EU Risk Management Plan
Tyenne (Tocilizumab)

Marketing Authorization Holder (MAH)	Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg Germany
EU RMP Version Number	1.1
Data lock point for this RMP	01-Apr-2026
Date of Final Sign-Off	See QPPV signature section below
Rationale for submitting an updated RMP	RMP has been updated in-line with the originator
Summary of significant changes in this RMP	Part I: Product(s) Overview: Updated as per data from originator and to ensure alignment with updated PI. Part II: Module SI - Epidemiology of the indication(s) and target population(s): Updated as per data from originator Part II: Module SIV - Population not studied in clinical trials: Updated as per data from originator Part II: Module SV - Post-authorisation experience is updated SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP updated with rationale for reclassification of *Thrombocytopenia and the potential risk of bleeding* and *Demyelinating disorders* as potential risks not categorized as important Part II: Module SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks: Details of important potential risk of *Thrombocytopenia and the Potential Risk of Bleeding* and *Demyelinating Disorders* have been deleted. Part II: Module SVIII - Summary of the safety concerns: Important potential risk of *Thrombocytopenia and the Potential Risk of Bleeding* and *Demyelinating Disorders* have been removed. Part V.1 Routine risk minimization measures updated Part V.2. Additional Risk Minimization Measures updated with new template requirement to present the rationale supporting the “Removal of additional risk minimization activities

	Part V.3 Summary of Risk Minimization measures: Important potential risk of *Thrombocytopenia and the Potential Risk of Bleeding* and *Demyelinating Disorders* have been removed, Annex 4 – Specific adverse drug reaction follow-up forms for demyelination events and spontaneous or serious/non-serious bleeding events have been removed due to reclassification of the risks Annex 6: Updated to remove the information related to the distribution of educational materials as additional risk minimization measures except the patient card.
Other RMP versions under evaluation	Not applicable
Details of the currently approved RMP	Version 0.2, Centralised procedure in EU, approved on 19 Feb 2024, procedure EMEA/H/C/005781/IB/0002
Deputy-QPPV name	Ana Rita Barata
Deputy QPPV signature	
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization applicant´s Deputy QPPV.

Confidential

The information contained in this report is confidential and is intended solely for the addressee and associated reviewers. Access to this report by anyone else is unauthorized. If you are not the intended recipient, any disclosure, copying, distribution or any action taken in reliance on it is prohibited and may be unlawful.

Table of contents

List of tables

Abbreviations

Abbreviation	Definition/Description
AESI	Adverse Event of Special Interest
AE	Adverse Events
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
CAR	Chimeric Antigen Receptor
COVID-19	Coronavirus disease 2019
CRS	Cytokine Release Syndrome
CS	Corticosteroids
DILI	Drug-induced Liver Injury
DNA	Deoxyribonucleic Acid
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicine Agency
EPAR	European Public Assessment Report
EU	European Union
EUAs	Emergency Use Authorizations
FDA	Food and Drug Administration
GCA	Giant Cell Arteritis
GI	Gastrointestinal
GM CSF	Granulocyte macrophage–colony stimulating factor
HLA	Human Leukocyte Antigen
IFN-γ	Interferon Gamma
IgG1	Immunoglobulin G1
IL-6	Interleukin-6
ILD	Interstitial Lung Disease
IV	Intravenous
JIA	Juvenile Idiopathic Arthritis
MA	Marketing Authorization
MAS	Macrophage Activation Syndrome

Abbreviation	Definition/Description
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mIL-6R	Membrane-bound IL-6 receptors
MTX	Methotrexate
NIAID	National Institute of Allergy and Infectious Diseases
NSAID	Non-Steroidal Anti-Inflammatory Drug
PBRER	Periodic Benefit-Risk Evaluation Report
pJIA	Polyarticular Juvenile Idiopathic Polyarthritis
PIL	Patient Information Leaflet
PT	Preferred Term
PY	Person Years
RA	Rheumatoid Arthritis
RDV	Remdesivir
RF	Rheumatoid Factor
RMM	Risk Minimization Measure
RMP	Risk Management Plan
SAEs	Serious Adverse Events
SC	Subcutaneous
sIL-6R	Soluble IL-6 Receptors
sJIA	Systemic Juvenile Idiopathic Arthritis
SmPC	Summary of Product Characteristics
SMQs	Standardized Medical Dictionary for Regulatory Activities Queries
STAT3	Signal transducer and activator of transcription 3
TB	Tuberculosis
TCZ	Tocilizumab
TNF	Tumour Necrosis Factor
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell

Part I: Product(s) Overview

Product(s) Overview

Active substance(s) **(INN or common name)**	Tocilizumab
Pharmacotherapeutic group(s) (ATC Code)	L04AC07
Marketing Authorization Applicant	Fresenius Kabi Deutschland GmbH
Medicinal products to which this RMP refers	1
Invented name(s)	TYENNE
Marketing authorization procedure	Centrally Authorized Procedure
Brief description of the product	Chemical class Immunosuppressants, Interleukin inhibitors/ Anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class
	Summary of mode of action Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of hemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.
	Important information about its composition Tocilizumab is a humanised IgG1 monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant deoxyribonucleic acid (DNA) technology
Hyperlink to the Product Information	Refer to Module 1.3.1 Product Information
Indication(s) (global)	Current:

	Intravenous (IV) Administration Rheumatoid arthritis (RA) Tyenne, in combination with methotrexate (MTX), is indicated for • the treatment of severe, active and progressive RA in adults not previously treated with MTX. • the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate. Coronavirus disease 2019 (COVID-19) Tyenne is indicated for the treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. Systemic juvenile idiopathic arthritis (sJIA) Tyenne is indicated for the treatment of active sJIA in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tyenne can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. Polyarticular juvenile idiopathic arthritis (pJIA) Tyenne in combination with MTX is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Cytokine release syndrome (CRS)

	Tyenne is indicated for the treatment of chimeric antigen receptor (CAR) T cell induced severe or life-threatening CRS in adults and paediatric patients 2 years of age and older. Subcutaneous (SC) Administration Rheumatoid arthritis (RA) Tyenne, in combination with methotrexate (MTX), is indicated for • the treatment of severe, active and progressive RA in adults not previously treated with MTX. • the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate. Systemic juvenile idiopathic arthritis (sJIA) Tyenne is indicated for the treatment of active sJIA in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Tyenne can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. Polyarticular juvenile idiopathic arthritis (pJIA) Tyenne in combination with MTX is indicated for the treatment of pJIA (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tyenne can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Giant cell arteritis (GCA) Tyenne is indicated for the treatment of GCA in adult patients.
	Proposed: Not Applicable

Dosages	Current: IV Administration *RA Patients* The recommended posology is 8 mg/kg body weight, given once every 4 weeks. For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended. *COVID-19 patients* The recommended posology for treatment of COVID-19 is a single 60-minute intravenous infusion of 8 mg/kg body weight in patients who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of tocilizumab 8 mg/kg may be administered. The interval between the two infusions must be at least 8 hours. *CRS (adults and paediatrics)* The recommended posology for treatment of CRS given as a 60-minute intravenous infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. Tocilizumab can be given alone or in combination with corticosteroids. If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses must be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients. Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the underlying malignancy, preceding lymphodepleting chemotherapy or the CRS. sJIA patients The recommended posology in patients above 2 years of age is 8 mg/kg once every 2 weeks in patients weighing greater than or equal to 30 kg or 12 mg/kg once every 2 weeks in patients weighing less than 30 kg. The dose must be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time.

	The safety and efficacy of intravenous tocilizumab in children below 2 years of age has not been established. *pJIA patients* The recommended posology in patients above 2 years of age is 8 mg/kg once every 4 weeks in patients weighing greater than or equal to 30 kg or 10 mg/kg once every 4 weeks in patients weighing less than 30 kg. The dose must be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time. SC Administration RA patients The recommended posology is subcutaneous 162 mg once every week. Limited information is available regarding switching patients from tocilizumab intravenous formulation to tocilizumab subcutaneous fixed dose formulation. The once every week dosing interval should be followed. Patients transitioning from intravenous to subcutaneous formulation should administer their first subcutaneous dose instead of the next scheduled intravenous dose under the supervision of a qualified healthcare professional. GCA patients The recommended posology is subcutaneous 162 mg once every week in combination with a tapering course of glucocorticoids. This medicinal product can be used alone following discontinuation of glucocorticoids. Tocilizumab monotherapy should not be used for the treatment of acute relapses. sJIA patients The recommended posology in patients above 1 year of age is subcutaneous 162 mg once every week in patients weighing greater than or equal to 30 kg or subcutaneous 162 mg once every 2 weeks in patients weighing less than 30 kg. Patients must have a minimum body weight of 10 kg when receiving tocilizumab subcutaneously. pJIA patients The recommended posology in patients above 2 years of age is subcutaneous 162 mg once every 2 weeks in patients weighing

	greater than or equal to 30 kg or subcutaneous 162 mg once every 3 weeks in patients weighing less than 30 kg.
	Proposed: Not Applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection, 162 mg/0.9 mL in pre-filled syringe or prefilled autoinjector Concentrate for solution for infusion, 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL in vials
	Proposed: Not applicable
Is/will the product be subject to additional monitoring?	Yes

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Rheumatoid Arthritis

Incidence

In adults aged 18 years and older, the overall incidence of rheumatoid arthritis (RA) is 45 per 100,000 person years (PY) (Gabriel et al. 2003).

Prevalence

The overall prevalence of RA in most industrialized countries is between 0.3% and 1% (Woolf 2003); 14/1000 female, 7.4/1000 male population (Gabriel et al. 1999). Rates are lower in developing countries and also relatively low in Japan (up to 2.4/1000 male and 2.0 to 7.0/1000 female) (Woolf 2003).

Demographics of the population in the proposed indication and risk factors for the disease

Approximately 73% of patients with RA are female (Gabriel et al. 2003). Age and sex distribution is largely similar across American and European populations (Abdel-Nasser et al.1997). Incidence and prevalence of RA rises with increasing age. Socioeconomic factors may influence the time between symptom presentation and diagnosis but not risk of RA.

The main existing treatment options

Numerous medications are available for the treatment of RA, which have varying efficacy and safety profiles in the treatment of the disease.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of RA but provide only symptomatic relief.

Conventional disease-modifying anti-rheumatic drugs (DMARDs), for example methotrexate (MTX), have been the cornerstone of RA treatment for many years and are recommended for early treatment as there is evidence that these agents may maintain or improve physical function and retard radiographic joint damage. These conventional DMARDs, in particular MTX, are often used in combination with biologic DMARDs (see below). However, treatment is limited by toxicity and/or ineffectiveness.

Several biologic DMARDs targeting the cytokine tumour necrosis factor alpha (TNFα) have been developed, but approximately 30% of patients fail to respond to these therapies. In addition to biologics targeting the interleukin (IL)-6 pathway and TNFα, biologics with different mechanisms of action have also been approved for the treatment of RA, including those that target cytokine pathways such as IL-1 inhibitors; CTLA4 to inhibit the full activation of T-cells; and anti-CD20 which depletes B-cells. Small molecules targeting Janus kinase have also been approved for the treatment of RA. These immunomodulatory treatments are not approved for use in combination with each other.

Risk Factors for the Disease

There is little evidence to suggest that socioeconomic or occupational factors contribute to risk of RA, although it may influence the time between symptom presentation and diagnosis and, thus, an early declaration of RA. Incidence and prevalence of RA rise with increasing age. Genetic susceptibility is a major determinant of susceptibility to RA; the majority of individuals who develop RA are Human Leukocyte Antigen (HLA) –DR4 or –DR1 or both.

Natural history of the indicated condition in the untreated population

Mortality: Compared with the general population, mortality is increased in patients with RA (SMR 1.27 – 2.03) (Björnadal et al. 2002; Gabriel et al. 2003; Young et al. 2007). Published mortality rates from large observational studies in RA patients not treated with biologic DMARDs range from 3.08 to 5.18 events per 100 PY. Corresponding mortality rates in RA patients treated with anti-TNF therapies were lower (range 0.70 to 1.61 events per 100 PY)

Discussion of the possible stages of disease progression to be treated: Early RA is typically defined as having RA symptoms of less than 2 years duration, however, it is not uncommon for early RA to be defined as symptoms in < 1, 3, or 5 years (Scott, 2007).

Outcome of the (untreated) target disease: Patients may initially present arthritis symptoms, but cannot immediately be classified into RA. A review of early arthritis cohorts revealed that 13% to 54% of patients initially classified as having undifferentiated arthritis went on to have a classification of RA after 1 year of follow-up, while 21% to 87% had persistent arthritis that remained unclassifiable (Hazes and Luime 2011).

Important comorbidities

As RA is associated with inflammation and changes of immunity, various comorbidities may be present. Comorbidities common among early RA patients include cardiovascular disease, anaemia, and depression. Coronary artery disease is the major cause of death in RA patients (SMR 1.79) (Björnadal et al. 2002). Gastrointestinal (GI) perforations, infections, malignancies, and cardiovascular disease are leading causes of increased mortality and morbidity in this population. Given the complexities of interstitial lung disease (ILD), it is a well-recognized comorbidity to be monitored in the context of serious and opportunistic infections.

SI.2 Systemic Juvenile Idiopathic Arthritis

Systemic juvenile idiopathic arthritis (sJIA) is a subset of juvenile idiopathic arthritis (JIA) that is characterized by the presence of arthritis and quotidian fever, accompanied by one or more of the following: rash, lymphadenopathy, hepatomegaly and/or splenomegaly, and serositis.

Incidence

In Europe, incidence of sJIA has been reported as 0.4-0.9 per 100,000 (Moe and Rygg 1998; Huemer et al. 2001; Bernston et al. 2003; Kaipianinen Seppanen and Savolainen 2001; Pruunslid et al. 2007; Modesto et al. 2010).

Prevalence

The prevalence of JIA in Europe has been reported as between 3.5-86/100,000 (Prieur et al. 1987; Gare and Fasth 1992; Modesto et al. 2010), and sJIA accounts for 6%-15% of children with JIA seen in clinics in North America and Europe (Cassidy et al. 2005; Woo 2006).

Demographics of the population in the proposed indication and risk factors for the disease

sJIA occurs throughout childhood, with a peak onset between 0 - 4 years (Ravelli and Martini 2007; Svantesson et al.1983; Gare and Fasth 1992; Bernston et al. 2003). Both sexes are equally affected (Cassidy and Petty 2005; Laxer and Schneider 1998; Symmons et al.1996).

The Main Existing Treatment Options

The initial treatment of sJIA varies depending on the extent of systemic symptoms and the number of joints with active arthritis.

Various non-biologic treatments for sJIA include NSAIDs, corticosteroids (CS) (oral or intravenous [IV]) and disease-modifying anti-rheumatic drugs (DMARDs) (such as MTX or leflunomide). MTX can be dosed orally or subcutaneously for sJIA. However, its use in sJIA is limited by its efficacy and safety profile. Adverse events (AEs) can include elevated liver function test results, anaemia, and teratogenicity. Based on clinical trial data, there is a lack of evidence to indicate that MTX is superior to placebo in the treatment of sJIA due to minimal effect on systemic features and active arthritis (Woo et al. 2000). Corticosteroids are often administered orally or intravenously to control severe disease. However, the AEs associated with the use of CS are numerous and include salt and water retention, weight gain, hypertension, peptic ulcer disease, mood swings, and bruising easily. Long-term use of CS is associated with complications such as osteoporosis, adrenal gland suppression, avascular necrosis, cataracts, lowered resistance to serious infection, insulin resistance, osteopenia, and growth failure. All of these factors contribute to long-term disability. Thus, the use of these medications in sJIA is limited by their side effect profile.

Anti-cytokine biologic therapies are highly effective in treating sJIA, and both canakinumab (anti-IL-1β) and tocilizumab (anti-IL-6R) are approved for the treatment of sJIA. Anakinra (anti-IL-1R), approved for adult RA, is also commonly used to treat sJIA. Patients may also receive other RA biologics, including αTNF inhibitors, although these are generally considered less effective than the other anti-cytokine therapies. NSAIDs, MTX, and CS are often used concomitantly with biologic therapies, and can be used concomitantly with tocilizumab.

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

Mortality: sJIA is associated with an increased risk of mortality compared with children with other types of JIA (Woo 2006) Almost two-thirds of all deaths that occur in JIA, occur in children with sJIA (Wallace and Levinson 1991). As reported for a variety of JIA cohorts from the 1970s and 1980s, mortality was 14% for sJIA and 3% for JIA (Laxer and Schneider 1998). Currently, JIA-related mortality is estimated at less than 1% in Europe (Cassidy and Petty 2005).

Important comorbidities

Important comorbid conditions are serious infections, impaired skeletal development in sJIA, Macrophage Activation Syndrome (MAS), and altered immune status.

SI.3 Polyarticular Juvenile Idiopathic Arthritis

Incidence

Projected European incidence = 4.9 - 6.6 per 100,000.

Based on (a) pJIA proportion of 27%-37% among all JIA in Europe (Bernston et al. 2003; Solau-Gervais et al. 2010; Nordal et al. 2011) and (b) JIA incidence average of approximately 18 per 100,000 (Bernston et al. 2003; Kaipianinen-Seppänen and Savolainen 2001; Danner et al. 2006; Pruunsild et al. 2007) and (c) Estonia incidences from study, Oligoarthritis of 11.7 per 100,000, and polyarticular juvenile idiopathic arthritis (pJIA) RF positive 4.4 per 100,000 (Pruunsild et al. 2007).

Projected worldwide incidence = 0.3 - 7.4 per 100,000.

Worldwide incidence approximately 33% of JIA (Ravelli and Martini 2007) and worldwide incidence 0.8 to 22.6 per 100,000 (Manners and Bower 2002).

