19, 2.07), 1.48 (1.21, 1.80), and 0.96 (0.66, 1.34).

In patients who were less than 65 years of age and had never smoked, the IR per 100 PY (95% CI) (based on total time) for malignancies excluding NMSC for tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.70 (0.38, 1.17), 0.31 (0.12, 0.68), 0.51 (0.31, 0.79), and 0.44 (0.20, 0.84).

VII.3.1.2.1.5. Preventability

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated NMSC) tofacitinib should only be used if no suitable treatment alternatives are available.

It is not recommended to initiate tofacitinib treatment in adult patients with a low neutrophil count (ie, absolute neutrophil count [ANC] < 1000 cells/mm^3). It is recommended not to initiate dosing in paediatric patients with an ANC less than 1200 cells/mm^3. Tofacitinib dose should be interrupted or adjusted based on ANC. Neutrophils should be monitored at baseline, 4-8 weeks after starting tofacitinib, and every 3 months thereafter.

It is not recommended to initiate tofacitinib treatment in adult and paediatric patients with a low lymphocyte count (ie, less than 750/mm^3). In patients who develop a confirmed absolute

lymphocyte count of less than 500/mm^3 treatment with tofacitinib is not recommended. Lymphocytes should be monitored at baseline and every 3 months thereafter.

Tofacitinib should not be used in combination with biologics such as TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators, IL 17 antagonists, IL 12/IL23 antagonists, and potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporin, and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

VII.3.1.2.1.6. Impact on the risk-benefit balance of the product

Malignancy can severely impact a patient's quality of life and can be fatal. Specific potential effects on an individual patient depend upon a variety of factors including site of malignancy and tolerance of therapy.

VII.3.1.2.1.7. Public health impact

Malignancy is a major public health problem. It is among the leading causes of morbidity and mortality worldwide.[296]

VII.3.1.2.2. Cardiovascular (CV) Risk (Excl MI)

VII.3.1.2.2.1. Potential mechanisms

Unknown.

VII.3.1.2.2.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.2.2.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: In RCTs, the IR (95% CI) per 100 PY of adjudicated Major Adverse Cardiac Event (MACE) related AEs for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.28 (0.11, 0.58), 0.42 (0.18, 0.83), 0.35 (0.20, 0.56). In the All RA population, the IR (95% CI) per 100 PY of adjudicated MACE related AEs for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.38 (0.26, 0.54), 0.37 (0.27, 0.48), 0.37 (0.30, 0.46). The IR (95% CI) per 100 PY of adjudicated events of non-fatal MI for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.17 (0.09, 0.29), 0.13 (0.08, 0.21), 0.15 (0.10, 0.21).

Study A3921133: The IRs of adjudicated MACE per 100 PY (95% CI) for the for the tofacitinib 5 mg, tofacitinib 10 mg, All Tofa, and TNFi groups, respectively, were 0.88 (0.64, 1.18), 1.02 (0.75, 1.34), 0.95 (0.76, 1.16), 0.70 (0.49, 0.97). The IRs of adjudicated non-fatal MACE per 100 PY (95% CI) for the for the tofacitinib 5 mg, tofacitinib 10 mg, All Tofa, and TNFi groups, respectively, were 0.62 (0.43, 0.88), 0.64 (0.44, 0.91), 0.63 (0.49, 0.81), 0.50 (0.32, 0.74). The most frequently reported MACE component was non-fatal MI for tofacitinib (Section VII.3.1.1.6 Myocardial Infarction).

PsA: The IRs per 100 PY (95% CI) of MACE related AEs from the RCTs for the 5 mg and 10 mg dose groups, respectively, were 0.00 (0.00, 2.39) and 0.66 (0.02, 3.69). In the All PsA population, the IRs per 100 PY (95% CI) of the MACE AEs for the 5 mg and 10 mg dose groups and the combined 5 mg and 10 mg dose groups, respectively, were 0.31 (0.08, 0.79), 0.25 (0.03, 0.91), 0.29 (0.11, 0.62).

UC: The IR per 100 PY (95% CI) of MACE related AEs from the RCTs (10 mg dose group for induction studies) was 1.26 (0.15, 4.56). The IRs per 100 PY (95% CI) for the RCTs (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups respectively for maintenance study) were 0.68 (0.02, 3.77), 0.64 (0.02, 3.54), 0.66 (0.08, 2.37).

The IRs per 100 PY (95% CI) of MACE related AEs from the All UC (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 0.51 (0.14, 1.30), 0.19 (0.05, 0.48), and 0.28 (0.12, 0.54). The IRs per 100 PY (95% CI) of nonfatal MACE from the All UC (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 0.51 (0.14, 1.30), 0.09 (0.01, 0.34), and 0.21 (0.08, 0.45).

JIA: There were no cases of MACE from the JIA integrated safety analysis population.

AS: No MACE cases were reported in the RCTs (Tofa 5 mg BID cohort) or in the All AS population (All Tofa 5 mg BID, All Tofa cohorts). The IR (95% CI) per 100 PY of MACE in the RCT (Tofa 5 mg BID) was 0.00 (0.00, 3.28). The IRs (95% CI) per 100 PY of MACE in the All AS population for All Tofa 5 mg BID and All Tofa, respectively, were 0.00 (0.00, 1.59) and 0.00 (0.00, 1.40).

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: Results are described for the 31 March 2018 datacut, the primary analyses. Results from the larger patient population included in the 31 January 2019 datacut were similar.

In the full sample (i.e., untrimmed/unmatched), there were 90 observed MACE events among the bDMARD group with a resulting crude incidence rate of 0.92 (95% CI=0.74-1.13) per 100 person-years. There were 15 observed MACE events among the tofacitinib group with a resulting crude incidence rate of 0.70 (95% CI=0.39-1.16) per 100 person-years.

Crude rates of MACE were similar in matched and trimmed cohorts. In the matched cohorts, there were 49 observed MACE events among bDMARD initiators for a crude incidence rate of 1.14 (95% CI=0.84-1.50) per 100 person-years; among tofacitinib initiators there were 10 MACE events for a crude incidence rate of 0.66 (95% CI=0.32-1.21) per 100 person-years.

Please see table below for the crude rates and 95% CI for safety events of interest (acute exposure) among eligible RA patients initiating tofacitinib, bDMARD, or csDMARD.

Table 119. Crude Rates (per 100 PY) and 95% CI for MACE and CV Events Among Eligible RA Patients Initiating Tofacitinib, bDMARD or csDMARD (Primary Analyses)

	31 March 2018 Datacut[a]								
	Tofacitinib			bDMARD			csDMARD		
	Rate	95% LL	95% UL	Rate	95% LL	95% UL	Rate	95% LL	95% UL
MACE									
Full sample	0.70	0.39	1.16	0.92	0.74	1.13	0.57	0.33	0.92
PS Trimmed	0.66	0.32	1.21	1.00	0.78	1.25	NR	NR	NR
PS Matched	0.66	0.32	1.21	1.14	0.84	1.5	NR	NR	NR
Total CVD	2.14	1.56	2.86	2.42	2.12	2.75	2.12	1.63	2.72
Cardiac Arrest	0	0	0.17	0.1	0.05	0.19	0	0	0.12
MI	0.28	0.1	0.61	0.3	0.21	0.43	0.3	0.14	0.58
CHF requiring hospitalisation	0.33	0.13	0.67	0.24	0.16	0.36	0.3	0.14	0.57

a. Primary analysis;
bDMARD=biologic disease modifying antirheumatic drug; CHF=congestive heart failure; csDMARD=conventional synthetic disease modifying antirheumatic drug; CVD=cardiovascular disease; LL=lower limit; MACE=major adverse cardiovascular event; MI=myocardial infarction; NR=not reported; PS=propensity score; PY=person-years; RA=rheumatoid arthritis; UL=upper limit
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Seriousness/outcome

RA: In the All RA population, there were 23 non-fatal CHF cases, of which 18 were serious and 5 were non-serious. In 21 of the non-fatal CHF cases, the event had resolved and in 2 cases the event was still present. There were 85 MACE cases, of which 79 were serious and 6 were non-serious. In 59 of the MACE cases, the event had resolved and in 6 cases the event was still present. There were 20 fatal outcomes.

Study A3921133: The outcomes for adjudicated MACE (all assessed as serious) for the following treatment groups were:

- Tofacitinib 5 mg BID: still present (6), resolved (26), death (13)
- Tofacitinib 10 mg BID: still present (8), resolved (23), death (18)
- All Tofa: still present (14), resolved (49), death (31)
- TNFi: still present (3), resolved (22), death (10)

PsA: In the All PsA population, there were 6 MACE cases, of which all 5 were serious and 1 was non-serious. In 4 of the MACE cases, the event resolved. There were 2 fatal outcomes.

UC: In the All UC population, there were 3 nonfatal CHF cases, of which 2 were serious and 1 was non-serious. All 3 nonfatal CHF cases had resolved. There were 8 MACE cases, all 8 of which were serious. In 6 of the MACE cases, the event resolved, and 1 case was still present. There was 1 fatal outcome.

JIA: There were no cases of MACE from the JIA integrated safety analysis population.

AS: There were no MACE cases in the AS programme.

Post-Marketing:

Table 120. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – CV Risk (Excl MI) (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Cerebrovascular accident	469	469	160	19	78	9	41	323
Transient ischaemic attack	65	65	17	0	20	0	1	44
Angina pectoris	60	60	12	0	22	0	6	32
Cerebral haemorrhage	37	37	21	3	9	6	1	18
Cerebral infarction	30	30	19	2	8	2	2	16
Coronary artery disease	27	22	8	2	3	0	1	21
Ischaemic stroke	22	22	7	0	8	0	0	14
Intracranial aneurysm	18	18	4	1	1	0	2	14
Haemorrhagic stroke	13	13	8	5	1	0	1	6
Myocardial ischaemia	12	12	3	2	2	1	0	7
Stress cardiomyopathy	12	11	5	1	4	0	2	5
Angina unstable	10	10	5	0	2	0	3	5
Hemiparesis	10	10	4	1	1	0	1	7
All others	144	141	62	15	27	11	15	76
Total	929	920	335	51	186	29	76	588

CV = cardiovascular; Excl = excluding; F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; MI = myocardial infarction; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 121. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – CV Risk (Excl MI) (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Cerebrovascular accident	377	377	117	10	50	5	30	284
Transient ischaemic attack	40	40	14	0	5	0	1	34
Angina pectoris	32	32	8	0	8	0	2	22
Coronary artery disease	24	18	10	3	2	0	0	19
Cerebral haemorrhage	18	18	10	1	3	0	0	14
Coronary arterial stent insertion	14	14	1	0	0	0	2	12
Coronary artery bypass	10	10	2	0	0	0	0	10
Intracranial aneurysm	10	10	0	1	1	0	0	8
Hemiparesis	9	9	1	1	2	0	1	5
Carotid artery occlusion	8	8	3	0	0	0	1	7
Arteriosclerosis coronary artery	7	7	2	0	1	0	0	6
Myocardial ischaemia	5	5	1	0	0	0	1	4
Stress cardiomyopathy	5	4	2	0	2	0	0	3
All others	59	58	33	2	7	3	9	38

Table 121. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – CV Risk (Excl MI) (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Total	618	610	204	18	81	8	47	466

CV = cardiovascular; Excl = excluding; F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; MI = myocardial infarction; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity[9] and nature of risk

RA: In the All RA population, 5 MACE cases were reported as mild, 19 were moderate, and 61 were severe. One case of non-fatal CHF was mild, 9 were moderate, and 13 were severe.

Study A3921133: The severity of adjudicated lymphoma for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (3), moderate (10), severe (32)
- Tofacitinib 10 mg BID: mild (1), moderate (9), severe (39)
- All Tofa: mild (4), moderate (19), severe (71)
- TNFi: mild (4), moderate (9), severe (22)

PsA: In the All PsA population, 1 MACE case was reported as mild, 2 were moderate, and 3 were severe. There were no cases of nonfatal CHF.

UC: In the All UC population, 1 MACE case was reported as mild, 1 was moderate, and 6 were severe. Of the 3 cases of nonfatal CHF, 1 was mild and 2 were moderate.

JIA: There were no cases of MACE from the JIA integrated safety analysis population.

AS: There were no MACE cases in the AS programme.

VII.3.1.2.2.4. Risk factors and risk groups

Patients with autoimmune diseases have an increased risk for cardiovascular disorders. The risk of cardiovascular events in general is increased in the elderly population. Tofacitinib has been associated with increased cholesterol, high blood pressure (hypertension), and weight gain, which are known risk factors for cardiovascular events.

In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an

[9] Severity definitions: mild = does not interfere with subject's usual function; moderate = interferes to some extent with subject's usual function; severe = interferes significantly with subject's usual function.

increased incidence of MACE was observed with tofacitinib compared to TNF inhibitors. Please refer to Section VII.3.1.1.6.4 for risk factors identified for MI in Study A3921133.

A post-hoc analysis of Study A3921133 identified age ≥65 years, current or past long-time smoking and, for MACE specifically, history of atherosclerotic cardiovascular disease (ASCVD, i.e., a composite of coronary artery disease, cerebrovascular disease, or peripheral artery disease) as risk factors accounting for the difference in adverse events of special interest between tofacitinib and TNF inhibitors.

Summary of results from the US Corrona RA Registry A3921205: The rates of MACE were higher in patients 65 and older than in patients younger than 65 in both tofacitinib and bDMARD initiator groups, with overlapping 95% CIs. The rate of MACE in patients 65 and older in tofacitinib initiators was 1.23 (95% CI=0.56, 2.34) and the rate in bDMARD initiators was 1.43 (95% CI=1.06, 1.89); the 95% CI overlapped.

VII.3.1.2.2.5. Preventability

It is recommended to monitor lipid parameters 8 weeks following initiation of tofacitinib therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia to reduce the risk of cardiovascular events.

MACE have been observed in patients taking tofacitinib.

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

VII.3.1.2.2.6. Impact on the risk-benefit balance of the product

These events may be serious and lead to hospitalisation.

VII.3.1.2.2.7. Public health impact

CVD is a major public health problem. It is among the leading causes of morbidity and mortality worldwide.

VII.3.1.2.3. Gastrointestinal (GI) Perforation

VII.3.1.2.3.1. Potential mechanisms

In evaluating whether tofacitinib could promote GI perforations, 2 potential mechanisms were considered most relevant, impaired wound healing and altered immune balance in the intestine.

VII.3.1.2.3.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.2.3.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: In RCTs, the IR (95% CI) per 100 PY of GI perforation AEs for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.00 (0.00, 0.14), 0.20 (0.05, 0.51), 0.09 (0.03, 0.22). In the All RA population, the IR (95% CI) per 100 PY of GI perforation AEs for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.06 (0.02, 0.13), 0.15 (0.09, 0.22), 0.11 (0.07, 0.16).

Study A3921133: The IRs per 100 PY (95% CI) for adjudicated GI perforation for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.17 (0.08, 0.33), 0.10 (0.03, 0.24), 0.14 (0.08, 0.23), 0.08 (0.02, 0.20).

PsA: The IRs per 100 PY (95% CI) of GI perforation AEs from the RCTs for the 5 mg and 10 mg dose groups, respectively, were 0.00 (0.00, 2.39) and 0.00 (0.00, 2.44). In the All PsA population, the IRs per 100 PY (95% CI) of GI perforation AEs for the 5 mg and 10 mg dose groups and the combined 5 mg and 10 mg dose groups, respectively, were 0.08 (0.00, 0.43), 0.00 (0.00, 0.46), and 0.05 (0.00, 0.27).

UC: The IR per 100 PY (95% CI) of GI perforation AEs (all) from the RCTs (10 mg dose group for induction studies) was 1.26 (0.15, 4.56). The IR per 100 PY (95% CI) of GI perforation AEs (revised definition[10]) was 0.63 (0.02, 3.51). The IRs per 100 PY (95% CI) of GI perforation AEs (all) for the RCTs (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups respectively for maintenance study) were 0.00 (0.00, 2.48), 0.00 (0.00, 2.35), and 0.00 (0.00, 1.21). The IRs per 100 PY (95% CI) of GI perforation AEs (revised definition[10]) were 0.00 (0.00, 2.48), 0.00 (0.00, 2.35), and 0.00 (0.00, 1.21).

The IRs per 100 PY (95% CI) of GI perforation AEs from the All UC (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 0.13 (0.00, 0.70), 0.28 (0.10, 0.62), and 0.24 (0.10, 0.49). The IRs per 100 PY (95% CI) of GI perforation AEs (revised definition[10]) were 0.13 (0.00, 0.70), 0.09 (0.01, 0.34), and 0.10 (0.02, 0.30).

JIA: There were no cases of GI perforation from the JIA integrated safety analysis population.

AS: No GI perforation cases were reported in the RCTs (Tofa 5 mg BID) or in the All AS population (All Tofa 5 mg BID, All Tofa). The IR (95% CI) per 100 PY of GI perforation in the RCTs (Tofa 5 mg BID) was 0.00 (0.00, 3.28). The IRs (95% CI) per 100 PY of GI

[10] Revised definition of GI perforation: Events that were confirmed by adjudication, excluding MedDRA PTs of Perirectal abscess, Rectal abscess, Anal abscess, Perineal abscess, Pilonidal cyst, and any PTs containing the term fistula regardless of the location of the fistula.

perforation in the All AS population for All Tofa 5 mg BID and All Tofa, respectively, were 0.00 (0.00, 1.59) and 0.00 (0.00, 1.40).

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: The crude incidence rates per 100 person-years (95% CI) for GI perforation in RA patients for tofacitinib, bDMARD, and csDMARD groups in the 31 March 2018 datacut are listed below.

Tofacitinib: 0.05 (95% CI=0, 0.26)
bDMARD: 0.05 (95% CI=0.02, 0.12)
csDMARD: 0.07 (95% CI=0.01, 0.24)

Seriousness/outcome

RA: In the All RA population, of the 27 cases of GI perforation, 26 were serious and 1 was non-serious). All 27 of GI perforation cases resolved. There was 1 appendicitis case for which the cause of death was attributed to appendicitis and sepsis.

Study A3921133: The outcomes for adjudicated GI perfortation (all assessed as serious) for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (9)
- Tofacitinib 10 mg BID: resolved (4), still present (1)
- All Tofa: resolved (13), still present (1)
- TNFi: resolved (4)

PsA: In the All PsA population, the single GI perforation case was serious. The outcome of the single GI perforation case was resolved.

