THE EU RISK MANAGEMENT PLAN FOR ROACTEMRA®(TOCILIZUMAB)

RMP version to be assessed as part of this application:

RMP Version number: 29.0

Data lock point for this RMP: October 2023

Date of final sign off: as in e-signatures below:

Date and Time (UTC)	Reason for Signing	Name
27-Nov-2023 09:42:23	Deputy QPPV	PPD
27-Nov-2023 16:27:12	Company Signatory (PV)	

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EU RMP FOR ROACTEMRA®

- **Rationale for Submitting an Updated RMP:**

This RMP version 29.0 is submitted in support of a post-approval measure (PAM) to characterize the safety profile of tocilizumab in the treatment of patients with chimeric antigen receptor (CAR) T-cell induced cytokine release syndrome (CRS) by collecting data on the timing of tocilizumab administration relative to the nature and onset of adverse events based on the data from completed ZUMA-8 Study.

The ZUMA-8 study added to the safety profile on the use of tocilizumab (TCZ) for the treatment of CAR-T induced CRS in patients taking Kite's brexucabtagene autoleucel drug. No AEs were observed as being related to TCZ in ZUMA-8, and no new safety signals were detected. The MAH sees this as further confirmation that benefit- risk balance of TCZ administration in this setting is positive. The MAH concludes to continue the monitoring with routine Pharmacovigilance activities that are already in place.

Summary of Significant Changes in This RMP:

Part II: Module SI.5 is being updated to add incidence language for cytokine release syndrome from ZUMA-8 study.

Part II: Module SIII is being updated to reflect the amended clinical trial exposure data for systemic juvenile idiopathic arthritis (sJIA) and polyarticular juvenile idiopathic polyarthritis (pJIA) indication from Study WA29231 (JIGSAW long-term extension study with tocilizumab SC).

Part II: Module SV is being updated to reflect the post-authorization exposure based on the last Periodic Benefit-Risk Evaluation Report (PBRER 1121480).

Part III is being updated to reflect the addition of Other Routine Pharmacovigilance activities with respect to ZUMA-8 study.

Annex 7 is being updated with other supporting data (Including Referenced Material).

Annex 8 was updated to reflect all changes made to the RMP.

Other RMP Versions under Evaluation: Not applicable.

Details of Currently Approved RMP:

RMP version number: 27.1

Approved with Procedure Number: EMEA/H/C/000955/II/0101

Date of approval (opinion date): 6 December 2021 (CHMP Opinion)

See Page 1 for e-signature and date

Dr. Birgitt Gellert (QPPV) Date
(Delegate: Dr. PPD . [Deputy QPPV])

See Page 1 for e-signature and date

PPD Date

PART I: PRODUCT(S) OVERVIEW

Active Substance(s) (INN or common name)	Tocilizumab
Pharmacotherapeutic group(s) (ATC code)	L04AC07
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	*One*
Invented name(s) in the European Economic Area (EEA)	*RoActemra*®
Marketing authorization procedure	Centrally Authorized Procedure
Brief description of the product including:	Chemical Class: Immunosuppressants, Interleukin inhibitors
	Summary of mode of action: Tocilizumab binds specifically to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signaling. 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 physiologic processes such as T cell activation, induction of immunoglobulin secretion, induction of hepatic acute-phase protein synthesis, and stimulation of haematopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis, and neoplasia.
	Important information about its composition: Tocilizumab, a humanised IgG1 monoclonal antibody against the human IL-6 receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.
Hyperlink to the product information	SmPC
Indication(s) in the EEA	**Current:** **Intravenous (IV) Formulation:** RoActemra (tocilizumab [TCZ]), in combination with methotrexate (MTX), is indicated for: • The treatment of severe, active, and progressive rheumatoid arthritis (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 tumor necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. • RoActemra is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. • RoActemra in combination with MTX is indicated for the treatment of polyarticular juvenile idiopathic polyarthritis (pJIA; rheumatoid factor [RF] positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. • RoActemra is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and paediatric patients 2 years of age and older. • RoActemra is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. <u>Subcutaneous (SC) Formulation:</u> RoActemra in combination with 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 DMARDs or TNF antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. • The treatment of Giant Cell Arteritis (GCA) in adult patients. • The treatment of juvenile idiopathic polyarthritis (pJIA; RF positive or negative and extended oligoarthritis) in patients 2 years of age and older,

	who have responded inadequately to previous therapy with MTX. • The treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given alone (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.
	• **Proposed: Not Applicable**
Dosage in the EEA	**Current**: **IV Formulation:** *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 *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 should 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. *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 should 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. *CRS Patients (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. RoActemra 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

	three additional doses of RoActemra may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CRS patients. *COVID-19* The recommended posology for treatment of adult patients with COVID-19 is a single 60-minute intravenous infusion of 8 mg/kg, with a maximum dose of 800 mg. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of RoActemra 8 mg/kg may be administered. There should be an interval of at least 8 hours between these two infusions. **SC Formulation:** *RA:* The recommended posology is subcutaneous 162 mg once every week. *GCA*: The recommended posology is subcutaneous 162 mg once every week in combination with a tapering course of glucocorticoids. RoActemra can be used alone following discontinuation of glucocorticoids. RoActemra monotherapy should not be used for the treatment of acute relapses. Based upon the chronic nature of GCA, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice. *pJIA:* 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. *sJIA*: • 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 between 1 year and 2 years of age must have a minimum body weight of 10 kg when receiving RoActemra subcutaneously.
Dosage in the EEA (continued)	**Proposed: Not Applicable**

Pharmaceutical form(s) and strengths	**Current**: **IV Formulation:** *Concentrate for Solution for Infusion* The IV formulation of RoActemra is a clear to opalescent, colourless to pale yellow solution, supplied in type I clear glass vials with a butyl rubber stopper. Each milliliter concentrate contains 20 mg tocilizumab. RoActemra IV is available in 4 mL, 10 mL, and 20 mL vials, containing 80 mg, 200 mg, and 400 mg of tocilizumab, respectively. **SC Formulation:** The SC formulation of RoActemra is a clear to opalescent, and colourless to slightly yellowish solution available in a pre-filled syringe (PFS) or pre-filled pen containing the unit dose of 162 mg/0.9 mL tocilizumab in L-histidine buffer, L-histidine monohydrochloride, polysorbate-80, L- arginine, L-arginine hydrochloride, L-methionine, and Water for Injections. The final commercial drug product configuration consists of the PFS assembled with the needle safety device (NSD). Note: Pharmaceutical form and strength of the PFS+NSD is identical to the pre-filled pen.
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the European Union?	No

CAR = chimeric antigen receptor; CHO = Chinese hamster ovary; COVID-19 = coronavirus disease 2019; CRS = cytokine release syndrome; DMARD = disease-modifying anti-rheumatic drug; EEA = European Economic Area; GCA = Giant Cell Arteritis; IV = intravenous; MTX=methotrexate; RA = rheumatoid arthritis; RF = rheumatoid factor; RMP = risk management plan; NSAID = nonsteroidal anti-inflammatory drug; NSD = needle safety device; pJIA = polyarticular juvenile idiopathic arthritis; PFS = pre-filled syringe; sJIA = systemic juvenile idiopathic arthritis; SC = subcutaneous; SmPC = Summary of Product Characteristics; TCZ = tocilizumab; TNF = tumor necrosis factor.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AI	autoinjector (also referred to as pre-filled pen/ACTPen/AI-1000G2/AI-G2)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CAR	chimeric antigen receptor
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
CRS	cytokine release syndrome
CS	corticosteroids
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DHPC	Direct Healthcare Professional Communication
DILI	drug-induced liver injury
DMARD	disease-modifying anti-rheumatic drug
ECDC	European Centre for Disease Prevention and Control
ECMO	extracorporeal membrane oxygenation
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GCA	giant cell arteritis
GI	gastrointestinal
HLA	human leukocyte antigen
HLT	high-level term
ICU	intensive care unit
IL	interleukin
ILD	interstitial lung disease
IV	intravenous
JIA	juvenile idiopathic arthritis
MAH	Marketing Authorization Holder
MAS	macrophage activation syndrome
MTX	methotrexate
NSAID	nonsteroidal anti-inflammatory drug

Abbreviation	Definition
PBO	placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PFS	pre-filled syringe
pJIA	polyarticular juvenile idiopathic arthritis
PSUR	Periodic Safety Update Report
PY	person years
QW	once weekly
RA	rheumatoid arthritis
RDV	remdesivir
RF	rheumatoid factor
RMP	Risk Management Plan
SAEs	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome
SC	subcutaneous
SCS	Summary of Clinical Safety
sJIA	systemic juvenile idiopathic arthritis
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
TCZ	tocilizumab
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal

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 (0.0 to 2.4/1000 male and 2.0 to 7.0/1000 female) (Woolf 2003).

- Demographics:

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 tumor 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 with 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, anemia, and depression. Coronary artery disease is the major cause of death in RA patients (SMR 1.79) (Björnadal et al. 2002). 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:

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 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, anemia, 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 IV 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 easy bruisability. 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 (TCZ; 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 aTNF 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 TCZ.

- Natural History of the Indicated Condition in the Untreated Population:

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) pcJIA 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; Kaipiainen-Seppänen and Savolainen 2001; Danner et al. 2006; Pruunsild et al. 2007) and (c) Estonia incidences from study: Oligoarthritis =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) pcJIA 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:

Oligoarthritis typically has an onset in children aged 2-4 years and predominately affects females (Dannecker and Quartier 2009; Ravelli and Martini 2007). Dannecker and Quartier 2009; Ravelli and Martini 2007). Polyarthritis RF+ occurs primarily in adolescent

girls (Dannecker and Quartier 2009; Ravelli and Martini 2007Dannecker 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 SC for pJIA. Its use in pJIA is limited by its safety profile, which can include elevated liver function test results, anemia, and teratogenicity.

Corticosteroids are often administered orally or IV 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 TCZ 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 TCZ) have provided therapeutic options for patients with moderate to severe pJIA; these options include etanercept (Enbrel), adalimumab (Humira), and abatacept (Orencia). 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 14% (predominantly related to MAS), 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 U.K.-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:
- 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.