Prevalence

Projected European prevalence for indicator conditions = 4.2 - 5.7 per 100,000.

Based on (a) pJIA proportion of 27%-37% among all JIA in Europe (Bernston et al. 2003; Solau-Gervais et al. 2010; Nordal et al. 2011) and (b) JIA prevalence 15.7 cases per 100,000 (Solau-Gervais et al. 2010)

Projected worldwide prevalence = 2.3 to 131.4 per 100,000.

Worldwide indicator ~34% of JIA (Ravelli and Martini 2007) and worldwide prevalence range of 7 to 401 per 100,000 (Manners and Bower 2002).

Demographics of the population in the proposed indication and risk factors for the disease

Oligoarthritis typically has an onset in children aged 2-4 years and predominately affects females (Dannecker and Quartier 2009; Ravelli and Martini 2007). Polyarthritis RF+ occurs primarily in adolescent girls (Dannecker and Quartier 2009; Ravelli and Martini 2007). The onset of Polyarthritis RF- has two peaks at 2 - 4 years and 6 - 12 years (Ravelli and Martini 2007). Predominance of males with oligoarthritis and sJIA was found in studies from India, Turkey, and Singapore (Aggarwal and Misra 1994; Ozen et al. 1998). South Africa reported equal sex ratio for JIA (Haffejee et al. 1984).

The Main Existing Treatment Options

Main treatment options include NSAIDs, MTX, and CS. NSAIDs are effective for many patients. If NSAIDs are ineffective, second-line medications may be considered such as MTX and CS.

Methotrexate can be dosed orally or subcutaneously for pJIA. Its use in pJIA is limited by its safety profile, which can include elevated liver function test results, anaemia, and teratogenicity.

Corticosteroids are often administered orally or intravenously to control severe disease. In addition, intra-articular steroid injections can also be utilized at the time of disease onset or during disease course. CS have a more limited role as systemic agents in the treatment of pJIA as compared with sJIA.

NSAIDs, MTX, and CS can continue to be used concomitantly with tocilizumab in the treatment of pJIA. Leflunomide, a reversible inhibitor of de novo pyrimidine synthesis has also been reported to be effective in children with pJIA.

Biological agents (other than tocilizumab) have provided therapeutic options for patients with moderate to severe pJIA; these options include etanercept, adalimumab, and abatacept. Two biologic agents are not used concomitantly.

Natural history of the indicated condition in the untreated population

Mortality: JIA-related mortality is estimated at less than 1% in Europe (Cassidy and Petty 2005). Mortality estimates specifically for the subtypes oligoarthritis and polyarthritis JIA are not available. However, it is unlikely that the mortality rate for these subtypes is higher, because together the oligoarticular JIA and pJIA subtypes constitute 40% - 53% of all JIA and generally patients with oligoarthritis have the best prognosis while those with polyarthritis have a varied prognosis; the worst outcomes are associated with joint erosions and serious complications of iridocyclitis (Guillaume et al. 2000; Ravelli and Martini 2007). Despite oligoarticular JIA and pJIA accounting for the majority of cases in JIA they have a much lower risk of mortality compared to sJIA, which has mortality of 0.6% (Hashkes et al. 2010), which constitutes 10%-20% of all JIA. The Dutch and Germany registry of JIA patients treated with etanercept reported no deaths among patients with oligoarticular JIA and pJIA (Prince et al. 2009; Horneff et al. 2009).

Important comorbidities

Important comorbidities include uveitis/iridocyclitis, osteopenia and osteoporosis, and leg-length discrepancy, contractures, and growth retardation.

SI.4 Giant Cell Arteritis

Incidence

The incidence of Giant Cell Arteritis (GCA) appears to have a geographic gradient; the disease is more frequently found in high latitudes. In the Northern hemisphere, there is a significant increase in both incidence and prevalence with increasingly northerly latitudes. The highest incidence rates have been reported in Scandinavia and the United Kingdom at 20 to 30 cases per 100,000 people aged 50 years or older. By contrast, studies from Southern Europe have consistently reported lower incidence rates than those from Scandinavia at 7 to 10 cases per 100,000 people aged 50 years or older (González-Gay et al. 2009; Watts and Scott 2014).

Prevalence

The sex ratio and incidence appear to vary. Studies from Northern and Western Europe report that women are 2 to 3 times more likely to be diagnosed with GCA than men (Watts and Scott 2014). In the study by Petri et al. (2015), the incidence in women was reported as twice that in men in a

UK-based patient population and within the reported range for studies in Northern and Western Europe. The ratio of females to males diagnosed with GCA is lower in studies from Southern Europe and can be close to 1:1 in other countries (Petri et al. 2015).

Demographics of the population in the proposed indication and risk factors for the disease

GCA primarily affects adults 50 years of age or older, and the risk for GCA increases with advancing age, with the highest rates observed in individuals between 70 and 79 years of age (González-Gay et al. 2009; Petri et al. 2015). In women, GCA incidence peaks from age 70 to 79 years. In men, GCA incidence increases but plateaus, with the peak at 80 years and older.

The Main Existing Treatment Options

Glucocorticoids (steroids) are the cornerstone of treatment for GCA (Mukhtyar et al. 2009; Broder et al. 2016). Oral steroids (usually prednisone/prednisolone) are initiated at a dose of 40 to 60 mg/day if a diagnosis of GCA is strongly suspected or confirmed by biopsy or imaging (Mukhtyar et al. 2009). Patients with complicated GCA, for example those with evolving vision loss or history of amaurosis fugax, are often treated with IV methylprednisolone 500 mg to 1 g daily for 3 days (Mazlumzadeh et al. 2006). Once the clinical signs and symptoms of GCA have subsided, typically after 2 to 4 weeks, the steroid dose is gradually tapered. Introduction of anti-platelet agents should be considered carefully owing to the risk of acute myocardial infarction, cerebral ischemia, hypertensive crisis, psychosis, and hyperosmolar decompensation of diabetes (Yates et al. 2014).

Despite their effectiveness at inducing remission of systemic inflammation and preventing acute damage (e.g., blindness), this comes with a high toxicity burden, with approximately 80% of patients suffering GC-related adverse clinical events at 10-year follow-up (Proven et al. 2003). In addition, GC are not as effective at maintaining remission, with many patients (up to 50%) experiencing relapse or flare-up of symptoms during reduction or discontinuation of glucocorticoids (Proven et al. 2003). Tocilizumab has been approved after demonstrating improved induction of remission compared to steroids alone and maintenance of steroid free remission resulting in reduced cumulative steroid dose. Other agents, including azathioprine, cyclophosphamide, MTX, infliximab, and etanercept, have shown conflicting or no evidence of benefit in the treatment of GCA. In spite of the paucity of evidence, MTX is used inconsistently as standard of care for glucocorticoid-sparing in relapsing patients.

Risk Factors for the Disease:

GCA primarily affects adults 50 years of age or older, and the risk for GCA increases with advancing age, with the highest rates observed in individuals between 70 and 79 years of age (González-Gay et al. 2009; Petri et al. 2015).

Susceptibility to GCA has been associated with an increased incidence of HLA-DR4 and HLA-DRB1*0401 (González-Gay et al. 2000). Other genetic factors, particularly those involved in the immune and inflammatory pathways, are likely also important in the susceptibility to GCA.

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

Outcome of the (untreated) target disease: The prognosis for patients with untreated GCA is extremely poor, with many patients suffering vision loss, or death from myocardial infarction, stroke, or dissecting aortic aneurysm (Foroozan et al. 2003; González-Gay et al. 2000)

Important comorbidities

GCA patients in the United Kingdom (UK) are reported as commonly experiencing aortic aneurysm, large vessel complications, polymyalgia rheumatica, visual disturbances, facial pain, osteoporosis, hypokalaemia, and various infections such as oral/oesophageal thrush and herpes zoster (Petri et al. 2015).

SI.5 Cytokine Release Syndrome

Cytokine release syndrome (CRS) is a potentially life-threatening symptom complex, caused by the excessive release of cytokines by immune effector or target cells during an exaggerated immune response. CRS can be triggered by infections or by therapeutic interventions, which activate the immune response, with the extent of severity most likely related to the degree and duration of immune activation. Severe or life-threatening CRS is a medical emergency, and if unsuccessfully managed, can result in significant morbidity or mortality.

Incidence

In ZUMA-1[1] (Phase 2), CRS occurred in 93% of the 101 subjects treated with axicabtagene ciloleucel. Of these subjects who experienced CRS, Grade 1 or 2 occurred in 80% and Grade 3 or higher occurred in 12%.

In ZUMA-8 (Phase 1), CRS occurred in 67% of the 15 subjects treated with brexucabtagene autoleucel infusion. Of these subjects who experienced CRS, Grade 1 or 2 occurred in 90% and Grade 3 or higher occurred in 10%.

Out of 203 patients infused with tisagenlecleucel across Studies[2] B2202[3], B2205J[4] and C2201[5], a total of 141 patients experienced CRS of any grade. Of the 141 patients, 50 required intervention with tocilizumab.

Demographics (ZUMA-1; Phase 2):

– There was no significant difference in incidence of CRS observed in subjects based on their performance status (i.e., Eastern Cooperative Oncology Group), age, or sex.

– Of the 101 subjects in ZUMA-1 (Phase 2), the age of the subjects ranged from 24 years to 77 years, with a median age of 58 years.

[1] A Phase 1-2 Multi-Center Study Evaluating Axicabtagene Ciloleucel in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1). Sponsor: Kite, A Gilead Company

[2] Studies B2202, B2205J and C2201 were sponsored by Novartis

[3] B2202: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia

[4] B2205J: A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in paediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia

[5] C2201: A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

– Of these 101 subjects, 68 subjects were male and 33 were female.

Demographics (B2202, B2205J, and C2201):

– The efficacy population for the tisagenlecleucel cohort included 28 males and 23 females (total 51 patients) of median age 17 years (range, 3–68 years)

Demographics (ZUMA-8; Phase 1):

– Of the 15 subjects in ZUMA-8 (Phase 1), the age of the subjects ranged from 52 years to 79 years, with a median age of 63 years.

– Of these 15 subjects, 10 subjects were male and 5 were female.

The Main Existing Treatment Options

Currently there are no drugs approved in the European Union for the treatment of chimeric antigen receptor (CAR) T cell-induced CRS. However, the Committee for Medicinal Products for Human Use has recently issued a positive opinion on the use of TCZ for the treatment of CRS.

Risk factors and risk groups:

Patient factors:

In some reports, the severity of CRS and elevation of serum cytokines have been related to disease burden, with higher disease burden predicting more toxicity presumably because this leads to higher levels of T cell activation (Almasbak et al. 2016; Brudno and Kochenderfer 2016). Maude et al. (2014) reported that the baseline disease burden (the percentage of blast cells in bone marrow before infusion) correlated with the severity of the CRS; a higher disease burden was significantly associated with severe CRS (p=0.002), (Maude et al. 2014). CRS associated with adoptive T cell therapies has been consistently associated with elevated interferon gamma (IFNγ), IL 6, and TNFα levels, and increases in IL 2, granulocyte macrophage–colony stimulating factor (GM CSF), IL 10, IL 8, IL 5, and fractalkine (Kalos et al. 2011; Kochenderfer et al. 2012; Grupp et al. 2013; Davila et al. 2014). CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS.

Dose-related (ZUMA-1; Phase 2):

– Subjects who received product with total T cell numbers greater than the population median had a higher incidence of Grade 3 or higher CRS (17.6% vs 8.0%).

– Subjects dosed with product potency (defined as IFN-γ production) greater than the population median had higher Grade 3 or higher CRS (20.0% vs 5.9%).

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

The cytokines implicated in CRS may be directly produced by the infused CAR T cells, as well as other immune cells such as macrophages that might produce large amounts of cytokines in response to cytokines produced by the infused CAR T cells. In contrast to neurologic AEs, Grade 3 or higher CRS was more robustly associated with a broad array of cytokine that can be produced

by activated myeloid and T cells rather than with the CAR T cell levels post-treatment. A wide variety of cytokines including IL-6, interferon γ, TNFα, IL-2, IL-2 receptorα (IL2Rα), IL 1 receptor antagonist (IL-1ra), IL-8, and IL-10 are elevated in the serum of patients experiencing fever, tachycardia, hypotension, and other toxicities after CAR T-cell infusions (Brudno and Kochenderfer 2016). The association of CRS with several of these cytokines and chemokines is likely related to their known functional activities. IL 6 and TNFα mediate vascular permeability, hypotension, fever, and tissue damage (Sprague and Khalil 2009); chemokines such as IL-8 trigger mobilization and redistribution of activated immune cells throughout the body (Griffith et al. 2014); and IL-1ra and IL-2Rα are indicative of macrophage and general immune activation (Ravelli et al. 2012). Levels of these cytokines decreased by 1 month post CAR T-cell infusion, a finding consistent with the timing and reversibility of CRS. In ZUMA-1 (Phase 2), CRS occurred in 93% of patients, 12% of whom experienced Grade 3 or higher (severe, life-threatening and fatal) CRS.

CAR T-related AEs, including fever, malaise, fatigue, anorexia, myalgia, arthralgia, nausea, vomiting, diarrhoea, headache, skin rashes, tachypnoea, hypoxemia, tachycardia, hypotension, increased or decreased cardiac output, renal impairment, elevated transaminases and bilirubin, and bleeding, can cause severe distress and require medical intervention. In the short-term CRS will impact the patient's quality of life although this is short lived and likely to be confined to the period of hospitalization with limited long-term effects. In severe cases, CRS related serious adverse events (SAEs) may be associated with death.

Important comorbidities (ZUMA-1; Phase 2):

Subjects with the following conditions were excluded from the studies:

– Hepatic impairment

– Renal impairment

– Cardiac impairment

– Pulmonary impairment

CRS has been known to be associated with end organ dysfunction (e.g. hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS.

SI.6 COVID-19

Incidence

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the most recently discovered coronavirus named novel severe acute respiratory syndrome (SARS-CoV-2) (WHO 2020a). As of 04 Oct 2021 (ie, based on WHO the most accurate numbers related to the DLP), approximately 237.9 million confirmed cases of COVID-19 had been reported globally by the WHO. The United States had 44.0 million confirmed cases followed by India with approximately 33.9 million confirmed cases, and Brazil with 21.5 million confirmed cases. In Europe, over 70.9 million cases were confirmed. The UK, France, and Italy were the most affected nations in Europe with over 8, 6 and 4 million confirmed cases, respectively (WHO 2020a).

Although most patients have mild symptoms and good prognosis, COVID-19 can develop to severe illnesses including pneumonia, pulmonary oedema, acute respiratory distress syndrome, multiple organ failure, or death (Li et al. 2020).

According to the data from the European Centre for Disease Prevention and Control (ECDC), pooled data from 25 countries for Week 25 (27 June 2021) showed that there were 6 patients per 100 000 population in hospital due to COVID-19. According to pooled weekly hospital admissions data from 18 countries, new admissions were 1 per 100 000 population (ECDC 2021).

The clinical spectrum of COVID-19 ranges from mild to critically ill cases leading to hospitalization and intensive care unit (ICU) admission (Yang X et al. 2020).

Demographics of the population in the proposed indication and risk factors for the disease

According to WHO, SARS-CoV-2 causing COVID-19, infects people of all ages. However, evidence suggests that older people (i.e., people over 60 years old) and those with underlying medical conditions (such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer) are at a higher risk of severe COVID-19 disease. The risk of severe disease gradually increases with age starting from around 40 years (WHO 2020c). A small number of cases of COVID-19 have been described in children. A study retrospectively enrolled 366 hospitalized children with respiratory symptoms from January 7 to 15, 2020 in China. COVID-19 was detected in 6 cases (1.6%), 4 of which showed typical viral pneumonia patterns, as assessed radiographically (Liu et al. 2020). Another report from the Centre for Disease Control (CDC) showed that the number of cases of COVID-19 in the United States between June and August 2020, was highest in the age group 20–29 years, accounting for more than 20% of the total (Venkatesan 2020). Among the laboratory-confirmed COVID-19–associated hospitalizations reported through COVID-NET in the US, the cumulative rate of hospitalization as of 3 July 2021 was reported to be: 100.4 per 100,000 (for age <18 years), 348 per 100,000 (for ≥18 years), 845.8 per 100,000 (for 50-64 years), and 1703.2 per 100,000 population for patients aged 65 years and older (COVID-NET).

Clinical Management of COVID-19

Prevention

To date, four vaccines have been granted conditional marketing authorization in the European Union: the Pfizer/BioNTech vaccine (Comirnaty®) was granted conditional MA on 21 December 2020 for the prevention of COVID-19 in individuals 16 years of age and older and, as of 04 October 2021, is approved for individuals aged 12 years and older. Subsequent conditional MAs were granted to the Moderna vaccine (Spikevax®) and the AstraZeneca/Oxford University vaccine (Vaxzevria®) in January 2021 and to the Janssen COVID-19 vaccine on 11 March 2021 for the prevention of COVID-19 in individuals 18 years of age or older.

Global efforts are underway to prioritize vaccination for adults most vulnerable to COVID-19. The long-term protection afforded by these vaccines is currently unknown.

Treatments

Treatment options for COVID-19 have been evolving since the pandemic was declared in March 2020. Initially, treatment was largely supportive in the outpatient or hospitalized setting and included the use of anti-pyretics, fluids, antibiotics if bacterial secondary or co-infection was suspected, and supplemental oxygen.