UC: In the All UC population, all 3 GI perforation cases (revised definition[10]) were serious. All 3 of the GI perforation cases (revised definition[10]) were resolved.

JIA: There were no cases of GI perforation from the JIA integrated safety analysis population.

AS: There were no GI perforation cases in the AS programme.

Post-Marketing:

Table 122. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – GI Perforation (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Diverticulitis	343	343	108	2	98	4	39	200
Colitis	217	81	42	1	46	0	34	136
Diverticulum	62	24	12	0	13	1	12	36
Intestinal perforation	58	58	21	4	8	0	5	41
Gastrointestinal perforation	50	50	12	1	7	3	1	38
Appendicitis	44	44	20	0	15	1	2	26
Large intestine perforation	32	32	21	2	12	1	2	15
Peritonitis	32	32	17	5	11	0	6	12
Appendicitis perforated	19	19	10	0	10	0	0	9
Diverticular perforation	17	17	8	0	5	0	2	10
Anal abscess	16	16	8	0	10	0	0	6
All others	142	137	69	10	41	1	19	71
Total	1032	853	348	25	276	11	122	600

F = fatal; GI = gastrointestinal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 123. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – GI Perforation (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Diverticulitis	233	233	65	0	50	0	20	164
Colitis	70	18	14	0	8	0	11	51
Diverticulum	27	9	4	0	2	0	8	17
Intestinal perforation	17	17	11	0	2	0	1	14
Large intestine perforation	17	17	12	0	4	0	1	12
Appendicitis	14	14	6	0	3	0	0	11
Gastrointestinal perforation	12	12	6	0	1	1	1	9
Appendicitis perforated	11	11	8	0	2	0	0	9
All others	60	59	22	0	9	0	7	44
Total	461	390	148	0	81	1	49	331

F = fatal; GI = gastrointestinal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity[11] and nature of risk

RA: In the All RA population 6 GI perforations were moderate and 21 were severe.

Study A3921133: The severity of adjudicated GI perforation for the following treatment groups were:

- Tofacitinib 5 mg BID: moderate (1), severe (8)
- Tofacitinib 10 mg BID: severe (5)
- All Tofa: moderate (1), severe (13)
- TNFi: moderate (2), severe (2)

PsA: In the All PsA population, the single GI perforation case was severe.

UC: In the All UC population, all 3 GI perforation cases (revised definition[10]) were severe.

JIA: There were no cases of GI perforation from the JIA integrated safety analysis population.

AS: There were no GI perforation cases in the AS programme.

VII.3.1.2.3.4. Risk factors and risk groups

Patients with painful inflammation of small pockets in the lining of the intestine (diverticulitis) or patients who also take nonsteroidal anti-inflammatory drugs or corticosteroids (eg, prednisone) may be at higher risk.

VII.3.1.2.3.5. Preventability

No data are available to identify specific measures that can be used to prevent the occurrence of GI perforation.

VII.3.1.2.3.6. Impact on the risk-benefit balance of the product

Depending on the location and severity of the event, the impact on an individual patient's quality of life may vary considerably. GI perforations are life-threatening emergencies and warrant prompt medical/surgical intervention. Fistulas can cause considerable patient morbidity and can have a profound impact on an individual patient's quality of life and may require prompt surgical/medical intervention to prevent or manage life-threatening complications.

[11] Severity definitions: mild = does not interfere with subject's usual function; moderate = interferes to some extent with subject's usual function; severe = interferes significantly with subject's usual function.

VII.3.1.2.3.7. Public health impact

GI perforation is not expected to have a significant impact on public health; however, these events can lead to hospitalisation or death, which may increase the burden on health care systems.

VII.3.1.2.4. Interstitial Lung Disease (ILD)

VII.3.1.2.4.1. Potential mechanisms

The most common cause of ILD is idiopathic. The relative contribution of tofacitinib vs. other factors including use of MTX and RA to the development of ILD is not known.

VII.3.1.2.4.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.2.4.3. Characterisation of the risk

Frequency

RA: In RCTs, the IR (95% CI) per 100 PY of possible or probable ILD AEs for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.12 (0.02, 0.34), 0.10 (0.01, 0.36), 0.13 (0.05, 0.27). In the All RA population, the IR of possible or probable ILD events (95% CI) per 100 PY for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.20 (0.12, 0.31), 0.18 (0.12, 0.26), 0.19 (0.14, 0.25).

Study A3921133: The IRs per 100 PY (95% CI) of adjudicated ILD for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.29 (0.16, 0.48), 0.35 (0.20, 0.56), 0.32 (0.22, 0.45), 0.34 (0.20, 0.54).

PsA: In the All PsA population, there were no events assessed as ILD by the review committee. The IR per 100 PY (95% CI) of possible or probable ILD events per 100 PY for the combined 5 mg and 10 mg dose group was 0.05 (0.00, 0.27).

UC: In the entire UC programme, there were no events assessed as ILD by the review committee.

JIA: There were no cases of ILD from the pJIA integrated safety analysis population.

AS: No ILD cases were reported in the RCTs (Tofa 5 mg BID) or in the All AS population (All Tofa 5 mg BID, All Tofa). The IR (95% CI) per 100 PY of ILD in the RCT (Tofa 5 mg BID) was 0.00 (0.00, 3.28). The IRs (95% CI) per 100 PY of ILD in the All AS population for All Tofa 5 mg BID and All Tofa, respectively, were 0.00 (0.00, 1.59) and 0.00 (0.00, 1.40).

Seriousness/outcome

RA: In the All RA population, there were 45 ILD cases, of which 19 events were considered serious and 26 were considered non-serious. The outcomes were resolved (21), still present (23), and fatal (1).

Study A3921133: The seriousness of adjudicated ILD for the following treatment groups were:

- Tofacitinib 5 mg BID: serious (2), non-serious (13)
- Tofacitinib 10 mg BID: serious (5), non-serious (12)
- All Tofa: serious (7), non-serious (25)
- TNFi: serious (5), non-serious (12)

The outcomes for adjudicated ILD for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (6), still present (6), unknown (2), death (1)
- Tofacitinib 10 mg BID: resolved (5), still present (9), unknown (3)
- All Tofa: resolved (11), still present (15), unknown (5), death (1)
- TNFi: resolved (6), still present (9), unknown (2)

PsA: In the All PsA population, there was 1 ILD case that was non-serious and the event resolved.

UC: In the entire UC programme, there were no events assessed as ILD by the review committee.

JIA: There were no cases of ILD from the pJIA integrated safety analysis population.

AS: There were no ILD cases in the AS programme.

Post-Marketing:

Table 124. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – ILD (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Interstitial lung disease	215	215	81	41	51	5	23	95
Pulmonary fibrosis	115	115	16	5	11	0	42	57
Pneumonitis	48	34	14	2	14	1	9	22
Rheumatoid lung	25	14	6	1	1	0	2	21
Acute respiratory distress syndrome	21	21	9	9	5	0	0	7
Organising pneumonia	16	16	6	0	10	0	1	5
Sarcoidosis	11	11	2	0	2	0	2	7
Lung infiltration	9	4	1	0	3	0	2	4
Hypersensitivity pneumonitis	7	5	3	0	4	0	2	1
Bronchiolitis	5	5	2	0	0	0	0	5

Table 124. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – ILD (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Lung opacity	5	2	0	0	1	0	1	3
All others	28	25	9	4	6	0	1	17
Total	505	467	149	62	108	6	85	244

F = fatal; H = hospitalisation; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 125. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – ILD (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Pulmonary fibrosis	53	53	8	1	3	1	12	36
Interstitial lung disease	31	31	3	2	1	0	4	24
Pneumonitis	14	6	2	0	1	0	2	11
Rheumatoid lung	13	8	2	0	1	0	4	8
Idiopathic pulmonary fibrosis	6	6	0	0	0	0	1	5
Bronchiolitis	5	5	0	0	0	0	0	5
Lung infiltration	3	1	0	0	1	0	0	2
Organising pneumonia	3	3	2	0	0	0	0	3
Sarcoidosis	3	3	0	0	0	0	0	3
All others	10	8	1	1	0	0	1	8
Total	141	124	18	4	7	1	24	105

F = fatal; H = hospitalisation; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity[12] and nature of risk

RA: In the All RA population 19 ILD cases were reported as mild, 18 were moderate, and 8 were severe.

Study A3921133: The severity of adjudicated ILD for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (8), moderate (4), severe (1), unknown (2)
- Tofacitinib 10 mg BID: mild (4), moderate (7), severe (3), unknown (3)

[12] Severity definitions: mild = does not interfere with subject's usual function; moderate = interferes to some extent with subject's usual function; severe = interferes significantly with subject's usual function.

- All Tofa: mild (12), moderate (11), severe (4), unknown (5)
- TNFi: mild (4), moderate (8), severe (3), unknown (2)

PsA: In the All PsA population, 1 ILD case was severe.

UC: In the entire UC programme, there were no events assessed as ILD by the review committee.

JIA: There were no cases of ILD from the JIA integrated safety analysis population.

AS: There were no ILD cases in the AS programme.

VII.3.1.2.4.4. Risk factors and risk groups

Patients living in some Asian countries.

VII.3.1.2.4.5. Preventability

No data are available to identify specific measures that can be used to prevent the occurrence of ILD. Tofacitinib should be used with caution in patients with prior history of ILD and Asian patients.

VII.3.1.2.4.6. Impact on the risk-benefit balance of the product

The potential impact on the patient ranges from benign infiltrates to life-threatening acute respiratory distress syndrome. ILD may be asymptomatic, detected only on x-ray or Computed Tomography scan or it may cause progressive respiratory symptoms resulting in hospitalisation and, in some cases, respiratory insufficiency that may be fatal.

VII.3.1.2.4.7. Public health impact

ILD is not expected to have a significant impact on public health.

VII.3.1.2.4.7.1. Interstitial Lung Disease in Asian Patients

The rates of ILD in subjects treated with tofacitinib in the RA clinical development programme analysed based on race are shown in the table below.

Table 126. Rheumatoid Arthritis Exposure Estimates and Incidence Rates of ILD in the All RA Population (P123LTE)

	White	Black	Asian	Other
Total pts exposure (n)	5170	252	1812	730
Unique pts with events (n)	24	2	15	4
Total pt-yr of exposure for event	15975.60	633.96	5192.81	2282.48
Incidence rate per 100 PY (95% CI)	0.15 (0.10, 0.22)	0.32 (0.04, 1.14)	0.29 (0.16, 0.48)	0.18 (0.05, 0.45)

CI = Confidence Interval. PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data

Table 126. Rheumatoid Arthritis Exposure Estimates and Incidence Rates of ILD in the All RA Population (P123LTE)

	White	Black	Asian	Other

cutoff date. Incidence rate (number of subjects with events per 100 subject-years). Exact Poisson (adjusted for Pt-yr) 95% confidence intervals are provided for the crude incidence rate.
Includes Protocols-A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
Final data 18 January 2019
Pt = patient, PY = patient-year
Source: Table 1614.10.1

Additionally, the exposure estimates and incidence rates for ILD for countries classified as Asian are shown in Table 127.

Table 127. Rheumatoid Arthritis Exposure and Incidence Rates for Interstitial Lung Disease Events by Geographic Region and Asian Country in the All RA Population (P123LTE)

By Region	Number of ILD Events	Patient-Years of Exposure	Incidence Rate (95% CI)
Asia	16	5620.04	0.28 (0.16, 0.46)
Europe	11	9120.28	0.12 (0.06, 0.22)
Latin America	9	4002.98	0.22 (0.10), 0.43)
US/Canada	9	5300.46	0.17 (0.08, 0.32)
Within Asian Countries			
Australia/New Zealand	1	515.20	0.19 (0.00, 1.08)
China/Taiwan	0	968.49	0.00 (0.00, 0.38)
[redacted]	1	577.05	0.17 (0.00, 0.97)
[redacted]	6	1806.55	0.33 (0.12, 0.72)
[redacted]	2	1063.70	0.19 (0.02, 0.68)
Thailand/Malaysia/ Philippines	6	689.04	0.87 (0.32, 1.90)
Non-Asian Regions Combined	29	18464.82	0.16 (0.11, 0.23)

CI = Confidence Interval. PY (subject-year): Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. Gaps in dosing between Index and LTE studies are included up to 28 days or to the data cutoff date. Events are counted up to 28 days beyond the last dose or to the data cutoff date. Incidence rate (number of subjects with events per 100 subject-years). Exact Poisson (adjusted for Pt-yr) 95% confidence intervals are provided for the crude incidence rate.
Includes Protocols-A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year), A3921073, A3921109, A3921129, A3921130, A3921152, A3921187, A3921192, A3921215, and A3921237.
Final data 18 January 2019
ILD = interstitial lung disease; US = United States
Source: Tables 1614.10.2, 1614.10.3, 1614.10.4

As shown in the tables, no clear differences between the IR of geographic regions were observed in the tofacitinib clinical development programme. Although the point estimates for Thailand/Malaysia/Philippines and Japan were higher than other countries and regions, the confidence interval was wide and overlapped with the majority of other estimates.

Based on data from the clinical development programme and published literature, Asian patients treated with tofacitinib do not appear to be at an increased risk of ILD above the background risk that has been associated with Asian race. However, the increased risk of ILD in Asian subjects is well established in the literature and approximately a third of patients reported with ILD in the tofacitinib programme were from Asian regions. Addition of a general warning regarding the risk of ILD in Asian subjects is included in Section 4.4 of the SmPC.

VII.3.1.2.5. Progressive Multifocal Leukoencephalopathy (PML)

PML is a rare demyelinating disorder caused by the JC polyoma virus (JCV). Considering tofacitinib is an immunosuppressant, although no occurrences of PML have been observed in tofacitinib-treated patients, the Applicant added PML as an important potential risk to the RMP and will continue to monitor for potential reports of PML in the on-going clinical trials, registries, and during post-approval use. No events of PML have been reported.

VII.3.1.2.5.1. Potential mechanisms

Decreased virus-specific immune surveillance allowing latent virus reactivation and development of viral associated diseases.

VII.3.1.2.5.2. Evidence source and strength of evidence

PML has been reported in some patients taking other medications that depress the immune system.

VII.3.1.2.5.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA, PsA, UC, JIA, and AS: No events of PML have been reported in the RA, PsA, UC, JIA, or AS clinical development programmes.

Study A3921133: No events of PML have been reported.

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: No events of PML have been reported in the US Corrona RA Registry.

Seriousness/outcome

RA, PsA, UC, JIA, and AS: Not applicable.

Study A3921133: Not applicable.

Post-Marketing:

Table 128. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – PML (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Progressive multifocal leukoencephalopathy	5	5	3	0	1	0	1	3
JC virus infection	3	3	1	0	1	0	2	0
JC polyomavirus test positive	2	1	0	0	0	0	0	2
Leukoencephalopathy	1	1	0	0	0	0	1	0
Total	11	10	4	0	2	0	4	5

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PML = progressive multifocal leukoencephalopathy; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 129. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – PML (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
JC virus infection	1	1	0	0	0	0	0	1
Total	1	1	0	0	0	0	0	1

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PML = progressive multifocal leukoencephalopathy; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk

RA, PsA, UC, JIA, and AS: Not applicable.

Study A3921133: Not applicable.

VII.3.1.2.5.4. Risk factors and risk groups

Patients taking other medications along with tofacitinib that also depress the immune system.

VII.3.1.2.5.5. Preventability

Tofacitinib must not be used in combination with biologic DMARDs or other potent immunosuppressive agents. Patients should be closely monitored for the development of signs and symptoms of infection.

VII.3.1.2.5.6. Impact on the risk-benefit balance of the product

PML is a life-threatening illness.

VII.3.1.2.5.7. Public health impact

No cases of PML have been observed with tofacitinib and the potential public health impact is currently considered low.

VII.3.1.2.6. All-cause Mortality

VII.3.1.2.6.1. Potential mechanisms

Mortality in patients treated with tofacitinib was mainly due to cardiovascular events, infections, and malignancies from A3921133. Serious and other important infections is an important identified risk and CV risk and malignancy are important potential risks for tofacitinib. The mechanism by which infection risk is increased in patients is likely to be multifactorial. In addition to the underlying disease, therapies used to treat the disease have effects on the immune system. Tofacitinib inhibits cytokines that are integral to lymphocyte activation, proliferation, and function, and inhibition of their signalling may thus result in modulation of multiple aspects of the immune response. The mechanism by which tofacitinib is associated with CV events is unknown. The potential role of Janus kinase inhibition in malignancies (excluding NMSC) is not known.

VII.3.1.2.6.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.2.6.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: For RA studies excluding A3921133, the IRs per 100 PY (95% CI) of all-cause mortality from the RCTs for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.31 (0.13, 0.61), 0.20 (0.05, 0.51), 0.26 (0.14, 0.46). The overall IR per 100 PY (95% CI) for all-cause mortality for the All RA population (excluding A3921133) for the 5 mg and 10 mg dose groups, and overall, respectively, were 0.32 (0.21, 0.46), 0.20 (0.13, 0.28), 0.24 (0.19, 0.32).

A3921133 final data: The IRs per 100 PY (95% CI) of all-cause mortality for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.50 (0.33, 0.74), 0.80 (0.57, 1.09), 0.65 (0.50, 0.82), 0.34 (0.20, 0.54).

PsA: For the RCTs, there were 0 deaths in 5 mg BID and 10 mg BID treatment groups. The IRs per 100 PY (95% CI) of all-cause mortality from the All PsA population for the 5 mg and 10 mg dose groups, respectively, were 0.55 (0.22, 1.14) and 0 (0.00, 0.48).

UC: For the RCTs (induction therapy P2P3 studies) the IR per 100 PY (95% CI) of all-cause mortality for the 10 mg BID dose group was 0.60 (0.02, 3.35). For the RCT (maintenance therapy P3 study) there were 0 deaths in 5 mg BID and 10 mg BID treatment groups. The IRs per 100 PY (95% CI) of all-cause mortality from the All UC population for the 5 mg and 10 mg dose groups, respectively, were 0.00 (0.00, 0.46) and 0.14 (0.03, 0.41).

JIA: No deaths occurred in the JIA integrated safety analysis population.

AS: No deaths were reported in the AS clinical programme. For the RCTs (Tofa 5 mg BID), the IR per 100 PY (95% CI) for mortality was 0.00 (0.00, 3.28). In the All AS population, the IRs per 100 PY (05% CI) for mortality in All Tofa 5 mg BID and All Tofa, respectively, were 0.00 (0.00, 1.41) and 0.00 (0.00, 1.24).