1. 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:
- *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 UK are reported as commonly experiencing aortic aneurysm, large vessel complications, polymyalgia rheumatica, visual disturbances, facial pain, osteoporosis, hypokalemia, and various infections such as oral/esophageal 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 experience CRS of any grade. Of the 141 patients, 50 required intervention with TCZ.
- Demographics (ZUMA-1; Phase 2):
  - There was no significant difference in incidence of CRS observed in subjects based on their performance status (i.e., ECOG), 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.
  - 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:

[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)

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

- 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, diarrhea, headache, skin rashes, tachypnea, 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.

- 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%).

- 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 18 May 2021, approximately 163.3 million confirmed cases of COVID-19 have been reported globally by the WHO. The United States has 32.6 million confirmed cases making one-quarter of all global confirmed cases followed by India with approximately 25.2 million confirmed cases, and Brazil with 15.6 million confirmed cases. In Europe, over 53.7 million cases were confirmed so far. The UK, France, and Italy are the most affected nations in Europe with over 4 million confirmed cases in each nation (WHO 2020a).

Although most patients have mild symptoms and good prognosis, COVID-19 can develop to severe illnesses including pneumonia, pulmonary edema, 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 et al. 2020b).

Demographics

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 United States, 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 31 May 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 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 - NONCLINICAL PART OF THE SAFETY SPECIFICATION

1.1 Toxicity

1.1.1 Local Tolerance Studies

Multiple-dose studies in primates, in which TCZ 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 TCZ and its formulation excipients (Study TOX00-0032; Study TOX03-0104; Study TOX03-0105; Study TOX03-0106; Study 1015671).

Relevance to human usage: Yes

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

1.1.2 Reproductive Toxicity Studies and Risk of Abortion

Tocilizumab was not teratogenic in an embryo-fetal toxicity study (Study TOX00-0012) 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-fetal 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-fetal 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 analog of tocilizumab into the milk of lactating mice has been observed (Report 1003—Mogi M. RO4877533).

Preclinical data in mice do not suggest an effect on fertility in mice treated with a mouse IL-6R surrogate antibody for tocilizumab (Report 1033493 – Arima A. RO4877533; Report 1033494 – Arima A. RO4877533). 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 (Report 1003492 – Arima A. RO4877533). 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 (Report 1029892 – Hoberman A).

Relevance to human usage: Unknown

Discussion: Although IL-6 does not seem to be a critical cytokine for either fetal growth or the immunological control of the maternal/fetal interface, the relevance of this observation for human pregnancy is unknown. However, a possible relation to tocilizumab cannot be excluded (Actemra RA Marketing Authorization Application [MAA]; EMEA) 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.

1.1.3 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 (Study TOX02-0161) multiple-dose study up to 50 mg/kg/day for 4 weeks (Study TOX02-0167) or at an IV dose of 100 mg/kg/week for 6 months (Study TOX02-0169). 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.

1.1.4 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 (Study TOX02-0172-JITSU97-0035; Study TOX02-0171-JITSU97-0086). 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 tumor progression, and the negative interference of STAT3-regulated gene products in tumor immunosurveillance (Yu 2007). Not only does STAT3, constitutively activated by malignant cells, inhibit the expression of mediators necessary for effective immune activation against tumor cells, but it also actively promotes the production of immunosuppressive factors that lead to a blockade of efficient anti-tumor response in situ.

Recently published data demonstrated that the functional maturation of dendritic cells in the tumor environment, which is necessary for an effective activation of an anti-tumor response, is blocked by tumor-secreted IL-6 (Park et al. 2004), an effect which significantly contributes to the widely observed clinical phenomenon of tumor tolerance rather than rejection. Conversely, the potential role of IL-6 as a therapeutic anti-tumor agent has been shown in a variety of preclinical tumor 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 tumor 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 (Study PHM02-0148) and effectively stops the IL-6 dependent growth of human myeloma cell lines in vitro (Study PHM02-0249) and KPMM2 tumor cells in vivo (Study PHM04-0089 [J97-0262]). The therapeutic effect of IL-6 receptor blockage under in vivo conditions was shown in various disease models with MR16-1, a rodent-specific analog 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 tumor 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 tumor growth and metastasis (immunosurveillance). The nonclinical data suggest an association between elevated levels of IL-6 and tissue/tumor 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 TCZ use. Refer to Module SVII.3.1 for details.

1.2 General Safety Pharmacology

1.2.1 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 (Study TOX02-0127; Study TOX02-0158).

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 TCZ 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.

1.2.2 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 of IL-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 TCZ group, and 3.72 (95% CI: 1.98, 6.37) in the 8 mg/kg TCZ group.

1.2.3 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 TCZ use, per data obtained in clinical trials. Refer to Module SVII.3.1 for more details.

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

Effects of a blockage of IL-6 signaling 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 analog 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, hematology, 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, estrous 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

Overview of Exposure Tables

Table 1 to Table 18 present patient exposure for the All Exposure Population, this includes any patients who have received at least one dose of TCZ in clinical trials (prior to marketing authorization approval) for the following indications: Adult RA, sJIA, pJIA, GCA, and COVID-19 .

Overview of Clinical Studies used for TCZ Exposure

Indication	Study	Data Cut Used for This RMP
Intravenous Administration		
Adult RA	WA17822	2 May 2012
	WA17823	
	WA18063	
	WA17824	
	WA18062	
	WP18663	
	WA18695	
	WA18696	
	WA19924	
	WA22762	12 October 2012
Adult Early RA	WA19926	Final CSR (Week 104)
sJIA	WA18221	Week 104 CSR
	NP25737	Final CSR (Week 52)
pJIA	WA19977	Week 40 CSR
COVID-19	WA42380 (COVACTA)	Final CSR (Day 60)
	ML42528 (EMPACTA)	Final CSR (Day 60)
	WA42511 (REMDACTA)	Final CSR (Day 60)
Subcutaneous Administration		
RA	WA22762	12 October 2012
	NA25220	29 October 2012
GCA	WA28119	Primary Analysis CSR (Week 52)
pJIA	WA28117	Final CSR (Week 52)
	WA29231	Week 156
sJIA	WA28118	Final CSR (Week 52)
	WA29231	Week 152

COVID-19 = coronavirus disease 2019; GCA = giant cell arteritis; pJIA = polyarticular juvenile idiopathic arthritis; RA = rheumatoid arthritis; sJIA = systemic juvenile idiopathic arthritis; TCZ = tocilizumab.

Extent of Exposure (days) is calculated by summing the actually received infusions + up to 28 days per infusion (for IV, depending on whether TCZ was given once every 2 weeks (Q2W) or once every 4 weeks [Q4W]) and by summing the actually received injections + up to 21 days per injection (for SC, depending on whether TCZ was given once weekly (QW), once every 10 days (Q10D), Q2W or once every 3 weeks [Q3W]); to obtain duration of exposure by month this value was then divided by 28 (as a month was

defined as 28 days for the purpose of analysis). Note: for COVID-19, the extent of exposure to TCZ is 28 days for all patients, apart from those who have a death recorded, for whom exposure is calculated as date of death – date of first dose administered +1 day or 28 days, whichever is less. Exposure in months is calculated in the same way as above. Patients are only counted in the age, sex, race, and special population outputs if they have provided a response, which allows them to be assigned to a category in the table. It should be noted that in the tables below, all values of person time have the unit PY, and the value “persons” denotes number (n) of patients. Person time was calculated by summing each patient exposure in days and dividing by 365.25. Minor variations up to 1 PY may be observed between the tables due to rounding differences. Table 1 and Table 2 provide a summary of duration of exposure by indication for the IV and SC formulation, in number of patients and by person time, for the patients in the clinical studies.

Table 1 Duration of IV Exposure by Indication

Duration of Exposure	Person (n)	Person Time (PY)
Adult RA		
≤ 3 months	303	45.7
4- ≤ 6 months	556	231.7
7 - ≤ 9 months	157	93.7
10 - ≤ 12 months	151	125.1
13 - ≤ 15 months	137	144.3
16 - ≤ 18 months	224	289.5
19 - ≤ 21 months	181	273.2
22 - ≤ 24 months	149	258.7
25 - ≤ 27 months	71	139.1
28 - ≤ 30 months	45	98.3
31 - ≤ 33 months	51	122.8
34 - ≤ 36 months	47	124.2
37 - ≤ 39 months	51	146.6
40 - ≤ 42 months	57	177.6
43 - ≤ 45 months	58	193.5
46 - ≤ 48 months	86	305.5
49 - ≤ 51 months	129	491.3
52 - ≤ 54 months	123	494.8
55 - ≤ 57 months	147	626.7
58 - ≤ 60 months	285	1280.8
61 - ≤ 63 months	467	2208.4
64 - ≤ 66 months	547	2698.4
67 - ≤ 69 months	382	1981
70 - ≤ 72 months	430	2318.6
73 - ≤ 75 months	10	56.2
76 - ≤ 78 months	5	29.4
79 - ≤ 81 months	3	18.4
82 - ≤ 84 months	1	6.2
Total	**4853**	**14979.7**
Adult Early RA (WA19926)		
≤ 3 months	64	10.1

Duration of Exposure	Person (n)	Person Time (PY)
4- ≤ 6 months	52	19.3
7 - ≤ 9 months	52	31.1
10 - ≤ 12 months	**237**	206.8
13 - ≤ 15 months	471	461.1
Total	**876**	**728.4**
sJIA		
≤ 3 months	7	0.8
4- ≤ 6 months	2	0.7
7 - ≤ 9 months	4	2.3
10 - ≤ 12 months	7	5.9
13 - ≤ 15 months	8	8.2
16 - ≤ 18 months	5	6.5
19 - ≤ 21 months	15	23.3
22 - ≤ 24 months	32	55.6
25 - ≤ 27 months	43	82.7
Total	**123**	**186**
pJIA		
≤ 3 months	8	1.4
4- ≤ 6 months	29	10.1
7 - ≤ 9 months	19	11.4
10 - ≤ 12 months	32	27
13 - ≤ 15 months	27	27.7
16 - ≤ 18 months	26	33.2
19 - ≤ 21 months	30	44.7
22 - ≤ 24 months	17	28.6
Total	**188**	**184.1**
COVID-19		
≤ 3 months	974	68.1
Total	**974**	**68.1**

COVID-19 = coronavirus disease 2019; GCA = giant cell arteritis; IV = intravenous; pJIA = polyarticular juvenile idiopathic arthritis; RA = rheumatoid arthritis;sJIA = systemic juvenile idiopathic arthritis; TCZ = tocilizumab

Notes: Patients are only assigned to the max duration category; they are not counted in previous duration categories.