Of note, systemic corticosteroids were not routinely recommended until emerging data from clinical trials, including the RECOVERY trial for the dexamethasone cohort (Horby et al. 2021) indicated a mortality benefit among patients requiring supplemental oxygen or mechanical ventilation. The RECOVERY trial demonstrated that dexamethasone resulted in an absolute reduction in mortality of 2.8% (22.9% for dexamethasone vs. 25.7% for Usual Care; age-adjusted rate ratio, 0.83 [95% CI: 0.75, 93]). The benefit was greatest for patients who were receiving invasive mechanical ventilation at the time of randomization with mortality of 29.3% for dexamethasone versus 41.4% for Usual Care (rate ratio, 0.64 [95% CI: 0.51-0.81]) (Horby et al. 2021). The European Medicines Agency (EMA) endorsed use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation on 18 September 2020 (EMA Webpage 2020).

Several other therapies for the treatment of severe or critical COVID-19 have been granted conditional approvals/Emergency Use Authorizations (EUAs) globally.

Remdesivir (RDV), a broad-spectrum antiviral, was granted conditional approval by the EMA on 25 June 2020 and is indicated for use in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen. The recommendation was mainly based on data from Study NIAID-ACTT-1, sponsored by the U.S. National Institute of Allergy and Infectious Diseases (NIAID), plus supporting data from other studies of RDV. Study NIAID-ACTT-1, a double-blind, placebo-controlled Phase III trial, showed that treatment with RDV resulted in clinically meaningful improvements across multiple outcome assessments (including shortening the time to recovery) compared with placebo in hospitalized patients with COVID-19 (Beigel et al. 2020).

On 29 April 2021, the EMA announced they had begun evaluation of a marketing authorization application to extend the use of the JAK inhibitor baricitinib (Olumiant®) to include treatment of COVID-19 in hospitalized patients from 10 years of age who require supplemental oxygen. The accelerated assessment is based on results from the two Phase III studies of baricitinib in hospitalized patients (COV-BARRIER and ACTT-2). However, uncertainty remains around the use of baricitinib with concomitant corticosteroids, and the Phase III COV-BARRIER study in hospitalized COVID-19 patients failed to meet its primary endpoint, a difference in the proportion of participants progressing to the first occurrence of non-invasive ventilation (including high flow oxygen) or invasive mechanical ventilation (including extracorporeal membrane oxygenation [ECMO]) or death by Day 28 (Lilly and Incyte Press Release 2021). Another Phase III study (ACTT-4) comparing baricitinib+RDV to dexamethasone+RDV was recently halted for futility (NIH Press Release 2021).

On 24 June 2021, the FDA issued an EUA for Actemra (tocilizumab) for the treatment of COVID-19 in hospitalized patients and paediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

Medical Need

Despite ongoing advances in the development of vaccines and treatments for COVID-19, significant unmet medical need remains in the treatment of COVID-19, especially in hospitalized patients with severe COVID-19 pneumonia who may progress to multiple organ failure and death and often require extensive healthcare resources, including ICU admission and mechanical ventilation.

Currently, the only treatment, which has been granted conditional MA for hospitalized COVID-19 patients in the EU is remdesivir; however, consistent benefits in mortality, need for mechanical ventilation and duration of hospital stay have not been observed across different studies (Beigel et al. 2020; WHO Solidarity Trial Consortium 2021). Additionally, the EMA endorsed use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation on 18 September 2020 (EMA Webpage 2020).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

Local Tolerance Studies

Multiple-dose studies in primates, in which tocilizumab was given IV in high doses, showed that tocilizumab was well tolerated. Additional local IV, SC, or intramuscular tolerance studies in rabbits also showed excellent local tolerability of tocilizumab and its formulation excipients.

Relevance to human usage: Yes

Discussion: Tolerance to tocilizumab has been confirmed by clinical data.

Reproductive Toxicity Studies and Risk of Abortion

Tocilizumab was not teratogenic in an embryo-foetal toxicity study in cynomolgus monkey at a daily dose of 50 mg/kg/day (highest dose) associated with a high systemic cumulative exposure of > 100 above the expected human efficacious concentration. A higher rate of abortion was however noted in this dose group compared with the placebo and other low dose groups. The abortion incidence was within the historical background for the cynomolgus monkey in captivity (Boot et al. 1985; Vogel and Bee 1999; Hendrie et. al. 1996) and the individual cases of abortions/embryo-foetal death did not show any consistent relationship to dosing or duration of dosing with tocilizumab. IL-6 does not appear to be a critical cytokine for embryo-foetal development since IL-6 deficient mice are fertile and their offspring show no abnormal phenotype. In addition, the difference in abortion rate in the cynomolgus monkey study was only marginally higher in the high dose group compared to the other treatment groups. Transfer of a murine analogue of tocilizumab into the milk of lactating mice has been observed.

Preclinical data in mice do not suggest an effect on fertility in mice treated with a mouse IL-6R surrogate antibody for tocilizumab. With this antibody, there was also no evidence for IL-6-inhibition-related effects on pre-natal and postnatal development, including on developing immune function in the F1 generation treated transplacentally. Similarly, there were no toxicologically relevant effects noted on fertility, pre- and postnatal development, and immune function in a combined fertility and pre- and postnatal development study in IL-6 knockout mice.

Relevance to human usage: Unknown

Discussion: Although IL-6 does not seem to be a critical cytokine for either foetal growth or the immunological control of the maternal/foetal interface, the relevance of this observation for human pregnancy is unknown. However, a possible relation to tocilizumab cannot be excluded as preclinical data suggests an increased risk of spontaneous abortion. Therefore, tocilizumab may represent a potential risk to pregnant women. No teratogenic effects have been identified with tocilizumab.

Single- and Multiple-Dose Toxicity Studies

Toxicity studies have shown tocilizumab to be well tolerated in cynomolgus monkeys when administered in an IV single dose study up to 100 mg/kg multiple-dose study up to 50 mg/kg/day for 4 weeks or at an IV dose of 100 mg/kg/week for 6 months. Although the exposure in these

studies exceeds the targeted human average efficacious concentrations by factors of 125 (4-week study) or 39 (6-month study), no adverse effects that would be considered clinically significant in man were seen in the clinical pathology investigations, the histopathological evaluation, or in any additional studies. Because tocilizumab is targeted at autoimmune disease, it is important to note that there were no treatment effects on the morphology of primary or secondary organs of the immune system. Two toxicology findings were observed in these experiments that warranted closer scrutiny. These included reductions of ANCs and B-cell counts in the peripheral blood. However, analysis showed that the reduction of ANC was mild and not associated with bone marrow manifestations or changes in neutrophil function. Similarly, the minor reduction in the CD20+ B-cell ratio observed in cynomolgus monkey studies with up to 4-weeks of exposure was not associated with detectable alterations of the tissue B-cell compartments in lymphoid organs.

Relevance to human usage: Yes

Discussion: These findings have been adequately addressed in the clinical development program of the originator.

Malignancies

A carcinogenicity study of tocilizumab has not been conducted. As tocilizumab does not bind to rodent IL-6R, conventional long-term carcinogenicity studies in rats or mice are thus, inappropriate to assess a function-associated carcinogenic potential of tocilizumab. A standard test set of in vitro genotoxicity studies conducted with tocilizumab has shown no evidence of genotoxic liabilities. IgG macromolecules do not penetrate cell walls or cell membranes and therefore, do not have direct interactions with cellular DNA. Because of this, IgG1 monoclonal antibodies do not have an intrinsic carcinogenic potential, and thus, such tests are not considered to be of relevance for a carcinogenic risk assessment of antibodies.

IL-6 is recognized as one of the most potent autocrine growth factors in the pathogenesis of numerous cancers, including thyroid carcinomas (Russell et al. 2004), prostate and ovarian cancer (Xiao et al. 2004; Hefler et al. 2003) and, in particular, hematologic malignancies such as multiple myeloma (Hilbert et al. 1995; Siegall et al.1990). Recently published data further demonstrated the contributing role of the sIL-6R transignalling in a colon cancer model (Becker et al. 2004; Becker et al. 2005; Landi et al. 2003), suggesting that under conditions of chronic inflammation, IL-6 may contribute to malignant progression and resistance of various malignancies (through activation of gp130), which do not per se express the membrane-bound IL-6 receptor.

While the direct stimulatory activity of IL-6 has long been recognized, recent studies have identified and characterized the role of IL-6 in the regulation of the signal transducer and activator of transcription 3 (STAT3), its critical role in tumour progression, and the negative interference of STAT3-regulated gene products in tumour immunosurveillance (Yu 2007). Not only does STAT3, constitutively activated by malignant cells, inhibit the expression of mediators necessary for effective immune activation against tumour cells, but it also actively promotes the production of immunosuppressive factors that lead to a blockade of efficient anti-tumour response in situ.

Recently published data demonstrated that the functional maturation of dendritic cells in the tumour environment, which is necessary for an effective activation of an anti-tumour response, is blocked by tumour-secreted IL-6 (Park et al. 2004), an effect which significantly contributes to the widely observed clinical phenomenon of tumour tolerance rather than rejection. Conversely, the

potential role of IL-6 as a therapeutic anti-tumour agent has been shown in a variety of preclinical tumour models although the use of recombinant IL-6 in patients was determined to be a multiple myeloma inducing growth factor (Mullen et al. 1992; Sun et al. 1992; Abroun et al. 2004; Salazar-Onfray et al. 2007).

Consistent with the role of IL-6 in tumour progression, nonclinical pharmacology studies conducted with tocilizumab showed clear anti-proliferative effects. These experiments demonstrated that tocilizumab inhibits the proliferation of cell lines induced by IL-6/sIL-6R complex such as BAF-h130 and effectively stops the IL-6 dependent growth of human myeloma cell lines *in vitro* and KPMM2 tumour cells *in vivo*. The therapeutic effect of IL-6 receptor blockage under in vivo conditions was shown in various disease models with MR16-1, a rodent-specific analogue antibody to tocilizumab. MR16-1 completely prevented the lymphoproliferative manifestations in an IL-6 transgenic mouse model of Castleman's Disease (Katsume et al. 2002) and halted the progression of tumour growth in a mouse model of colon carcinoma (Becker et al. 2004).

No lesions with a proliferative characteristic or any other type of pre-neoplastic findings have been seen in a cynomolgus monkey study of 6-months, in which the animals were continuously exposed to tocilizumab at serum concentrations more than 30-fold above the clinical effective serum levels. As suggested by the role of IL-6 in the physiology of cell regulation, chronic and complete IL-6 depletion in vivo in IL-6 knockout mice does not lead to a higher spontaneous malignancy rate. Reports from experiments conducted in aged IL-6 knockout mice are particularly notable, as the life span was not compromised nor was there any palpable mass reported in these animals (Gomez et al. 2006; Dovi et al. 2003), although tissues of these animals were not histopathologically screened for the presence of early-stage malignant disease. There is no direct evidence that tocilizumab would induce malignant transformation. On the contrary, other available evidence that IL-6 is a growth factor for tissue maintenance and regeneration under conditions of insult (direct damage or inflammation), and in malignant cells, IL-6 per se does not seem to disrupt the balance of the immunological control of tumour growth and metastasis (immunosurveillance). The nonclinical data suggest an association between elevated levels of IL-6 and tissue/tumour growth, but do not suggest that an inhibition of the IL-6R signalling pathways via chronic treatment with tocilizumab would lead to an increased risk of malignancies in patients.

Relevance to human usage: Yes

Discussion: The risk of malignancy is known to be increased in patients with RA and with some treatments commonly used in RA, such as MTX and biologic DMARDs (Bongartz et al. 2006). A Food and Drug Administration (FDA) alert was published requiring the manufacturers of TNF blockers to update the Boxed Warning in the prescribing information to alert healthcare professionals of an increased risk of lymphoma and other malignancies in children and adolescents treated with TNF blockers. EMA 2010 priorities also identified the risk of malignancy as one of the potential long-term adverse effects of immunomodulators, including the anti-TNFs, rituximab, and tocilizumab. Malignancies are considered an important potential risk associated with tocilizumab use. Refer to Module SVII.3.1 for details.

General Safety Pharmacology

Pharmacology Studies

The cardiovascular safety of tocilizumab has been investigated in a series of rigorously designed preclinical in vivo studies. These results indicate that tocilizumab does not adversely affect either cardiac integrity or electrophysiology; an alteration of blood pressure was also not observed in any of the preclinical studies.

Relevance to human usage: No

Discussion: Tocilizumab has not demonstrated an impact on cardiac integrity or electrophysiology in the clinical setting. Cardiovascular concerns are an important potential risk because tocilizumab treatment is associated with increases in LDL cholesterol and triglycerides, and RA patients are at increased risk of cardiovascular disease. See important potential risk of elevated lipid levels and the potential risk of cardiovascular/cerebrovascular events in Module SVII.3.1.

Effects on Bone Turnover and Quality

IL-6 has been shown to stimulate osteoclast activity and bone resorption by an indirect mechanism, increasing interactions between osteoblast and osteoclast activities. The effects of IL-6 on bone destruction and the potentially therapeutic benefit on IL-6 inhibition were studied in an IL-6 transgenic mouse model. IL-6 over expression in pre-pubertal mice induced the uncoupling of osteoclast and osteoblast activities which in turn manifested as decreased trabecular and cortical bone growth, delayed ossification, and impaired skeletal growth (De Benedetti et al. 2006). Other studies in the transgenic juvenile mouse model demonstrated that effective inhibition of IL-6 was able to correct the IL-6-induced pathology (De Benedetti et al. 2001).

While treatment with tocilizumab is expected to block IL-6-induced osteoclastic activities and thereby normalize the physiologic process of bone remodelling, there are no preclinical data to suggest that IL-6 inhibition *per se* generates an abnormal imbalance of this process. The studies in juvenile animals are also relevant for adults as the fast-growing body weight at this age requires a constant adaptation of the skeletal system via length-growth, increase in bone mass, but also bone shaping and adaptation to the constantly changing biomechanical strains. Therefore, studies of this type offer a more appropriate means than those in adults of assessing the effect ofIL-6 deprivation on bone remodelling. The phenotype of these mice did not show any irregularity and therefore, provides no evidence for an IL-6 deficiency-induced underlying abnormal bone remodelling process. Nonclinical safety studies conducted with tocilizumab are in concordance with these data, showing that bone morphology was normal in primate toxicity studies over a tocilizumab exposure for up to 6 months. The histopathology of bone in these young adult animals with ongoing skeletal growth showed no morphological/developmental abnormalities. Overall, the preclinical data demonstrate that IL-6 is a key regulatory factor in osteoclast activation and contributes to the osteopenic manifestations frequently associated with chronic inflammatory diseases. Preclinical studies showed that inhibition of IL-6 normalizes inflammation-driven osteoclastic bone destruction, and nonclinical safety studies conducted with tocilizumab demonstrated that IL-6 inhibition, induced by continuous chronic exposure to tocilizumab, maintains a morphologically and functionally normal bone homeostasis.

Relevance to human usage: Yes

Discussion: The incident rate of fractures (events per 100 PY) at 1 year in LITHE were 3.12 (95% CI: 1.35, 6.15) in the placebo group, 2.42 (95% CI: 1.05, 4.8) in the 4 mg/kg tocilizumab group, and 3.72 (95% CI: 1.98, 6.37) in the 8 mg/kg tocilizumab group.

Effects of IL-6 Depletion on Maintenance of Mucosal Integrity of the GI Tract

IL-6 is known to play an important role in maintenance of mucosal integrity and the depletion of IL-6 may impede that function (Dann et al. 2008). In IL-6 knockout mice, an IL-6 deficiency was found to exacerbate mucosal inflammation and damage caused by bacteria and chemical irritants, and in vitro, IL-6 protected colonic epithelial cells against inducible apoptosis by increasing expression of anti-apoptotic proteins. Therefore, IL-6 depletion may be associated with impairment of the maintenance of mucosal integrity. On the other hand, the downregulation of IL-6 in animal models of colitis (direct chemically induced colitis and immune-transfer colitis) has been proven to ameliorate symptoms and histologic inflammatory consequences of these experimentally induced colitis models thus proving a potential benefit of an anti-IL-6R antibody in colitis (Ishiguro et al. 2010).

Relevance to human usage: Yes

Discussion: Complications of diverticulitis is an identified risk of tocilizumab use, per data obtained in clinical trials. Refer to Module SVII.3.1 for more details.

Effects of a Blockage of IL-6 Signalling with a Surrogate Antibody in Juvenile Mice

Effects of a blockage of IL-6 signalling in juvenile animals have been investigated with a murine surrogate antibody of tocilizumab, termed MR16-1. MR16-1, a rat anti-mouse IL-6R monoclonal antibody (IgG1) has been thoroughly characterized in pharmacologic models as a suitable rodent analogue of human anti-IL-6 antibodies. For this safety assessment purpose, juvenile mice were treated once every 3 days from weaning (postnatal Day 22) until sexual maturation (postnatal Day 79). Effects of MR16-1 were investigated on postnatal development and growth, immune system, skeletal development, and sexual maturation after IV administration of MR16-1 in juvenile mice. Toxicokinetic investigations yielded evidence that the study was done under full blockage of IL-6 signalling. The observation of anti-drug antibodies did not impair the assessment.

No adverse effects were observed in body weight, food consumption, haematology, necropsy, organ weights, or histopathology in any treatment group during dosing or recovery period.

With respect to immune system in juvenile animals, there were no adverse effects in immunocompetence, NK cell activities in any treatment group. The following results were obtained: 50- and 15-mg/kg groups, a decrease in CD3e+CD4+CD8a− ratio and peripheral blood count in males and females at end of the dosing period; decrease in CD3e+ ratio and count; increase in CD3e+CD4+CD8a− ratio and peripheral blood count in males and females and increase in CD49b/Pan-NK cells+CD3e− ratio in females in the 50-mg/kg group at end of the recovery period, was observed. These changes are considered to have a minor impact on the immune system, since no adverse effects on immunocompetence (serum IgG and IgM production to KLH) was observed in any treatment group.