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: In the full sample, crude and age- and sex- adjusted incidence rates of death events were similar among the tofacitinib group when compared with the bDMARD group and the CIs overlapped. Across the trimmed and matched populations, incidence rates of death were similar among the tofacitinib and bDMARD treated patients with overlapping CIs.

Please see table below for the crude rates and 95% CI for death events among eligible RA patients initiating tofacitinib, bDMARD, or csDMARD.

Table 130. Crude Rates (per 100 PY) and 95% CI for Death Among Eligible RA Patients Initiating Tofacitinib, bDMARD, or csDMARD (31 January 2019, Primary Analyses)

Latent Exposure	31 January 2019 Datacut														
	Tofacitinib					bDMARD					csDMARD				
	N	PY	Rate	95% LL	95% UL	N	PY	Rate	95% LL	95% UL	N	PY	Rate	95% LL	95% UL
Death															
Full	3	4505	0.80	0.56	1.11	112	16665	0.67	0.55	0.81	30	549	0.55	0.37	0.78
Sample	6	3205	0.72	0.45	1.08	80	12624	0.63	0.50	0.79	NR	2	NR	NR	NR
PS	2	3173	0.69	0.43	1.05	61	8252	0.74	0.57	0.95	NR	NR	NR	NR	NR
Trimmed	3											NR			
PS	2														
Matched	2														

bDMARD=biologic disease modifying antirheumatic drug; csDMARD=conventional synthetic disease modifying antirheumatic drug; LL=lower limit; N=count; NR=not reported; PS=propensity score; PY=person-years; RA=rheumatoid arthritis; UL=upper limit
Corrona RA Registry (study A3921205) final report: Table 15, Table 24

Seriousness/outcome

Post-Marketing: In the post-marketing dataset, there were 2913 fatal outcomes in the immediate-release or unknown formulations dataset and 1055 fatal outcomes in the prolonged-release formulation dataset. The events resulting in fatal outcomes in the immediate-release or unknown formulations dataset (≥20) were coded to the PTs Death (1560), Pneumonia (90), COVID-19 (66), Sepsis (49), Myocardial infarction (46), Respiratory failure (45), Interstitial lung disease (41), Lung neoplasm malignant (28), COVID-19 pneumonia (25), Pulmonary embolism (24), Condition aggravated (23), Cardiac arrest (22). The events resulting in fatal outcomes outcomes in prolonged-release formulation dataset (≥5) were coded to the PTs Death (951), COVID-19 (30), Myocardial infarction (11), Cerebrovascular accident, Pneumonia (10 each), COVID-19 pneumonia,

Sepsis (9 each), Multiple organ dysfunction syndrome (6) Acute respiratory failure, Cardiac arrest, and Chronic obstructive pulmonary disease (5 each).

VII.3.1.2.6.4. Risk factors and risk groups

Mortality in patients treated with tofacitinib was mainly due to cardiovascular events, infections, and malignancies. Risk factors/groups for serious infections include patients who are elderly or diabetic, patients that use medicinal products along with tofacitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts, and patients from certain Asian countries (eg, Japan, Korea). The risk of cardiovascular events independently of tofacitinib is increased in the elderly population. Tofacitinib has been associated with increased cholesterol, high blood pressure (hypertension), and weight gain, which are known risk factors for cardiovascular events. The risk of malignancy (cancer) in general is increased in the elderly population.

In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increase in non-fatal MI, lung cancer, lymphoma, VTE, and NMSC was observed in patients treated with tofacitinib compared to TNF inhibitor. Please refer to Section VII.3.1.1.1, Section VII.3.1.1.4, Section VII.3.1.1.5, Section VII.3.1.1.6, and Section VII.3.1.1.8 for the discussion of risk factors for VTE, lung cancer, lymphoma, MI, and NMSC respectively.

Summary of results from the US Corrona RA Registry A3921205: The risk factors found to be associated with an increased risk of mortality events were in general similar among tofacitinib initiators and bDMARD initiators with moderate-to-severe disease (such as history of hypertension, history of coronary artery disease, history of VTE, age 70+, age 60+). In patients aged 50 years and older with moderate-to-severe disease with at least one CV risk factor, the incidence rates (95% CI) were comparable among tofacitinib initiators and bDMARD initiators.

VII.3.1.2.6.5. Preventability

In Study A3921133 (a randomised active-controlled post authorisation safety surveillance study of RA patients who were 50 years of age and older and had at least one additional CV risk factor), increased mortality within 28 days of last treatment was observed in patients treated with tofacitinib compared to TNF inhibitors. CV risk factors were defined as current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anaemia of chronic disease, pulmonary manifestations.

Preventive measures for serious infections may include screening for infections prior to initiation of tofacitinib treatment and monitoring lymphocytes counts during therapy (it is not recommended to initiate or continue tofacitinib treatment in patients with a confirmed lymphocyte count less than 750 cells/mm^3 and if absolute lymphocyte count less than 500 cells/mm^3 is confirmed by repeat testing within 7 days, dosing should be discontinued). It is

recommended to monitor lipid parameters for CV risk. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia to reduce the risk of cardiovascular events. There are no known preventable actions for malignancy.

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular or malignancy risk factors, tofacitinib should only be used if no suitable treatment alternatives are available. Please refer to the preventability sections of serious and other important infections, lung cancer, lymphoma, MI, and malignancy (Section VII.3.1.1.2.5, Section VII.3.1.1.4.5, Section VII.3.1.1.5.5, Section VII.3.1.1.6.5, and Section VII.3.1.2.1.5, respectively).

VII.3.1.2.6.6. Impact on the risk-benefit balance of the product

Based on the established benefits of tofacitinib as described in the prescribing information where there is an approved indication and the list of routine and additional risk mitigation measures to manage the important identified risks and important potential risks (including serious and other important infections, CV risk, and malignancy), the benefit:risk balance for tofacitinib in treating patients with RA, PsA, and UC at the recommended doses remains favourable.

VII.3.1.2.6.7. Public health impact

The tofacitinib post-marketing dataset contained 1360 fatal outcomes out of a total of 67,075 cases (reporting proportion of 2.0%) with an estimated cumulative worldwide post-authorisation exposure to tofacitinib of 209,081 patient-years (estimated reporting rate of 0.65 per 100 patient-years). Given the background risk of mortality in patients with RA, PsA, and UC, mortality associated with tofacitinib is not expected to have a significant public health impact.

VII.3.1.2.7. Fractures

VII.3.1.2.7.1. Potential mechanisms

Potential mechanisms are unknown. Nonclinical and literature data [297] suggest that tofacitinib is likely to have protective properties on bone in an osteoporosis setting as has been seen in RA.

VII.3.1.2.7.2. Evidence source and strength of evidence

Corrona RA registry Study A3921205 and Study A3921133.

VII.3.1.2.7.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: In RCTs, the IR per 100 PY (95% CI) of fractures for the 5 mg and 10 mg dose groups, and overall, respectively, were 2.55 (1.97,3.25), 2.81 (2.12,3.66), and 2.69 (2.26,3.18). In the All RA population, the IRs per 100 PY (95% CI) of fractures for the 5 mg and 10 mg dose

groups, and overall, respectively, were 2.62 (2.29, 2.99), 2.26 (2.02, 2.52), and 2.39 (2.20, 2.60).

Study A3921133: The IRs per 100 PY (95% CI) of fractures for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 2.79 (2.34, 3.30), 2.87 (2.40, 3.40), 2.83 (2.50, 3.19), and 2.27 (1.87, 2.74).

PsA: The IRs per 100 PY (95% CI) of fractures from the RCTs for the 5 mg and 10 mg dose groups, respectively, were 4.59 (1.85, 9.46) and 3.35 (1.09, 7.81). In the All PsA population, the IRs per 100 PY (95% CI) of fractures for the 5 mg and 10 mg dose groups and the combined 5 mg and 10 mg dose groups, respectively, were 1.89 (1.21, 2.82), 2.32 (1.37, 3.66), and 2.05 (1.48, 2.78).

UC: The IR per 100 PY (95% CI) of fractures from the RCTs (induction studies, 10 mg dose group) was 3.62 (1.33, 7.89). The IRs per 100 PY (95% CI) of fractures from the RCT (maintenance study, 5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 2.72 (0.74, 6.97), 1.92 (0.40, 5.62), and 2.31 (0.93, 4.76). The IRs per 100 PY (95% CI) of fractures in the All UC population (5 mg, 10 mg, and combined 5 mg and 10 mg dose groups, respectively) were 1.58 (0.81, 2.75), 1.89 (1.33, 2.59), and 1.80 (1.34, 2.37).

JIA: The IR per 100 PY (95% CI) from the integrated safety analysis population for fractures was 1.65 (0.61, 3.59).

AS: The IR per 100 PY (95% CI) of fractures from the RCTs (Tofa 5 mg BID) was 1.76 (0.00, 5.89). In the All AS population, the IRs per 100 PY (95% CI) of fractures for All Tofa 5 mg BID and All Tofa, respectively, were 0.87 (0.11, 3.14) and 0.76 (0.09, 2.76).

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: The crude incidence rates per 100 person-years (95% CI) for fractures in RA patients for tofacitinib, bDMARD, and csDMARD groups in the 31 March 2018 datacut are listed below.

Tofacitinib: 3.51 (95% CI=2.75, 4.41)
bDMARD: 2.45 (95% CI=2.15, 2.79)
csDMARD: 2.24 (95% CI=1.73, 2.85)

Seriousness/outcome

RA: In the All RA population, 156 fractures were serious and 392 were non-serious. The outcomes reported were resolved (453), still present (90), and unknown (5).

Study A3921133: The seriousness of fractures for the following treatment groups were:

- Tofacitinib 5 mg BID: serious (44), non-serious (92)
- Tofacitinib 10 mg BID: serious (29), non-serious (103)

- All Tofa: serious (73), non-serious (195)
- TNFi: serious (36), non-serious (73)

The outcomes for fractures for the following treatment groups were:

- Tofacitinib 5 mg BID: resolved (118), still present (17), unknown (1)
- Tofacitinib 10 mg BID: resolved (109), still present (23)
- All Tofa: resolved (227), still present (40), unknown (1)
- TNFi: resolved (95), still present (14)

PsA: In the All PsA population, 10 fractures were serious and 32 were non-serious. The outcomes reported were resolved (38), still present (3), and unknown (1).

UC: In the All UC population, 16 fractures were serious and 34 were non-serious. The outcomes reported were resolved (44) and still present at the time of report (6).

JIA: In the JIA integrated safety analysis population, 6 fractures were reported and all 6 were non-serious and all 6 resolved.

AS: In the All AS population (All Tofa), 1 fracture was serious and 1 was non-serious; both resolved.

Post-Marketing:

Table 131. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Fractures (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Hip fracture	190	190	97	1	45	1	23	121
Lower limb fracture	159	149	47	3	38	0	27	91
Foot fracture	136	119	17	0	30	0	28	78
Spinal fracture	126	126	39	0	20	2	31	73
Upper limb fracture	120	114	22	0	20	1	18	81
Rib fracture	119	108	26	1	22	1	20	75
Femur fracture	109	109	61	1	29	0	11	68
Fracture	107	99	27	0	18	0	17	72
Ankle fracture	103	97	21	0	28	0	14	61
Wrist fracture	81	73	3	0	8	0	17	56
Pelvic fracture	78	78	38	0	20	1	17	41
Shoulder fracture	54	53	14	0	13	0	6	35
All others	353	336	101	2	90	6	76	180
Total	1735	1651	513	8	381	12	305	1032

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 132. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Fractures (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Hip fracture	150	150	65	0	24	0	11	115
Lower limb fracture	138	133	45	0	18	0	20	100
Foot fracture	131	126	14	0	13	0	13	105
Spinal fracture	107	107	24	0	9	1	13	84
Ankle fracture	98	94	24	0	16	0	9	75
Upper limb fracture	90	88	14	0	13	0	7	70
Rib fracture	87	84	19	0	14	1	10	62
Wrist fracture	78	71	10	0	14	0	9	55
Femur fracture	62	62	27	0	10	1	12	39
Fracture	44	42	4	0	4	0	9	31
Shoulder fracture	43	42	6	0	5	1	6	31
All others	255	247	57	0	39	0	35	181
Total	1283	1246	309	0	179	4	154	948

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk

RA: In the All RA population 143 fractures were mild, 306 were moderate, and 99 were severe.

Study A3921133: The severity of fractures for the following treatment groups were:

- Tofacitinib 5 mg BID: mild (32), moderate (70), severe (34)
- Tofacitinib 10 mg BID: mild (22), moderate (90), severe (20)
- All Tofa: mild (54), moderate (160), severe (54)
- TNFi: mild (24), moderate (53), severe (32)

PsA: In the All PsA population, 8 fractures were mild, 23 were moderate, and 11 were severe.

UC: In the All UC population 16 fractures were mild, 24 were moderate, and 10 were severe.

JIA: In the JIA integrated safety analysis population, 2 fractures were mild and 4 were moderate.

AS: In the All AS population (All Tofa), 2 fractures were moderate.

VII.3.1.2.7.4. Risk factors and risk groups

Based on the review of clinical data, an increased risk of fracture was observed in patients with known risk factors for fractures, such as in elderly patients, female patients, and patients with corticosteroid use.

VII.3.1.2.7.5. Preventability

Caution should be used in patients with known risk factors for fractures such as elderly patients, female patients, and patients with corticosteroid use.

VII.3.1.2.7.6. Impact on the risk-benefit balance of the product

Based on the established benefits of tofacitinib as described in the prescribing information and the list of routine and additional risk mitigation measures, the benefit:risk balance for tofacitinib in treating patients with RA, PsA, UC, and JIA at the recommended doses remains favourable.

VII.3.1.2.7.7. Public health impact

The public health impact of fractures includes increases in physical impairments and psychological symptoms of fear of re-injury and post-traumatic stress disorder.

VII.3.1.2.8. Increased Risk of Adverse Events (AEs) When Tofacitinib is Administered in Combination with Methotrexate (MTX) in RA or PsA Patients

VII.3.1.2.8.1. Potential mechanisms

The increased rate of AEs in patients treated with tofacitinib in combination use of MTX is likely due to the additive effect of combining agents. MTX is known to be associated with many AEs, eg, infections, GI toxicity.

MTX may be hepatotoxic, particularly at high dosage or with prolonged therapy. Methotrexate therapy in patients with impaired renal function should be undertaken with extreme caution because impairment of renal function will decrease methotrexate elimination. The most common adverse reactions for methotrexate include ulcerative stomatitis, leukopenia, vasculitis, eye-irritation and loss of libido/impotence, nausea and abdominal distress.

VII.3.1.2.8.2. Evidence source and strength of evidence

Clinical trial data and post-marketing data.

VII.3.1.2.8.3. Characterisation of the risk

Frequency

Interventional Clinical Trials:

RA: In RCTs, the incidence rate of treatment-emergent AEs in RA patients treated with tofacitinib 5 mg BID in combination with MTX was 145.36 per 100 PYs (95% CI: 137.11,

153.98), as compared to 164.77 per 100 PYs in patients treated with tofacitinib 5 mg BID monotherapy (95% CI: 151.23, 179.20).

Study A3921133: Not applicable. All subjects entering the study must have taken MTX continuously for at least 4 months prior to the Screening visit and have been taking a stable, weekly dose of MTX for at least 6 weeks prior to the Baseline visit and continued taking that dose throughout the study, unless modification was clinically indicated.

PsA: In the All PsA population, all patients treated with tofacitinib were treated with a background csDMARD, most frequently MTX. In the RCTs background csDMARD treatment was mandatory. Whilst subjects may have received tofacitinib monotherapy in the LTE, in the All PsA population that integrates data from both the LTE and RCT, no patients were treated with tofacitinib monotherapy.

UC: Tofacitinib is not used in combination with MTX in treatment of UC.

JIA: The data in the JIA program did not show an increased risk of treatment-emergent AEs in patients treated with tofacitinib 5 mg BID in combination with MTX as compared to patients treated with tofacitinib 5 mg BID monotherapy.

AS: In the All AS population, patients treated with tofacitinib were permitted concomitant csDMARDs, including MTX.

Frequency Results from Non-interventional PASS

US Corrona RA Registry A3921205: Counts, PY, crude rates of events of interest, and 95% CI for acute exposure events by subgroup of interest among tofacitinib and bDMARD exposed RA patients are found in the table below. The rates of MACE were higher in the monotherapy groups among the tofacitinib initiators and bDMARD initiators, although the 95% CIs overlapped. The rates of serious infection events were numerically higher in the combination group among the tofacitinib initiators and monotherapy group among the bDMARD initiators with overlapping 95% CIs. The rates of total HZ were higher in the monotherapy group among the tofacitinib initiators with overlapping 95% CIs; please note these were non-serious HZ events.

Table 133. Crude Rates (per 100 PY) and 95% CI for Safety Events of Interest Among Eligible RA Patients Initiating Tofacitinib or bDMARD (31 March 2018, Primary Analyses) Subgroup Analysis: Use of csDMARD

Event of interest	Tofacitinib initiators					bDMARD initiators				
	N	PY	Rate	95% CI LL	95% CI UL	N	PY	Rate	95% CI LL	95% CI UL
MACE by use of csDMARD										
Monotherapy	7	929.42	0.75	0.3	1.55	30	2710.83	1.11	0.75	1.58
Combination	8	1199.58	0.67	0.29	1.31	60	7119.83	0.84	0.64	1.08
Serious infection event by use of csDMARD										
Monotherapy	20	913.08	2.19	1.34	3.38	87	2663.75	3.27	2.62	4.06
Combination	44	1171.92	3.75	2.73	5.04	201	7020.17	2.86	2.48	3.29
Total HZ by use of csDMARD										

Table 133. Crude Rates (per 100 PY) and 95% CI for Safety Events of Interest Among Eligible RA Patients Initiating Tofacitinib or bDMARD (31 March 2018, Primary Analyses) Subgroup Analysis: Use of csDMARD

Event of interest	Tofacitinib initiators					bDMARD initiators				
	N	PY	Rate	95% CI LL	95% CI UL	N	PY	Rate	95% CI LL	95% CI UL
Monotherapy	17	917.67	1.85	1.08	2.97	20	2721.17	0.73	0.45	1.14
Combination	17	1194.83	1.42	0.83	2.28	52	7121.42	0.73	0.55	0.96
Serious HZ by use of csDMARD										
Monotherapy	0	930.67	0	0	0.4	2	2732.75	0.07	0.01	0.26
Combination	0	1207.5	0	0	0.31	2	7170	0.03	0	0.1
Non-serious HZ by use of csDMARD										
Monotherapy	17	917.67	1.85	1.08	2.97	18	2722	0.66	0.39	1.05
Combination	17	1194.83	1.42	0.83	2.28	50	7122.75	0.7	0.52	0.93
DVT or PE by use of csDMARD										
Monotherapy	2	929.25	0.22	0.03	0.78	9	2726.42	0.33	0.15	0.63
Combination	2	1207.17	0.17	0.02	0.6	21	7152.83	0.29	0.18	0.45

bDMARD=biologic disease modifying antirheumatic drug; CI=confidence interval; csDMARD=conventional synthetic disease modifying antirheumatic drug; DVT=deep vein thrombosis, HZ=herpes zoster; LL=lower limit; MACE=major adverse cardiovascular event; N=count; PE=pulmonary embolism; PY=person years; UL=upper limit
Corrona RA Registry (study A3921205) final report: Table 17, Table 20, Table 21

Seriousness/outcome

RA: In the RCT population, there were 1276 treatment-emergent AEs in RA patients treated with tofacitinib 5 mg BID in combination with MTX, of which 194 events were considered serious and 1081 were considered non-serious, one was considered unknown. The outcomes were resolved (911), still present (332), unknown (13), and fatal (20).