Patient exposure is rounded up to the next month before it is categorized. A month is considered as 28 days.

Duration of exposure is rounded up to the next month.

Source : L11935E/STmt_exp_rmp_dur.out, WA22762/Stmt_exp_rmp_dur.out WA18221/Stmt_exp_rmp_dur.out, WA19977/STmt_exp_rmp_dur.out, WA19926/STmt_exp_rmp_dur.out, NP25737/STmt_exp_rmp_dur_SA966_SE.out
t_dur_rmp_wa42380_SETCZ
t_ex_dur_rmp_ml42528_SETCZ
t_ex_dur_rmp_wa42511_SETCZ

Table 2 Duration of SC Exposure by Indication (RA, GCA, pJIA, and sJIA)

Duration of Exposure	Number of Patients	Person Years of Exposure (PY)
RA		
≤ 3 months	125	19.4
4- ≤ 6 months	120	46.2
7 - ≤ 9 months	109	63.9
10 - ≤ 12 months	149	122.2
13 - ≤ 15 months	315	325.8
16 - ≤ 18 months	297	374.9
19 - ≤ 21 months	178	265.1
22 - ≤ 24 months	85	146.4
Total	**1378**	**1364.2**
GCA		
≤ 3 months	8	1.0
4 - ≤ 6 months	10	3.8
7 - ≤ 9 months	6	3.5
10 - ≤ 12 months	4	3.4
13 - ≤ 15 months	121	118.6
Total	**149**	**130.1**
pJIA		
≤ 3 months	0	0.0
4- ≤ 6 months	0	0.0
7 - ≤ 9 months	4	2.1
10 - ≤ 12 months	2	1.6
13 - ≤ 15 months	2	2.0
16 - ≤ 18 months	1	1.3
19 - ≤ 21 months	1	1.6
22 - ≤ 24 months	0	0.0
25 - ≤ 27 months	0	0.0
28 - ≤ 30 months	3	6.5
31 - ≤ 33 months	1	2.4
34 - ≤ 36 months	1	2.7
37 - ≤ 39 months	0	0.0
40 - ≤ 42 months	0	0.0
43 - ≤ 45 months	1	3.3
46 -≤ 48 months	3	10.9

Duration of Exposure	Number of Patients	Person Years of Exposure (PY)
49 - ≤ 51 months	2	7.6
52 - ≤ 54 months	1	4.1
55 - ≤57 months	1	4.2
58 - ≤ 60 months	0	0.0
61 - ≤ 63 months	1	4.8
64 - ≤ 66 months	2	9.8
67 - ≤ 69 months	3	15.3
70 - ≤ 72 months	5	27.1
73 - ≤75 months	5	27.9
76 - ≤ 78 months	13	76.0
79 - ≤ 81 months	0	0.0
Total	**52**	**211.2**
sJIA		
≤ 3 months	4	0.4
4- ≤ 6 months	1	0.3
7 - ≤ 9 months	3	1.9
10 - ≤ 12 months	1	0.8
13 - ≤ 15 months	5	5.0
16 - ≤ 18 months	1	1.3
19 - ≤ 21 months	1	1.6
22 - ≤ 24 months	1	1.7
25 - ≤ 27 months	0	0.0
28 - ≤ 30 months	0	0.0
31 - ≤ 33 months	0	0.0
34 - ≤ 36 months	4	10.7
37 - ≤ 39 months	1	3.0
40 - ≤ 42 months	4	12.5
43 - ≤ 45 months	1	3.3
46 - ≤ 48 months	1	3.7
49 - ≤ 51 months	1	3.7
52 - ≤ 54 months	1	4.0
55 - ≤ 57 months	4	17.0
58 - ≤ 60 months	1	4.5
61 - ≤ 63 months	0	0.0
64 - ≤ 66 months	4	19.9
67 - ≤ 69 months	3	15.6

Duration of Exposure	Number of Patients	Person Years of Exposure (PY)
70 - ≤ 72 months	1	5.4
73 - ≤ 75 months	1	5.7
76 - ≤ 78 months	6	35.1
79 - ≤ 81 months	1	6.0
Total	**51**	**163.1**

GCA = giant cell arteritis; pJIA = polyarticular juvenile idiopathic arthritis; RA = rheumatoid arthritis; sJIA = systemic juvenile idiopathic arthritis.

Notes: Patients are only assigned to the max duration category; they are not counted in previous duration categories.

Patient exposure is rounded up to the next month before it is categorized. A month is considered as 28 days.

Source: WA22762 /STmt_exp_rmp_dur.out, NA25220/Stmt_exp_rmp_dur_SA978.out, WA28119/STmt_exp_rmp_dur_all_ah128, pool_Jigsaw117_118_LTE/prod/output/pool_STmt_exp_rmp_dur.out

Table 3 and Table 4 provide an overall summary of duration of exposure in months, by number of patients and by person time, for the IV and SC formulations, for all patients in the studied populations.

Table 3 Duration of IV Exposure (Total)

Total Exposure	Persons (n)	Person Time (PY)
≤ 3 months	1356	126.1
4- ≤ 6 months	639	261.8
7 - ≤ 9 months	232	138.5
10 - ≤ 12 months	427	364.8
13 - ≤ 15 months	643	641.3
16 - ≤ 18 months	255	329.2
19 - ≤ 21 months	226	341.2
22 - ≤ 24 months	198	342.9
25 - ≤ 27 months	114	221.8
28 - ≤ 30 months	45	98.3
31 - ≤ 33 months	51	122.8
34 - ≤ 36 months	47	124.2
37 - ≤ 39 months	51	146.6
40 - ≤ 42 months	57	177.6
43 - ≤ 45 months	58	193.5
46 - ≤ 48 months	86	305.5
49 - ≤ 51 months	129	491.3
52 - ≤ 54 months	123	494.8
55 - ≤ 57 months	147	626.7
58 - ≤ 60 months	285	1280.8
61 - ≤ 63 months	467	2208.4
64 - ≤ 66 months	547	2698.4
67 - ≤ 69 months	382	1981
70 - ≤ 72 months	430	2318.6
73 - ≤ 75 months	10	56.2
76 - ≤ 78 months	5	29.4
79 - ≤ 81 months	3	18.4
82 - ≤ 84 months	1	6.2
Total	**7014**	**16146.3**

IV = intravenous.

Notes: Patients are only assigned to the max duration category; they are not counted in previous duration categories.

Patient exposure is rounded up to the next month before it is categorized. A month is considered as 28 days.

Table 4 Duration of SC Exposure (Total)

Total Exposure	Number of Patients	Person Years of Exposure (PY)
≤ 3 months	137	20.8
4- ≤ 6 months	131	50.3
7 - ≤ 9 months	122	71.4
10 - ≤ 12 months	156	128.0
13 - ≤ 15 months	443	451.4
16 - ≤ 18 months	299	377.5
19 - ≤ 21 months	180	268.3
22 - ≤ 24 months	86	148.1
25 - ≤ 27 months	0	0
28 - ≤ 30 months	3	6.5
31 - ≤ 33 months	1	2.4
34 - ≤ 36 months	5	13.4
37 - ≤ 39 months	1	3.0
40 - ≤ 42 months	4	12.5
43 - ≤ 45 months	2	6.6
46 - ≤ 48 months	4	14.6
49 - ≤ 51 months	3	11.3
52 - ≤ 54 months	2	8.1
55 - ≤ 57 months	5	21.2
58 - ≤ 60 months	1	4.5
61 - ≤ 63 months	1	4.8
64 - ≤ 66 months	6	29.7
67 - ≤ 69 months	6	30.9
70 - ≤ 72 months	6	32.5
73 - ≤ 75 months	6	33.6
76 - ≤ 78 months	19	111.1
79 - ≤ 81 months	1	6.1
Total	**1,630**	**1,868.6**

SC = subcutaneous

Notes: Patients are only assigned to the max duration category; they are not counted in previous duration categories.

Patient exposure is rounded up to the next month before it is categorized. A month is considered as 28 days.

Source: root/clinical_studies/RO4877533/CDPT3724/WA29767/data_analysis/CSRFinal_wk96/prod/output/PR12681_t_ex_dur_SE_ILD.out, root/clinical_studies/RO4877533/CDPT3489/share/pool_Jigsaw117_118_LTE/prod/output/pool_STmt_exp_rmp_dur.out

Table 5 and Table 6 provide an overview of duration of exposure by indication, for IV and SC formulations, by the dose level received, for all patients in the studied populations. Table 5 includes all dose levels that an individual patient may have received.

Table 5 Exposure of IV Dose (by Indication)

Dosing Regimen	Persons (n)	Person time (PY)
Adult RA		
TCZ 4 mg/kg Q4W	1591	1133.8
TCZ 8 mg/kg Q4W	4711	13844
TCZ 10 mg/kg Q4W	23	1.8
Total	**4853***	**14979.6**
Adult Early RA (WA19926)		
TCZ 4 mg/kg Q4W	295	241.9
TCZ 8 mg/kg Q4W	583	486.5
Total	**876***	**728.4**
sJIA		
TCZ 8 mg/kg Q2W	72	98.9
TCZ 12 mg/kg Q2W	71	87
Total	**123***	**186**
pJIA		
TCZ 8 mg/kg Q4W	160	153.3
TCZ 10 mg/kg Q4W	38	30.8
Total	**188***	**184.1**
COVID-19		
TCZ 8 mg/kg - 1 or 2 doses	974	68.1
Total	**974**	**68.1**

COVID-19 = coronavirus disease 2019; GCA = giant cell arteritis; IV = intravenous; pJIA=polyarticular juvenile idiopathic arthritis; Q2W = once every 2 weeks; Q4W = once every 4 weeks; RA=rheumatoid arthritis; sJIA=systematic juvenile idiopathic arthritis; TCZ=tocilizumab.

Notes:

*Total is less than the sum of patients receiving each dose as some patients received multiple doses.

Patients can be included in more than one category, if they receive more than one dose at any time during the study.