With respect to sexual maturation and skeletal development in juvenile animals, there were no adverse effects in the morphological differentiation of external genitalia, oestrous cycle, sperm examination, crown-rump length, or skeletal development in any treatment group.

From these study results, it is concluded that MR16-1 did not induce any toxicologically meaningful changes on postnatal development, growth, immune system, skeletal development, or sexual maturation in juvenile animals.

Relevance to human usage: No

Discussion: The applicability of these results to humans is limited because they were conducted with a murine surrogate antibody.

Part II: Module SIII - Clinical trial exposure

NOTE: MSB11456 was the development code of Tyenne.

Overview of Clinical Studies used for Tocilizumab Exposure

The clinical studies used to calculate patient exposure to MSB11456 (tocilizumab) as of 04-Oct-2021 are the following:

- FKS456-001: A randomized, double-blind, multiple-dose, parallel-group, two-arm study to evaluate the efficacy, safety and immunogenicity of MSB11456 compared to European Union-approved RoActemra in patients with moderately to severely active rheumatoid arthritis (APTURA I study).
- FKS456-002: A randomized, double-blind, parallel-group, single-dose study to compare the pharmacokinetics, safety, tolerability and immunogenicity of intravenous administration of MSB11456 (proposed tocilizumab biosimilar) versus US-licensed Actemra in healthy volunteers (APTURA II study);
- FKS456-003: A randomized, open-label, fixed dose, cross-over study to compare pharmacokinetics, safety and tolerability of prefilled syringe and auto-injector presentations of MSB11456 in healthy subjects (APTURA III study);
- MS200740-0001: Randomized, double-blind, parallel-group, single-dose study to compare the pharmacokinetics, pharmacodynamics, safety, tolerability and immunogenicity of MSB11456, US-licensed Actemra and EU-approved RoActemra in healthy adult subjects.

Overview of Exposure Tables

The following tables present cumulative patient exposure per treatment duration in subject-years, age Group, gender, and race.

Table 1 Duration of exposure to MSB11456 per study

Study Identifier	Treatment Groups	Number of subjects	Subject-Years on Study
MS200740-0001	162 mg sc MSB11456	231	30.41
FKS456-001	162 mg sc MSB11456	441	330.2
FKS456-002	8 mg/kg IV MSB11456	62	8.00
FKS456-003	MSB11456 PFS 162 mg sc – MSB11456 AI 162 mg sc	51	11.29
	MSB11456 AI 162 mg sc – MSB11456 PFS 162 mg sc	49	10.53
	Total	834	-

Source:
For FKS456-001 - SDTM.DM, SDTM.DS, SDTM.EX, SDTM.EC
For FKS456-002 - SDTM.DM, SDTM.DS, SDTM.EX, SDTM.EC
For FKS456-003 - SDTM.DM, SDTM.DS, SDTM.EX
For MS200740-0001 - ADaM.ADSL

Table 2 Exposure to MSB11456 by age group and gender

Study Identifier	Treatment Groups	Age Group (Years)	Male n (%*)	Female n (%*)	Total n
MS200740-0001	162 mg sc MSB11456	18 - 55	121 (52.4)	110 (47.6)	231
FKS456-001	162 mg sc MSB11456	18 - 55	26 (5.9)	215 (48.8)	441
		>55	50 (11.3)	150 (34.0)	
FKS456-002	8 mg/kg IV MSB11456	18 - 55	41 (66.1)	21 (33.9)	62
FKS456-003	MSB11456 AI 162 mg sc - MSB11456 PFS 162 mg sc	18 - 55	29 (59.2)	20 (40.8)	49
	MSB11456 PFS 162 mg sc - MSB11456 AI 162 mg sc	18 - 55	33 (64.7)	18 (35.3)	51
	Total	**-**	**300 (36.0)**	**534 (64.0)**	**834**

*Percentages in parenthesis reflect relative exposure based on total numbers of subjects exposed to the IMP MSB11456 only in the respective study.

n=number of subjects exposed to MSB11456

Source:
For MS200740-0001 - ADaM.ADSL
For FKS456-001 - SDTM.DM
For FKS456-002 - SDTM.DM
For FKS456-003 - SDTM.DM

Table 3 Exposure to MSB11456 by race

Race Group	Study Identifier	Number of Subjects
White	MS200740-0001	165
	FKS456-001	441
	FKS456-002	62
	FKS456-003	100
	Total	**768**
Black or African American	MS200740-0001	0
	FKS456-001	0

	FKS456-002	0
	FKS456-003	0
	Total	**0**
Asian	MS200740-0001	18
	FKS456-001	0
	FKS456-002	0
	FKS456-003	0
	Total	**18**
American Indian or Alaska Native	MS200740-0001	1
	FKS456-001	0
	FKS456-002	0
	FKS456-003	0
	Total	**1**
Native Hawaiian or Other Pacific Islander	MS200740-0001	12
	FKS456-001	0
	FKS456-002	0
	FKS456-003	0
	Total	**12**
Other	MS200740-0001	34
	FKS456-001	0
	FKS456-002	0
	FKS456-003	0
	Total	**34**
Not Collected	MS200740-0001	1
	FKS456-001	0
	FKS456-002	0
	FKS456-003	0
	Total	**1**

Source:
For MS200740-0001 - ADaM.ADSL
For FKS456-001 - SDTM.DM
For FKS456-002 - SDTM.DM
For FKS456-003 - SDTM.DM

Part II: Module SIV - Population not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 4 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Severe allergic or anaphylactic reactions	To ensure general safety of patients with known severe hypersensitivity to monoclonal antibodies when treated with MSB11456.	No	Hypersensitivity is contraindicated in the EU SmPC.
Active severe infections	Patients with a history of recurring or chronic infections or with active underlying conditions, may potentially be predisposed to infections when exposed to MSB11456.	No	For RA, sJIA, pJIA, and CRS, active severe infections are contraindicated in the EU SmPC. Patients with COVID-19 who simultaneously also have other, serious active infections are contraindicated in the EU SmPC
Current or previous (within the past 2 years) evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal,hepatic, endocrine (including uncontrolled diabetes mellitus) or gastrointestinal disease	To ensure general safety of patients to be treated with MSB11456 in the clinical trial setting.	No	There is no data to suggest that tocilizumab has an effect on pulmonary, renal, or endocrine function. Active hepatic disease /hepatic impairment, neurological disorders, cardiovascular risk, and complications of diverticulitis are listed as special warnings and precautions in the EU SmPC.

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Uncontrolled disease states, such as asthma or inflammatory bowel disease where flares are commonly treated with oral or parenteral corticosteroids	Potential for patients to be unable to adhere to study protocol. Oral steroids had to remain stable and parenteral steroids were prohibited in MSB11456 RA clinical trials to enable accurate assessment of MSB11456 efficacy.	No	This exclusion criterion was not related to the safety of the patient population
History of diverticulitis, diverticulosis requiring antibiotic treatment, or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose to perforations	To ensure general safety of patients to be treated with MSB11456 in the clinical trial setting	No	Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with tocilizumab in RA patients. Complications of diverticulitis is listed as a special warning and precaution in the EU SmPC and is included as an important identified risk in this RMP (refer to Module SVII.3.1).
Current liver disease as determined by the investigator	To ensure general safety of patients to be treated with MSB11456 in the clinical trial setting.	No	Treatment with tocilizumab, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases. This has been listed in the EU SmPC under Special Warnings and Precautions for use. Hepatotoxicity is classified as an important identified risk in this RMP (see Module SVII.3.1).

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Active TB requiring treatment within the previous 3 years and no evidence of active TB infection at enrolment	To ensure general safety of patients to be treated with MSB11456 in the clinical trial setting.	No	Tuberculosis is listed as a special warning and precaution in the EU SmPC.
Primary or secondary immunodeficiency (history of or currently active)	To ensure general safety of patients to be treated with MSB11456 in the clinical trial setting.	No	These patients may be more prone to infections; infections are listed as a special warning and precaution in the EU SmPC.
Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (including hematologic malignancies and solid tumours, except basal cell carcinoma of theskin that has been excisedand cured), or breast cancer diagnosed within the previous 20 years	To ensure general safety of patients to be treated with MSB11456 in the clinical trial setting.	No	Malignancy is listed as a special warning and precaution in the EU SmPC. Malignancies are included as an important potential risk in this RMP (see Module SVII.3.1).
Pregnant women or nursing (breast feeding) mothers	To ensure the safety of pregnant women or nursing (breast feeding) mothers and their child.	No	Information on the use of tocilizumab in pregnant women or nursing (breast feeding) mothers is provided in the EU SmPC including guidance on contraceptive use and advice that tocilizumab should not be used during pregnancy unless necessary.Healthcare providers are advised to assess the risk/ benefit of discontinuation of breastfeeding for the child

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
			versus therapy discontinuation risk/benefit.
History of alcohol, drug, or chemical abuse within the 6 months prior to screening visit. Neuropathies or other painful conditions that might interfere with pain evaluation	Potential for patients to be unable to adhere to study protocol or have conditions that would affect efficacy assessments.	No	This exclusion criterion was not related to the safety of the patient population.
Patients with lack of peripheral venous access	Potential for patients to be unable to adhere to study protocol/receive studymedication.	No	This exclusion criterion was not related to the safety of the patient population.
History of MAS within 3 months prior to the screening visit*	To ensure general safety of patients to be treated with MSB11456 in the clinical trial setting.	No	MAS is listed in the special warnings and precautions for use section in the EU SmPC.
Active uveitis (absence of uveitis must be documented by a slitlamp ophthalmology examination within 12 weeks prior to baseline)**	To ensure general safety of patients to be treated with MSB11456 in the clinical trial setting.	No	Uveitis is not a labelled indication for tocilizumab, treatment for uveitis might interact with study medication.

COVID-19 = coronavirus disease 2019; CRS = cytokine release syndrome; GI = gastrointestinal; MAS=Macrophage Activation Syndrome; MTX = methotrexate; pJIA=polyarticular juvenile idiopathic arthritis; RA=rheumatoid arthritis; RMP = risk management plan; SmPC = Summary of Product Characteristics; sJIA =systemic juvenile idiopathic arthritis; TB=Tuberculosis.

*Criteria specific to sJIA

**Criteria specific to pJIA

SIV.2 Limitations to detect adverse reactions in clinical trials development program

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

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development program

Table 5 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women and breastfeeding women	Not included in the MSB11456 clinical development program. However, in Study FKS456-002, 1 patient was found pregnant at the end of study; per investigator, the reason for pregnancy occurrence was a contraception failure. The Originator's clinical development program (RoActemra EU-RMP, Roche) included: - IV administration: 55 patients - SC administration: 5 patients.
Patients with Relevant Comorbidities	
Patients with hepatic impairment	Not included in the MSB11456 clinical development program. The Originator's clinical development program (RoActemra EU-RMP, Roche) included: - IV administration: 24 patients.
Patients with renal impairment	Not included in the MSB11456 clinical development program. The Originator's clinical development program (RoActemra EU-RMP, Roche) included: - IV administration: 152 patients.
Patients with cardiacimpairment	Not included in the MSB11456 clinical development program. The Originator's clinical development program (RoActemra EU-RMP, Roche) included: - IV administration: 221 patients.

Type of special population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical trial programs of tocilizumab (both MSB11456 and RoActemra) recruited RA patients with moderate to severe disease.
Subpopulations carrying relevant genetic polymorphisms	There is no known association between the use of tocilizumab (both MSB11456 and RoActemra) and polymorphisms.
Combination with other biologics	Not included in the MSB11456 clinical development program. The use of tocilizumab (RoActemra) in combination with rituximab in RA patients was investigated in one trial (WX21956). However, the trial was terminated early for reasons unrelated to safety, and the number of patients recruited at the time of study termination was too small to determine the efficacy and safety of the combination therapy.
Other	
Elderly patients (≥75 years)	Not included in the MSB11456 clinical development program. The Originator's clinical development program (RoActemra EU-RMP, Roche) included: - IV administration: 286 patients; - SC formulation: 74 patients.
Paediatric Patients	Not included in the MSB11456 clinical development program. The Originator's clinical development program (RoActemra EU-RMP, Roche) included: - IV formulation: 311 patients; - SC formulation: 103 patients.

Part II: Module SV - Post-authorization experience

Cumulatively, patient exposure for Tyenne (tocilizumab) is 117,653 patient treatment years since the first registration of the product in Sep. 2023.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for Misuse for Illegal Purposes

No studies on the effects of the potential for tocilizumab to cause dependence have been performed. However, there is no evidence from the available data that tocilizumab treatment results in dependence. Drugs that have the potential for misuse for illegal purposes are accepted to share some general characteristics such as psychoactivity, less commonly, anabolic effects, and enhancement of haemoglobin levels.

IL-6 signalling blockade, through the use of tocilizumab, would not reasonably be considered as a potential drug of misuse for illegal purposes as it does not share any characteristics with drugs that are commonly associated with illegal misuse. Furthermore, there is no evidence from completed clinical studies that tocilizumab has been associated with any clinical event that might suggest the potential for misuse for illegal purposes. There is also no evidence from the available data that tocilizumab treatment gives rise to dependence.

Erythropoetins have been associated with illegal use, primarily in athletes, in order to stimulate the bone marrow to increase red blood count production thereby achieving the performance enhancement associated with training at high altitude. Results from clinical trials with tocilizumab have demonstrated improvement in anaemia of chronic disease, associated with chronic inflammatory conditions, but no increase in healthy volunteers or in patients with normal haemoglobin labels. Additionally, supraphysiological levels of haemoglobin have not been recorded in patients receiving tocilizumab. Therefore, tocilizumab is not considered to be of use as a performance enhancing drug in this context.

The data collected in the clinical studies of Tyenne are in accordance with established scientific and medical knowledge, that tocilizumab does not relevantly impact haemoglobin levels.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Following a comprehensive review of the Tyenne safety data and based on clinical experience with the originator product Roche's RoActemra (tocilizumab), the following are considered important risks:

- Important identified risks: Serious Infections, Complications of Diverticulitis, Neutropenia, Hepatotoxicity.
- Important potential risks: Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events, Malignancies, Immunogenicity.

The safety concerns Serious Infection and Complications of Diverticulitis are considered important identified risks for chronic tocilizumab dosing but are assessed as important potential risks for the indication of COVID-19.

Further details on the safety concerns are provided in section SVII.3.1.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

In alignment with the current safety concerns of Roche's RoActemra (tocilizumab) (RMP version 30.4), the MAH has proposed the reclassification of the important risks of thrombocytopenia and the potential risk of bleeding and demyelinating disorders to not important risks. The cumulative post-marketing safety data of RoActemra, since 2009 to date, provides a stable and well-characterized risk profile for tocilizumab (TCZ). The long-term safety review identified no new significant safety information that would alter the established characteristics of the known risks, nor did it reveal any new safety signals. Information regarding thrombocytopenia and the potential risk of bleeding, and demyelinating disorders, have been adequately captured in Section 4.4 Warning and Precautions of the EU SmPC.

There are no additional risk minimization measures and additional pharmacovigilance activities for these risks that are ongoing or proposed. These risks will be reviewed under important risks in the PBRER and monitored through routine PV processes, such as literature review and regular signal detection. The MAH considers these current routine PV activities, including the information provided in the EU SmPC, adequate.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Table 6. Details of important identified and potential risks of tocilizumab

Important identified risk **Serious Infections** **This safety concern is considered an important identified risk for chronic tocilizumab dosing, but is assessed as important potential risk for the indication of COVID-19. For ease of review, all data related to COVID-19 are included below together with data related to chronic tocilizumab dosing.**	
Potential mechanism	Patients with RA, GCA, pJIA, and sJIA are at a higher risk of infection than the general population because of altered immunological function as well as concomitant therapies used to treat the underlying disease (e.g., corticosteroids and immunomodulating agents). Biologic therapies have been shown to be associated with infections, particularly serious infections, including tuberculosis and opportunistic infections. Patients with COVID-19 are at higher risk of secondary bacterial or fungal infection. Superinfections and co-infections are common in respiratory viral illnesses including COVID-19, particularly in severe hospitalized cases. Acute suppression of IL-6 may increase the infection risk due to IL-6's role in the acute-phase response and overall defence mechanism against infectious organisms.
Evidence source(s) and strength of evidence	The source of information is clinical/safety data and medical literature.
Characterization of the risk	**Background incidence/prevalence** ***RA, sJIA, pJIA, GCA, and CAR T-cell CRS*** Incidence rates of serious infections in RA patients treated with TNF antagonists ranged from 6.0 to 10.1 events per 100 PY (Johnston et al. 2011; Nguyen-Khoa et al. 2010; Thyagarajan et al. 2012). Deaths due to infections: incidence rate ranged from 0.069 to 0.24 events per 100 PY (Lunt et al. 2010; Carmona et al. 2007). **COVID-19** The incidence of secondary infections or co-infection (bacterial, fungal, or viral) in patients hospitalized with COVID-19 in China ranged from 1% to 15% (Chen et al. 2020; Fu et al. 2020; Huang et al. 2020; Lin et al. 2020a;

Zhou et al. 2020). Common bacterial and fungal co-infections reported were *Acinetobacter baumannii, Klebsiella pneumoniae, Mycoplasma pneumoniae, Candida albicans, and Aspergillus flavus*, while common viral infections were influenza A, influenza B, respiratory syncytial virus, parainfluenza, Epstein-Barr virus, and adenovirus (Chen et al. 2020; Huang et al. 2020; Lin et al. 2020a; Zhou et al. 2020). A retrospective study reported 101 patients with confirmed COVID-19 admitted to the Zhijiang Medical Centre, China including 36 patients in the ICU. In total, 5 patients in the ICU (5.0%, 5 of 101 for all patients; 13.9%, 5 of 36 for patients in the ICU) were diagnosed with secondary bacterial infection (Fu et al. 2020). Another retrospective study of 393 hospitalized COVID-19 patients in the United States (New York) between 3 March and 27 March 2020 reported an incidence of 1% and 5.6% of viral co-infection and bacteraemia respectively (Goyal et al. 2020). A single centre study in the United States (Stanford) from 3 to 25 March 2020 identified a 20% prevalence of other viral respiratory infections among 115 hospitalized COVID-19 patients. The most common co-infections were rhinovirus/enterovirus (6.9%), respiratory syncytial virus (5.2%), and non-SARS-CoV-2 Coronaviridae (4.3%) (Kim et al. 2020). Zhou et al. (2020) observed an incidence of 59% for sepsis and 20% for septic shock in 191 patients hospitalized with COVID-19 (Zhou et al. 2020). Chen et al. (2020) reported the prevalence of 4% for septic shock in 99 patients with COVID-19−associated pneumonia (Chen et al. 2020).