Study A3921133: Not applicable.

PsA: In the All PsA population, all patients treated with tofacitinib were treated with a background csDMARD, most frequently MTX.

UC: Tofacitinib is not used in combination with MTX in the treatment of UC.

JIA: In the JIA integrated safety analysis population, 139 treatment-emergent AEs were reported in patients treated with tofacitinib 5 mg BID in combination with MTX, of which 10 events were considered serious and 129 were considered non-serious. The outcomes were resolved (111), still present (27), and unknown (1).

AS: In the All AS population, patients treated with tofacitinib were permitted concomitant csDMARDs, including MTX.

Post-Marketing:

Table 134. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Increased Risk of AEs When Tofacitinib is Administered in Combination with MTX in RA or PsA Patients (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Drug ineffective	3342	387	56	8	222	0	534	2580
Condition aggravated	1847	382	65	4	399	0	580	893
Therapeutic product effect incomplete	1502	50	7	1	151	0	215	1135
Headache	1321	98	35	6	470	2	358	486
Arthralgia	1239	174	47	3	222	0	484	549
Pain	1194	152	52	4	229	2	407	553
Fatigue	1151	101	31	5	160	1	445	542
Nausea	978	93	28	1	350	0	243	386
Pain in extremity	830	93	28	2	152	1	322	359
Off label use	818	84	21	7	8	0	52	752
Diarrhoea	813	97	37	3	322	0	184	306
Nasopharyngitis	762	43	13	4	223	2	213	321
All others	41477	13293	4675	974	8368	114	10817	21260
Total	57274	15047	5095	1022	11276	122	14854	30122

AE = adverse event; F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; PsA = psoriatic arthritis; PT = Preferred Term; R = resolved/resolving; RA = rheumatoid arthritis; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 135. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Increased Risk of AEs When Tofacitinib is Administered in Combination with MTX in RA or PsA Patients (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Drug ineffective	948	18	3	0	31	0	116	803
Pain	750	28	16	0	90	2	184	477
Condition aggravated	725	60	18	0	86	1	217	433
Arthralgia	620	25	13	0	71	2	144	407
Headache	442	10	6	0	113	2	101	227
Pain in extremity	395	17	9	0	49	0	106	245
Fatigue	382	15	8	0	58	0	82	242
Product dose omission issue	363	6	3	0	4	0	9	350
Therapeutic product effect incomplete	332	2	1	0	24	0	40	268
Joint swelling	254	10	3	0	38	0	52	166
Musculoskeletal stiffness	251	5	2	0	33	0	48	172
All others	15557	3065	909	60	2545	32	2510	10429
Total	21019	3261	991	60	3142	39	3609	14219

AE = adverse event; F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; MTX = methotrexate; PsA = psoriatic arthritis; PT = Preferred Term; R = resolved/resolving; RA = rheumatoid arthritis; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk

RA: In the RCT population, there were 1276 treatment-emergent AEs in RA patients treated with tofacitinib 5 mg BID in combination with MTX, of which 542 cases were reported as mild, 576 were moderate, and 158 were severe.

Study A3921133: Not applicable.

PsA: In the All PsA population, all patients treated with tofacitinib were treated with a background csDMARD, most frequently MTX.

UC: Tofacitinib is not used in combination with MTX in the treatment of UC.

JIA: In the JIA integrated safety analysis population, 139 treatment-emergent AEs were reported in patients treated with tofacitinib 5 mg BID in combination with MTX, of which 68 were reported as mild, 64 were moderate, and 7 were severe.

AS: In the All AS population, patients treated with tofacitinib were permitted concomitant csDMARDs, including MTX.

VII.3.1.2.8.4. Risk factors and risk groups

Subjects on tofacitinib and methotrexate together may be at higher risk of developing adverse events.

VII.3.1.2.8.5. Preventability

When tofacitinib is used in combination with MTX, cautions should be exercised, and patients should be monitored carefully for any potential AEs.

VII.3.1.2.8.6. Impact on the risk-benefit balance of the product

AEs may lead to morbidity and mortality, resulting in significant impact on quality of life of individual patients.

VII.3.1.2.8.7. Public health impact

The impact of AEs on public health may be significant both in terms of lost time at work and increased burden on medical care.

VII.3.1.2.9. Primary Viral Infection Following Live Vaccination

VII.3.1.2.9.1. Potential mechanisms

Unknown.

VII.3.1.2.9.2. Evidence source and strength of evidence

A3921237 study report.

VII.3.1.2.9.3. Characterisation of the risk

Frequency

RA: Not available; in the RA clinical programme, a patient with no previous history of varicella infection and no anti-varicella antibodies at baseline experienced dissemination of the vaccine strain of varicella 16 days after vaccination.

Study A3921133: Not available. As per the study protocol, live or live-attenuated vaccines were not given concurrently with study medication.

PsA: Not available. Per PsA study protocol, any subject who had been vaccinated with live or attenuated vaccines within the 6 weeks prior to the first dose of study medication or was to be vaccinated with these vaccines at any time during treatment or within 6 weeks following discontinuation of study medication was ineligible to participate.

UC: Not available. There were no events of primary viral infection following live vaccination in the UC clinical programme.

JIA: Not available. As per the JIA protocol, any subjects vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of study drug, or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of study drug were ineligible to participate.

AS: Not available. Vaccination with live or live attenuated components was prohibited within the 6 weeks prior to the first dose, during the study period, and for 6 weeks after last dose.

Seriousness/outcome

RA: The event was assessed as serious and the patient recovered after treatment with standard doses of antiviral medication. This patient subsequently made a robust, though delayed, humoral and cellular response to the vaccine.

Study A3921133: Not available.

PsA: Not available.

UC: There were no events of primary viral infection following live vaccination in the UC clinical programme.

JIA: Not available.

AS: There were no events of primary viral infection following live vaccination in the AS clinical programme.

Post-Marketing:

Table 136. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Primary Viral Infection Following Live Vaccination (Immediate-Release or Unknown Formulations)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Herpes zoster	28	3	0	0	9	0	3	16
Influenza	10	0	0	0	5	0	1	4
Nasopharyngitis	5	0	0	0		0	2	3
Cystitis	2	0	0	0	1	0	1	
Infection	2	1	0	0		0	0	2
Lower respiratory tract infection	2	2	0	0	1	0	0	1
Varicella zoster virus infection	2	2	2	0	1	0	0	1
Viral infection	2	0	0	0	0	0	0	2
All others	11	6	0	0	2	0	3	6
Total	64	14	2	0	19	0	10	35

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Table 137. Reported Events, Seriousness, and Outcomes for Post-Marketing Cases – Primary Viral Infection Following Live Vaccination (Prolonged-Release Formulation)

MedDRA PT	No. Events	Serious Events	H	F	R	RS	NR	U
Herpes zoster	8	0	0	0	0	1	1	6
Influenza	3	0	0	0	0	0	0	3
Sinusitis	2	0	0	0	0	0	0	2
All others	4	1	0	0	0	0	0	4
Total	17	1	0	0	0	1	1	15

F = fatal; H = hospitalisation; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; R = resolved/resolving; RS = resolved with sequelae; NR = not resolved; U = unknown

Severity and nature of risk

RA: The event was assessed as moderate.

Study A3921133: Not available.

PsA: Not available.

UC: There were no events of primary viral infection following live vaccination in the UC clinical programme.

JIA: Not available.

AS: There were no events of primary viral infection following live vaccination in the AS clinical programme.

VII.3.1.2.9.4. Risk factors and risk groups

In general, patients treated with medications that depress the immune system are at an increased risk of developing a viral infection after getting a live vaccine. This is possible when there is not enough time between live vaccination and the start of the medication that depresses the immune system or with zoster vaccination, where the patients have not had chicken pox in the past.

VII.3.1.2.9.5. Preventability

Prior to initiating tofacitinib, it is recommended that all patients, particularly pJIA patients and juvenile PsA patients, be brought up to-date with all immunisations in agreement with current immunisation guidelines. It is recommended that live vaccines not be given concurrently with tofacitinib. The decision to use live vaccines prior to treatment should take into account the degree of immunocompetence of a given patient.

Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding RA who have received 2 or more prior bDMARDs. If live zoster vaccine is administered; it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus. If the history of chickenpox is considered doubtful or unreliable it is recommended to test for antibodies against varicella zoster virus. Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of tofacitinib or in accordance with current vaccination guidelines regarding immunomodulatory agents such as tofacitinib.

VII.3.1.2.9.6. Impact on the risk-benefit balance of the product

Primary viral infection may be mild, moderate, or severe and sometimes life-threatening.

VII.3.1.2.9.7. Public health impact

Primary viral infection can lead to morbidity and mortality. The impact of the infections on public health is significant both in terms of lost time at work and increased burden on medical care.

VII.3.2. Presentation of the Missing Information

Table 138. Effects on Pregnancy and the Foetus

Evidence source and strength of evidence	There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women. The use of tofacitinib during pregnancy is contraindicated.
Anticipated risk/consequence of the missing information	Guidance against the use of tofacitinib during pregnancy is provided in the Summary of Product Characteristics (Section 4.6). There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women. Even though the use of tofacitinib during pregnancy is contraindicated, all pregnancies can't be prevented. Therefore, effects on pregnancy and the foetus will be monitored via routine pharmacovigilance.

Table 139. Use in Breastfeeding

Evidence source and strength of evidence	Tofacitinib was secreted in the milk of lactating rats. It is not known whether tofacitinib is secreted in human milk. A risk to the breast-fed child cannot be excluded. The use of tofacitinib during breastfeeding is contraindicated.
Anticipated risk/consequence of the missing information	Guidance against the use of tofacitinib during breast-feeding is provided in the Summary of Product Characteristics (Section 4.6). A risk to the breast-fed child cannot be excluded.

Table 140. Effect on Vaccination Efficacy and the Use of Live/Attenuated Vaccines

Evidence source and strength of evidence	Three vaccine studies (A3921129, A3921024, A3921237) that were designed to evaluate the immune response following administration of influenza, pneumococcal, and zoster vaccines were completed. No data are available on the secondary transmission of infection by live vaccines to patients receiving tofacitinib. It is recommended that live vaccines not be given concurrently with tofacitinib.
Anticipated risk/consequence of the missing information	The risk of secondary infection by live vaccines to patients receiving tofacitinib is currently not well understood.

Table 141. Use in Patients with Mild, Moderate, or Severe Hepatic Impairment

Evidence source and strength of evidence	Tofacitinib has not been studied in patients with severe hepatic impairment.
Anticipated risk/consequence of the missing information	Tofacitinib should not be used in patients with severe hepatic impairment. Film-coated tablets: in patients with moderate hepatic impairment, tofacitinib dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily in patients with moderate hepatic impairment. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily. Prolonged-release tablets: in patients with moderate hepatic impairment, tofacitinib dose should be reduced to 5 mg film-coated tablets once daily when the indicated dose in the presence of normal hepatic function is 11 mg prolonged release tablet once daily.

Table 141. Use in Patients with Mild, Moderate, or Severe Hepatic Impairment

	Oral solution: in patients with moderate hepatic impairment, tofacitinib dose should be reduced to 5 mg or weight-based equivalent once daily when the indicated dose in the presence of normal hepatic function is 5 mg or weight based equivalent twice daily.

Table 142. Use in Patients with Moderate or Severe Renal Impairment

Evidence source and strength of evidence	The impact of use of tofacitinib in patients with severe renal impairment remains unknown.
Anticipated risk/consequence of the missing information	Tofacitinib dose should be reduced in patients with severe renal impairment. In patients with severe renal impairment: Film-coated tablets: in patients with severe renal impairment, tofacitinib dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis. Prolonged-release tablets: in patients with severe renal impairment, tofacitinib dose should be reduced to 5 mg film-coated tablet once daily when the indicated dose in the presence of normal renal function is 11 mg prolonged release tablet once daily. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis. Oral solution: in patients with severe renal impairment, tofacitinib dose should be reduced to 5 mg or weight-based equivalent once daily when the indicated dose in the presence of normal renal function is 5 mg or weight based equivalent twice daily. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis.

Table 143. Use in Patients with Evidence of Hepatitis B or Hepatitis C Infection

Evidence source and strength of evidence	Tofacitinib has not been studied in patients with evidence of hepatitis B or hepatitis C infection.
Anticipated risk/consequence of the missing information	The impact of use of tofacitinib in patients with pre-existing hepatitis B or hepatitis C infection remains unknown.

Table 144. Use in Patients with Malignancy

Evidence source and strength of evidence	Patients with history of malignancy except adequately treated NMSC or cervical carcinoma in situ were excluded from clinical studies.
Anticipated risk/consequence of the missing information	The impact of use of tofacitinib in patients with history of malignancy remains unknown. The risks and benefits of tofacitinib treatment should be considered prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated NMSC or when considering continuing tofacitinib in patients who develop a malignancy. The possibility exists for tofacitinib to affect host defences against malignancies.

NMSC = non-melanoma skin cancer

Table 145. Long-term Safety in pJIA Patients and Juvenile PsA Patients (e.g., Growth or Development Disturbances)

Evidence source and strength of evidence	Long-term safety of tofacitinib in pJIA patients and juvenile PsA patients has not been studied.
Anticipated risk/consequence of the missing information	The impact of the long-term safety of tofacitinib in pJIA patients and juvenile PsA patients remains unknown.

pJIA = polyarticular juvenile idiopathic arthritis; PsA = psoriatic arthritis

Module SVIII. Summary of the Safety Concerns

Table 146. Summary of Safety Concerns

Important identified risks	Venous thromboembolic events (DVT/PE)
	Serious and other important infections
	HZ reactivation
	Lung cancer
	Lymphoma
	Myocardial infarction
	Decrease in Hgb levels and anaemia
	NMSC
	Transaminase elevation and potential for DILI
	Higher incidence and severity of AEs in the elderly
Important potential risks	Malignancy
	Cardiovascular risk (excl MI)
	GI perforation
	ILD
	PML
	All-cause mortality
	Fractures
	Increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients
	Primary viral infection following live vaccination
Missing information	Effects on pregnancy and the foetus
	Use in breastfeeding
	Effect on vaccination efficacy and the use of live/attenuated vaccines
	Use in patients with mild, moderate, or severe hepatic impairment
	Use in patients with moderate or severe renal impairment
	Use in patients with evidence of hepatitis B or hepatitis C infection
	Use in patients with malignancy
	Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)

AE = adverse event; DILI = drug-induced liver injury; DVT = deep vein thrombosis; Excl = excluding; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IBD = inflammatory bowel disease; ILD = interstitial lung disease; JIA = juvenile idiopathic arthritis; MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma skin cancer; pJIA = polyarticular juvenile idiopathic arthritis; PE = pulmonary embolism; PML = progressive multifocal leukoencephalopathy; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RMP = risk management plan

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities include adverse drug reaction (ADR) reporting and signal detection.

Specific adverse reaction follow-up questionnaires for safety concerns:

None.

Other forms of routine pharmacovigilance activities for safety concerns:

None.

III.2. Additional Pharmacovigilance Activities

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
ARTIS A3921314 Category 3	Prospective, non-interventional active surveillance study embedded within the Antirheumatic Therapies in Sweden (ARTIS) registry (RA)	To describe safety outcomes among RA patients treated with Xeljanz versus other new advanced targeted therapies in real-world clinical use in ARTIS (Sweden). This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[b] MI, GI perforation, PML, all-cause mortality, fractures, higher incidence of AEs in elderly patients (≥65 years) including infections.	Non-interventional, prospective, active surveillance	Swedish patients prescribed tofacitinib for rheumatoid arthritis	Study start: 15/09/2019 Interim report: Year 2, 4, 6 Study finish: 14/09/2025 Final report: 14/08/2026
BSRBR A3921312 Category 3	Prospective, non-interventional active surveillance study embedded within the British Society for Rheumatology Biologics	To describe safety outcomes among RA patients treated with Xeljanz versus other new advanced targeted therapies in real-world clinical use in BSRBR (UK)	Non-interventional, prospective, active surveillance	UK patients prescribed tofacitinib for rheumatoid arthritis	Study start: 15/09/2019 Interim report: Year 2, 4, 6 Study finish: 14/09/2025 Final report:

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
	Register (BSRBR) (RA)	This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[b] MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence of AEs in elderly patients (≥65 years) including infections.			14/08/2026
RABBIT A3921317 Category 3	Prospective, non-interventional active surveillance study embedded within the Rheumatoide Arthritis – Beobachtung der Biologika-Therapie (RABBIT) registry (RA)	To describe safety outcomes among RA patients treated with Xeljanz versus other new advanced targeted therapies in real-world clinical use in RABBIT (Germany) This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[b] MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of AEs in elderly patients (≥65 years) including infections.	Non-interventional, prospective, active surveillance	German patients prescribed tofacitinib for rheumatoid arthritis	Study start: 15/09/2019 Interim report: Year 2, 4, 6 Study finish: 14/09/2025 Final report: 14/08/2026
BIOBADASER A3921316 Category 3	Prospective, non-interventional active surveillance study embedded within the Registro Español de	To describe safety outcomes among RA patients treated with Xeljanz versus other new advanced targeted therapies in real-world clinical use in	Non-interventional, prospective, active surveillance	Spanish patients prescribed tofacitinib for rheumatoid arthritis	Study start: 15/09/2019 Interim report: Year 2, 4, 6 Study finish: 14/09/2025

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
	Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas (BIOBADASER) (RA)	BIOBADASER (Spain). This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[b] MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence of AEs in elderly patients (≥65 years) including infections.			Final report: 14/08/2026
Drug utilisation study (DUS) A3921321 Category 3	An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)	The research question is: Is there evidence that prescribers in the EU are compliant with the recommendations and limitations for use described in the tofacitinib aRMM materials? The primary objectives are to: 1. Describe the characteristics of patients treated with tofacitinib, stratified by study country (i.e., Sweden, Hungary, the Netherlands and Germany) and indication (i.e., RA, PsA, and UC; off-label indications), in terms of: • Demographics (e.g., age, sex); and • Comorbidities and prior and current medication use. 2. Evaluate prescribers' adherence to the tofacitinib aRMMs, specifically:	Longitudinal descriptive study	All patients with a prescription for tofacitinib identified in EHR/registry databases in 4 European countries	Start of data collection[e]: 30/09/2022 End of data collection[e]: 31/10/2026 Interim study report 1: 30/01/2024 Interim study report 2: 31/08/2025 Final study report: 31/10/2027[f]

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones

		• Compliance to the recommended posology per indication (average daily dose) and duration of use;
		• Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment; and
		• Compliance to recommendations for limitations of use, including:
		  • Use in patients with VTE risk factors;
		  • Use in patients aged 65 years and older;
		  • Use in patients with CV risk factors;
		  • Use in patients with malignancy risk factors;
		  • Contraindicated use; and
		  • Use with concomitant medications not compatible with tofacitinib.
		