Source:

L11935E/STmt_exp_rmp_dur.out, WA18221/Stmt_exp_rmp_dur.out, WA22762/STmt_exp_rmp_dur.out, WA19977/STmt_exp_rmp_dur.out

WA19926/STmt_exp_rmp_dur.out, NP25737/STmt_exp_rmp_dur_SA966_SE.out

t_dose_rmp_wa42380_SETCZ

t_ex_dose_rmp_ml42528_SETCZ

t_ex_dose_rmp_wa42511_SETCZ

Table 6 Exposure of SC Dosing Regimen (by Indication)

Dosing Regimen	Persons (n)	Person Time (PY)
Adult RA		
TCZ SC 162 mg QW	820	908.7
TCZ SC 162 mg Q2W	558	455.5
Total	**1378**	**1364.2**
GCA		
TCZ SC 162 mg QW	100	86.4
TCZ SC 162 mg Q2W	49	43.7
Total	**149**	**130.1**
pJIA		
TCZ SC 162 mg Q2W	42	138.4
TCZ SC 162 mg Q3W	27	72.8
Total	**52***	**211.2**
sJIA		
TCZ SC 162 mg QW	37	103.3
TCZ SC 162 mg Q10D	8	11.7
TCZ SC 162 mg Q2W	22	48.1
Total	**51***	**163.1**

GCA = giant cell arteritis; pJIA = polyarticular juvenile idiopathic arthritis; QW = once weekly; Q2W = once every 2 weeks; Q10D = once every 10 days; RA = rheumatoid arthritis; SC = subcutaneous; sJIA = systematic juvenile idiopathic arthritis; TCZ=tocilizumab.

Notes:

*Total is less than the sum of patients receiving each dose as some patients received multiple doses

Patients can be included in more than one category, if they receive more than one dose at any time during the study.

Source: WA22762/STmt_exp_rmp_dur.out, NA25520/Stmt_exp_rmp_dur_SA978.out, WA28119/STmt_exp_rmp_dur_all_ah128_SE.out, pool_Jigsaw117_118_LTE/pool_STmt_exp_rmp_dur.out

Table 7 includes all dose levels that an individual patient may have received.

Table 7 Exposure of IV Dose (Total)

Dosing Regimen	Persons (n)	Person Time (PY)
Total Exposure		
TCZ 4 mg/kg Q4W	1886	1375.7
TCZ 8 mg/kg Q4W or Q2W	5526	14582.7
TCZ 8 mg/kg one dose or two doses	974	68.1
TCZ 10 mg/kg Q4W	61	32.6
TCZ 12 mg/kg Q2W	71	87
Total	**8518***	**16146.1**

IV = intravenous; Q2W = twice weekly; Q4W = four times weekly; TCZ = tocilizumab.

* Some patients received multiple doses and were counted under each dosing regimen and so the total is greater than the number of individual patients. Patients can be included in more than one category, if they receive more than one dose at any time during the study.

Source: L11935E/STmt_exp_rmp_dur.out, WA18221/Stmt_exp_rmp_dur.out, WA22762/STmt_exp_rmp_dur.out, WA19977/STmt_exp_rmp_dur.out

WA19926/STmt_exp_rmp_dur.out, NP25737/STmt_exp_rmp_dur_SA966_SE.out

t_dose_rmp_wa42380_SETCZ

t_ex_dose_rmp_ml42528_SETCZ

t_ex_dose_rmp_wa42511_SETCZ

Table 8 Exposure of SC Dose (Total)

Dosing Regimen	Persons (n)	Person Time (PY)
TCZ SC 162 mg QW	957	1098.4
TCZ SC 162 mg Q10D	8	11.7
TCZ SC 162 mg Q2W	671	685.7
TCZ SC 162 mg Q3W	27	72.8
Total	**1630***	**1868.6**

PY = person years; QW = once weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q10D = once every 10 days; SC = subcutaneous; TCZ = tocilizumab.

Note: Patients can be included in more than one category, if they receive more than one dose at any time during the study.

*Total is less than the sum of patients receiving each dosing regimen as some patients received multiple regimens.

Source: WA22762/STmt_exp_rmp_dur.out, NA25220/STmt_exp_rmp_dur_SA978.out

i28119a/STmt_exp_rmp_dur_all_ah128_SE.out,
pool_Jigsaw117_118_LTE/prod/output/pool_STmt_exp_rmp_dur.out

Table 9 and Table 10 provide an overview of number of patients exposed by indication, age group, and sex, in number of patients and person time, for the patients in the clinical studies.

Table 9 Exposure by Age and Sex (by IV Indication)

Age Group (years)	Persons (n)		Person Time (PY)	
	Male	Female	Male	Female
Adult RA				
≥18< 50	297	1579	924.7	5052.8
≥ 50<65	413	1768	1303.1	5606.1
≥ 65<75	149	510	397.3	1400.6
≥ 75	20	117	42.8	252
Total	**879**	**3974**	**2667.9**	**12311.5**
Adult Early RA (WA19926)				
≥18< 50	75	315	59.8	259.9
≥ 50<65	89	280	73	240.4
≥ 65<75	24	69	20.5	56.6
≥ 75	11	13	8.7	9.5
Total	**199**	**677**	**161.9**	**566.5**
sJIA				
< 2	4	7	2.1	3.5
≥ 2 < 5	9	12	13.5	19.8
≥ 5 < 12	27	22	43.1	37.2
≥ 12 < 18	20	22	31.1	35.7
Total	**60**	**63**	**89.8**	**96.2**
pJIA				
≥ 2 < 5	2	12	0.8	9.3
≥ 5 < 12	21	66	16.3	70
≥ 12 < 18	21	66	19.6	68.2
Total	**44**	**144**	**36.7**	**147.4**

Age Group (years)	Persons (n)		Person Time (PY)	
	Male	Female	Male	Female
COVID-19				
≥18< 50	153	86	11.3	6.4
≥ 50< 65	239	121	17.5	8.9
≥ 65< 75	155	95	10.1	6.4
≥ 75	75	50	4.5	3.0
Total	**622**	**352**	**43.4**	**24.7**

COVID-19 = coronavirus disease 2019; GCA = giant cell arteritis; pJIA=polyarticular juvenile idiopathic arthritis; RA=rheumatoid arthritis; sJIA=systematic juvenile idiopathic arthritis.

Source: L11935E/STmt_exp_rmp_age.out, WA18221/Stmt_exp_rmp_age.out, WA22762/STmt_exp_rmp_age.out, WA19977/STmt_exp_rmp_age.out WA19926/STmt_exp_rmp_age.out, NP25737/STmt_exp_rmp_sex_SA966_SE.out

t_age_sex_rmp_wa42380_SETCZ

t_ex_age_sex_rmp_ml42528_SETCZ

t_ex_age_sex_rmp_wa42511_SETCZ

Table 10 Exposure by Age and Sex (by SC Indication)

Age Group (years)	Number of Patients		Patient Year (PY)	
	Male	Female	Male	Female
Adult RA				
≥18< 50	67	436	63.8	437.2
≥ 50<65	115	537	115.1	525.4
≥ 65<75	40	153	37.2	153.3
≥ 75	8	22	8.2	24.1
Total	**230**	**1148**	**224.3**	**1140**
GCA				
≥18< 50	0	0	0.0	0.0
≥ 50<65	10	39	9.3	37.2
≥ 65<75	15	41	13.2	34.8
≥ 75	12	32	9.0	26.7
Total	**37**	**112**	**31.4**	**98.7**
pJIA				
< 2	0	1	0.0	5.8
≥ 2 < 5	2	5	1.6	23.8
≥ 5 < 12	8	15	34.8	74.7
≥ 12 < 18	6	15	26.1	44.4

Age Group (years)	Number of Patients		Patient Year (PY)	
	Male	Female	Male	Female
Total	**16**	**36**	**62.5**	**148.6**
sJIA				
< 2	1	2	3.0	4.4
≥ 2 < 5	3	**5**	13.4	19.2
≥ 5 < 12	10	10	35.3	24.6
≥ 12 < 18	8	12	20.7	42.4
Total	**22**	**29**	**72.5**	**90.6**

GCA = giant cell arteritis; pJIA=polyarticular juvenile idiopathic arthritis; RA=rheumatoid arthritis; sJIA=systematic juvenile idiopathic arthritis.

Note: Extent of Exposure = Sum of actually received injections + up to 14 days per injection.

Source: WA22762/STmt_exp_rmp_age.out, NA25220/STmt_exp_rmp_age.out, WA28119/STmt_exp_rmp_age_all_ah128_SE.out, pool_Jigsaw117_118_LTE/prod/output/pool_STmt_exp_rmp_age.out

Table 11 and Table 12 provides an overall summary of total number of patients by age group and gender, for IV and SC formulations, in number of patients and person time, for the patients in the clinical studies.

Table 11 Exposure by Age and Sex (IV Total)

Age Group (years)	Persons (n)		Person Time (PY)	
	Male	Female	Male	Female
< 2	4	7	2.1	3.5
≥ 2 < 5	11	24	14.3	29.1
≥ 5 < 12	48	88	59.4	107.2
≥ 12 < 18	41	88	50.7	103.9
≥ 18< 50	525	1980	995.8	5319.1
≥ 50< 65	741	2169	1393.6	5855.4
≥ 65< 75	328	674	427.9	1463.6
≥ 75	106	180	56.0	264.5
Total	**1804**	**5210**	**2999.8**	**13146.3**

Source: L11935E/STmt_exp_rmp_age.out, WA18221/Stmt_exp_rmp_age.out, WA22762/STmt_exp_rmp_age.out, WA19977/STmt_exp_rmp_age.out

WA19926/STmt_exp_rmp_age.out, NP25737/STmt_exp_rmp_sex_SA966_SE.out

t_age_sex_rmp_wa42380_SETCZ

t_ex_age_sex_rmp_ml42528_SETCZ

t_ex_age_sex_rmp_wa42511_SETCZ

Table 12 Exposure by Age and Sex (SC Total)

Age Group (years)	Number of Patients (n)		Person Years of Exposure (PY)	
	Male	Female	Male	Female
< 2	1	3	3.0	10.2
≥ 2 < 5	5	10	15.0	43.0
≥ 5 < 12	18	25	70.1	99.3
≥ 12 < 18	14	27	46.8	86.8
≥18< 50	67	436	63.8	437.2
≥ 50<65	125	576	124.4	562.6
≥ 65<75	55	194	50.4	188.1
≥ 75	20	54	17.2	50.8
Total	**305**	**1325**	**390.7**	**1477.9**
Source: L11935E/STmt_exp_rmp_age.out, WA18221/Stmt_exp_rmp_age.out, WA22762/STmt_exp_rmp_age.out, WA19977/STmt_exp_rmp_age.out WA28119/STmt_exp_rmp_age_all_ah128_SE.out, pool_Jigsaw117_118_LTE/prod/output/pool_STmt_exp_rmp_age.out				

Table 13 and Table 14 provide an overview of exposure of patients by ethnic and racial origin, for IV and SC formulations, by indication, in number of patients and person time, for the patients in the clinical studies.