Severity and nature of risk

In the IV RA all exposure population, upper respiratory tract infection was the most commonly reported type of infection and pneumonia and cellulitis were the most commonly reported types of serious infection. Reported serious infections, some with fatal outcome, included active tuberculosis, which may present with intrapulmonary or extrapulmonary disease, invasive pulmonary infections, including candidiasis, aspergillosis, coccidioidomycosis and pneumocystis jirovecii, pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arthritis. Cases of opportunistic infections have been reported. There is no evidence to date of an increasing risk of infection, serious infection, opportunistic infection, or tuberculosis over time. The most commonly reported fatal infections are pneumonia and sepsis.

Impact on Quality of Life

Tocilizumab may reduce resistance to infections; therefore, patients will be monitored for any signs or symptoms of infections. Patients may experience severe infections, which can sometimes be fatal. Vigilance for the timely detection of serious infection is recommended for patients receiving biologic treatments for moderate to severe RA, GCA, pJIA, or sJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute-phase reaction. The effects of

	tocilizumab on C-reactive protein, neutrophils, and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Similar monitoring requirements and recommendations for vigilance apply for COVID-19 patients.
Risk group or risk factors	Patients with diabetes reported a higher rate of serious infections compared to patients without diabetes. Patients treated with tocilizumab and taking background corticosteroids reported a higher rate of serious infections compared to patients not taking background corticosteroids. The rate of serious infections appears to increase with body weight. Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions (e.g., diverticulitis, diabetes, or ILD which may predispose patients to infections). Vigilance for timely detection of serious infections is recommended as signs and symptoms of acute inflammation may be lessened due to suppression of the acute-phase reactants.
Preventability	Prescribing information (EU SmPC) warnings caution when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions (e.g., diverticulitis, diabetes, and ILD) which may predispose patients to infections. Prescribing information warnings of need for increased vigilance regarding infections (including screening for latent tuberculosis [TB]) and recommendation to administer prophylactic treatment with standard antibacterial therapy in patients with latent TB prior to start of treatment with tocilizumab. Exclusion of any possibility of an active infection before initiating therapy in RA, sJIA, pJIA, and CRS (including screening for latent TB). Interruption of tocilizumab if a patient develops a serious infection until the infection resolves in these indications. Exclusion of any possibility of any concurrent active serious infection before initiating therapy in COVID-19. In the prescribing information, patients with COVID-19 are recommended to contact a healthcare professional immediately should they identify symptoms suggesting infection emergence to assure rapid evaluation and appropriate treatment.
Impact on the risk-benefit balance of the product	Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab. Patients may experience severe infection or frequent minor infections. There have been a number of serious infections reported including cellulitis (inflammation of the deep layers of skin), pneumonia, shingles (herpes zoster), sepsis (toxins in the blood or tissues), and reactivation of a viral infection

	(Epstein-Barr). The EU SmPC, Patient Information Leaflet (PIL) and the Educational Materials for Healthcare professionals and patients, mitigate the risk and severity, and also provide information regarding managing the risk.
Public health impact	Considering the preventability and the possibility to identify and manage patients with pre-existing risk factors, the public health impact is considered low.
Important identified risk **Complications of Diverticulitis** **This safety concern is considered an important identified risk for chronic tocilizumab dosing, but is assessed as important potential risk for the indication of COVID-19. For ease of review, all data related to COVID-19 are included below together with data related to chronic tocilizumab dosing.**	
Potential mechanism	Potential infectious aetiology (diverticulitis)
Evidence source(s) and strength of evidence	The source of information is clinical/safety data and medical literature.
Characterization of the risk	**Background incidence/prevalence** ***RA, sJIA, pJIA, GCA, and CAR T-cell CRS*** Myllykangas-Luosujärvi found a 6-fold excess mortality in patients with RA as a result of diverticular disease and postulated a link to medications used to treat RA (Myllykangas-Luosujärvi et al.1995). As corticosteroids are known to be associated with abscess development, and since both corticosteroids and NSAIDs have been implicated in perforated diverticular disease, Mpofu et al. undertook a case control study to investigate their association with the development of sigmoid diverticular abscess perforation in patients with and without RA (Mpofu et al. 2004). This demonstrated a strong association between corticosteroid treatment in the development of sigmoid diverticular abscess perforation in both rheumatic and non-rheumatic patients. Data from claims databases suggest that treatment with corticosteroids may be associated with an increased risk of gastrointestinal (GI) perforations with rates of 0.19 for biologics administered concomitantly with corticosteroids, and 0.3 for corticosteroids (Curtis et al.2012). **COVID-19**

	Limited information is available for GI perforation in patients with COVID-19. Associations between GI symptoms and COVID-19 have been evidenced but restricted to diarrhoea (CDC 2020a; WHO 2020a; WHO 2020b). In a retrospective cross-sectional study of 412 COVID-19 patients in Boston, United States, bowel wall perforation was observed in 1 patient (0.2%) (Bhayana et al. 2020). Zangrillo et al. (2020) reported a single case of GI perforation in a case series of 73 mechanically ventilated patients with confirmed COVID-19 admitted to the ICU in Milan, Italy (Zangrillo et al. 2020). A retrospective study included 81 adult COVID-19 patients with abdominal computed tomography performed from 1 April 2020 to 1 May 2020 in Brazil. A single case of intestinal perforation was observed on abdominal imaging accounting for the prevalence of 1% (Horvat et al. 2021). More individual case reports have been published as Alnabwani et al, who reported a case of a 72 year old patient with severe COVID 19 infection who developed perforation and Argan et al who reported 3 cases of gastrointestinal perforations secondary to COVID 19 (Alnabwani et al. 2022; Argan et al. 2021) **Mortality** No study described the mortality due to GI perforation in COVID-19 patients. **Seriousness/outcomes:** Most events resolved without sequelae (23/33). Two events were fatal. **Severity and nature of risk** Over 50% of the events involved diverticular perforation. There has been no change in the pattern or types of GI perforation events over time. **Impact on Quality of Life** Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation.
Risk group or risk factors	Tocilizumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. No study described the risk factors associated with GI perforation in COVID-19 patients.
Preventability	Prescribing information (EU SmPC) warning that tocilizumab should be used with caution in patients with a history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, should be evaluated promptly for early identification of GI perforation. Patients to be alerted to

	seek care in case of symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage, and/or unexplained change in bowel habits with fever.
Impact on the risk-benefit balance of the product	The rare event of perforation of the large bowel has been seen in subjects who had large bowel infections. Perforations may occur in the absence of clear symptoms or clinical signs. Tocilizumab should not be administered to patients with a history of complicated diverticulitis and should be used with caution in patients with a history of diverticulitis. The EU SmPC, Patient Information Leaflet and Educational Materials for Healthcare professionals and patients, mitigate the risk and severity and also provide information regarding managing the risk.
Public health impact	None.
Important identified risk **Neutropenia**	
Potential mechanism	The potential cause of neutropenia could be due to marginalization of neutrophils; however, the exact cause is uncertain.
Evidence source(s) and strength of evidence	The source of information is clinical/safety data and medical literature.
Characterization of the risk	***Background Incidence/Prevalence*** **COVID-19** In a pooled analysis of 66 paediatric patients with COVID-19, available from 12 studies (11 conducted in China and 1 in Singapore), neutropenia was reported in 6% of the patients (Henry et al. 2020). A retrospective study in Wuhan, China included 213 (mild/moderate: 175, severe: 38) COVID-19 patients who had been discharged or died by 15 March 2020. On laboratory examinations, overall, 20.2% patients reported lower neutrophil count [mild/moderate: (21.1%), severe: (15.8%)] (Hu et al. 2020). **Seriousness/outcomes:** Grade 3 and 4 CTCAE Grade data are provided above for both the IV and SC populations. In all indications studied to date, other than COVID-19, no correlation was observed between events of Grade 3 and 4 neutropenia and the occurrence of serious infections. There was a higher incidence of Grade 1 or 2

	neutropenia among patients weighing less than < 60 kg compared with patients in the other body weight categories. **Severity and nature of risk** Severe neutropenia may be associated with an increased risk of serious infections, although there has been no association between decreases in neutrophils and the occurrence of serious infections in clinical trials with TCZ to date for all indications other than COVID-19. **Impact on Quality of Life:** Decreases in neutrophil counts have been observed in RA, GCA, pJIA, and sJIA patients following treatment with TCZ.
Risk group or risk factors	Patients with an absolute neutrophil count (ANC) below 2 x 10^9/L have increased risks.
Preventability	In patients not previously treated with tocilizumab for all indications other than COVID-19, initiation is not recommended in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L. Monitoring during treatment is recommended and dose modification or treatment discontinuation is recommended based upon ANC. In patients who develop an ANC < 0.5 x 10^9/L continued treatment is not recommended. For patients with COVID-19 who develop an ANC <1 x 10^9/L, administration of treatment is not recommended. For patients with COVID-19, monitoring of neutrophil counts according to current standard clinical practices is recommended.
Impact on the risk-benefit balance of the product	Decreases in neutrophil and other white blood cell (WBC) counts have been associated with tocilizumab treatment. The EU SmPC, Patient Information Leaflet and Educational Materials for Healthcare professionals and patients, mitigate the risk and severity, and also provide information regarding managing the risk.
Public health impact	None
Important identified risk **Hepatotoxicity**	
Potential mechanism	It has been suggested that RA may be associated with non-alcoholic steatohepatitis (Ahmed et al. 2006) which may be mediated by the action of pro-inflammatory cytokines such as IL-6 and TNFα. IL-6 is elevated in patients with hepatitis (Hill et al.1992) and alcoholic liver disease (Hill et al.1992). Therefore, IL-6 and TNFα are involved in liver injury. Paradoxically, IL-6 is also considered a hepatoprotective factor because it

	stimulates hepatocyte proliferation and mediates the regeneration of liver tissue after injury (Taub et al. 2003; Cressman et al. 1996). IL-6-deficient mice develop increased liver injury in response to CCl4 in a TNFα mediated model of liver injury (Czaja et al.1995), suggesting IL-6 may function downstream of TNFα to ameliorate the injury response.
Evidence source(s) and strength of evidence	Based on a comprehensive, cumulative review of the clinical and safety data, FDA Adverse Event Reporting System and Eudravigilance databases and peer reviewed literature, a causal association between tocilizumab and serious hepatotoxicity has been identified. The assessment was further validated by an independent drug-induced liver injury (DILI) expert panel on selected cases.
Characterization of the risk	***Background Incidence/Prevalence*** ***RA, sJIA, pJIA, GCA, and CAR T-cell CRS*** The overall worldwide incidence rate of DILI variously specified in the general population is low (13.9-24.0 per 100,000 people). The incidence of acute and clinically significant DILI (requiring hospitalization or requiring specialist referral), however, is even lower (2.3-2.4 per 100,000 persons per year). At the more severe end of the spectrum, the occurrence of all-cause acute liver failure in the developed world is considered very rare (1 to 6 cases per 1,000,000 people every year). There is wide variability in the incidence rates of DILI in populations. This is due to the following reasons: • difficulty in recognizing and diagnosing DILI (e.g., there are no widely accepted criteria for diagnosis of DILI, instead it is a diagnosis of exclusion) • difficulty in attribution of the event to a drug. There are multiple drug agents commonly in use among the general population, and in particular among patients with RA, where many DMARDs as well as over-the-counter drugs frequently used (e.g., anti-inflammatories) are recognized to have hepatotoxic effects • under-ascertained predisposing factors (such as heavy alcohol consumption, use of herbal agents), as well as other factors prevalent in the RA population, such as obesity, diabetes, etc., that may impact individual background risk • trade-offs in undertaking population-level studies that of necessity cover less detail on larger numbers of individuals, versus undertaking small studies with comprehensive data detail on more circumscribed populations but with multiple exclusions, which by default are less representative of patients receiving medical care under real-world conditions or of target populations.

	Thus, the epidemiology data presented contains limitations which make the generalizability of these results, including extrapolation to the RA population challenging. This was further compounded by inconsistent definition of DILI across different publications examined, and reporting of results for only a single drug comparator, further limiting the generalization of the results for the RA population with or without biological DMARD. As MTX is used as background therapy in a large number of RA patients, the observations with this agent are relevant in this context. In the MTX SmPC (Nordimet 2022), MTX is described as hepatotoxic, particularly at high doses or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes, and periportal fibrosis have been reported. Changes may occur without prior signs of toxicity, so it is imperative that hepatic function be determined before treatment is started and monitored regularly throughout therapy. In addition, the MTX SmPC, describes that temporary increases in transaminases to 2-3 times of the upper limit of normal (ULN) have been reported by patients at a frequency of 13 - 20 %, however MTX should not be started or should be discontinued if there are any clinically relevant abnormalities of liver function tests or liver biopsy. **COVID-19** Liver injury is commonly associated in patients infected with coronavirus (COVID-19, SARS, and Middle East Respiratory Syndrome). A review of 12 studies from China found that in COVID-19 patients, the incidence of liver injury ranged from 14.8% to 53%, abnormal ALT from 13.3% to 28% and abnormal AST from 22.2% to 58% (Xu et al. 2020). A prospective cohort study reported on 1611 hospitalized patients with confirmed SARS-CoV-2 infection from 15 April 2020 through 31 July 2020 in 38 different hospitals from 11 Latin American countries. Abnormal liver tests on admission were present in 45.2% (95% CI: 42.7–47.7) of the cohort. Patients with elevated ALT, total bilirubin, and alkaline phosphatase accounted for 35.3%, 6.3%, and 19.4%, respectively. Among patients with elevated ALT, 32.6% of the cases presented moderate injury (2–5 times ULN) and 10.7% were severe (>5 times ULN) (Mendizabal et al. 2021). Retrospective laboratory diagnosis of 1099 Chinese COVID-19 patients from 11 December 2019 to 29 January 2020 showed ALT elevation (> 40 U/L) occurred in 21.3% (158/741) and AST elevation (> 40 U/L) in 22.2% (168/757) of patients. Severe COVID-19 patients had a higher probability of ALT elevation, and AST elevations compared with non-severe patients (28.1% vs. 19.8% and 39.4% vs. 18.2%, respectively). 10.5% (76/722)

	patients presented with abnormal bilirubin (> 17.1 µmol/liter) (Guan et al. 2020). Another retrospective study in China (from 20 January 2020 to 17 February 2020) evaluated laboratory findings of 202 clinically confirmed hospitalized COVID-19 patients. Elevated ALT (< 30 U/L for males and 19 U/L for females) was present in 101 (50.0%) patients. Elevated AST and total bilirubin were found in 16.8% and 8.4% of the patients, respectively. 67 (33.2%) patients had persistent abnormal liver function from admission till the last day of follow-up. Non-alcoholic fatty liver disease, identified as hepatic steatosis index >36 points and/or by abdominal ultrasound examination, was present in 37.6% of the patients (Ji et al. 2020). A retrospective study of 5700 COVID-19 patients in the United States (March-April 2020) identified 19 patients (0.4%) with cirrhosis, and 0.1% each with chronic hepatitis B and C as prevalent comorbidity before hospitalization (Richardson et al. 2020). Patients with liver injury were at 9-fold greater risk of severe COVID-19 (OR 9.04) (Cai et al. 2020). In addition, immune-mediated inflammation, such as cytokine storm and pneumonia-associated hypoxia, might also contribute to liver injury or even develop into liver failure in patients with COVID-19 who are critically ill (Zhang et al. 2020a). **Adverse Reactions in Double-Blind RA Studies** The approximate incidence of MTX-attributed (i.e., placebo-rate subtracted) adverse reactions in 12 to 18-week double-blind studies of patients (n=128) with RA treated with low dose oral (7.5 to 15 mg/week) pulse MTX, are listed in the MTX US package insert and include 15% of patients with elevated liver function tests (LFTs). Persistent abnormalities in LFTs were reported to precede appearance of fibrosis or cirrhosis in this population. Virtually all of these patients were on concomitant NSAIDs and some were also taking low dosages of corticosteroids. It is unknown whether even longer use will increase these risks. **Seriousness/outcomes** Mild and moderate elevations of hepatic transaminases have been observed with tocilizumab treatment. Increased frequency of these elevations was observed when drugs, which are known to cause hepatotoxicity (e.g. MTX), were used in combination with tocilizumab. Serious DILI, including acute liver failure, hepatitis, and jaundice, have been observed with tocilizumab. Cases of liver failure resulting in liver transplantation have been reported. In post-marketing analysis of study WA25204, one serious event of drug-induced hepatitis with hyperbilirubinemia was reported in association with tocilizumab treatment which resolved. **Severity and nature of risk:**

	Eight cases were assessed as TCZ-related moderate-severe liver injury. Overall the median latency for these cases was 98 days (range: 14 to 1825 days). The cases include two cases of acute liver failure/liver transplant, five cases of CTCAE Grade 4 hepatotoxicity, and one case with Grade 2 hepatotoxicity. These eight TCZ-related DILI cases represent a small proportion of the estimated 1,066,849 patients exposed to TCZ to date, resulting in a crude rate of ~8 cases/1,000,000 patients, representing a rare event frequency. **Impact on Quality of Life** Serious DILI, including acute liver failure, hepatitis, and jaundice, have been observed with tocilizumab. Cases of liver failure resulting in liver transplantation have been reported. In RA, GCA, pJIA, and sJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. The recommended dose modifications, including tocilizumab discontinuation, should be based on transaminases levels, in line with SmPC Section 4.2. For ALT or AST elevations □ 3–5 x ULN, RoActemra treatment should be interrupted (RoActemra EU SmPC). In COVID-19 patients, ALT/AST should be monitored according to current standard clinical practices.
Risk group or risk factors	Treatment with tocilizumab particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases; therefore, caution should be exercised when considering treatment of any patients with active hepatic disease or hepatic impairment. Patients hospitalized with COVID-19 frequently have elevated ALT or AST levels. Multiorgan failure with involvement of the liver is recognized as a complication of severe COVID-19. (Zhang et al. 2020a).
Preventability	In all indications other than COVID-19, caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated transaminases ALT or AST above 1.5 × ULN. In patients with elevated ALT or AST above 5 × ULN, treatment is not recommended. In RA, GCA, pJIA, and sJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. The recommended dose modifications, including tocilizumab discontinuation, based on transaminases levels, in line with SmPC Section 4.2. For ALT or AST elevations > 3–5 x ULN, tocilizumab treatment should be interrupted. In patients with COVID-19, monitoring of ALT/AST according to current standard clinical practices is recommended. In patients with COVID-19 with elevated ALT or AST > 10 × ULN, initiation of treatment with tocilizumab is not recommended.