		The secondary objectives are to:
		1. Describe prescribing patterns over time; and
		2. To describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral and the 2021 signal evaluation procedure, specifically:
		• Use in patients with VTE risk factors;
		• Use in the elderly (patients aged 65 years and older);			

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
		• Use in patients with CV risk factors; and • Use in patients with malignancy risk factors			
European UC registry study (SWIBREG) A3921344 Category 3	Prospective, non-interventional active surveillance study SWIBREG (Swedish Quality Register for Inflammatory Bowel Disease)	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting. Safety concerns addressed include venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), MACE, MI, GI perforation, PML, all-cause mortality, fractures, higher incidence and severity of incidence of adverse events in elderly patients (≥65 years) including infections. Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.	Prospective, non-interventional active surveillance study	European patients prescribed tofacitinib for ulcerative colitis	Study start: 31/03/2021[a] Interim reports: years 2 and 4 Study finish: 31/03/2026 Final report: 31/03/2027

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
European UC registry study (UR-CARE) A3921352 Category 3	Prospective, non-interventional active surveillance study using the United Registries for Clinical Assessment and Research (UR-CARE)	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting. Safety concerns addressed include venous thromboembolism (DVT/PE), serious infections, HZ reactivation, lymphoma, lung cancer, NMSC, malignancy, cardiovascular risk (specifically MACE), MI, GI perforation, PML, all-cause mortality, fractures, higher incidence of adverse events in elderly patients (≥65 years) including infections. Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.	Prospective, non-interventional active surveillance study	European patients prescribed tofacitinib for ulcerative colitis	Study start: 31/01/2024 Interim report: 31/08/2024 Study finish: 31/03/2026 Final report: 31/03/2027
Drug utilisation and active surveillance study in the US A3921347 Category 3	A drug utilisation and active surveillance, post-authorisation study to assess tofacitinib utilisation patterns in the US and to characterise the safety of tofacitinib use in patients with moderately to severely active ulcerative colitis in the real-world setting using data from a US administrative healthcare claims database	To understand the patterns of tofacitinib use in the US, as well as assess the risk of safety events of interest that may be associated with its use, a non-interventional, drug utilisation and active surveillance study will be conducted using data from an administrative healthcare claims database. The drug utilisation study will assess overall patterns of tofacitinib use, as well as potential off-label use among non-approved indications, use of 10 mg BID in	Descriptive, drug utilisation and active surveillance study	For the drug utilisation portion of the study, all patients enrolled in the US claims database during the study period who have received ≥1 prescription of tofacitinib will be included. For the active surveillance portion of the study, a sub-population will be created, which will consist of US patients	Start of data collection: 30/06/2020[d] End of data collection: 30/06/2025 Interim report 1: 30/06/2022 Interim report 2: 30/06/2024 Final report: 30/06/2026

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
		patients without a recorded diagnosis of UC, and use of 10 mg maintenance therapy among UC patients at a high risk for thrombosis. Safety concerns include venous thromboembolism (DVT/PE), mortality,[c] fractures, malignancies (including lymphoma and lung cancer), opportunistic and serious infections, herpes zoster, MACE, MI, and gastrointestinal perforations Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.		prescribed tofacitinib for UC.	
Shingrix study A3921427 Category 3	Observational Study of Effectiveness and Safety of Recombinant Zoster Vaccine (Shingrix) in Moderately-to-Severely Active Ulcerative Colitis (UC) or Rheumatoid Arthritis (RA) Patients Treated with Tofacitinib (Xeljanz) in Real-World Clinical Care Settings	To evaluate among patients with UC or RA receiving treatment with tofacitinib, the incidence of HZ and UC or RA disease flare among patients who received at least one dose of Recombinant Zoster Vaccine (RZV) relative to the incidence rate among patients who did not receive RZV.	Non-interventional, observational cohort study among real-world patients with UC and RA treated with tofacitinib, using US claims data	UC and RA patients in the US treated with tofacitinib	Start of data collection: 02/01/2024 End of data collection: 14/09/2024 Final report: 14/09/2025
German Biologics in Pediatric Rheumatology Registry (BIKER) and Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry A3921407	Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and	To contextualise the rates of safety events observed among tofacitinib-treated polyarticular JIA patients and juvenile PsA patients. The primary objective of the study would be to estimate the	Active safety surveillance program encompassing 2 existing JIA registries	pJIA patients and juvenile PsA patients	Start of data collection: 01/03/2026 End of data collection: 01/11/2032 Final study report: 01/05/2033

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
Category 3	Juvenile PsA within the BIKER and JuMBO Registry	postmarking incidence rate of venous thromboembolism, serious infections, and other important infections (including opportunistic infection, tuberculosis and vaccine preventable infections), all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer, among patients with polyarticular JIA or juvenile PsA patients who initiate tofacitinib. **Secondary objective 1:** to estimate the postmarketing incidence rates of gastrointestinal perforations, major adverse cardiac events (including MI), hypersensitivity, long-term safety in pJIA patients and juvenile PsA patients (e.g. growth or development disturbances), fractures, PML, all-cause mortality, HZ reactivation, NMSC, and ILD. To assess long-term safety, a minimum of 5 years follow-up is planned. **Secondary objective 2:** To compare the risk of outcomes of interest listed under the primary objective and the secondary objective 1 among patients with pJIA or juvenile PsA who initiate tofacitinib			

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
		(Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort). This comparison will be restricted to the outcomes of interest, where there are adequate data.			
Nationwide Swedish HealthCare Registers A3921408 Category 3	Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers	To contextualise the rates of safety events observed among tofacitinib-treated polyarticular JIA patients and juvenile PsA patients. The primary objective of the study would be to estimate the postmarking incidence rate of venous thromboembolism, serious infections, and other important infections (including opportunistic infection, tuberculosis), all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer among patients with polyarticular JIA or juvenile PsA patients who initiate tofacitinib. **Secondary objective 1:** to estimate the postmarketing incidence rates of gastrointestinal perforations, major adverse cardiac events (including MI), fractures, PML, all-cause mortality, HZ reactivation, NMSC, and ILD. To assess long-term safety, a minimum of	Active safety surveillance program	pJIA patients and juvenile PsA patients	Start of data collection: 01/03/2026 End of data collection: 01/11/2030 Final study report: 01/05/2031

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
		5 years follow-up is planned. **Secondary objective 2:** To compare the risk of outcomes of interest listed under the primary objective and the secondary objective 1 among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort). This comparison will be restricted to the outcomes of interest, where there are adequate data.			
UK JIA Biologics Register A3921409 Category 3	Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register	To contextualise the rates of safety events observed among tofacitinib-treated polyarticular JIA patients and juvenile PsA patients. The primary objective of the study would be to estimate the postmarking incidence rate of venous thromboembolism, serious infections, and other important infections (including opportunistic infection, tuberculosis and vaccine preventable infections), all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer among patients with polyarticular JIA or juvenile PsA patients who initiate tofacitinib.	Active safety surveillance program	pJIA patients and juvenile PsA patients	Start of data collection: 01/03/2026 End of data collection: 01/11/2030 Final study report: 01/05/2031

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
		Secondary objective 1: To estimate the postmarketing incidence rates of gastrointestinal perforations, major adverse cardiac events (including MI), hypersensitivity, long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances), fractures, PML, all-cause mortality, HZ reactivation, NMSC, and ILD. To assess long-term safety, a minimum of 5 years follow-up is planned. **Secondary objective 2:** To compare the risk of outcomes of interest listed under the primary objective and the secondary objective 1 among patients with pJIA or juvenile PsA who initiate tofacitinib (Tofacitinib cohort) and patients with pJIA or juvenile PsA treated with approved bDMARDs (Comparator cohort). This comparison will be restricted to the outcomes of interest, where there are adequate data.			

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones
Long-term observational safety study in paediatric patients 2-17 years of age with polyarticular JIA (pJIA) treated with tofacitinib A3921371 Category 3	An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry	To evaluate for the risk of thrombosis, infections (including opportunistic infections and serious infections), all malignancies combined (excluding nonmelanoma skin cancer [NMSC]), NMSC, lymphoma, lung cancer, growth effects, and fractures, MACE (including MI), and vaccine preventable infections. To assess long-term safety, 5 years follow-up is planned.	An active surveillance post-authorisation safety study	pJIA patients	Start of data collection: 31/01/2026 End of data collection: 28/02/2030 Final study report: 30/09/2030
A3921145 Category 3	A Long Term, Open Label Follow Up Study of Tofacitinib for Treatment of JIA	The primary objective of this study is to determine the long term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA. The secondary objective of this study is to evaluate the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA.	Long term, open label, follow up study	pJIA patients and juvenile PsA patients	Study start: 18/03/2013 Study finish: TBD Final report: TBD
Drug utilisation study in France[g] A3921403 Category 3	A Post-Authorisation Safety Study of the Utilisation and Prescribing Patterns of Xeljanz (tofacitinib) Using an Administrative Healthcare Database in France	TBD	Longitudinal descriptive study	Patients of all ages who are new initiators of tofacitinib in France	Start of data collection: TBD End of data collection: TBD Interim report: TBD Final study report: TBD

a. Study protocol approved on 01/03/2021. Study start date does not impact patient accrual as data can be obtained retrospectively.
b. Specifically, MACE
c. Due to limitations related to the claims database, only in-hospital mortality can be assessed

Table 147. Additional Pharmacovigilance Activities

PASS short name summary	Study Title	Rationale and Study Objectives	Study design	Study populations	Milestones

d. This represents start of data collection for the active surveillance portion of the study. Start of data collection for the drug utilisation study will be 31 March 2021.
e. Start and end of data collection refer to the start and end of data extraction, respectively, due to the approximate 2-year data lag associated with the databases. Interim study report 1 will cover data from 01 April 2016 through 31 December 2020. Interim study report 2 will cover data from 01 April 2016 through 31 December 2022. The final study report will cover data from 01 April 2016 through 31 December 2024.
f. If it is necessary to extend the study observation period for a country because the minimum number of tofacitinib patients (100 patients) per indication has not been met for all three indications by the end of the study observation period, the study observation period will be extended for those countries as the data are available and the MAH will submit the final study report later than 31 October 2027. For those countries that have met the minimum patient threshold of at least 100 tofacitinib patients per indication for all three indications at the end of the study observation period, a second interim study report will be submitted within 12 months after the planned end of data collection.
g. Objectives and milestones are "TBD" as the protocol is under assessment (EMEA/H/C/004214/MEA/025.1).
AE = adverse event; ARTIS = Anti-rheumatic Therapies in Sweden; aRMM = additional risk minimisation measure; AS = ankylosing spondylitis; BID = twice daily; BIKER = German Biologics in Pediatric Rheumatology Registry; BIOBADASER = Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas; BSRBR = British Society for Rheumatology Biologics Register; CARRA = Childhood Arthritis and Rheumatology Research Alliance;bDMARD = biologic disease-modifying antirheumatic drug; CV = cardiovascular; DUS = drug utilization study; DVT= deep vein thrombosis; EHR = electronic health care record; ENEIDA = Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales; EU = European Union; GI = gastrointestinal; HZ = herpes zoster; JIA = juvenile idiopathic arthritis; JuMBO = Juvenile Arthritis Methotrexate/Biologics long-term Observation; MACE = major adverse cardiac event; MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma skin cancer; OI = opportunistic infection; PAM = Post-Authorisation Measure; PASS = post-authorisation safety study; PE = pulmonary embolism; ; pJIA = polyarticular juvenile idiopathic arthritis; PML = progressive multifocal leukoencephalopathy; PRAC = Pharmacovigilance Risk Assessment Committee; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RABBIT = Rheumatoide Arthritis–Beobachtung Der Biologika-Therapie; RMP = Risk Management Plan; RZV = Recombinant Zoster Vaccine; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease, TB = tuberculosis; TBD = to be determined; TNF = tumour necrosis factor; UC = ulcerative colitis; UR-CARE = United Registries for Clinical Assessment and Research; UK = United Kingdom; US = United States; VTE = venous thromboembolism

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-going and Planned Additional Pharmacovigilance Activities

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
None				
Category 3 – Required additional pharmacovigilance activities				
Prospective, non-interventional active surveillance study embedded within the ARTIS registry (RA) (A3921314) On-going	To describe safety outcomes among RA patients treated with Xeljanz and other new advanced targeted therapies in real-world clinical use in ARTIS (Sweden). This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[a] MI, GI perforation, PML, all-cause mortality, fractures, higher incidence of AEs in elderly patients (≥65 years) including infections.	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk[a] (excl MI) - MI - GI perforation - PML - all-cause mortality - fractures - higher incidence and severity of AEs in the elderly[g]	Study start Interim report Study finish Final report	15/09/2019 Year 2, 4, 6 14/09/2025 14/08/2026
Prospective, non-interventional active surveillance study embedded within the BSRBR registry (RA) (A3921312) On-going	To describe safety outcomes among RA patients treated with Xeljanz versus other new advanced targeted therapies in real-world clinical use in BSRBR (UK). This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[a] MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk[a] (excl MI) - MI - GI perforation - PML - all-cause mortality - fractures - increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients[h]	Study start Interim report Study finish Final report	15/09/2019 Year 2, 4, 6 14/09/2025 14/08/2026

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	incidence of AEs in elderly patients (≥65 years) including infections.	- higher incidence and severity of AEs in the elderly[g]		
Prospective, non-interventional active surveillance study embedded within the RABBIT registry (RA) (A3921317) On-going	To describe safety outcomes among RA patients treated with Xeljanz versus other new advanced targeted therapies in real-world clinical use in RABBIT (Germany) This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[a] MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of AEs in elderly patients (≥65 years) including infections.	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk[a] (excl MI) - MI - GI perforation - PML - all-cause mortality - fractures - increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients[h] - higher incidence and severity of AEs in the elderly	Study start Interim report Study finish Final report	15/09/2019 Year 2, 4, 6 14/09/2025 14/08/2026
Prospective, non-interventional active surveillance study embedded within the BIOBADASER registry (RA) (A3921316) On-going	To describe safety outcomes among RA patients treated with Xeljanz versus other new advanced targeted therapies in real-world clinical use in BIOBADASER (Spain). This study will address the concerns of venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk,[a] MI, GI	- venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk[a] (excl MI) - MI - GI perforation - PML - all-cause mortality - fractures - increased risk of AEs when	Study start Interim report Study finish Final report	15/09/2019 Year 2, 4, 6 14/09/2025 14/08/2026

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence of AEs in elderly patients (≥65 years) including infections.	tofacitinib is administered in combination with MTX in RA or PsA patients[h] - higher incidence and severity of AEs in the elderly[g]		
Drug utilisation study A3921321 On-going	The research question is: Is there evidence that prescribers in the EU are compliant with the recommendations and limitations for use described in the tofacitinib aRMM materials? The primary objectives are to: 1. Describe the characteristics of patients treated with tofacitinib, stratified by study country (i.e., Sweden, Hungary, the Netherlands and Germany) and indication (i.e., RA, PsA, and UC; off-label indications), in terms of: • Demographics (e.g., age, sex); and • Comorbidities and prior and current medication use. 2. Evaluate prescribers' adherence to the tofacitinib aRMMs, specifically: • Compliance to the recommended posology per indication (average daily dose) and duration of use;	- venous thromboembolism (DVT/PE)[i] - use in patients with mild, moderate, or severe hepatic impairment - MI[j] - use in patients with malignancy	Start of data collection[e] End of data collection[e] Interim study report 1 Interim study report 2 Final study report	30/09/2022 31/10/2026 30/01/2024 31/08/2025 31/10/2027[f]

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates

	• Compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment; and
	• Compliance to recommendations for limitations of use, including:
	  • Use in patients with VTE risk factors;
	  • Use in patients aged 65 years and older;
	  • Use in patients with CV risk factors;
	  • Use in patients with malignancy risk factors;
	  • Contraindicated use; and
	  • Use with concomitant medications not compatible with tofacitinib.
	
	The secondary objectives are to:
	1. Describe prescribing patterns over time; and
	2. To describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral and the 2021 signal evaluation procedure, specifically:
	• Use in patients with VTE risk factors;
	• Use in the elderly (patients aged 65 years and older);
	• Use in patients with CV risk factors; and
	• Use in patients with malignancy risk factors.			