Table 13 Exposure by Ethnic/Racial Origin (IV; by Indication)

Ethnic/Racial Origin	Persons (n)	Person Time (PY)
Adult RA		
White	3635	10923.6
Asian	350	1300.2
American Indian or Alaska Native	306	1061.1
Black	211	596.1
Other	351	1098.4
Total	**4853**	**14979.4**
Adult Early RA (WA19926)		
White	673	555.9
Asian	67	56.3
American Indian or Alaska Native	17	14.4
Black	23	17.0

Ethnic/Racial Origin	Persons (n)	Person Time (PY)
Other	96	84.8
Total	**876**	**728.4**
sJIA		
White	108	164.6
Asian	1	0.1
American Indian or Alaska Native	2	2.9
Black	2	1.9
Other	10	16.4
Total	**123**	**186**
pJIA		
White	150	147.4
Asian	3	3.7
American Indian or Alaska Native	1	1.5
Black	4	4.0
Other	30	27.5
Total	**188**	**184.1**
COVID-19		
White	591	41.2
Asian	51	3.8
American Indian Or Alaska Native	63	4.5
Black	127	8.6
Other	142	9.8
Total	**974**	**67.9**

COVID-19 = coronavirus disease 2019; GCA = giant cell arteritis; pJIA=polyarticular juvenile idiopathic arthritis; RA=rheumatoid arthritis; sJIA=systematic juvenile idiopathic arthritis.

Source: L11935E/STmt_exp_rmp_race.out, WA18221/Stmt_exp_rmp_race.out, WA22762/STmt_exp_rmp_race.out, WA19977/STmt_exp_rmp_race.out

WA19926/STmt_exp_rmp_race.out, NP25737/STmt_exp_rmp_sex_SA966_SE.out

t_race_rmp_wa42380_SETCZ

t_ex_race_rmp_ml42528_SETCZ

t_ex_race_rmp_wa42511_SETCZ

Table 14 Exposure by Ethnic/Racial Origin (SC; by Indication)

Ethnic/Racial Origin	Number of Patients (n)	Person Years of Exposure (PY)
Adult RA		
White	1034	1022.1
Asian	54	67.0
American Indian or Alaska Native	34	39.9
Black	66	62.6
Other	190	172.5
Total	**1378**	**1364.1**
GCA		
White	143	126.2
Asian	1	0.6
American Indian or Alaska Native	0	0.0
Black	1	1.0
Other	2	1.1
Unknown	2	1.2
Total	**149**	**130.1**
pJIA		
White	47	185.1
Asian	0	0.0
American Indian or Alaska Native	0	0.0
Black	0	0.0
Other	5	26.1
Total	**52**	**211.2**
sJIA		
White	41	133.8
Asian	1	6.0
American Indian or Alaska Native	1	3.3
Black	1	2.8
Other	7	17.3
Total	**51**	**163.1**

GCA = giant cell arteritis; pJIA=polyarticular juvenile idiopathic arthritis; RA=rheumatoid arthritis; sJIA=systematic juvenile idiopathic arthritis.

Source: WA22762/STmt_exp_rmp_race.out, NA25520/Stmt_exp_rmp_race.out, WA28119/STmt_exp_rmp_rac_all_ah128_SE.out, pool_Jigsaw117_118_LTE/prod/output/pool_STmt_exp_rmp_race.out

Table 15 and Table 16 provides an overall summary of exposure of patients by ethnic and racial origin, for IV and SC formulations, in number of patients and person time, for the patients in the clinical studies.

Table 15 Exposure by Ethnic/Racial Origin (Total IV; All Indications)

Ethnic/Racial Origin	Persons (n)	Person Time (PY)
Total Exposure		
White	5157	11832.7
Asian	472	1364
American Indian or Alaska Native	389	1084.4
Black	367	627.6
Other	719	1236.9
Total	**7014**	**16145.6**

IV = intravenous

Source: L11935E/STmt_exp_rmp_race.out, WA18221/Stmt_exp_rmp_race.out, WA22762/STmt_exp_rmp_race.out, WA19977/STmt_exp_rmp_race.out; WA19926/STmt_exp_rmp_race.out, NP25737/STmt_exp_rmp_sex_SA966_SE.out

t_race_rmp_wa42380_SETCZ

t_ex_race_rmp_ml42528_SETCZ

t_ex_race_rmp_wa42511_SETCZ

Table 16 Exposure by Ethnic/Racial Origin (Total SC, All Indications)

Ethnic/Racial Origin	Number of Patients	Person Years of Exposure (PY)
Total Exposure		
White	1265	1467.2
Asian	56	73.6
American Indian or Alaska Native	35	43.2
Black	68	66.4
Other	199	200.8
Unknown	7	17.4
Total	**1630**	**1868.6**

SC = subcutaneous

Source: WA22762/Stmt_exp_rmp_race.out, NA25220/STmt_exp_rmp_race.out, W28119/STmt_exp_rmp_rac_all_ah128_SE.out, pool_Jigsaw117_118_LTE/prod/output/pool_STmt_exp_rmp_race.out

Table 17 and Table 18 present exposure by indication, in number of patients and person time, for IV and SC formulations, for the special populations in the clinical studies. It should be noted that, with the exception of WA42380 (to exclude only patients

with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >10 x upper limit of normal (ULN)), ML42528, and WA42511 (to exclude only patients with ALT or AST >5 x ULN), patients with a history of liver impairment, defined as current ALT or AST elevations >1.5 ULN, positive hepatitis BsAg or hepatitis C antibody, or total bilirubin > ULN, were excluded from the Roche studies. Patients with renal impairment, defined as patients with elevated serum creatinine (>124 µmol/L in female patients and >141 µmol/L in male patients) were also excluded from the Roche studies. For these reasons, data from such patients are available for inclusion in Table 17 only from WA42380, ML42528, and WA42511 (patients with eGFR <30 mL/min were excluded in WA42511).

Table 17 Exposure Special Population (by IV Indication)

Special Population	Persons (n)	Person Time (PY)
Adult RA		
Pregnant women	48	129.9
Elderly (≥ 75 years old)	137	294.8
Renal impairment	0	0
Liver impairment	0	0
Total	**185**	**424.7**
Adult Early RA		
Pregnant women	7	4.2
Elderly (≥ 75 years old)	24	18.2
Renal impairment	0	0
Liver impairment	0	0
Total	**31**	**22.4**
sJIA		
Pregnant women	0	0
Renal impairment	0	0
Liver impairment	0	0
Total	**0**	**0**
pJIA		
Pregnant women	0	0
Renal impairment	0	0
Liver impairment	0	0
Total	**0**	**0**

Special Population	Persons (n)	Person Time (PY)
COVID-19		
Elderly (≥ 75 years old)	125	7.7
Pregnant women	0	0
Renal impairment	152	9.6
Liver impairment	24	1.8
Cardiac impairment	221	14.5
Total	**391***	**25.8***

COVID-19 = coronavirus disease 2019; IV = intravenous; pJIA=polyarticular juvenile idiopathic arthritis; RA=rheumatoid arthritis; sJIA=systematic juvenile idiopathic arthritis.
Notes:
* Total is less than the sum of patients/PYs in each special population as patients could be counted under multiple categories.
Pregnancy defined by the preferred terms with a primary SOC of Pregnancy, Puerperium, and Perinatal Conditions or Terms included in the High-Level Term of Induced Abortion. Pregnancy could also be collected from a positive pregnancy test.
Renal, Hepatic and Cardiac Impairment defined as MedDRA basket 'PBRER SD AE Terms Suggesting {Renal/Hepatic/Cardiac} Impairment' respectively.
Patients with a history of liver impairment, current ALT or AST elevations >1.5 upper limit of normal (ULN), positive hepatitis BsAg or hepatitis C antibody, or total bilirubin > ULN were previously excluded from the Roche studies; however, exclusion criteria were updated for Study WA42380 (to exclude only patients with ALT or AST >10 x ULN) and for studies ML42528 and WA42511 (to exclude only patients with ALT or AST >5 x ULN).
Patients with renal impairment: patients with elevated serum creatinine (>124 µmol/L in female patients and >141 µmol/L in male patients) were previously excluded from the Roche studies; however, exclusion criteria were updated for Studies WA42380, ML42528, and WA42511 (please note that patients with eGFR <30 mL/min were excluded in WA42511).
Source: L11935E/STmt_exp_rmp_prg.out, WA18221/Stmt_exp_rmp_prg.out, WA22762/STmt_exp_rmp_prg.out, WA19977/STmt_exp_rmp_prg.out, L11935E/STmt_exp_rmp_age.out, WA18221/Stmt_exp_rmp_age.out, WA22762/STmt_exp_rmp_age.out, WA19977/STmt_exp_rmp_age.out, WA19926/STmt_exp_rmp_prg.out
t_speclpop_rmp_wa42380_SETCZ
t_ex_speclpop_rmp_ml42528_SETCZ
t_ex_speclpop_rmp_wa42511_SETCZ
Note that data on pregnant patients were obtained from patients who became pregnant after entering Roche clinical studies and who were subsequently discontinued from the study per protocol.

Table 18 Exposure Special Population (by SC)

Special Population	Persons (n)	Person Time (PY)
Adult RA		
Pregnant women	5	2.7
Elderly (≥ 75 years old)	30	32.3
Renal impairment	0	0.0
Liver impairment	0	0.0

Special Population	Persons (n)	Person Time (PY)
Total	**35**	**35**
GCA		
Pregnant women	0	0.0
Elderly (≥ 75 years old)	44	35.7
Renal impairment	0	0.0
Liver impairment	0	0.0
Total	**44**	**35.7**
pJIA		
Pregnant women	**1***	**0.0**
Renal impairment	0	0.0
Liver impairment	**0**	**0.0**
Total	**0**	**0.0**
sJIA	**0**	**0.0**
Pregnant women		
Renal impairment	**0**	**0.0**
Liver impairment	0	0.0
Total	**0**	**0.0**

GCA = giant cell arteritisa; pJIA=polyarticular juvenile idiopathic arthritis; RA=rheumatoid arthritis; SC = subcutaneous; sJIA=systematic juvenile idiopathic arthritis.