Impact on the risk-benefit balance of the product	The frequency of the observed serious hepatotoxicity events is considered rare and the benefit-risk profile of tocilizumab in the approved indications remains favourable. The risk of hepatotoxicity is described in the EU SmPC, Patient Information Leaflet and Educational Materials for Healthcare professionals and patients and also provides information regarding AST/ALT monitoring to help mitigate and manage the risk. The recommended tocilizumab dose modification (reduction, interruption or discontinuation) are already mentioned in the approved labels. Given the well-described and managed safety profile of tocilizumab and the known efficacy, benefit risk of tocilizumab in the indicated treatment populations remains positive.
Public health impact	None
Important potential risk **Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events**	
Potential mechanism	As observed with other biological DMARDs, increases in lipid parameters may reflect the pharmacodynamic effect of tocilizumab on suppression of inflammation in patients with RA.
Evidence source(s) and strength of evidence	The source of information is clinical/safety data and medical literature.
Characterization of the risk	**Background incidence/prevalence** ***RA, sJIA, pJIA, GCA, and CAR T-cell CRS*** Myocardial infarction (MI): 10 per 1000 PY in RA patients; 7.1/1000 PY in patients without arthritis (Watson et al. 2003); MI in RA patients: 0.53 per 100 PY compared with 0.28 per 100 PY in non-RA patients (Solomon et al.2006, Suissa et al. 2006). Cerebrovascular events: 0.51 per 100 PY (Solomon et al.2006, Solomon et al.2012). Congestive heart failure: to 0.5 per 100 PY in the general population with a steep rise with increasing age (Murray-Thomas and Cowie et al. 2003) 2.0 per 100 PY in RA (Nicola et al. 2005).

COVID-19

The prevalence of elevated lipid levels such as hyperlipidaemia, dyslipidaemia, and hypercholesterolemia in patients with COVID-19 ranged from 5% to 46.2% (Zhang et al. 2020b; Grasselli et al. 2020; Lodigiani et al. 2020; Petrilli et al. 2020). The low prevalence of 5% for hyperlipidemia was observed from a study of 140 hospitalized COVID-19 patients in China (Zhang et al. 2020b). In Europe, a retrospective case series of 1,591 Italian ICU patients with laboratory-confirmed COVID-19 found 18% had hypercholesterolemia (Grasselli et al. 2020). Among 388 Italian COVID-19 patients admitted to either ICU or general ward, 19.6% had dyslipidemia (Lodigiani et al. 2020). Studies from the United States found relatively higher prevalence of elevated lipid profiles compared to studies from Europe and China: of 5,279 COVID-19 patients identified between 1 March 2020 and 8 April 2020 in New York, 32.5% had hyperlipidemia (Petrilli et al. 2020).

The COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) estimated that as of 28 February 2021, in the United States, the prevalence of CVD was 36.7% in adults and 5.5% in paediatric COVID-19 hospitalized patients (COVID-NET). A retrospective study of 393 COVID-19 patients in the United States between 3 and 27 March 2020, reported 54 (13.7%) patients had coronary artery disease at the baseline. Heart failure and myocardial infarction was reported in 1.8% and 3.6% of patients, respectively as an in-hospital complication (Goyal et al. 2020).

Mortality

In a study on 107 COVID-19 patients, 2 patients died due to acute myocardial infarction and sudden cardiac arrest respectively, accounting for an overall mortality of 2.0% due to CVD. Cardiovascular disease was found to be associated with increased risk (OR: 7.972) of death in COVID-19 patients as compared to patients without underlying CVD (Wang et al. 2020). COVID-19 patients with pre-existing cardiac injury had a significantly higher in-hospital mortality rate (42 of 82 [51.2%]) compared with those without myocardial injury (15 of 335 [4.5%]). Among patients with myocardial injury, Troponin I elevation was associated with higher mortality rates (Shi et al. 2020).

Seriousness/outcomes

In the TCZ clinical trials, no association between increases in lipids and cardiovascular morbidity has been identified to date.

Severity and nature of risk

Elevations in LDL cholesterol responded to treatment with lipid-lowering agents.

In the TCZ clinical trials, no association between increases in lipids and cardiovascular morbidity has been identified to date.

	Impact on Quality of Life Increases in total cholesterol, LDL, and triglyceride levels have been observed in patients following treatment with TCZ. The relationship of these elevations and the risk for cardiovascular/cerebrovascular disease is unknown.
Risk group or risk factors	Patients with underlying CVD are at higher risk for severe illness from COVID-19 (CDC 2020b). Of 41 Chinese COVID-19 patients admitted to hospital, 6 (15%) had underlying CVD; patients with CVD comprised 23% of those requiring ICU care and 11% of those who did not (Huang et al. 2020).
Preventability	Lipid parameters such as total cholesterol, triglycerides, and/or low LDL should be monitored during the first 4-8 weeks of tocilizumab treatment. Patients should be managed according to clinical guidelines for management of hyperlipidaemia.
Impact on the risk-benefit balance of the product	Increases in total cholesterol, LDL, and triglycerides have been observed following tocilizumab treatment. The EU SmPC, Patient Information Leaflet and Educational Materials for Healthcare professionals and patients, mitigate the risk severity and also provide information regarding managing the risk.
Public health impact	Potential impact on public health is minimal given the low frequency of cardiovascular/cerebrovascular complications attributable to tocilizumab.
Important potential risk **Malignancies**	
Potential mechanism	Tocilizumab is an immunosuppressive agent and may therefore result in an increased risk of malignancy.
Evidence source(s) and strength of evidence	The source of information is clinical/safety data and medical literature.
Characterization of the risk	**Background incidence/prevalence** ***RA, sJIA, pJIA, GCA, and CAR T-cell CRS*** A higher risk of cancer has consistently been reported in RA patients compared with the general population. This risk appears to be particularly higher for lymphoproliferative malignancies such as non-Hodgkin's lymphoma and multiple myeloma in RA patients compared with the general population (Mellemkjaer et al.1996; Prior et al.1985).

	Incidence rates for the TNFα inhibitor users from observational studies ranged from 0.38 events per 100 PY (Du Pan et al. 2009) to 1.9 events per 100 PY (excluding non- malignant skin cancer (NMSC); CIs not reported) (Setoguchi et al. 2006) **COVID-19** In a systematic review of 17 studies involving 32,404 patients worldwide, the pooled prevalence of malignancies was 3.5% (95% CI: 1.7, 5.8), and ranged from 0.5% to 21% in COVID-19 patients (Ofori-Asenso et al. 2020). A meta-analysis was performed of 11 studies including a total of 3,661 Chinese COVID-19 patients. In studies with less than 100 patients, the overall prevalence of malignancies was 3.0% (95% CI: 1%, 6%), but in studies with more than 100 patients, the overall prevalence was 2.0% (95% CI: 1%, 3%) (Desai 2020). In a retrospective study of 388 hospitalized Italian COVID-19 patients between 13 February and .10 April 2020, 6.4% of patients had active cancer. Prevalence was 3.3% and 7.0%, in ICU patients and general ward patients, respectively (Lodigiani 2020). A retrospective multicenter study including 105 COVID-19 patients with cancer reported a case fatality of 11.4%. COVID-19 patients with cancer had an odds ratio of 2.17 (95% CI: □ 0.806, 5.149; p □ 0.064) for fatality as compared to the patients without cancer (Dai 2020). Another retrospective study from Turkey reported that among 4489 patients hospitalized with COVID-19, 1.6% of the patients had cancer. The mortality among cancer patients due to COVID-19 was significantly higher as compared to non-cancer patients (23.9% vs. 1.51%) (Erdal et al. 2021). **Severity and nature of risk** The rates and types of malignancies observed in the IV and SC TCZ all exposure populations were consistent over time. Impact on Quality of Life: There have been reports of cancer in patients treated with TCZ; no individual type of tumor was more common than expected in this population.
Risk group or risk factors	None identified.
Preventability	Not applicable.
Impact on the risk-benefit balance of the product	There have been very few reports of cancer with tocilizumab, and no individual tumour type predominates. Despite the low event rate, a potential risk cannot be excluded. Tocilizumab treatment should not be started in subjects with cancer. The EU SmPC, Patient information leaflet and

	Educational Materials for Healthcare professionals and patients, provide information regarding the risk.
Public health impact	The risk of malignancy is known to be increased in patients with RA and with some treatments commonly used in RA, such as MTX and biologic DMARDs. A Food and Drug Administration (FDA) alert was published requiring the manufacturers of TNF blockers to update the Boxed Warning in the prescribing information to alert healthcare professionals of an increased risk of lymphoma and other malignancies in children and adolescents treated with TNF blockers. Europe, Middle East, and Africa 2010 priorities also identified the risk of malignancy as one of the potential long-term adverse effects of immunomodulators, including the anti-TNFs, rituximab, and tocilizumab. Concern is high because of the seriousness of the risk; however, the public health impact is considered low because of the low frequency of such events.
Important potential risk **Immunogenicity**	
Potential mechanism	Immune response to the infusion or injection of a protein (IgG)
Evidence source(s) and strength of evidence	The source of information is clinical/safety data.
Characterization of the risk	No correlation between the development of anti-tocilizumab antibodies and serious hypersensitivity or anaphylaxis has been observed in clinical trials with Tyenne.
Risk group or risk factors	None identified.
Preventability	Not known.
Impact on the risk-benefit balance of the product	The incidence of anti-drug antibodies to TCZ is low in patients with adult RA, pJIA, GCA, or sJIA. No correlation between the development of anti-TCZ antibodies and the safety and efficacy response to TCZ has been observed in clinical trials with TCZ (IV or SC).
Public health impact	Not applicable.

SVII.3.2 Presentation of the missing information

There is no missing information for Tyenne (tocilizumab) requiring further characterization.

Part II: Module SVIII - Summary of safety concerns

Table 7. Details of important identified and potential risks of Tyenne

Safety Concerns	
Important identified risks	• Serious Infections* • Complications of Diverticulitis* • Neutropenia • Hepatotoxicity
Important potential risks	• Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events • Malignancies • Immunogenicity
Missing information	None

*The safety concerns Serious Infection and Complications of Diverticulitis are considered important identified risks for chronic tocilizumab dosing but are assessed as important potential risks for the indication of COVID-19.

Part III: Pharmacovigilance Plan

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities will be carried out for the important identified and potential risks described above.

The robust pharmacovigilance system established by Fresenius Kabi enables collection and analysis of safety data from multiple sources including spontaneous notification, literature, regulatory authorities, commercial partners as well as detection and management of signals and risks. When safety information is received, it is triaged and entered into a safety database. Individual case safety reports are reviewed by a safety physician on a case-by-case basis for completeness and accuracy and to assess the seriousness, causal relationship between an adverse event and the drug, as well as the expectedness. If relevant information is missing, Fresenius Kabi will conduct follow-up investigations to collect additional data such as outcome, concomitant medications, concurrent disease(s), etc.

Aggregate safety data is reviewed periodically and compared to the previous period, taking into account the accumulated safety knowledge for the product to identify any safety signals or trends. Furthermore, a list of adverse events of special interest (AESI) will be closely monitored on an ongoing basis using appropriate Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) or relevant Preferred Terms (PT) when no SMQ is available. If a signal is detected, Fresenius Kabi will assess the data in order to validate the signal taking into account previous awareness, strength of the evidence, as well as clinical relevance.

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

Specific adverse reaction follow-up forms for:

- Serious infections
- Complications of diverticulitis (including GI perforation)
- Hepatotoxicity
- Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events
- Malignancies

The purpose of these Specific adverse drug reaction follow-up forms is to collect information in a standardized manner and monitor the frequency and nature of AEs emerging during post-marketing use.

For further details on the specific adverse reaction follow-up forms please see Annex 4 of the RMP.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be carried out for Tyenne at this point.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for Post-authorization Efficacy Studies

IV.1 Planned and ongoing post-authorization imposed efficacy studies that are conditions of the marketing authorization or that are specific obligations

There are currently no planned post-authorization efficacy studies for Tyenne for IV or SC administration for COVID-19, RA, early RA, GCA, pJIA, and sJIA.

Part V: Risk Minimization Measures

Risk Minimization Plan

V.1 Routine risk minimization measures

Table 8 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risk: **Serious infections***	**Routine risk communication:** SmPC IV and SC administration: Section 4.3 Contraindications: Active, severe infections with the exception of COVID-19 (see Section 4.4) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet IV and SC administration: Section 2 Warnings and precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine.
Important identified risk: **Complications of Diverticulitis***	**Routine risk communication**: SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet Section 2 Warnings and precautions. Section 4 Possible side effects

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: None **Other risk minimization measures beyond the Product Information**: Pack size: None Medicine's legal status: prescription only medicine.
Important identified risk: **Neutropenia**	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects/Laboratory evaluations Patient Information leaflet Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine.
Important identified risk: **Hepatoxicity**	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet Section 2 Warnings and precautions. Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimization activities
	In patients with RA, GCA, pJIA, sJIA, ALT, and AST should now be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine.
Important potential risk: **Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events**	**Routine risk communication:** SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet Section 2 Warnings and precautions. Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine.
Important potential risk: **Malignancies**	**Routine risk communication:** SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet Section 2 Warnings and precautions. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None

Safety concern	Routine risk minimization activities
	Other risk minimization measures beyond the Product Information: Pack size: None Medicine's legal status: prescription only medicine.
Important potential risk: **Immunogenicity**	**Routine risk communication:** SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine.

*The safety concerns Serious infection and Complications of Diverticulitis are considered important identified risks for chronic tocilizumab dosing but are assessed as important potential risks for the indication of COVID-19.

V.2 Additional risk minimization measures

Additional risk minimization measures are targeted for the indications of RA, GCA, pJIA, and sJIA. The CRS indication, an acute life-threatening condition treated in the hospital setting by oncologists, has a different benefit-risk profile relative to previously approved indications. Given this therapeutic context, no additional risk minimization measure is required for treatment of CRS. Use of Tyenne for CRS and its risk profile are in line with those specified in the EU SmPC. The additional risk-minimization measures in Table 9 are not applicable for COVID-19 indication.

Table 9 Additional risk minimization measures by safety concern

Important identified risk **Serious Infections***	
Additional Risk Minimization Measure	Patient Card

Objectives	The objective of the measure is to ensure that patients seek medical attention early, to facilitate timely diagnosis and treatment of serious infections.
Rationale for the additional risk minimization activity	To inform both the patient and health care providers that tocilizumab increases the risk of getting infections which can become serious if not treated and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of infections.
Target audience and planned distribution path	Patient
Plans for evaluating the effectiveness of the interventions and criteria for success	The intervention will be assessed as effective if risk/benefit assessment remains unchanged over time as per PBRER.
Important identified risk **Complications of Diverticulitis***	
Additional Risk Minimization Measure	Patient Card
Objectives	The objective of the measure is to ensure that patients seek medical attention early, to facilitate timely diagnosis and treatment of complications of diverticulitis.
Rationale for the additional risk minimization activity	To inform both the patient and health care providers that patients using tocilizumab may develop complications of diverticulitis which can become serious if not treated, and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of such events.
Target audience and planned distribution path	Patient
Plans for evaluating the effectiveness of the interventions	The intervention will be assessed as effective, if risk/benefit assessment remains unchanged over time per PBRER.

and criteria for success	
Important identified risk **Hepatoxicity**	
Additional Risk Minimization Measure	Patient Card
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and to facilitate timely diagnosis and treatment of hepatoxicity.
Rationale for the additional risk minimization activity	To inform both the patient and health care providers that patients using tocilizumab may develop hepatotoxicity, and on rare occasions, patients have experience serious life-threatening liver problems, some of which have required liver transplant. Patients will be monitored closely for changes in blood liver enzyme level.
Target audience and planned distribution path	Patient
Plans for evaluating the effectiveness of the interventions and criteria for success	The intervention will be assessed as effective, if risk/benefit assessment remains unchanged over time per PBRER.