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Prospective, non-interventional active surveillance study (SWIBREG) A3921344 On-going	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting. Safety concerns addressed include venous thromboembolism (DVT/PE), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), MACE, MI, GI perforation, PML, all-cause mortality, fractures, higher incidence of adverse events in elderly patients (≥65 years) including infections. Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.	- fractures - venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk[a] (excl MI) - MI - GI perforation - PML - all-cause mortality - higher incidence and severity of adverse events in the elderly[g]	Study start Interim report Study finish Final report	31/03/2021[d] Years 2 and 4 31/03/2026 31/03/2027
Prospective, non-interventional active surveillance study (UR-CARE) A3921352 Planned	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting. Safety concerns addressed include venous thromboembolism (DVT/PE), serious infections, HZ reactivation, lymphoma, lung cancer, NMSC, malignancy, cardiovascular risk (specifically MACE), MI, GI perforation, PML, all-cause mortality, fractures, higher incidence of adverse events in elderly patients (≥65 years) including infections. Safety outcomes with 10 mg BID dose during	- fractures - venous thromboembolic events (DVT/PE) - serious and other important infections - HZ reactivation - NMSC - malignancy - lymphoma - lung cancer - CV risk[a] (excl MI) - MI - GI perforation - PML - all-cause mortality - higher incidence and severity of adverse events in the elderly[g]	Study start Interim report Study finish Final report	31/01/2024 31/08/2024 31/03/2026 31/03/2027

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	maintenance will be evaluated in a separate sub-analysis.			
Drug utilisation and active surveillance, post-authorisation study examining utilisation patterns and tofacitinib safety in UC (US) A3921347 On-going	To understand the patterns of tofacitinib use in the US, as well as assess the risk of safety events of interest that may be associated with its use, a non-interventional, drug utilisation and active surveillance study will be conducted using data from an administrative healthcare claims database. This study will assess overall patterns of tofacitinib use, as well as potential off-label use among non-approved indications, use of 10 mg BID in patients without a recorded diagnosis of UC, and use of 10 mg maintenance therapy among UC patients at a high risk for thrombosis. Safety concerns include venous thromboembolism (DVT/PE), mortality, [b] fractures, malignancies (including lymphoma and lung cancer), opportunistic and serious infections, herpes zoster, MACE, MI, and GI perforations Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.	- fractures - venous thromboembolic events (DVT/PE) - all-cause mortality[b] - malignancy - lymphoma - lung cancer - serious and other important infections - HZ reactivation - cardiovascular risk (excl MI)[a] - MI - GI perforations	Start of data collection End of data collection Interim report 1 Interim report 2 Final report	30/06/2020[c] 30/06/2025 30/06/2022 30/06/2024 30/06/2026
Observational Study of Effectiveness and Safety of Recombinant	To evaluate among patients with UC or RA receiving treatment with	- primary viral infection following live vaccination	Start of data collection	02/01/2024

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Zoster Vaccine (Shingrix) in Moderately-to-Severely Active UC or RA Patients Treated with Tofacitinib (Xeljanz) in Real-World Clinical Care Settings A3921427 Planned	tofacitinib, the incidence of HZ and UC or RA disease flare among patients who received at least one dose of RZV relative to the incidence rate among patients who did not receive RZV.		End of data collection Final report	14/09/2024 14/09/2025
Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry A3921407 Planned	To contextualise the rates of safety events observed among tofacitinib-treated polyarticular JIA and juvenile PsA patients	- fractures - venous thromboembolism (DVT/PE) - serious and other important infections - malignancies - lymphoma - lung cancer - MI - GI perforation - CV risk[a] (excl MI) - long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances) - PML - all-cause mortality - HZ reactivation - NMSC - ILD	Start of data collection End of data collection Final study report	01/03/2026 01/11/2032 01/05/2033

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers A3921408 Planned	To contextualise the rates of safety events observed among tofacitinib-treated polyarticular JIA and juvenile PsA patients	- fractures - venous thromboembolic events (DVT/PE) - serious and other important infections - malignancies - lymphoma - lung cancer - MI - GI perforation - CV risk[a] (excl MI) - PML - all-cause mortality - HZ reactivation - NMSC - ILD	Start of data collection End of data collection Final study report	01/03/2026 01/11/2030 01/05/2031
Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register A3921409 Planned	To contextualise the rates of safety events observed among tofacitinib-treated polyarticular JIA and juvenile PsA patients	- fractures - venous thromboembolic events (DVT/PE) - serious infections and other important infections - malignancies - lymphoma - lung cancer - MI - GI perforation - CV risk[a] (excl MI) - long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances) - PML - all-cause mortality - HZ reactivation - NMSC - ILD	Start of data collection End of data collection Final study report	01/03/2026 01/11/2030 01/05/2031
An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile	To evaluate risks (malignancies, serious infections [including opportunistic infections], and thrombosis) in pJIA patients in the US	- fractures - malignancies - NMSC - lymphoma - lung cancer - MI - serious and other important infections	Start of data collection End of data collection Final study report	31/01/2026 28/02/2030 30/09/2030

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry A3921371 Planned		- venous thromboembolic events (DVT/PE) - long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)		
A3921145 On-going	To determine the long-term safety and tolerability of tofacitinib for treatment of the signs and symptoms of JIA. To evaluate the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA.	- long-term safety in pJIA and juvenile PsA patients (e.g., growth or development disturbances)	Study start Study finish Final report	18/03/2013 TBD TBD
A Post-Authorisation Safety Study of the Utilisation and Prescribing Patterns of Xeljanz (tofacitinib) Using an Administrative Healthcare Database in France[k] A3921403 Planned	TBD	- venous thromboembolic events (DVT/PE)[i] - use in patients with mild, moderate, or severe hepatic impairment - MI[j] - use in patients with malignancy	Start of data collection End of data collection Interim report Final study report	TBD TBD TBD TBD

a. Specifically, MACE
b. Due to limitations related to the claims database, only in-hospital mortality can be assessed
c. This represents start of data collection for the active surveillance portion of the study. Start of data collection for the drug utilisation study will be 31 March 2021.
d. Study protocol approved on 01/03/2021. Study start date does not impact patient accrual as data can be obtained retrospectively.
e. Start and end of data collection refer to the start and end of data extraction, respectively, due to the approximate 2-year data lag associated with the databases. Interim study report 1 will cover data from 01 April 2016 through 31 December 2020. Interim study report 2 will cover data from 01 April 2016 through 31 December 2022. The final study report will cover data from 01 April 2016 through 31 December 2024.
f. If it is necessary to extend the study observation period for a country because the minimum number of tofacitinib patients (100 patients) per indication has not been met for all three indications by the end of the study observation period, the study observation period will be extended for those countries as the data are available and the MAH will submit the final study report later than 31 October 2027. For those countries that have met the minimum patient threshold of at least 100 tofacitinib patients per indication for all three indications at the end of the study observation period, a second interim study report will be submitted within 12 months after the planned end of data collection.

Table 148. On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates

g. Higher incidence of AEs in the elderly will be assessed only. Severity cannot be assessed due to dataset limitations.
h. Increased risk of AEs when tofacitinib is administered in combination with MTX will be assessed in RA patients only. PsA patients are not included in the registry.
i. This study does not directly estimate the incidence of DVT/PE, but describes the use of tofacitinib among patients with VTE risk factors.
j. This study does not directly estimate the incidence of MI, but describes the use of tofacitinib among patients with cardiovascular risk factors.
k. Objectives and milestones are "TBD" as the protocol is under assessment (EMEA/H/C/004214/MEA/025.1).
AE = Adverse Event; ARTIS = Anti-rheumatic Therapies In Sweden; AS = ankylosing spondylitis; bDMARD = biologic disease-modifying antirheumatic drug; BID = twice daily; BIKER = German Biologics in Pediatric Rheumatology Registry; BIOBADASER = Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas; BSRBR = British Society For Rheumatology Biologics Register; CARRA = Childhood Arthritis and Rheumatology Research Alliance; CV = cardiovascular; EHR = electronic health care records; ENEIDA = Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales; EU = European Union; excl = excluding; GI = gastrointestinal; HZ = herpes zoster; JuMBO = Juvenile Arthritis Methotrexate/Biologics long-term Observation; MACE = major adverse cardiac event; MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma Skin Cancer; OI = opportunistic infection; PAM = Post-Authorisation Measure; pJIA = polyarticular juvenile idiopathic arthritis; PML = progressive multifocal leukoencephalopathy; PRAC = Pharmacovigilance Risk Assessment Committee; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RABBIT = Rheumatoide Arthritis–Beobachtung Der Biologika-Therapie; RMP = Risk Management Plan; RZV = Recombinant Zoster Vaccine; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease, TB = tuberculosis; TBD = to be determined; TNF = tumour necrosis factor; UC = ulcerative colitis; UR-CARE = United Registries for Clinical Assessment and Research; US = United States; VTE = venous thromboembolism

PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 149. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Important Identified Risks	
Venous thromboembolic events (DVT/PE)	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Text for evaluating patients with signs and symptoms of venous thromboembolism (DVT/PE) and discontinuation of tofacitinib therapy in patients with suspected venous thromboembolism (DVT/PE) is included in SmPC Section 4.4.
Serious and other important infections	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties

Table 149. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for interruption of tofacitinib therapy in patients with serious and other important infections are included in SmPC Section 4.2 Serious and other important infections for which Tofacitinib is contraindicated is included in SmPC Section 4.3 (active TB, serious infections such as sepsis, or opportunistic infections are contraindications). Special warnings and precautions for Serious and other important infections are described in SmPC Section 4.4, including text such as not initiating treatment in patients with active infections, including localised infections, closely monitoring patients for the development of signs and symptoms of infection, recommendations for TB. In patients 65 years of age and older tofacitinib should only be used if no suitable treatment alternatives are available. Dose interruption and discontinuation in laboratory abnormalities including neutropenia and lymphopenia are included in SmPC Section 4.2. Information about ANC monitoring for Decrease in neutrophil counts and neutropenia is included in SmPC Section 4.4. Information about ALC monitoring for Decrease in lymphocyte counts and lymphopenia is included in SmPC Section 4.4. SmPC Section 4.4 states tofacitinib has not been studied and its use should be avoided in combination with biologics because of the possibility of increased immunosuppression and increased risk of infection.
HZ reactivation	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Risk factors for HZ reactivation are included in SmPC Section 4.4.
Lung cancer	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Risk factors for lung cancer are included in SmPC Section 4.4. In addition, Section 4.4 states that in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.

Table 149. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
Lymphoma	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Risk factors for lymphoma are included in SmPC Section 4.4. In addition, Section 4.4 states that in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.
Myocardial infarction	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Risk factors for MI are included in SmPC Section 4.4. In addition, Section 4.4, under MACE (including MI), states that in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease and other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.
Decrease in haemoglobin levels and anaemia	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Dose interruption and discontinuation in laboratory abnormalities including anaemia are included in SmPC Section 4.2 Information about Hgb monitoring for Decrease in Hgb levels and anaemia is included in SmPC Section 4.4.
NMSC	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects

Table 149. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for periodic skin examinations for all patients particularly those who are at an increased risk for skin cancer are included in SmPC Section 4.4.
Transaminase elevation and potential for DILI	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Text for monitoring liver enzymes and treatment interruption when drug-induced liver injury is suspected until diagnosis has been excluded is included in SmPC Section 4.4.
Higher incidence and severity of AEs in the elderly	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4, under Use in patients 65 years of age and older, states that considering the increased risk of serious infections, myocardial infarction, malignancies, and all-cause mortality with tofacitinib in patients 65 years of age and older, tofacitinib should only be used if no suitable treatment alternatives are available.
Important potential risks	
Malignancy	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.1 Pharmacodynamic properties

Table 149. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidelines for patients with current or a history of malignancy included in SmPC Section 4.4. In addition, Section 4.4 states that in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated NMSC) tofacitinib should only be used if no suitable treatment alternatives are available. Dose interruption and discontinuation in laboratory abnormalities including neutropenia and lymphopenia are included in SmPC Section 4.2. Information about ANC monitoring for Decrease in neutrophil counts and neutropenia is included in SmPC Section 4.4. Information about ALC monitoring for Decrease in lymphocyte counts and lymphopenia is included in SmPC Section 4.4. SmPC Section 4.4 states tofacitinib has not been studied and its use should be avoided in combination with biologics because of the possibility of increased immunosuppression and increased risk of infection.
Cardiovascular risk (excl MI)	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.1 Pharmacodynamic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Risk factors for MI are included in SmPC Section 4.4. In addition, Section 4.4, under MACE (including MI), states that in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease and other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available. Recommendations for lipid monitoring for Lipid elevations and hyperlipidaemia is included in SmPC Section 4.4.
GI perforation	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Text regarding the prompt evaluation of patients presenting with new onset abdominal signs and symptoms is included in SmPC Section 4.4.
ILD	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None.
PML	Not applicable

Table 149. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
All-cause mortality	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.1 Pharmacodynamic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 states that considering the increased risk of all-cause mortality with tofacitinib in patients 65 years of age and older, tofacitinib should only be used if no suitable treatment alternatives are available.
Fractures	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None.
Increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None.
Primary viral infection following live vaccination	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Text for patients to be brought up to date with all immunisations in agreement with current immunization guidelines prior to initiating treatment is included in SmPC Section 4.4.
Missing information	
Effects on pregnancy and the foetus	Routine risk communication SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy, and lactation
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Use in pregnant women is contraindicated and described in SmPC Section 4.3. Information for Effects on pregnancy and the foetus is included in SmPC Section 4.6 including text for the use of effective contraception during treatment with tofacitinib and for at least 4 weeks after the last dose in women of childbearing potential.
Use in breastfeeding	Routine risk communication SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy, and lactation

Table 149. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Use in breastfeeding is contraindicated and described in SmPC Section 4.3.
Effect on vaccination efficacy and the use of live/attenuated vaccines	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 includes text for patients to be brought up to date with all immunisations in agreement with current immunization guidelines.
Use in patients with mild, moderate, or severe hepatic impairment	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 5.2 Pharmacokinetic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Dosing recommendations for use in patients with moderate hepatic impairment is included in SmPC Section 4.2 Contraindication for use in patients with severe hepatic impairment is included in SmPC Section 4.3.
Use in patients with moderate or severe renal impairment	Routine risk communication SmPC Section 4.2 Posology and method of administration SmPC Section 5.2 Pharmacokinetic properties
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Dosing recommendations for use in patients with severe renal impairment is included in SmPC Section 4.2
Use in patients with evidence of hepatitis B or C infection	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 includes text for screening for viral hepatitis in accordance with clinical guidelines before starting therapy with tofacitinib.
Use in patients with malignancy	Routine risk communication SmPC Section 4.4 Special warnings and precautions for use

Table 149. Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidelines for patients with current or a history of malignancy is included in SmPC Section 4.4.
Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)	Routine risk communication None
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None

AE = adverse event; ALC = absolute leukocyte count; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DILI = drug-induced liver injury; DVT = deep vein thrombosis; Excl = excluding; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IBD = inflammatory bowel disease; ILD = interstitial lung disease; JIA = juvenile idiopathic arthritis; MACE = major adverse cardiovascular events; MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma skin cancer; PE = pulmonary embolism; pJIA = polyarticular juvenile idiopathic arthritis; PML = progressive multifocal leukoencephalopathy; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SmPC = Summary of Product Characteristics; TB = tuberculosis; UC = ulcerative colitis

V.2. Additional Risk Minimisation Measures

Patient Alert Card

Objectives:

The objective of the proposed additional measure is to provide an appropriate tool designed to enhance the awareness and knowledge of patients about the following safety concerns and to ensure the optimal use of tofacitinib.

- Venous thromboembolism (DVT/PE)
- Serious and other important infections
- Herpes zoster (HZ) reactivation
- Nonmelanoma skin cancer (NMSC)
- Transaminase elevation and potential for potential for drug-induced liver injury (DILI)
- Myocardial infarction
- Malignancy excluding NMSC
- Lung cancer
- Lymphoma

- Gastrointestinal (GI) Perforation
- Interstitial lung disease (ILD)
- Increased immunosuppression when used in combination with biologics and immunosuppressants including B-lymphocyte depleting agents
- Increased risk of AEs when tofacitinib is administered in combination with methotrexate (MTX) in RA or PsA
- Effects on pregnancy and the foetus
- Use in breastfeeding
- Effect on vaccination efficacy and the use of live/attenuated vaccines
- That patients 65 years of age and older should only use tofacitinib if no suitable treatment alternatives are available

Rationale for the additional risk minimisation activity:

Additional awareness and knowledge of patients about the risk will help to mitigate this risk.

Target audience and planned distribution path:

The target audience is patients via their prescribing physicians. The communication plan varies by local legal and regulatory requirements.

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

Routine pharmacovigilance activities to identify new safety signals and monitor reporting trends. Observational data sources (eg, prescriber survey and drug utilisation study) will be used to evaluate overall RMM effectiveness.

Risk Minimisation Measures (RMMs) are judged effective if no negative trends or worsening outcomes are identified.

Xeljanz Prescriber Brochure

Objectives:

The objective of the proposed additional measure is to provide an appropriate tool designed to enhance the awareness and knowledge of prescribers and patients about the following safety concerns and to ensure the optimal use of tofacitinib.

To accomplish the objective, Prescriber Information Pack was developed to inform prescribers about the risks and provide recommendations on how to mitigate the risk through appropriate monitoring and management.

- Venous thromboembolism (DVT/PE)
- Serious and other important infections
- HZ reactivation
- Decrease in Hgb levels and anaemia
- NMSC
- Transaminase elevation and potential for potential for DILI
- Cardiovascular risk (excl MI)
- MI
- Malignancy (excluding NMSC)
- Lymphoma
- Lung cancer
- GI Perforation
- ILD
- All-cause mortality
- Increased immunosuppression when used in combination with biologics and immunosuppressants including B-lymphocyte depleting agents
- Increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA
- Primary viral infection following live vaccination

- Higher incidence and severity of AEs in the elderly (≥65 years) including serious infections, myocardial infarction, malignancies, and all-cause mortality and that tofacitinib should only be used in these patients if no suitable treatment alternatives are available

- Effects on pregnancy and the foetus

- Use in breastfeeding

- Effect on vaccination efficacy and the use of live/attenuated vaccines

- Use in RA patients with mild, moderate, or severe hepatic impairment

Rationale for the additional risk minimisation activity:

Additional awareness and knowledge of physicians about the risks help to mitigate the risks.

Target audience and planned distribution path:

The target audience is prescribing physicians. The communication plan varies by local legal and regulatory requirements.

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

Routine PV activities to identify new safety signals and monitor reporting trends. Observational data sources (eg, prescriber survey and drug utilisation study) will be used to evaluate overall RMM effectiveness.

RMMs are judged effective, if no negative trends or worsening outcomes are identified from the registry studies. In addition, effectiveness of the aRMMs communication of the key risk messages associated with the use of tofacitnib to HCPs will be studied in the European prescriber survey. The European drug utilisation study will evaluate if there is evidence that prescribers in Europe are compliant with the recommendations and limitations for use described in the tofacitinib aRMM materials.