Notes: Pregnancy defined by the preferred terms with a primary SOC of Pregnancy, Puerperium, and Perinatal Conditions or Terms included in the High-Level Term of Induced Abortion. Pregnancy could also be collected from a positive pregnancy test.

* One pJIA patient in Study WA29231 with positive pregnancy test on Study Day 637 withdrew from the study due to pregnancy. The pregnancy continued following the patient's discontinuation from the study and the patient gave birth to a live born baby at full term (38 weeks).

Patients with a history of liver impairment , current ALT or AST elevations >1.5 upper limit of normal (ULN), positive hepatitis BsAg or hepatitis C antibody, or total bilirubin > ULN were excluded from the Roche studies.

Patients with renal impairment: patients with elevated serum creatinine (>124 µmol/L in female patients and >141 µmol/L in male patients) were excluded from the Roche studies.

Source: WA22762/STmt_exp_rmp_prg.out, NA25220/Stmt_exp_rmp_prg.out, WA22762//STmt_exp_rmp_age.out, NA25220/Stmt_exp_rmp_age.out, i28119a/STmt_exp_rmp_age_all_ah128_SE.out

Note that data on pregnant patients were obtained from patients who became pregnant after entering Roche clinical studies and who were subsequently discontinued from the study per protocol.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

Table 19 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 TCZ.	No	Hypersensitivity is contraindicated in the 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 TCZ.	No	For RA, sJIA, pJIA, and CRS, active severe infections are contraindicated in the SmPC. Patients with COVID-19 who simultaneously also have other, serious active infections are contraindicated in the 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 TCZ in the clinical trial setting.	No	There is no data to suggest that TCZ 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 SmPC.
Uncontrolled disease states, such as asthma or inflammatory bowel	Potential for patients to be unable to adhere to study protocol. Oral steroids had to remain stable and parenteral	No	This exclusion criterion was not related to the safety of the patient population

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
disease where flares are commonly treated with oral or parenteral corticosteroids.	steroids were prohibited in TCZ RA clinical trials to enable accurate assessment of TCZ efficacy.		
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 TCZ in the clinical trial setting	No	Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with TCZ in RA patients. Complications of diverticulitis is listed as a special warning and precaution in the 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 TCZ in the clinical trial setting.	No	Treatment with TCZ, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases. This has been listed in the SmPC under Special Warnings and Precautions for use. Hepatotoxicity is classified as an important identified risk in this RMP (see Module SVII.3.1)
Active TB requiring treatment within the previous 3 years and no evidence of active TB infection at enrollment.	To ensure general safety of patients to be treated with TCZ in the clinical trial setting.	No	Tuberculosis is listed as a special warning and precaution in the SmPC.
Primary or secondary immunodeficiency (history of or currently active).	To ensure general safety of patients to be treated with TCZ 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 SmPC.

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (including hematologic malignancies and solid tumors, except basal cell carcinoma of the skin that has been excised and cured), or breast cancer diagnosed within the previous 20 years.	To ensure general safety of patients to be treated with TCZ in the clinical trial setting	No	Malignancy is listed as a special warning and precaution in the 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.	No	Information on the use of TCZ in pregnant women or nursing (breast feeding) mothers is provided in the SmPC including guidance on contraceptive use and advice that TCZ should not be used during pregnancy unless necessary. Healthcare providers are advised to consider discontinuation of therapy in breastfeeding women, or discontinuation of treatment.
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

Criterion	Reason for exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with lack of peripheral venous access	Potential for patients to be unable to adhere to study protocol/receive study medication	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 TCZ in the clinical trial setting	No	There is no data to suggest that TCZ has any effect on MAS. MAS is listed in the special warnings and precautions for use section in the 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 TCZ in the clinical trial setting.	No	There are insufficient data to suggest that TCZ has an effect on uveitis.

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; TCZ= tocilizumab.

* Criteria specific to sJIA

**Criteria specific to pJIA

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

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 Underrepresented in Clinical Trial Development Programs

Table 20 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant or breastfeeding women	IV formulation: 55 patients SC formulation: 5 patients
Patients with Relevant Comorbidities	
Patients with hepatic impairment	IV formulation: 24
Patients with renal impairment	IV formulation: 152
Patients with cardiac impairment	IV formulation: 221
Patients with a disease severity different from inclusion criteria in clinical trials	The clinical trial program for tocilizumab in RA recruited patients with moderate to severe disease (mean baseline DAS28 score in the adult RA All Exposure population was 6.4 [source: LTE safety update report No. 1053329 Section 3.2]).
Subpopulations carrying known and relevant genetic polymorphisms	There is no known association between the use of tocilizumab and polymorphisms
Combination with other biologics	The use of tocilizumab in combination with rituximab in RA patients has been investigated in one trial (WX21956). However, this 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)	IV formulation: 286 patients SC formulation: 74 patients
Paediatric Patients	IV formulation: 311 patients SC formulation: 103 patients

IV=intravenous; LTE=long-term extension; RA= rheumatoid arthritis; SC=subcutaneous.

Notes: Renal, Hepatic, and Cardiac Impairment defined as MedDRA basket 'PBRER SD AE Terms Suggesting {Renal/Hepatic/Cardiac} Impairment' respectively.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

The Marketing Authorization Holder (MAH) outlines in detail the method used to calculate post-authorization exposure in each respective Periodic Safety Update Report (PSUR)/Periodic Benefit-Risk Evaluation Report (PBRER).

SV.1.2 Exposure

The estimated cumulative post-authorization exposure to tocilizumab from the International Birth Date (11 April 2005) to 10 April 2023 (inclusive) are presented in the PBRER (data lock point 10 April 2023). The estimated cumulative market exposure to TCZ until 10 April 2023is 3,947,326 patients (3,447,231 PY) of which 397,379 patients (332,041 PY) were estimated to have received TCZ during the reporting interval (from 11 April 2022 to 10 April 2023).

IV Formulation

The combined cumulative post-marketing exposure of patients to IV tocilizumab is estimated to be 2,653,023 patients (2,394,764 PY).

SC Formulation

The combined cumulative post-marketing exposure of patients to SC tocilizumab is 1,243,053 patients (1,010,969 PY).

PART II: MODULE SVI - ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

No studies on the effects of the potential for TCZ to cause dependence have been performed. However, there is no evidence from the available data that TCZ 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 hemoglobin levels.

IL-6 signaling blockade, through the use of TCZ, 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 nonclinical and clinical studies that TCZ 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 TCZ treatment gives rise to dependence.

Erythropoietins have been associated with illegal use, primarily in athletes, in order to stimulate the bone marrow to increase RBC production thereby achieving the

performance enhancement associated with training at high altitude. Results from clinical trials with TCZ have demonstrated improvement in anemia of chronic disease, associated with chronic inflammatory conditions, but no increase in healthy volunteers or in patients with normal hemoglobin labels. Additionally, supraphysiological levels of hemoglobin have not been recorded in patients receiving TCZ. Therefore, TCZ is not considered to be of use as a performance enhancing drug in this context.

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

Not applicable

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

Not applicable.

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

Information on Important Identified Risks

Serious Infections

The safety concern “serious infection” is considered an important identified risk for chronic TCZ 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 under the Section Information on Important Identified Risks, together with data related to chronic TCZ dosing.

MedDRA terms: SOC Infections and Infestations

Potential mechanisms:
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 defense mechanism against infectious organisms.

Evidence source(s) and strength of evidence:
Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.

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 Center, 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 bacteremia respectively (Goyal et al. 2020). A single center 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).

Frequency with 95 % CI

Rates of Serious Infections

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population	• Placebo (PBO) + DMARD: 3.13/100PY (95% CI: 1.83, 5.02) • TCZ 4 mg/kg + MTX: 3.51/100PY (95% CI: 1.97, 5.80) • TCZ 8 mg/kg + DMARD: 5.11/100PY (95% CI: 3.70, 6.88) • Source: Summary of Clinical Safety (SCS): RA (IV), Table 76 (p.204)
IV RA all exposure population (2 May 2012)	• 4.42/100PY (95% CI: 4.11, 4.76)
IV Early RA WA19926 (Week 52)	• PBO + MTX: 2.4/100PY (95% CI: 0.9, 5.1) • TCZ 4 mg/kg + MTX: 4.2/100PY (95% CI: 2.1, 7.5) • TCZ 8 mg/kg + MTX: 3.8/100PY (95% CI: 1.8, 7.0) • TCZ 8 mg/kg + PBO MTX: 3.0/100PY (95% CI: 1.3, 5.9)
SC RA (Week 24)	• TCZ 162mg QW + DMARD: 3.11/100PY (95% CI: 1.42, 5.89) • TCZ 162mg Q2W + DMARD: 6.57/100PY (95% CI: 3.39, 11.47) • PBO + DMARD: 6.11/100PY (95% CI: 1.98, 14.26) • Source: Summary of Clinical Safety (SCS) RA (SC) Table 33 (p.78)
• ***SC RA all exposure population (4MSU October 2012)***	• 4.61/100PY (95% CI: 3.62, 5.78)
SC GCA (Week 52)	• PBO QW + 26-week prednisone taper: 4.2/100PY (95% CI: 0.5, 15.2) • PBO QW + 52-week prednisone taper: 12.5/100PY (95% CI: 4.6, 27.2) • TCZ 162 mg QW + 52-week prednisone taper: 9.7/100PY (95% CI: 4.4, 18.4) • TCZ 162 mg Q2W + 52-week prednisone taper: 4.4/100PY (95% CI: 0.5, 15.9)
IV pJIA (Week 104)	• 5.2/100PY (95% CI: 3.0, 8.5) Source: WA19977 Final CSR (p.34)
SC pJIA (Week 52)	• 4.0/100PY (95% CI: 0.48, 14.33) Source: Summary of Clinical Safety pJIA Section 2.1.5.2.2 (p.69)

IV sJIA (Week 12)

- PBO: 0
- All TCZ: 11.5/100PY (95% CI: 1.4, 41.5)

Source: Summary of Clinical Safety sJIA Table 20 (p.69)

IV sJIA (Week 260)

- All TCZ: 10.1/100PY (95% CI: 7.1, 14.0)

Source: WA18221 Week 260 CSR Table 32

IV sJIA <2 Years (Week 52)

- TCZ IV 12 mg/kg: 13.6/100PY (95% CI: 0.3, 75.7)

Source: NP25737 Final CSR Table 3

SC sJIA (Week 52)

- All TCZ: 10.7/100PY (95% CI: 3.5, 25.0)
- Source: WA28118 Final CSR output t_ae_rate_SE_SAE_INF.out

TCZ indications with acute dosing regimen:

- ***COVID-19 (Day 60)*** [6]

  - Pooled data from WA42380, ML42528, and WA42511

    - Pooled Safety-Evaluable Population:
    - PBO: 22.8%
    - TCZ: 18.6%
    - Baseline Steroid Use subgroup:
    - PBO: 22.9%
    - TCZ: 18.1%
    - Source: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_SE_SINF.out
    - root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_aesi_bsteroid_SE.out

[6] The safety concern “serious infection” is considered an important identified risks for chronic TCZ dosing, but is assessed as important potential risk for the indication of COVID 19. CIs are not available for the COVID studies.