*The safety concerns Serious infection and Complications of Diverticulitis are considered important identified risks for chronic tocilizumab dosing, but are assessed as important potential risks for the indication of COVID-19.

Removal of Additional Risk-Minimization Activities

The implementation of additional risk minimisation measures (aRMMs) for tocilizumab as outlined in the EU RMP for the reference product has historically supported the safe use of the active substance through targeted educational materials. These materials contributed to increased awareness among healthcare professionals regarding potential risks and appropriate risk minimisation actions.
Based on the totality of available data, including post-marketing experience with tocilizumab and the well-characterised safety profile of the active substance, no increase in reporting trends for the relevant risks has been observed, and no impact on the overall benefit–risk balance has been identified.

For TYENNE (tocilizumab), the MAH considers that the identified risks are adequately addressed through routine risk minimisation measures as described in the SmPC and package leaflet. Therefore, the continued distribution of certain educational materials (HCP brochure, dosing guide, and patient brochure) is not considered warranted.
This position is supported by evidence generated for the reference product, including a Drug Safety Report (DSR) (Report No. 1148065), which evaluated the relevance of these additional risk minimisation measures.

V.3 Summary of risk minimization measures

Table 10 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk: **Serious infections***	**Routine risk minimization measures:** SmPC (IV and SC formulation): • Section 4.3 Contraindications Active, severe infections (see Section 4.4) • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information leaflet (IV and SC formulation): • Section 2 Warnings and precautions • Section 4 Possible side effects: tell a doctor straightaway. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up forms **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** Patient Card	
Important identified risk: **Complications of Diverticulitis***	**Routine risk minimization measures:** SmPC: • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information leaflet • Section 2 Warnings and precautions. • Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up forms **Additional pharmacovigilance activities:** • None
Important potential risk: **Neutropenia**	**Routine risk minimization measures:** SmPC:	**Routine pharmacovigilance activities beyond adverse**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects/Laboratory evaluations Patient Information leaflet • Section 2 Warnings and precautions. • Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** • Pack size: None • Legal status: prescription only medicine • **Additional risk minimization measures:** NA	**reactions reporting and signal detection:** Specific adverse drug reaction follow-up forms, i.e. for events of special interest will collect neutrophil data in cases of serious infection **Additional pharmacovigilance activities:** • None
Important identified risk: **Hepatoxicity**	**Routine risk minimization measures:** SmPC: • Section 4.2 Posology and method of administration (IV administration) • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information Leaflet (IV/SC administration)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up forms **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Section 2 Warnings and precautions. • Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: In patients with RA, GCA, pJIA, sJIA, ALT and AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. **Other risk minimization measures beyond the Product Information:** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • Patient Card	

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important potential risk: **Elevated Lipid Levels and Potential Risk of Cardiovascular/ Cerebrovascular Events**	**Routine risk minimization measures:** SmPC: • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information leaflet • Section 2 Warnings and precautions. • Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other risk minimization measures beyond the Product Information:** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** NA	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up forms **Additional pharmacovigilance activities:** • None
Important potential risk: **Malignancies**	**Routine risk minimization measures:** SmPC: • Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Patient Information leaflet • None **Routine risk minimization activities recommending specific**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up forms **Additional pharmacovigilance activities:** • None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	clinical measures to address the risk: None **Other risk minimization measures beyond the Product Information:** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** NA	
Important potential risk: **Immunogenicity**	**Routine risk minimization measures:** SmPC: • Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** • Pack size: None • Legal status: prescription only medicine **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

*The safety concerns Serious infection and Complications of Diverticulitis are considered important identified risks for chronic tocilizumab dosing but are assessed as important potential risks for the indication of COVID-19.

Part VI: Summary of the Risk Management Plan for Tyenne (tocilizumab)

This is a summary of the Risk Management Plan for Tyenne . The RMP details important risks of Tyenne , how these risks can be minimized, and how more information will be obtained about Tyenne risks and uncertainties (missing information).

The SmPC and PIL give essential information to healthcare professionals and patients, respectively on how tocilizumab should be used.

This summary of the RMP for Tyenne 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 Tyenne RMP.

I. The medicine and what it is used for

Tyenne is authorized for rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, giant cell arteritis, cytokine release syndrome induced by CAR T-cell therapies and COVID-19 infection. It contains tocilizumab as the active substance and it is given by intravenous infusion or subcutaneous injection.

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

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Tyenne, together with measures to minimize such risks, are outlined below.

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

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

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PBRER 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 Tyenne is not yet available, it is listed under 'missing Information' below.

II.A List of important risks and missing information

Important risks of Tyenne are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tyenne. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Serious Infections* • Complications of Diverticulitis* • Neutropenia • Hepatotoxicity
Important potential risks	• Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events • Malignancies • Immunogenicity
Missing information	None

*The safety concerns Serious infection and Complications of Diverticulitis are considered important identified risks for chronic tocilizumab dosing but are assessed as important potential risks for the indication of COVID-19.

II.B Summary of important risks

Important identified risk **Serious Infections***	
Evidence for linking the risk to the medicine	The source of information is clinical/safety data and medical literature.
Risk factors and risk groups	Patients with diabetes reported a higher rate of serious infections compared to patients without diabetes. Patients treated with tocilizumab and taking background corticosteroids reported a higher rate of serious infections compared to patients not taking background corticosteroids. The rate of serious infections appears to increase with body weight. Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring or chronic infections

	or with underlying conditions (e.g., diverticulitis, diabetes, or ILD which may predispose patients to infections).
Risk minimization measures	**Routine risk communication:** SmPC IV and SC administration: Section 4.3 Contraindications: - Active, severe infections (see Section 4.4) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet IV and SC administration: Section 2 Warnings and precautions Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** Patient Card
Additional pharmacovigilance activities	None
Important identified risk **Complications of Diverticulitis***	
Evidence for linking the risk to the medicine	The source of information is clinical/safety data and medical literature.
Risk factors and risk groups	Tocilizumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis.

Risk minimization measures	**Routine risk communication:** SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet Section 2 Warnings and precautions. Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** Patient Card
Additional pharmacovigilance activities	None
Important identified risk **Neutropenia**	
Evidence for linking the risk to the medicine	The source of information is clinical/safety data and medical literature.
Risk factors and risk groups	Risk group - patients with an absolute neutrophil count (ANC) below 2 x 10^9/L.
Risk minimization measures	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects/Laboratory evaluations Patient Information leaflet

	Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** NA
Additional pharmacovigilance activities	None
Important identified risk **Hepatoxicity**	
Evidence for linking the risk to the medicine	Based on a comprehensive, cumulative review of the clinical and safety data, FDA Adverse Event Reporting System and EudraVigilance databases and peer reviewed literature, a causal association between tocilizumab and serious hepatotoxicity has been identified. The assessment was further validated by an independent drug-induced liver injury (DILI) expert panel on selected cases.
Risk factors and risk groups	Treatment with tocilizumab particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases; therefore, caution should be exercised when considering treatment of any patients with active hepatic disease or hepatic impairment.
Risk minimization measures	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet Section 2 Warnings and precautions. Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:**

	In patients with RA, GCA, pJIA, sJIA, ALT, and AST should now be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** Patient Card
Additional pharmacovigilance activities	None
Important potential risk **Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events**	
Evidence for linking the risk to the medicine	The source of information is clinical/safety data and medical literature.
Risk factors and risk groups	None identified.
Risk minimization measures	**Routine risk communication:** SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet Section 2 Warnings and precautions. Section 4 Possible side effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** NA

Additional pharmacovigilance activities	None
Important potential risk **Malignancies**	
Evidence for linking the risk to the medicine	The source of information is clinical/safety data and medical literature.
Risk factors and risk groups	None identified.
Risk minimization measures	**Routine risk communication:** SmPC Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Patient Information leaflet Section 2 Warnings and precautions. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** NA
Additional pharmacovigilance activities	None
Important potential risk **Immunogenicity**	
Evidence for linking the risk to the medicine	The source of information is clinical/safety data.

Risk factors and risk groups	None identified.
Risk minimization measures	**Routine risk communication:** SmPC Section 4.8 Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: prescription only medicine. **Additional risk minimization measures:** NA
Additional pharmacovigilance activities	None

*The safety concerns Serious infection and Complications of Diverticulitis are considered important identified risks for chronic tocilizumab dosing but are assessed as important potential risks for the indication of COVID-19.

II.C Post-authorization development plan

II.C.1 Studies that are conditions of the Marketing Authorization

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

II.C.2 Other studies in post-authorization development plan

There are no studies planned.

Annex 4 – Specific adverse drug reaction follow-up forms

Complications of diverticulitis (including GI perforation)

Hepatotoxicity

Serious Infections

Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events

Malignancies

Tocilizumab Guided Questionnaire
Gastrointestinal Perforation and Related Events

AER:		Local Case ID:	
Site No:		Patient Date of Birth (dd-MMM-yyyy):	
Patient ID/Initials:		Patient Gender:	☐ M ☐ F
Patient Weight	☐ kg ☐ lb	Patient Height	☐ cm ☐ inch

Gastrointestinal perforations and related events have been observed in some patients treated with Tocilizumab.

By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Reporter Information
Name of reporter completing this form: (if other than addressee, provide contact information below)
Health Care Provider? ☐ Yes ☐ No Specify:
Phone Number: Fax Number: Email Address:

Reported Term

Description of the event
Hospital Admission ☐ Yes (Admission Date MM/DD/YYYY): ☐ No (Discharge Date MM/DD/YYYY):
Onset Date (MM/DD/YYYY)
Stop Date (MM/DD/YYYY)
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐ Death Date of Death (MM/DD/YYYY) ☐ **Life-Threatening** (use only if patient was at immediate risk of death due to event) ☐ **Initial/Prolonged Hospitalization** ☐ **Congenital Anomaly/Birth Defect** ☐ **Persistent or Significant Disability** ☐ **Medically Significant** (important medical events that may jeopardize the patient and may require

Page 1 of 5

medical/surgical intervention to prevent the other outcomes) ☐ **Non-Serious**	
Related to Tocilizumab?	☐Yes ☐ No
Event led to surgery	☐Yes Please specify: ☐No
Outcome of the event:	☐Persisting ☐ Improved ☐Recovered with sequelae ☐Resolved ☐Unknown ☐Worsened ☐ Death

Drug therapy details – Tocilizumab			
Indication:			
Start Date (MM/DD/YYYY)			
Starting Dose	_____ mg/kg _____ Total monthly dose (mg)		
Route			
Frequency	☐ Monthly ☐Other, please specify:		
History of 4 most recent Infusions prior to Adverse Event (AE)	Date (MM/DD/YYYY)	Dose	Action Taken in response to AE?
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued

Treatment for the event		
What treatment was initiated for the event? (including any pre-hospitalization treatment)		
Treatment	Dosing Regimen	Dates of Therapy (MM/DD/YYYY tc MM/DD/YYYY)

Page 2 of 5

Risk Factors			
Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.			
Gastric ulcers Specify:	☐History	☐Concurrent	☐Not present
Duodenal ulcers Specify:	☐History	☐Concurrent	☐Not present
Inflammatory bowel disease Specify:	☐History	☐Concurrent	☐Not present
Diverticulosis Specify:	☐History	☐Concurrent	☐Not present
Diverticulitis Specify:	☐History	☐Concurrent	☐Not present
Gastrointestinal obstruction Specify:	☐History	☐Concurrent	☐Not present
Abdominal pain	☐History	☐Concurrent	☐Not present
Abdominal abscess	☐History	☐Concurrent	☐Not present
Fistula	☐History	☐Concurrent	☐Not present
Gastrointestinal bleeding Specify:	☐History	☐Concurrent	☐Not present
Cancer Specify:	☐History	☐Concurrent	☐Not present
Smoking	☐History	☐Concurrent	☐Not present
Alcohol abuse	☐History	☐Concurrent	☐Not present
Abdominal Surgery Specify:	☐History	☐Concurrent	☐Not present
Colonoscopy	☐History	☐Concurrent	☐Not present
Endoscopy	☐History	☐Concurrent	☐Not present
Other Please Specify:	☐History	☐Concurrent	☐Not present

Page 3 of 5

Laboratory tests/ Imaging
Please provide SI (International System of Units) if available. Otherwise, as reported.
Please attach all laboratory results and imaging tests. ☐Labs Attached

Please indicate if any of the following tests have been performed, and the result:

	Baseline Value (Prior to TCZ Use)	Date of Baseline Test (MM/DD/YYYY)	Date of Test (MM/DD/YYYY)	Test Results (include units)	Reference Range (If Applicable)	Pending?
CBC						☐Yes
Laparoscopy						☐Yes
Colonoscopy						☐Yes
Sigmoidoscopy						☐Yes
EGD (Esophagogastro-duodenoscopy)						☐Yes
CT Scan						☐Yes
MRI						☐Yes
Other						☐Yes

Past/Concomitant Medications
☐Medication List Attached

		Dose	Route	Frequency	Past, Concomitant, or N/A
Methotrexate	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Other DMARDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Biologic DMARDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
NSAIDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Corticosteroids Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
PPIs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
H2 blockers Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Stool softeners Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Antibiotics	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Surgery	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Other Please specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A

Page 4 of 5

Please provide any further relevant information about the Adverse Event. Please indicate if there have been any significant changes from the initial report.

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Page 5 of 5

Tocilizumab Guided Questionnaire
Medically Significant Hepatic Event

AER:		Local Case ID:	
Site No:		Patient Date of Birth (dd-MMM-yyyy):	
Patient ID/Initials:		Patient Gender:	☐ M ☐ F
Patient Weight	☐ kg ☐ lb	Patient Height	☐ cm ☐ inch

Hepatic events have been observed in some patients treated with Tocilizumab.
By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Reporter Information
Name of reporter completing this form: (If other than addressee, provide contact information below)
Health Care Provider? ☐ Yes ☐ No Specify:
Phone Number: Fax Number: Email Address:

Reported Term

Description of the event
Hospital Admission ☐ Yes (Admission Date MM/DD/YYYY): ☐ No (Discharge Date MM/DD/YYYY):
Onset Date (MM/DD/YYYY)
Stop Date (MM/DD/YYYY)
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐ **Death** Date of Death (MM/DD/YYYY) ☐ **Life-Threatening** (use only if patient was at immediate risk of death due to event) ☐ **Initial/Prolonged Hospitalization** ☐ **Congenital Anomaly/Birth Defect** ☐ **Persistent or Significant Disability** ☐ **Medically Significant** (important medical events that may jeopardize the patient and may require medical/surgical intervention to prevent the other outcomes) ☐ **Non-Serious**
Related to Tocilizumab? ☐ Yes ☐ No

Page 1 of 5

Outcome of the event:	☐Persisting ☐ Improved ☐Recovered with sequelae ☐Resolved ☐Unknown ☐Worsened ☐Death
Was the hepatic event associated with ALT/AST >3xULN?	☐No ☐Yes: Provide Date of abnormal labs (MM/DD/YYYY): ☐Unknown
Was the hepatic event associated with total bilirubin of >2xULN?	☐No ☐Yes: Provide Date of abnormal labs (MM/DD/YYYY): ☐Unknown
Did TCZ dose modification occur in association with lab abnormality?	☐No ☐Yes: Provide Date of dose modification (MM/DD/YYYY): ☐Unknown
Did DMARD dose modification occur in association with lab abnormality?	☐No ☐Yes: Provide Date of dose modification (MM/DD/YYYY): ☐Unknown

Drug therapy details – Tocilizumab			
Indication:			
Start Date (MM/DD/YYYY)			
Starting Dose	_____ mg/kg _____ Total monthly dose (mg)		
Route			
Frequency	☐ Monthly ☐Other, please specify:		
History of 4 most recent Infusions prior to Adverse Event (AE)	Date (MM/DD/YYYY)	Dose	Action Taken in response to AE?
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued

Page 2 of 5

Treatment for the event		
What treatment was initiated for the event? (including any pre-hospitalization treatment)		
Treatment	**Dosing Regimen**	**Dates of Therapy (MM/DD/YYYY to MM/DD/YYYY)**

Risk Factors			
Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.			
Pre-existing hepatobiliary Disorder Specify:	☐History	☐Concurrent	☐Not present
Pancreatic Disorder Specify:	☐History	☐Concurrent	☐Not present
Drug Allergy Specify:	☐History	☐Concurrent	☐Not present
Previous Drug Reactions Specify:	☐History	☐Concurrent	☐Not present
Auto-Immune Disease Specify:	☐History	☐Concurrent	☐Not present
Surgical Procedures Specify:	☐History	☐Concurrent	☐Not present
Blood Transfusion Specify:	☐History	☐Concurrent	☐Not present
Alcohol use Specify:	☐History	☐Concurrent	☐Not present
Tattoo Specify:	☐History	☐Concurrent	☐Not present
Acupuncture Specify:	☐History	☐Concurrent	☐Not present
IV Drug Abuse Specify:	☐History	☐Concurrent	☐Not present
Sexually Transmitted Diseases Specify:	☐History	☐Concurrent	☐Not present
Diabetes Mellitus Specify:	☐History	☐Concurrent	☐Not present

Page 3 of 5

Obesity Specify:	☐History	☐Concurrent	☐Not present
Non-alcoholic steatohepatitis Specify:	☐History	☐Concurrent	☐Not present
Viral hepatitis Specify:	☐History	☐Concurrent	☐Not present
Family History of Liver Disease Specify:	☐History	☐Concurrent	☐Not present
Recent Travel to Endemic areas for viral hepatitis Specify:	☐History	☐Concurrent	☐Not present
CHF	☐History	☐Concurrent	☐Not present
Other: Please specify:	☐History	☐Concurrent	☐Not present

Please attach all laboratory results (ALT, ALT, Indirect bilirubin, INR, Alkaline phosphatise, albumin, CBC, CRP, eosinophils etc) and imaging tests. Please provide SI (International System of Units) if available. Otherwise, as reported.