Prescriber Checklist

Objectives:

The objective of the proposed additional measure is to provide an appropriate tool designed to enhance the awareness and knowledge of prescribers about the safety concerns and to ensure the optimal use of tofacitinib.

To accomplish the objective, 2 treatment checklists: initiation checklist and maintenance checklists, were developed to be used prior to and during tofacitinib treatment. They intend to remind the prescriber of the risks associated with use of tofacitinib and the recommended tests before and during the tofacitinib treatment.

- Venous thromboembolism (DVT/PE)
- Serious and other important infections
- Decrease in Hgb levels and anaemia
- Transaminase elevation and potential for potential for DILI
- Cardiovascular risk (excl MI)
- MI
- Malignancy
- Lymphoma
- Lung cancer
- NMSC
- GI perforation
- ILD
- All-cause mortality
- Increased immunosuppression when used in combination with biologics and immunosuppressants including B-lymphocyte depleting agents
- Primary viral infection following live vaccination
- Effects on pregnancy and the foetus
- Use in breastfeeding
- Effect on vaccination efficacy and the use of live/attenuated vaccines
- Use in patients with mild, moderate, or severe hepatic impairment
- The existing key element of "relevant comorbidities for which caution is advised when tofacitinib is administered and conditions in which tofacitinib should not be administered" includes details on the patients at risk for MACE/MI and malignancy events (i.e., to avoid use of tofacitinib in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other cardiovascular risk factors or patients with risk factors for malignancies).

Rationale for the additional risk minimisation activity:

The rationale of the proposed additional measures is that additional awareness and knowledge of prescribers about the risks will help to mitigate this risk.

Target audience and planned distribution path:

The target audience is prescribing physicians. The communication plan varies by local legal and regulatory requirements.

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

Routine PV activities to identify new safety signals and monitor reporting trends. Observational data sources (eg, prescriber survey and drug utilisation study) will be used to evaluate overall RMM effectiveness.

RMMs are judged effective, if no negative trends or worsening outcomes are identified from the registry studies. In addition, effectiveness of the aRMMs communication of the key risk messages associated with the use of tofacitnib to HCPs will be studied in the European prescriber survey. The European drug utilisation study will evaluate if there is evidence that prescribers in Europe are compliant with the recommendations and limitations for use described in the tofacitinib aRMM materials.

V.3. Summary of Risk Minimisation Measures

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Venous thromboembolic events (DVT/PE)	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (Swedish National Quality Registry for Inflammatory Bowel Disease [SWIBREG] – A3921344, and the United Registries for Clinical Assessment and Research [UR-CARE] – A3921352), over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database. •A3921403: A drug utilisation study using French claims database (SNDS)
Serious and other important infections	<u>Routine risk minimisation measures:</u> SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
HZ reactivation	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
Lung cancer	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		[A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
Lymphoma	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	<u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
Myocardial infarction	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database. •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment)

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•A3921403: A drug utilisation study using French claims database (SNDS)
Decrease in Hgb levels and anaemia	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
NMSC	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years.

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
Transaminase elevation and potential for DILI	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Higher incidence and severity of AEs in the elderly	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years (incidence only for ARTIS, BIOBADASER, BSRBR) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years (incidence only).
Important Potential Risks		
Malignancy	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
Cardiovascular risk (excl MI)	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
GI perforation	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		•A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database.
ILD	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register
PML	Routine risk minimisation measures: Not applicable Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
All-cause mortality	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: • A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (in-hospital mortality)

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Fractures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (Swedish National Quality Registry for Inflammatory Bowel Disease [SWIBREG] – A3921344, and the United Registries for Clinical Assessment and Research [UR-CARE] – A3921352), over 5 years. •A3921347 (UC): A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database. •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry
Increased risk of AEs when tofacitinib is	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
administered in combination with MTX in RA or PsA patients	Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).	None Additional pharmacovigilance activities: •Prospective, non-interventional active surveillance safety study using 3 European RA registries (BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years (RA only).
Primary viral infection following live vaccination	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921427: Observational Study of Effectiveness and Safety of Recombinant Zoster Vaccine (Shingrix) in Moderately-to-Severely Active UC or RA Patients Treated with Tofacitinib (Xeljanz) in Real-World Clinical Care Settings
Missing Information		
Effects on pregnancy and the foetus	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy, and lactation Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Use in breastfeeding	Routine risk minimisation measures: SmPC Section 4.3 Contraindications SmPC Section 4.6 Fertility, pregnancy, and lactation Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Effect on vaccination efficacy and the use of live/attenuated vaccines	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).	Additional pharmacovigilance activities: None
Use in patients with mild, moderate, or severe hepatic impairment	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 4.3 Contraindications SmPC Section 5.2 Pharmacokinetic properties Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •A3921403: A drug utilisation study using French claims database (SNDS)
Use in patients with moderate or severe renal impairment	Routine risk minimisation measures: SmPC Section 4.2 Posology and method of administration SmPC Section 5.2 Pharmacokinetic properties Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with evidence of hepatitis B or C infection	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with malignancy	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •A3921403: A drug utilisation study using French claims database (SNDS)
Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or	Routine risk minimisation measures: None Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Additional pharmacovigilance activities:

Table 150. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
development disturbances)		•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Study A3921145: A Long Term, Open Label Follow Up Study of Tofacitinib for Treatment of JIA

AE = adverse event; ARTIS = Anti-rheumatic Therapies In Sweden; BIKER = German Biologics in Pediatric Rheumatology Registry; BIOBADASER = Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas; BSRBR = British Society For Rheumatology Biologics Register; CARRA = Childhood Arthritis and Rheumatology Research Alliance; DILI = drug-induced liver injury; DVT = deep vein thrombosis; EU = European Union; Excl = excluding; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IBD = inflammatory bowel disease; ILD = interstitial lung disease; JIA = juvenile idiopathic arthritis; JuMBO = Juvenile Arthritis Methotrexate/Biologics long-term Observation;MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma skin cancer; PASS = post-authorisation safety study; PE = pulmonary embolism; pJIA = polyarticular juvenile idiopathic arthritis; PML = progressive multifocal leukoencephalopathy; PRAC = Pharmacovigilance Risk Assessment Committee; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RABBIT = Rheumatoide Arthritis–Beobachtung Der Biologika-Therapie; RMM = risk minimisation measure; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease, TNF = tumour necrosis factor; UC = ulcerative colitis; UR-CARE = United Registries for Clinical Assessment and Research; US = United States

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Xeljanz (tofacitinib)

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

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

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

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

I. The Medicine and What It Is Used For

XELJANZ is authorised for the treatment of adults with moderate to severe active rheumatoid arthritis, active psoriatic arthritis, moderately to severely active ulcerative colitis, active polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis, and ankylosing spondylitis (see SmPC for the full indication). It contains tofacitinib citrate as the active substance and it is given by oral route of administration.

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

https://www.ema.europa.eu/en/medicines/human/EPAR/xeljanz

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

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

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

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly

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

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

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

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

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

II.A. List of Important Risks and Missing Information

Important risks of XELJANZ are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of XELJANZ. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 151. List of Important Risks and Missing Information

Important identified risks	Venous thromboembolic events (DVT/PE)
	Serious and other important infections
	HZ reactivation
	Lung cancer
	Lymphoma
	Myocardial infarction
	Decrease in Hgb levels and anaemia
	NMSC
	Transaminase elevation and potential for DILI
	Higher incidence and severity of AEs in the elderly
Important potential risks	Malignancy
	Cardiovascular risk (excl MI)
	GI perforation
	ILD
	PML
	All-cause mortality
	Fractures
	Increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients
	Primary viral infection following live vaccination
Missing information	Effects on pregnancy and the foetus
	Use in breastfeeding

Table 151. List of Important Risks and Missing Information

	Effect on vaccination efficacy and the use of live/attenuated vaccines
	Use in patients with mild, moderate, or severe hepatic impairment
	Use in patients with moderate or severe renal impairment
	Use in patients with evidence of hepatitis B or hepatitis C infection
	Use in patients with malignancy
	Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)

AE = adverse event; DILI = drug-induced liver injury; DVT = deep vein thrombosis; Excl = excluding; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IBD = inflammatory bowel disease; ILD = interstitial lung disease; JIA = juvenile idiopathic arthritis; MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma skin cancer; pJIA = polyarticular juvenile idiopathic arthritis; PE = pulmonary embolism; PML = progressive multifocal leukoencephalopathy; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RMP = risk management plan

II.B. Summary of Important Risks and Missing Information

Table 152. Summary of Important Risks and Missing Information

Important Identified Risk: Venous thromboembolic events (DVT/PE)	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Venous thromboembolism was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors in Study A3921133 (patients with RA aged 50 years and older with at least one CV risk factor). No differential risk factors were identified for the increased risk relative to TNF inhibitors. Numerous VTE risk factors are known in the general population. These known VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (body mass index [BMI] ≥30), diabetes, hypertension, smoking status should also be considered. Pediatric JIA patients can experience many of the risk factors seen in adults. In a review article it is noted that in children aged 2 to <18 years with JIA, cardiovascular risk factors including hypertension, dyslipidaemia and being less physically active are more frequent than in their healthy peers. JIA patients may also have other cardiovascular risk factors seen in adult RA such as obesity, diabetes, and smoking. JIA patients potentially could have other risk factors (e.g., adolescent contraceptive hormone use, major surgeries, immobilization, congenital and acquired thrombophilias), which may increase their risk of such events. Published literature suggest a higher prevalence of anticardiolipin antibodies positive, or elevated levels of coagulation factors in JIA patients compared with non-JIA patients; however, these findings were not correlated with clinical features such as abnormal clotting test or anticardiolipin antibody syndrome. Data also suggest an increased risk of malignancy among JIA patients compared with non-JIA patients. In a retrospective cohort study based in the Swedish Cancer Register, the HR (95% CI) for all pediatric malignancies in JIA vs the general population was 1.43 (0.71-2.88). Summary of results from the US Corrona RA Registry A3921205: The overall number of VTE events in the tofacitinib group with moderate-to-severe disease was small and the rate [0.18 (0.04, 0.51)] was similar to the bDMARD group [0.32 (0.20, 0.47)]. The

Table 152. Summary of Important Risks and Missing Information

	risk factors associated with VTE were generally similar between tofacitinib and bDMARD groups and were consistent with the known risk factors for VTE (e.g., advanced age). In patients with moderate-to-severe disease aged 50 years and older with at least one CV risk factor, the crude incidence rate (95% CI) was 0.22 (0.03, 0.78) in tofacitinib initiators compared with 0.51 (0.31, 0.80) for bDMARDs initiators.
Risk minimisation measures	Routine risk communication: SmPC Sections 4.4, 4.8, and 5.1 Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC) •A3921403: A drug utilisation study using French claims database (SNDS)
Important Identified Risk: Serious and other important infections	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Risk factors/groups for serious infections include patients who are elderly or diabetic, patients that use drugs along with tofacitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts in their blood, and patients from certain Asian countries. Summary of results from the US Corrona RA Registry A3921205: The risk factors associated with serious infection events were similar between tofacitinib and bDMARD groups in patients with moderate-to-severe disease (such as history of hypertension, history of diabetes mellitus, age 70+, age 60+). The rates of serious infection events were higher without overlapping 95% CI in patients 65 and older than in patients younger than 65 in both tofacitinib initiators [<65 years: 2.03 (1.35, 2.94); ≥65 years: 5.1 (3.57, 7.06)] and bDMARD initiators [<65 years: 2.15 (1.8, 2.54); ≥65

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	years: 4.54 (3.85, 5.33)]. The 95% CI overlapped between the tofacitinib group ≥65 years and bDMARD group ≥65 years.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, 4.8, and 5.1 Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Identified Risk: HZ reactivation	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	There is a higher rate of herpes zoster in Japanese and Korean patients. Patients who have had rheumatoid arthritis for many years, were elderly or have previously used two or more medicines that depress the immune system, including so called targeted biologic (antibody) therapies, such as those that inhibit tumour necrosis factor, and corticosteroids also have an increased risk. Patients with a low white blood cell (lymphocyte) count may have an increased risk of herpes zoster.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register

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	•Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Identified Risk: Lung cancer	
Evidence for linking the risk to the medicine	Clinical trial data (A3921133)
Risk factors and risk groups	Patients with RA may be at higher risk than the general population for the development of lung cancer. In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer, lymphoma, and an increase in NMSC was observed with tofacitinib compared to TNF inhibitors. Summary of Study A3921133 results: an increase in malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with tofacitinib compared to TNF inhibitor. The IRs of lung cancer per 100 PY (95% CI) (based on total time) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All tofacitinib, and TNFi groups, respectively, were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), 0.28 (0.19, 0.39), 0.13 (0.05, 0.26).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)

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Important Identified Risk: Lymphoma	
Evidence for linking the risk to the medicine	Clinical trial data (A3921133)
Risk factors and risk groups	Patients with RA, particularly those with highly active disease, may be at higher risk (up to several fold) than general population for the development of lymphoma. In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer, lymphoma, and an increase in NMSC was observed with tofacitinib compared to TNF inhibitors. Summary of Study A3921133 results: an increase in malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with tofacitinib compared to TNF inhibitor. The IRs of lymphoma per 100 PY (95% CI) (based on total time) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All tofacitinib, and TNFi groups, respectively, were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), 0.09 (0.04, 0.17), 0.02 (0.00, 0.10).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Identified Risk: Myocardial infarction	
Evidence for linking the risk to the medicine	Clinical trial data (A3921133)
Risk factors and risk groups	In Study A3921133, a large, randomised active-controlled post authorisation safety surveillance study of RA patients who were 50 years of age and older and had at least

Table 152. Summary of Important Risks and Missing Information

	one additional cardiovascular risk factor, the following predictive factors for development of MI (fatal and non-fatal) were identified using a multivariate Cox model with backward selection: age ≥65 years, male, current or past smoking, history of diabetes, and history of coronary artery disease (which includes myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures). Summary of Study A3921133 results: an increase in incidence of non-fatal MI was observed with tofacitinib compared to TNFi. The IRs of adjudicated non-fatal MI per 100 PY (95% CI) (based on 60 days risk period) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All tofacitinib, and TNFi groups, respectively, were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), 0.35 (0.24, 0.48), 0.16 (0.07, 0.31). The IRs of adjudicated fatal MI per 100 PY (95% CI) (based on 60 days risk period) for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All tofacitinib, and TNFi groups, respectively, were 0.00 (0.00, 0.07), 0.06 (0.01, 0.18), 0.03 (0.01, 0.09), 0.06 (0.01, 0.17).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •A3921403: A drug utilisation study using French claims database (SNDS)
Important Identified Risk: Decrease in Hgb levels and anaemia	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	No risk groups have been identified.

Table 152. Summary of Important Risks and Missing Information

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8. Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None.
Important Identified Risk: NMSC	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	In the RA programme, NMSC primarily occurred in sun-exposed areas of the body including the face/head and hands. The commonly reported risk factors of NMSC include sun exposure (i.e., ultraviolet), medications that suppress the immune system, light therapy, virus infections (eg, human papilloma virus), age, and certain types of radiation. In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer, lymphoma, and an increase in NMSC was observed with tofacitinib compared to TNF inhibitors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
Important Identified Risk: Transaminase elevation and potential for DILI	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.

Table 152. Summary of Important Risks and Missing Information

Risk factors and risk groups	Use of other medications (called DMARDs) to treat RA or to treat PsA at the same time as tofacitinib.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None
Important Identified Risk: Higher incidence and severity of AEs in the elderly	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, patients 65 years of age and older had an increased risk of serious infections, MI, malignancies, and all-cause mortality with tofacitinib.
Risk minimisation measures	Routine risk communication: SmPC Sections 4.2, 4.4, 4.8, and 5.1. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years (incidence only for ARTIS, BIOBADASER, BSRBR) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years (incidence only).
Important Potential Risk: Malignancy	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	The risk of malignancy (cancer) in general is increased in the elderly population. In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies particularly NMSC, lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors. The following predictive factors for development of malignancies excluding NMSC were identified using a Multivariate Cox model with backward selection: age ≥65 years and current or past smoking. Summary of results from the US Corrona RA Registry A3921205: The rates of malignancy excluding NMSC were higher without overlapping 95% CI in patients 65 and older than in patients younger than 65 in both tofacitinib and bDMARD initiator groups. The rate of malignancy excluding NMSC in patients 65 and older in tofacitinib initiators was 1.77 (95%CI=1.17, 2.57) and the rate in bDMARD initiators was 1.22 (95% CI=0.95, 1.55); the 95% CI overlapped.

Table 152. Summary of Important Risks and Missing Information

	Summary of Study A3921133 results: an increase in malignancies (excluding NMSC), particularly lymphoma and lung cancer, was observed with tofacitinib compared to TNFi. This increased risk was predominantly observed in older patients and in patients who are current or past smokers. The IR per 100 PY (95% CI) (based on total time) of adjudicated malignancies (excluding NMSC) in adults aged ≥65 years or who had ever smoked for the tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 1.38 (1.01, 1.82), 1.59 (1.19, 2.07), 1.48 (1.21, 1.80), and 0.96 (0.66, 1.34). In patients who were less than 65 years of age and had never smoked, the IR per 100 PY (95% CI) (based on total time) for malignancies excluding NMSC for tofacitinib 5 mg BID, tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.70 (0.38, 1.17), 0.31 (0.12, 0.68), 0.51 (0.31, 0.79), and 0.44 (0.20, 0.84).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. SmPC Section 5.1. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Potential Risk: Cardiovascular risk (excl MI)	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Patients with autoimmune diseases have an increased risk for cardiovascular disorders. The risk of cardiovascular events in general is increased in the elderly population. Tofacitinib has been associated with increased cholesterol, high blood pressure (hypertension), and weight gain, which are known risk factors for cardiovascular events.

Table 152. Summary of Important Risks and Missing Information

	In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of MACE was observed with tofacitinib compared to TNF inhibitors. Summary of results from the US Corrona RA Registry A3921205: The rates of MACE were higher in patients 65 and older than in patients younger than 65 in both tofacitinib and bDMARD initiator groups, with overlapping 95% CIs. The rate of MACE in patients 65 and older in tofacitinib initiators was 1.23 (95%CI=0.56, 2.34) and the rate in bDMARD initiators was 1.43 (95% CI=1.06, 1.89); the 95% CI overlapped.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. SmPC Section 5.1. Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Potential Risk: GI perforation	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Patients with painful inflammation of small pockets in the lining of the intestine (diverticulitis) or patients who also take nonsteroidal anti-inflammatory drugs or corticosteroids (eg, prednisone) may be at higher risk.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).