Seriousness/outcomes[7]

Rates of Fatal Infections

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population

- PBO + DMARD: 0.18/100PY (95% CI: 0.00, 1.03)
- TCZ 4 mg/kg + MTX: 0
- TCZ 8 mg/kg + DMARD: 0.48/100PY (95% CI: 0.13, 1.22)
- Source: Summary of Clinical Safety RA (IV), Section 5.9.2 (pp. 209 and 802)

IV RA all exposure population (2 May 2012)

- 0.16/100 PY (95% CI: 0.10, 0.24)

IV Early RA WA19926 (Week 52)

- PBO + MTX: 0.78/100 PY (95% CI: 0.10, 2.83)
- TCZ 4 mg/kg + MTX: 0.76/100 PY (95% CI: 0.09, 2.74)
- TCZ 8 mg/kg + MTX: 0
- TCZ 8 mg/kg +PBO: 0

SC RA (Week 24)

- TCZ 162 mg QW + DMARD: 0
- TCZ 162 mg Q2W + DMARD: 1.4/100 PY (95% CI: 0.28, 3.95)
- PBO + DMARD: 0
- Source: Summary of Clinical Safety RA (SC), Tables 20-21;33, (pp. 51-52;78)

- ***SC RA all exposure population (4MSU October 2012)***

- 0.31/100 PY (95% CI: 0.10, 0.73)

SC GCA (Week 52)

- PBO + 26-week prednisone taper: 0
- PBO + 52-week prednisone taper: 0
- TCZ 162 mg QW+ 52-week prednisone taper: 0
- TCZ 162 mg Q2W+ 52-week prednisone taper: 0

IV pJIA (Week 104)

- 0 - No deaths occurred during the study

Source: WA19977 Final CSR (p.34)

[7] Rates of Serious infections with an outcome of death are presented in this section

SC pJIA (Week 52)

- 0 - No deaths occurred during the study

Source: Summary of Clinical Safety pJIA (SC) Section 2.1.5.2.2 (p.69)

IV sJIA (Week 12)

- PBO: 0
- All TCZ: 0

Source: Summary of Clinical Safety sJIA (IV) Table 20, pp 54

IV sJIA (Week 260)

- All TCZ: 0.3/100PY (95% CI: 0.01, 1.53)

Source: WA18221 Week 260 CSR, Table 32

IV sJIA <2 Years (Week 52)

- 0 - No deaths occurred during the study

Source: NP25737 Final CSR, Table 3

SC sJIA (Week 52)

- All TCZ: 2.1/100PY (95% CI: 0.05, 11.92)

Source: WA28118 Final CSR, output t_ae_rate_SE_SAE_INF.out

- ***TCZ indications with acute dosing regimen:***
- ***COVID-19 (Day 60)*** [8]

Pooled data from WA42380, ML42528, and WA42511

- PBO: 14.7%
- TCZ: 13.8%
- Source: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_dth_SE.out

[8] The safety concern “serious infection” is considered an important identified risks for chronic TCZ dosing, but is assessed as important potential risk for the indication of COVID 19. CIs are not available for the COVID studies. These fatal cases occurred in the context of an indication (COVID 19) involving a severe underlying respiratory infection. There were 12.2% patients with the Preferred Term of COVID-19 or COVID-19 pneumonia in the PBO group and 10.4% in the TCZ group.

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

TCZ 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 TCZ 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 factors and risk groups:

Patients with diabetes reported a higher rate of serious infections compared to patients without diabetes. Patients treated with TCZ 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 TCZ 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 warning caution when considering the use of RoActemra 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 and Patient Information Leaflet warning 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 TCZ
- Exclusion of any possibility of an active infection before initiating therapy in RA, sJIA, pJIA, and CRS (including screening for latent TB). Interruption of TCZ 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 benefit-risk balance of the product:
Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including TCZ. 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 TCZ Summary of Product Characteristics (SmPC), Patient Information Leaflet, 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:
There is no public health impact.

Complications of Diverticulitis

The safety concern “complications of diverticulitis” is considered an important identified risk for chronic TCZ 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 under the Section Information on Important Identified Risks, together with data related to chronic TCZ dosing.

MedDRA terms: GI Perforation Standardised MedDRA Query (SMQ) (narrow); GI Perforation SMQ (wide)

Potential mechanisms:
Potential infectious etiology (diverticulitis)

Evidence source(s) and strength of evidence:
Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.

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-Luosujarvi 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 diarrhea (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 1patient (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).

Risk factors and risk groups

No study described the risk factors associated with GI perforation in COVID-19 patients.

Mortality

No study described the mortality due to GI perforation in COVID-19 patients.

Rates of Medically Confirmed GI perforation[9]

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population	• PBO+MTX: 0 • TCZ 4 mg/kg +MTX: 0.23/100PY (95% CI: 0.01, 1.31) • TCZ 8 mg/kg + DMARD: 0.12/100PY (95% CI: 0.00, 0.66) Source: Summary of Clinical Safety, RA (IV) Table 53, (p.161)
IV RA all exposure population (2 May 2012)	• 0.20/100PY (95% CI: 0.14, 0.29) • Source: Safety Update of IV TCZ Adult RA Studies (Data cutoff date 2 May 2012), Table 19, (p.75)
IV Early RA WA19926 (Week 52)	• PBO+MTX: 0.40/100PY (0.0, 2.2) • All TCZ: 0 Source: Summary of Clinical Safety, RA (IV) Table 50, (p.128)
SC RA (Week 24)	• TCZ 162 mg QW + DMARD: 0 • TCZ 162 mg Q2W + DMARD: 0 • PBO + DMARD: 0
• ***SC RA all exposure population (4MSU October 2012)***	• 0.06 events per 100 PY (95% CI: 0.00, 0.35) • Source: Four Month Safety Update, RA (SC) Table 18 (p.32)
SC GCA (Week 52)	• PBO + 26-week prednisone taper: 0 • PBO + 52-week prednisone taper: 0 • TCZ 162 mg QW+ 52-week prednisone taper: 0 • TCZ 162 mg Q2W+ 52-week prednisone taper: 0
IV pJIA (Week 40)	• 0 – No GI perforations were reported in this study Source: WA19977 Final CSR, Section 7.3.3, pp128

[9] Medically Confirmed GI Perforation: Because the events captured by the GI perf SMQ are considered nonspecific an unblinded medical review was performed by the Sponsor to identify cases medically consistent with GI perforation

IV pJIA (Week 104)

- 0 – No GI perforations were reported in this study

Source: WA19977 Final CSR, Section 7.3.3, pp128

SC pJIA (Week 52)

- 0- No GI Perforations were reported in this study
- Source: Summary of Clinical Safety Section 2.1.5.1 pp63

IV sJIA (Week 12)

- 0- No GI Perforations were reported in this study
- Source: Summary of Clinical Safety Section 7.4.7.2 (p.178)

IV sJIA (Week 104)

- 0-No GI Perforations were reported in this study
- Source: Summary of Clinical Safety Section 7.4.7.2 (p.178)

IV sJIA (Week 260)

Not assessed
Source: WA18221 Week 260 Final CSR Section 3.6.7.1 (p.45)

IV sJIA <2 Years (Week 12)

- 0 - No GI Perforations were reported in this study
- Source: NP25737 Final CSR Section 6.8.8

IV sJIA <2 Years (Week 52)

0- No GI Perforations were reported in this study
Source: NP25737 Final CSR Section 7.9.6

SC sJIA (Week 52)

- 0 - No GI Perforations were reported in this study
- Source: NP25737 Final CSR Section 6.8.7

TCZ indications with acute dosing regimen:

COVID-19 (Day 60) [10]

- Pooled data from WA42380, ML42528, and WA42511

-
- Pooled Safety-Evaluable Population:
- PBO: 0.6%
- TCZ: 0.5%
- Baseline Steroid Use subgroup:
- PBO: 0.3%
- TCZ: 0.5%

Source: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_SE_GASTR.out root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_aesi_bsteroid_SE.out

[10] The safety concern “complications of diverticulitis” is considered an important identified risks for chronic TCZ dosing, but is assessed as important potential risk for the indication of COVID 19. The three COVID-19 studies used wide SMQ for relevant outputs, which included non-medically confirmed cases.

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 factors and risk groups:
Tocilizumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis.

Preventability:
Prescribing information warning that TCZ 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, hemorrhage, and/or unexplained change in bowel habits with fever.

Impact on the benefit-risk 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 TCZ 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

Neutropenia

MedDRA terms: Neutropenia High-Level Term (HLT), Neutrophil count decreased Preferred Term
Laboratory data analysis based on Common Terminology Criteria for Adverse Events (CTCAE) grades:

– Grade 1: 1.5 x 10^9/L - < lower limit of normal (LLN)

- Grade 2: 1.0 - < 1.5 x 10^9/L
- Grade 3: 0.5 - < 1.0 x 10^9/L
- Grade 4: <0.5 x 10^9/L

Potential mechanisms:
The potential cause of neutropenia could be due to marginalization of neutrophils; however, the exact cause is uncertain. Neutrophil function and distribution was studied in Study WA29049, and Study ML25243.

Evidence source(s) and strength of evidence:
Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.

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).