☐**Labs Attached**

Please indicate if any of the following tests have been performed, and the result:

	Baseline Value (Prior to TCZ Use)	Date of Baseline Test (MM/DD/YYYY)	Date of Test (MM/DD/YYYY)	Test Results (Include units)	Reference Range (If Applicable)	Pending?
ANA						☐ Yes
Liver biopsy* Please obtain biopsy report if available						☐ Yes
CT Scan						☐ Yes
MRI						☐ Yes
Ultrasound						☐ Yes
Other: Please specify:						☐ Yes

Serology Results

Please indicate if any of the following tests have been performed, and the result:

Test	Conducted?	Results	Date (MM/DD/YYYY)
Hepatitis A	☐ Yes ☐ No		
Hepatitis B	☐ Yes ☐ No		
Hepatitis C	☐ Yes ☐ No		

Page 4 of 5

Hepatitis D	☐ Yes ☐ No		
Anti-CMV	☐ Yes ☐ No		
Anti-EBV	☐ Yes ☐ No		
Anti-Nuclear Ab	☐ Yes ☐ No		
Anti-mitochondrial Ab	☐ Yes ☐ No		
Other: Please specify:	☐ Yes ☐ No		

Past/Concomitant Medications
☐ Medication List Attached

		Dose	Route	Frequency	Past, Concomitant, or N/A
Methotrexate	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A
Other DMARDs Specify:	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A
Biologic DMARDs Specify:	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A
Corticosteroids Specify:	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A
Statins Specify:	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A
Acetaminophen	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A
Antibiotic Specify:	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A
Other: Please specify:	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Page 5 of 5

Tocilizumab Guided Questionnaire
Infections (Including Opportunistic Infections)

AER:		Local Case ID:	
Site No:		Patient Date of Birth (dd-MMM-yyyy):	
Patient ID/Initials:		Patient Gender:	☐ M ☐ F
Patient Weight	☐ kg ☐ lb	Patient Height	☐ cm ☐ inch

Infections have been observed in some patients treated with Tocilizumab.

By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Reporter Information
Name of reporter completing this form: (if other than addressee, provide contact information below)
Health Care Provider? ☐ Yes ☐ No Specify:
Phone Number: Fax Number: Email Address:

Reported Term

Description of the event
Hospital Admission ☐ Yes (Admission Date MM/DD/YYYY): (Discharge Date MM/DD/YYYY): ☐No
Onset Date (MM/DD/YYYY)
Stop Date (MM/DD/YYYY)
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐**Death** Date of Death (MM/DD/YYYY) ☐**Life-Threatening** (use only if patient was at immediate risk of death due to event) ☐**Initial/Prolonged Hospitalization** ☐**Congenital Anomaly/Birth Defect** ☐**Persistent or Significant Disability** ☐**Medically Significant** (important medical events that may jeopardize the patient and may require medical/surgical intervention to prevent the other outcomes)

Page 1 of 5

☐ Non-Serious	
Related to Tocilizumab?	☐Yes ☐No
Outcome of the event:	☐Persisting ☐Improved ☐Recovered with sequelae ☐Resolved ☐Unknown ☐Worsened ☐Death
Was the patient neutropenic at the current time of the serious or opportunistic infectious event ?	☐No ☐Yes: Provide lab results including Date of abnormal labs if available(MM/DD/YYYY): ☐Unknown
Was the infection associated with an ANC of <1000?	☐No ☐Yes: Provide Date of abnormal labs (MM/DD/YYYY): ☐Unknown
Did dose modification occur in association with lab abnormality?	☐No ☐Yes: Provide Date of dose modification (MM/DD/YYYY): ☐Unknown

Drug therapy details – Tocilizumab			
Indication:			
Start Date (MM/DD/YYYY)			
Starting Dose	_____ mg/kg _____ Total monthly dose (mg)		
Route			
Frequency	☐ Monthly ☐Other, please specify:		
History of 4 most recent Infusions prior to Adverse Event (AE)	Date (MM/DD/YYYY)	Dose	Action Taken in response to AE?
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued

Page 2 of 5

Treatment for the event		
What treatment was initiated for the event? (including any pre-hospitalization treatment)		
Treatment	Dosing Regimen	Dates of Therapy (MM/DD/YYYY to MM/DD/YYYY)

Please attach all laboratory results [blood, sputum, all available cultures, gram stain, Complete Blood Count with Differential, CRP, ESR] and imaging tests. Please provide SI (International System of Units) if available. Otherwise, as reported.

☐ **Labs Attached**

Please indicate if any of the following tests have been performed, and the result below:

	Baseline Value (Prior to TCZ Use)	Date of Baseline Test (MM/DD/YYYY)	Lab results at time of event including Date of Test (MM/DD/YYYY)	Test Results (include units)	Reference Range (If Applicable)	Pending?
Blood Culture/Stool/Urine/ Cerebrospinal fluid						☐Yes
Complete Blood Count with Differential						☐Yes
Chest X-Ray						☐Yes
CT Scan						☐Yes
CRP (C-reactive protein)						☐Yes
ESR (erythrocyte sedimentation rate)						☐Yes
PPD Results						☐Yes
PCR						☐Yes
Acid Fast Bacilli						☐Yes
Histology						☐Yes
Other Please specify:						☐Yes

Page 3 of 5

Risk factors			
Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.			
Diabetes Mellitus	☐History	☐Concurrent	☐Not present
HIV Infection	☐History	☐Concurrent	☐Not present
Felty's syndrome: long standing RA, splenomegaly, and low WBC Specify:	☐History	☐Concurrent	☐Not present
Splenectomy	☐History	☐Concurrent	☐Not present
Indwelling catheter	☐History	☐Concurrent	☐Not present
Previous Infection? Specify:	☐History	☐Concurrent	☐Not present
Recent Travel? Specify:	☐History	☐Concurrent	☐Not present
Other Please specify:	☐History	☐Concurrent	☐Not present

Has the patient ever received TB prophylaxis or active treatment? If yes, provide details below.				
Product Name	**Prophylactic or Active Treatment?**	**Dose**	**Date started**	**Date stopped**

Past/Concomitant Medications ☐Medication List Attached					
		Dose	Route	Frequency	Past, Concomitant, or N/A
Methotrexate	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Other DMARDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Biologic DMARDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
NSAIDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Corticosteroids Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Other	☐Yes				☐Past ☐Concomitant ☐N/A

Page 4 of 5

Please specify:	☐ No				

In the few weeks following the infection, what was the specific Immunoglobulin titer to the infectious agent (if available):		
IgG	Date (MM/DD/YYYY)	Result:
IgM	Date (MM/DD/YYYY)	Result:
IgA	Date (MM/DD/YYYY)	Result:
Other tests: Please specify:	Date (MM/DD/YYYY)	Result:

Please provide any further relevant information about the Adverse Event. Please indicate if there have been any significant changes from the initial report.

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Page 5 of 5

Tocilizumab Guided Questionnaire
Myocardial Infarction/Acute Coronary Syndrome

AER:		Local Case ID:	
Site No:		Patient Date of Birth (dd-MMM-yyyy):	
Patient ID/Initials:		Patient Gender:	☐ M ☐ F
Patient Weight	☐ kg ☐ lb	Patient Height	☐ cm ☐ inch

Myocardial infarction and acute coronary syndrome have been observed in some patients treated with Tocilizumab.

By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Reporter Information
Name of reporter completing this form: (If other than addressee, provide contact information below)
Health Care Provider? ☐ Yes ☐ No Specify:
Phone Number: Fax Number: Email Address:

Reported Term

Description of the event
Hospital Admission ☐ Yes (Admission Date MM/DD/YYYY): ☐ No (Discharge Date MM/DD/YYYY):
Onset Date (MM/DD/YYYY)
Stop Date (MM/DD/YYYY)
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐ **Death** Date of Death (MM/DD/YYYY) ☐ **Life-Threatening** (use only if patient was at immediate risk of death due to event) ☐ **Initial/Prolonged Hospitalization** ☐ **Congenital Anomaly/Birth Defect** ☐ **Persistent or Significant Disability** ☐ **Medically Significant** (Important medical events that may jeopardize the patient and may require medical/surgical intervention to prevent the other outcomes)

Position:

Page 1 of 5

☐ Non-Serious					
Related to Tocilizumab?	☐Yes	☐ No			
Outcome of the event:	☐Persisting	☐ Improved	☐Recovered with sequelae		
	☐Resolved	☐Unknown	☐Worsened	☐Death	

Drug therapy details – Tocilizumab			
Indication:			
Start Date (MM/DD/YYYY)			
Starting Dose	_____ mg/kg	_____ Total monthly dose (mg)	
Route			
Frequency	☐ Monthly	☐Other, please specify:	
History of 4 most recent infusions prior to Adverse Event (AE)	Date (MM/DD/YYYY)	Dose	Action Taken in response to AE?
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued
			☐Dose maintained ☐Dose decreased ☐Dose interrupted ☐Dose increased ☐Dose discontinued

Page 2 of 5

Treatment for the event		
What treatment was initiated for the event? (including any pre-hospitalization treatment)		
Treatment	Dosing Regimen	Dates of Therapy (MM/DD/YYYY to MM/DD/YYYY)

Please attach all laboratory results (fasting cholesterol panel, cardiac enzymes, platelets) and imaging tests. Please provide SI (International System of Units) if available. Otherwise, as reported.

☐ **Labs Attached**

Please indicate if any of the following tests have been performed, and the result:

	Baseline Value (Prior to TCZ Use)	Date of Baseline Test (MM/DD/YYYY)	Date of Test (MM/DD/YYYY)	Test Results (Include units)	Reference Range (If Applicable)	Pending?
Coronary Angiography						☐ Yes
CT Scan						☐ Yes
Echocardiography						☐ Yes
Electrocardiogram						☐ Yes
Stress Test						☐ Yes
PTCA						☐ Yes
CABG						☐ Yes
Stent						☐ Yes
Other Please specify:						☐ Yes

Risk Factors			
Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.			
Family history of cardiovascular disease Specify:	☐ History	☐ Concurrent	☐ Not present
Coronary Artery Disease Specify:	☐ History	☐ Concurrent	☐ Not present

Page 3 of 5

Previous Myocardial Infarction	☐History	☐Concurrent	☐Not present
Cardiac Valve Disease	☐History	☐Concurrent	☐Not present
Diabetes Mellitus	☐History	☐Concurrent	☐Not present
Hypertension	☐History	☐Concurrent	☐Not present
Hypercholesterolemia	☐History	☐Concurrent	☐Not present
Smoking	☐History	☐Concurrent	☐Not present
Obesity	☐History	☐Concurrent	☐Not present
Other Please specify:	☐History	☐Concurrent	☐Not present

Past/Concomitant Medications
☐**Medication List Attached**

		Dose	Route	Frequency	Past, Concomitant, or N/A
Methotrexate	☐ Yes ☐ No				☐Past ☐Concomitant ☐N/A
Other DMARDs Specify:	☐ Yes ☐ No				☐Past ☐Concomitant ☐N/A
Biologic DMARDs Specify:	☐ Yes ☐ No				☐Past ☐Concomitant ☐N/A
Corticosteroids Specify:	☐ Yes ☐ No				☐Past ☐Concomitant ☐N/A
Lipid lowering Medications Specify:	☐ Yes ☐ No				☐Past ☐Concomitant ☐N/A
Antihypertensive medication Specify:	☐ Yes ☐ No				☐Past ☐Concomitant ☐N/A
Aspirin/ anti-platelet Specify:	☐ Yes ☐ No				☐Past ☐Concomitant ☐N/A
Other Please specify:	☐ Yes ☐ No				☐Past ☐Concomitant ☐N/A

Please provide any further relevant information about the Adverse Event. Please indicate if there have been any significant changes from the initial report.

Page 4 of 5

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Page 5 of 5

Tocilizumab Guided Questionnaire
Malignancy

AER:		Local Case ID:	
Site No:		Patient Date of Birth (dd-MMM-yyyy):	
Patient ID/Initials:		Patient Gender:	☐ M ☐ F
Patient Weight	☐ kg ☐ lb	Patient Height	☐ cm ☐ inch

Malignancy has been observed in some patients treated with Tocilizumab.
By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Reporter Information		
Name of reporter completing this form: (if other than addressee, provide contact information below)		
Health Care Provider? ☐ Yes ☐ No	Specify:	
Phone Number:	Fax Number:	Email Address:

Reported Term

Provide anatomical site **(Please provide biopsy, pathology, and biomarker results if available)**	

Description of the event		
Event led to 1. surgery	☐Yes	☐ No
2. radiotherapy	☐Yes	☐ No
3. chemotherapy	☐Yes	☐ No
Hospital Admission ☐ Yes (Admission Date MM/DD/YYYY): (Discharge Date MM/DD/YYYY):		☐No
Onset Date (MM/DD/YYYY)		
Stop Date (MM/DD/YYYY)		

Position:

Page 1 of 4

Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐ **Death** Date of Death (MM/DD/YYYY) ☐ **Life-Threatening** (use only if patient was at immediate risk of death due to event) ☐ **Initial/Prolonged Hospitalization** ☐ **Congenital Anomaly/Birth Defect** ☐ **Persistent or Significant Disability** ☐ **Medically Significant** (important medical events that may jeopardize the patient and may require medical/surgical intervention to prevent the other outcomes) ☐ **Non-Serious**	
Related to Tocilizumab?	☐ Yes ☐ No
Outcome of the event:	☐ Persisting ☐ Improved ☐ Recovered with sequelae ☐ Resolved ☐ Unknown ☐ Worsened ☐ Death

Drug therapy details – Tocilizumab			
Indication:			
Start Date (MM/DD/YYYY)			
Starting Dose	_____ mg/kg	_____ Total monthly dose (mg)	
Route			
Frequency	☐ Monthly	☐ Other, please specify:	
History of 4 most recent infusions prior to Adverse Event (AE)	Date (MM/DD/YYYY)	Dose	Action Taken in response to AE?
			☐ Dose maintained ☐ Dose decreased ☐ Dose interrupted ☐ Dose increased ☐ Dose discontinued
			☐ Dose maintained ☐ Dose decreased ☐ Dose interrupted ☐ Dose increased ☐ Dose discontinued
			☐ Dose maintained ☐ Dose decreased ☐ Dose interrupted ☐ Dose increased ☐ Dose discontinued
			☐ Dose maintained ☐ Dose decreased ☐ Dose interrupted ☐ Dose increased ☐ Dose discontinued

Page 2 of 4

Treatment for the event		
What treatment was initiated for the event? (including any pre-hospitalization treatment)		
Treatment	Dosing Regimen	Dates of Therapy (MM/DD/YYYY to MM/DD/YYYY)

Risk Factors			
Please indicate if the following conditions are either part of the patient's medical history or are still active conditions.			
Smoking	☐History	☐Concurrent	☐Not present
Alcohol use	☐History	☐Concurrent	☐Not present
Family history of cancer Specify:	☐History	☐Concurrent	☐Not present
Chemical exposure	☐History	☐Concurrent	☐Not present
Sunlight exposure (UV) Specify:	☐History	☐Concurrent	☐Not present
Ionizing radiation exposure Specify:	☐History	☐Concurrent	☐Not present
HIV infection	☐History	☐Concurrent	☐Not present
EBV infection	☐History	☐Concurrent	☐Not present
HTLV infection	☐History	☐Concurrent	☐Not present
Other infections Specify:	☐History	☐Concurrent	☐Not present

Past/Concomitant Medications
☐**Medication List Attached**

		Dose	Route	Frequency	Past, Concomitant, or N/A
Methotrexate	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Other DMARDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Biologic DMARDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Corticosteroids Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A

Page 3 of 4

Chemotherapy Specify:	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A
Other Please specify:	☐ Yes ☐ No				☐ Past ☐ Concomitant ☐ N/A

Please attach all laboratory results and imaging tests. Please provide SI (International System of Units) if available. Otherwise, as reported.

☐ **Labs Attached**

Please provide any further relevant information about the Adverse Event. Please indicate if there have been any significant changes from the initial report.

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Annex 6 – Details of proposed additional risk minimisation activities

Additional Risk Minimization Measures for the relevant tocilizumab indications, namely RA, sJIA, pJIA and GCA, include a Patient Card.

The Patient Information Pack should contain the following key elements:

- Package leaflet covering all approved indications (with instructions for use for the SC formulation)
- Patient Card

- To address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear. Patients should seek guidance from their healthcare professional in case they develop an infection of any kind (even a head cold) at the time of their scheduled treatment with tocilizumab.
- To address the risk that patients using tocilizumab may develop complications of diverticulitis which can become serious if not treated. Patients should inform their doctor immediately if they experience signs and symptoms of stomach pain, or colic with a change in bowel habits, or notice blood in their stool. The patient should inform the healthcare professional if they have or have had intestinal ulceration or diverticulitis (inflammation in parts of the large intestine).
- To address the risk that patients using tocilizumab may develop serious hepatic injury. Patients' liver function would be monitored for changes in the level of liver enzymes through liver function tests during treatment with tocilizumab. Patients should inform their doctor immediately if they experience signs and symptoms of liver toxicity including tiredness, confusion, abdominal pain, pain or swelling in the upper right side of the stomach area and jaundice (yellowing of the skin and eyes, and have dark brown coloured urine).