Table 152. Summary of Important Risks and Missing Information

Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Potential Risk: ILD	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Patients living in Asian countries.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register
Important Potential Risk: PML	
Evidence for linking the risk to the medicine	PML has been reported in some patients taking other medications that depress the immune system.
Risk factors and risk groups	Patients taking other medications along with tofacitinib that also depress the immune system.
Risk minimisation measures	Routine risk communication: Not applicable Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry

Table 152. Summary of Important Risks and Missing Information

	•A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
Important Potential Risk: All-cause mortality	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Mortality in patients treated with tofacitinib was mainly due to cardiovascular events, infections, and malignancies. Risk factors/groups for serious infections include patients who are elderly or diabetic, patients that use drugs along with tofacitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts, and patients from certain Asian countries. The risk of cardiovascular events in general is increased in the elderly population. Tofacitinib has been associated with increased cholesterol, high blood pressure (hypertension), and weight gain, which are known risk factors for cardiovascular events. The risk of malignancy (cancer) in general is increased in the elderly population. There are no known tofacitinib-associated risk factors for malignancy (cancer). In Study A3921133, a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increase in non-fatal MI, lung cancer, lymphoma, VTE, and NMSC was observed in patients treated with tofacitinib compared to TNF inhibitor. Summary of results from the US Corrona RA Registry A3921205: The risk factors found to be associated with an increased risk of mortality events were in general similar among tofacitinib initiators and bDMARD initiators with moderate-to-severe disease (such as history of hypertension, history of coronary artery disease, history of VTE, age 70+, age 60+). In patients aged 50 years and older with moderate-to-severe disease with at least one CV risk factor, the incidence rates (95% CI) were comparable among tofacitinib initiators and bDMARD initiators.
Risk minimisation measures	<u>Routine risk communication</u> SmPC Section 4.4 SmPC Section 5.1 <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers

Table 152. Summary of Important Risks and Missing Information

	•A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Potential Risk: Fractures	
Evidence for linking the risk to the medicine	Corrona RA registry Study A3921205 and Study A3921133
Risk factors and risk groups	Elderly patients, female patients, and patients with corticosteroid use.
Risk minimisation measures	Routine risk communication SmPC Section 4.4. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	•Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (Swedish National Quality Registry for Inflammatory Bowel Disease [SWIBREG] – A3921344, and the United Registries for Clinical Assessment and Research [UR-CARE] – A3921352), over 5 years. •A3921347: A drug utilization and active surveillance post-authorisation study in the US using data from an administrative health claims database (UC) •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry
Important Potential Risk: Increased risk of AEs when tofacitinib is administered in combination with MTX in RA or PsA patients	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Subjects on tofacitinib and methotrexate together may be at higher risk of developing adverse events.

Table 152. Summary of Important Risks and Missing Information

Risk minimisation measures	Routine risk communication: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).
Additional pharmacovigilance activities	•Prospective, non-interventional active surveillance safety study using 3 European RA registries (BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years (RA only).
Important Potential Risk: Primary viral infection following live vaccination	
Evidence for linking the risk to the medicine	A3921237 study report.
Risk factors and risk groups	In general, patients treated with medications that depress the immune system are at an increased risk of developing a viral infection after getting a live vaccine. This is possible when there is not enough time between live vaccination and starting the medication that depresses the immune system or with zoster vaccination, where the patients have not had chicken pox in the past.
Risk minimisation measures	Routine risk communication: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921427: Observational Study of Effectiveness and Safety of Recombinant Zoster Vaccine (Shingrix) in Moderately-to-Severely Active UC or RA Patients Treated with Tofacitinib (Xeljanz) in Real-World Clinical Care Settings
Missing Information: Effects on pregnancy and the foetus	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.3 and 4.6. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None
Missing Information: Use in breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.3 and 4.6. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None

Table 152. Summary of Important Risks and Missing Information

Missing Information: Effect on vaccination efficacy and the use of live/attenuated vaccines	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None
Missing Information: Use in patients with mild, moderate, or severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, and 5.2. Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •A3921403: A drug utilisation study using French claims database (SNDS)
Missing Information: Use in patients with moderate or severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2. Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	None
Missing Information: Use in patients with evidence of hepatitis B or hepatitis C infection	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	None
Missing Information: Use in patients with malignancy	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	•A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •A3921403: A drug utilisation study using French claims database (SNDS)c

Table 152. Summary of Important Risks and Missing Information

Missing Information: Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Study A3921145: A Long Term, Open Label Follow Up Study of Tofacitinib for Treatment of JIA

ARTIS = Anti-rheumatic Therapies in Sweden; BID = twice daily; BIKER = German Biologics in Pediatric Rheumatology Registry; BIOBADASER = Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas; BSRBR = British Society for Rheumatology Biologics Register; CARRA = Childhood Arthritis and Rheumatology Research Alliance; CI = confidence interval; CV = cardiovascular; DMARD = disease-modifying anti-rheumatic drug; EU = European Union; Excl = excluding; IR = incidence rate; JIA = juvenile idiopathic arthritis; JuMBO = Juvenile Arthritis Methotrexate/Biologics long-term Observation; MI = myocardial infarction; NMSC = non-melanoma skin cancer; OI = opportunistic infection; PASS = post-authorisation safety studies; PE = pulmonary embolism; pJIA = polyarticular juvenile idiopathic arthritis; PML = progressive multifocal leukoencephalopathy; PRAC = Pharmacovigilance Risk Assessment Committee; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RABBIT = Rheumatoide Arthritis: Beobachtung der Biologika-Therapie; RMM = risk minimisation measure; RMP = Risk Management Plan; SmPC = summary of product characteristics; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease; TNF = tumour necrosis factor; UC = ulcerative colitis; UR-CARE = United Registries for Clinical Assessment and Research; US = United States

II.C. Post-Authorisation Development Plan

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

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

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

- Category 3 (required additional pharmacovigilance activities): 17

    - Study A3921321 is an EU-based drug utilisation study using electronic health care records. The research question is: Is there evidence that prescribers in the EU are compliant with the recommendations and limitations for use described in the tofacitinib aRMM materials? The primary objectives include 1. Describe the characteristics of patients treated with tofacitinib, stratified by study country (i.e., Sweden, Hungary, the Netherlands and Germany) and indication (i.e., RA, PsA, and UC; off-label indications), in terms of demographics (e.g., age, sex) and

comorbidities and prior and current medication use. 2. Evaluate prescribers' adherence to the tofacitinib aRMMs, specifically compliance to the recommended posology per indication (average daily dose) and duration of use; compliance to patient screening and laboratory monitoring prior to and during tofacitinib treatment; and compliance to recommendations for limitations of use, including use in patients with VTE risk factors, use in patients aged 65 years and older, use in patients with CV risk factors, use in patients with malignancy risk factors, contraindicated use, and use with concomitant medications not compatible with tofacitinib. The secondary objectives are to 1. Describe prescribing patterns over time; and 2. To describe changes in the utilisation of tofacitinib following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral and the 2021 signal evaluation procedure, specifically: use in patients with VTE risk factors; use in the elderly (patients aged 65 years and older), use in patients with CV risk factors, and use in patients with malignancy risk factors.

- Study A3921314 is a prospective, non-interventional active surveillance study embedded within the ARTIS registry. This study is being conducted to describe safety outcomes among RA patients treated with tofacitinib and other new advanced targeted therapies in real-world clinical use in ARTIS (Sweden). It will address the concerns of venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, higher incidence of AEs in elderly patients (≥65 years) including infections.

- Study A3921312 is a prospective, non-interventional active surveillance study embedded within the BSRBR registry. This study is being conducted to describe safety outcomes among RA patients treated with tofacitinib versus other new advanced targeted therapies in real-wold clinical use in BSRBR (UK). It will address the concerns of venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence of AEs in elderly patients (≥65 years) including infections.

- Study A3921317 is a prospective, non-interventional active surveillance study embedded within the RABBIT registry. This study is being conducted to describe safety outcomes among RA patients treated with tofacitinib versus other new advanced targeted therapies in real-wold clinical use in RABBIT (German). It will address the concerns of venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of AEs in elderly patients (≥65 years) including infections.

- Study A3921316 is a prospective, non-interventional active surveillance study embedded within the BIOBADASER registry. This study is being conducted to describe safety outcomes among RA patients treated with tofacitinib versus other new advanced targeted therapies in real-wold clinical use in BIOBADASER (Spain). It will address the concerns of venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with tofacitinib in combination use of MTX, higher incidence of AEs in elderly patients (≥65 years) including infections.

- Study A3921344 and Study A3921352 are prospective, non-interventional active surveillance studies in 2 European UC registries (SWIBREG and UR-CARE, respectively) over at least 5 years to further understand and characterise the safety profile of tofacitinib within the clinical practice setting. Safety concerns addressed include venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), cardiovascular risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, higher incidence and severity of adverse events in elderly patients (≥65 years) including infections. Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.

- Study A3921347 is a drug utilisation and active surveillance, post-authorisation study in the US, to assess tofacitinib utilisation patterns in the US and to characterise the safety of tofacitinib use in patients with moderately to severely active UC in the real-world setting using data from a US administrative healthcare claims database. Safety concerns for the active surveillance portion of the study include venous thromboembolism (deep vein thrombosis and pulmonary embolism), in-hospital mortality, fractures, malignancies (including lymphoma and lung cancer), opportunistic and serious infections, herpes zoster, major adverse cardiovascular endpoints, MI, and gastrointestinal perforations. Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.

- A3921427: Observational Study of Effectiveness and Safety of Recombinant Zoster Vaccine (Shingrix) in Moderately-to-Severely Active UC or RA Patients Treated with Tofacitinib (Xeljanz) in Real-World Clinical Care Settings. This study will address safety outcomes following vaccination with recombinant adjuvanted zoster vaccine. .

- Study A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and the Juvenile Arthritis Methotrexate/Biologics long-term Observation [JuMBO] registryA3921407. This study is a planned study in the EU that will help to contextualise the rates of safety events [venous thromboembolism, serious infections and other important infections (including opportunistic infection, tuberculosis and vaccine preventable infections), all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer, GI perforations, major adverse cardiac events

(including MI), long-term safety in pJIA patients and juvenile PsA patients (for example, growth or development disturbances), PML, hypersensitivity, all-cause mortality, fractures, HZ reactivation, NMSC, and ILD observed among tofacitinib-treated pJIA patients and juvenile PsA patients. To assess long-term safety, a minimum of 5 years follow-up is planned.

- Study A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers. This study will help to contextualise the rates of safety events [venous thromboembolism, serious infections and other important infections (including opportunistic infection, tuberculosis), all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer, GI perforations, major cardiac adverse events (including MI), long-term safety in pJIA patients and juvenile PsA patients [PML, all-cause mortality, fractures, HZ reactivation, NMSC, and ILD] observed among tofacitinib-treated pJIA patients and juvenile PsA patients. To assess long-term safety, a minimum of 5 years follow-up is planned.

- Study A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register. This study will help to contextualise the rates of safety events [venous thromboembolism, serious infections and other important infections (including opportunistic infections, tuberculosis and vaccine preventable infections), all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer, GI perforations, major cardiac adverse events (including MI), long-term safety in pJIA patients and juvenile PsA patients [for example, growth or development disturbances], hypersensitivity, PML, all-cause mortality, fractures, HZ reactivation, NMSC, and ILD observed among tofacitinib-treated pJIA patients and juvenile PsA patients. To assess long-term safety, a minimum of 5 years follow-up is planned.

- Study A3921371: An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry: this planned study is a long-term observational safety study to evaluate the risk of all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer, major cardiac adverse events (including MI), serious infections (including opportunistic infections), venous thromboembolism, fractures, and long-term safety in pJIA patients (for example, growth or development disturbances) in the US.

- Study A3921145 (A Long Term, Open Label Follow Up Study of Tofacitinib for Treatment of JIA) is an on-going Phase 2/3 study being conducted to address long-term safety and tolerability in pJIA and juvenile PsA patients (e.g., growth or development disturbances). This study will also evaluate the persistence of efficacy of tofacitinib for treatment of the signs and symptoms of JIA.

- Study A3921403: A Post-Authorisation Safety Study of the Utilisation and Prescribing Patterns of Xeljanz (tofacitinib) Using an Administrative Healthcare Database in France. This is a drug utilisation study that complements Study A3921321 to assess the effectiveness of aRMMs using secondary data. Safety concerns include venous thromboembolic events (eg, use of tofacitinib in patients with VTE risk factors), patients with mild, moderate, or severe hepatic impairment, MI (eg, use of tofacitinib patients with cardiovascular risk factors), and use in patients with malignancy risk factors.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated Summary of Planned, On-going, and Completed Pharmacovigilance Study Programme

Annex 3 – Protocols for Proposed, On-going, and Completed Studies in the Pharmacovigilance Plan

Annex 4 – Specific Adverse Drug Reaction Follow-up Forms

Annex 5 – Protocols for Proposed and On-going Studies in RMP Part IV

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 – Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Approved key messages of the additional risk minimisation measures

Prior to launch of XELJANZ in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The MAH shall ensure that in each Member State where XELJANZ is marketed, healthcare professionals who intend to prescribe XELJANZ have been provided with an educational package.

The main objective of the programme is to increase awareness about the risks of the product, specifically in regards to all-cause mortality, serious infections, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), cardiovascular risk (excluding myocardial infarction [MI]), MI, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy (particularly lymphoma and lung cancer), NMSC, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities.

The MAH shall ensure that in each Member State where XELJANZ is marketed, all healthcare professionals and patients/carers who are expected to prescribe or use XELJANZ have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

- **The physician educational material** should contain:
    - The Summary of Product Characteristics
    - Guide for healthcare professionals
    - Prescriber checklist
    - Patient alert card
    - A reference to the website with the educational material and patient alert card

- **The Guide for healthcare professionals** shall contain the following key elements:
    - Relevant information of the safety concerns addressed by the aRMM (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable)
    - Details of the population at higher risk for the safety concern addressed by the aRMM (i.e. contraindications, risk factors, increased risk by interactions with certain medicine)
    - Details of the populations at higher risk for VTE, cardiovascular risk including MI, and malignancy (including lymphoma and lung cancer)
    - Details on use of XELJANZ in patients 65 years of age and older, including information on the specific risks in this population (e.g. serious infections, myocardial infarction, malignancy, all-cause mortality), and details on how to

minimise the risks of tofacitinib in patients 65 years of age and older in clinical practice, i.e. the recommendation that tofacitinib should only be used in patients 65 years of age and older if no suitable treatment alternatives are available.
    - Details on how to minimise the safety concerns addressed by the aRMM through appropriate monitoring and management (i.e. who may receive the medicine, what to do, what not do, and who is most likely be impacted according to different scenarios, like when to limit or stop prescribing/ingestion, how to administer the medicine, when to increase/decrease the dose according to laboratory measurements, signs and symptoms)
    - Details on how to minimise the risks of VTE, cardiovascular risk including MI, and malignancy (including lymphoma, lung cancer and NMSC) in clinical practice, i.e.:
        - VTE: Tofacitinib should be used with caution in patients with known VTE risk factors.
        - MACE and MI: In patients 65 years of age and older, patients who are current or past long-time smokers and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.
        - Malignancies: In patients 65 years of age and older, patients who are current or past long-time smokers and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer), tofacitinib should only be used if no suitable treatment alternatives are available.
        - Posology UC maintenance treatment: Tofacitinib 10 mg twice daily is not recommended for maintenance treatment in patients with UC who have known VTE, MACE and malignancy risk factors, unless there is no suitable alternative treatment available.
    - Key message to convey in patients counselling
    - Instructions on how to handle possible adverse events
    - Information about the BSRBR, ARTIS, RABBIT, BIODABASER, UC registries, and polyarticular juvenile idiopathic arthritis (pJIA) and juvenile psoriatic arthritis registries and the importance of contributing to these
    - Vaccination course to be completed before treatment as it is recommended that live vaccines not be given concurrently with tofacitinib

- **The Prescriber checklist** shall contain the following key messages:
    - Lists of tests to be conducted during the initial screening and maintenance of the patient
    - Vaccination course to be completed before treatment
    - A specific reference to the fact that the patient has been informed and understands that tofacitinib is contraindicated during pregnancy and breast-feeding and women of childbearing potential should use effective contraception during treatment with tofacitinib and for at least 4 weeks after the last dose
    - That the benefit risk of tofacitinib should be discussed with the patient, and the patient alert card should be given to and discussed with the patient

- Relevant comorbidities for which caution is advised when XELJANZ is administered and conditions in which XELJANZ should not be administered
- Guidance to minimise the risk of cardiovascular events including MI and malignancy (lymphoma, lung cancer, and NMSC), i.e.:
    - MACE and MI: In patients 65 years of age and older, patients who are current or past long-time smokers and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.
    - Malignancies: In patients 65 years of age and older, patients who are current or past long-time smokers and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer), tofacitinib should only be in these patients if no suitable treatment alternatives are available.
    - Guidance that in patients 65 years of age and older tofacitinib should only be used in these patients if no suitable treatment alternatives are available.
- List of concomitant medications which are not compatible with treatment with XELJANZ
- The need to discuss with the patients the risks associated with the use of XELJANZ, specifically in regards to all-cause mortality, infections, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), cardiovascular risk (excluding MI), MI, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy (including lymphoma and lung cancer), gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities
- The need to monitor for any signs and symptoms and laboratory abnormalities for early identification of the abovementioned risks

- **The Patient alert card** shall contain the following key messages:
    - A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using XELJANZ
    - That treatment with XELJANZ may increase the risk of infections, malignancies (including lung cancer, lymphoma), and non-melanoma skin cancer
    - That patients should inform health professionals if they are planning to receive any vaccine or become pregnant
    - Signs or symptoms of the following safety concern and/or when to seek attention from a HCP: infections, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), myocardial infarction (MI), herpes zoster reactivation, malignancies (including lung cancer, lymphoma), non-melanoma skin cancer, transaminase elevation and potential for drug-induced liver injury, gastrointestinal perforation, interstitial lung disease, increased immunosuppression when used in combination with biologics and immunosuppressants including B lymphocyte depleting agents, increased risk of adverse events when XELJANZ is administered in combination with MTX, effects on pregnancy and foetus, use in breast-feeding, effect on vaccination efficacy and the use of live/attenuated vaccines.
    - Contact details of the prescriber

- **The website repository** shall contain:
    - The educational material in digital format
    - The patient alert card in digital format

- **The patient information pack** should contain:
    - Patient information leaflet
    - The patient alert card
    - Instructions for use