Neutrophil Laboratory Data

TCZ indications with a periodic chronic dosing regimen:

IV RA all exposure population (2 May 2012)	n=4163 • Normal: 2256 (54.2%) • Grade 1: 900 (21.6%) • Grade 2: 757 (18.2%) • Grade 3: 223 (5.4%) • Grade 4: 27 (<1%) Source: Safety Update of IV TCZ Adult RA Studies (Data cutoff date 2 May 2012)
• ***SC RA (Week 24)***	• Grade 3 and 4 • TCZ 162 mg QW + DMARD: 18/631 (2.9%) • TCZ 162 mg Q2W + DMARD: 16/437 (3.7%) • Placebo + DMARD: 0/218
SC RA all exposure population (4MSU Data Cut October 2012) •	Grade 3 and 4 • TCZ 162 mg QW + DMARD: 29/521 (5.6%) • TCZ 162 mg Q2W PFS[11]: 6/170 (3.5%) • TCZ 162 mg Q2W PFS to TCZ 162 mg Q2W AI[12]: 7/168 (4.2%) • Placebo PFS Q2W to TCZ 162 mg Q2W PFS: 2/60 (3.3%) • Placebo PFS Q2W to TCZ 162 mg Q2W AI: 4/59 (6.8%)
SC GCA (Week 52)	• Grade 3 and 4 • PBO + 26-week prednisone taper: 0/50 (0.0%) • PBO + 52-week prednisone taper: 0/51 (0.0%) • TCZ 162 mg QW+ 26-week prednisone taper: 4/100 (2.0%) • TCZ 162 mg Q2W+ 26-week prednisone taper: 2/49 (4.1%)

[11] 162 mg SC administered via the pre-filled syringe (PFS)
[12] 162 mg SC administered via the autoinjector (AI)

IV pJIA (Week 104)

- n=188
- Grade 3: 11 (5.9%)
- Grade 4: 0
- Source: WA19977 final week 104 CSR Section 7.10.1 Table 37

SC pJIA (Week 52)

- n=52
- Grade 3-4: 8 (15.4%)
- Source: Summary of Clinical Safety, Table 33 (p.90)

IV sJIA (Week 12)

Grade 3:
Placebo: 0
All TCZ: 5/75 (6.7%)
Grade 4:
Placebo: 0
All TCZ: 1/75 (1.3%)
Source: WA18221 Week 12 Final CSR, Table 57

IV sJIA (Week 260)

- n=112
- Grade 3: 28 (25.0%)
- Grade 4: 7 (6.3%)
- Source: WA18221 Week 260 Final CSR, Table 43 (p.139)

IV sJIA <2 Years (Week 52)

- n=11
- Grade 3: 3 (27.3%)
- Grade 4: 0
- Source: NP 25737 CSR data output: t_lb_shift_SE.out

SC sJIA (Week 52)

- n=51
- Grade 3: 12 (23.5%)
- Grade 4: 0

Source: WA 28118 Final CSR data outputs: t_lb_grade_SE. t_lb_shift_SE_HEM.out

TCZ indications with acute dosing regimen:

COVID-19 (Day 60) [13]

- WA42380

- PBO (n=115):
- Grade 1: 2 (1.7%)
- Grade 2: 0
- Grade 3: 1 (0.9%)
- Grade 4: 0
- TCZ (n=245):
- Grade 1: 18 (7.3%)
- Grade 2: 22 (9%)
- Grade 3: 9 (3.7%)
- Grade 4: 3 (1.2%)

Source: WA42380 Final CSR

- ML42528

- PBO (n=80):
- Grade 1: 8 (10%)
- Grade 2: 1 (1.3%)
- Grade 3: 0
- Grade 4: 0

TCZ (n=170):
Grade 1: 48 (28.2%)
Grade 2: 2 (1.2%)
Grade 3: 2 (1.2%)
Grade 4: 0
Source: ML42528 Final CSR

[13] Data are limited to those that were “not low” at baseline from the shift table. A pooled assessment was not conducted as the frequency and timing of scheduled laboratory measurements was different. Individual study data are presented.

- WA42511

- PBO+RDV (n=168):
- Grade 1: 3 (1.8%)
- Grade 2: 3 (1.8%)
- Grade 3: 1 (0.6%)
- Grade 4: 0
- TCZ+RDV (n=309):
- Grade 1: 17 (5.5%)
- Grade 2: 18 (5.8%)
- Grade 3: 4 (1.3%)
- Grade 4: 3 (1.0%)
- Source: WA42511 Final CSR

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.

Preventability:
In patients not previously treated with TCZ for all indications other than, COVID-19, initiation is not recommended in patients with an 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 benefit-risk balance of the product:
Decreases in neutrophil and other WBC counts have been associated with TCZ treatment. The TCZ 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 identified.

Hepatotoxicity

MedDRA terms: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ narrow), Liver related investigations, signs and symptoms (SMQ narrow), Cholestasis and jaundice of hepatic origin (SMQ narrow), Hepatocellular damage and hepatitis NEC (HLT)

Potential mechanisms:
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, the MAH has identified a causal association between TCZ and serious hepatotoxicity. The assessment was further validated by an independent drug-induced liver injury (DILI) expert panel on selected cases (Hepatotoxicity and Tocilizumab, Drug Safety Report [DSR] No. 1084454, 2019) (Addendum CSR, Study WA25204 [ENTRACTE]; Report 1093548).

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 (Drug Safety Report No. 1084454, 2019).

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, 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 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.

MTX background rates for liver enzyme elevations from the US package insert are cited below (Methotrexate = Rheumatrex US package insert).

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.

Laboratory Abnormalities in the Clinical Trials Setting:

ALT/AST shift from baseline

TCZ indications with a periodic chronic dosing regimen:

Indication and Route	*ALT shift from baseline*	*AST shift from baseline*
IV RA DMARD-IR all control population	Placebo + DMARD (n=929) >3 to 5x ULN: 9 (1.0%) >5 ×ULN: 3 (0.3%) All TCZ (n=1858) >3 to 5x ULN: 89 (4.8%) > 5 ×ULN: 30 (1.6%) Source: Summary of Clinical Safety RA (IV), Table 46 (p.149)	Placebo + DMARD (n=971) >3 to 5 x ULN: 4 (0.4%) > 5 × ULN: 1 (0.1%) All TCZ (n=1921) >3 to 5 x ULN: 31 (1.6%) > 5 × ULN: 3 (0.2%) Source: Summary of Clinical Safety RA (IV), Table 46 (p.149)
IV RA All Exposure (02 May 2012)	1 to ≤ 3 × ULN:70.6% (2712/3839) > 5 × ULN: 2.9%	1 to ≤ 3 × ULN: 59.4% (2357/3965) > 5 × ULN: 0.9%
IV Early RA WA19926 (Week 52)	ALT >ULN -≤ 3x ULN: • PBO +MTX: 36.9% • TCZ 8 mg/kg + PBO: 35.6% • TCZ 4 mg/kg +MTX:39.1% • TCZ 8 mg/kg +MTX: 48.6% ALT > 3 ULN ≤ 5 x ULN • highest frequency in the TCZ 8 mg/kg + MTX and TCZ 4 mg/kg + MTX ALT > 5 ULN ≤ 8 x ULN • highest frequency in the TCZ 8 mg/kg + MTX and TCZ 4 mg/kg + MTX	AST >ULN -≤ 3 x ULN • PBO +MTX: 36.9% • TCZ 8 mg/kg + PBO: 35.6% • TCZ 4 mg/kg +MTX:39.1% • TCZ 8 mg/kg +MTX: 48.6% AST > 3 ULN ≤ 5 x ULN • frequency (at least twice higher) in the TCZ 8 mg/kg + MTX AST > 5 ULN ≤ 8 x ULN • highest frequency in the TCZ 8 mg/kg + MTX

- ***SC RA (Week 24)***

ALT >3x ULN-5xULN
- PBO + DMARD: 4/218 (1.8%)
- TCZ 162 mg QW + DMARD: 24/631 (3.8%)
- TCZ 162 mg Q2W + DMARD: 7/437 (1.6%)

ALT > 5xULN:
- PBO + DMARD: 0/218
- TCZ 162 mg QW + DMARD: 6/631 (1.0%)
- TCZ 162 mg Q2W + DMARD: 1/437 (0.2%)

AST > 3x ULN-5xULN
- PBO + DMARD: 2/218 (0.9%)
- TCZ 162 mg QW + DMARD: 5/631 (0.8 %)
- TCZ 162 mg Q2W + DMARD: 2/437 (0.5%)

AST > 5xULN:
- PBO + DMARD: 0/218
- TCZ 162 mg QW + DMARD: 1/631 (0.2%)
- TCZ 162 mg Q2W + DMARD: 0/437

SC RA all exposure population (4MSU Data Cut October 2012)

ALT >3x ULN- 5x ULN
- PBO PFS Q2W to TCZ PFS Q2W: 2/60 (3.3%)
- PBO PFS Q2W to TCZ AI Q2W: 2/59 (3.4%)
- TCZ 162 mg QW + DMARD: 30/521 (5.8%)
- TCZ 8 mg/kg IV to TCZ 162 mg QW: 12/186 (6.5%)
- TCZ 162 mg QW to TCZ 8 mg/kg IV: 4/48 (8.3%)
- TCZ PFS Q2W: 4/170 (2.4%)
- TCZ PFS Q2W to TCZ AI Q2W: 4/168 (2.4%)

> 5xULN:
- PBO PFS Q2W to TCZ PFS Q2W: 1/60 (1.7%)
- PBO PFS Q2W to TCZ AI Q2W: 2/59 (3.4%)
- TCZ 162 mg QW + DMARD: 6/521 (1.2%)
- TCZ 8 mg/kg IV to TCZ 162 mg QW: 4/186 (2.2%)
- TCZ 162 mg QW to TCZ 8 mg/kg IV: 1/48 (2.1%)
- TCZ PFS Q2W: 1/170 (0.6%)
- TCZ PFS Q2W to TCZ AI Q2W: 2/168 (1.2%)

AST > 3x ULN- 5x ULN
- PBO PFS Q2W to TCZ PFS Q2W: 1/60 (1.7%)
- PBO PFS Q2W to TCZ AI Q2W: 2/59 (3.4%)
- TCZ 162 mg QW + DMARD: 3/521 (0.6%)
- TCZ 8 mg/kg IV to TCZ 162 mg QW: 3/186 (1.6%)
- TCZ PFS Q2W: 2/170 (1.2%)
- TCZ PFS Q2W to TCZ AI Q2W: 2/168 (1.2%)

AST > 5xULN:
- PBO PFS Q2W to TCZ AI Q2W: 1/59 (1.7%)
- TCZ 162 mg QW + DMARD: 3/521 (0.6%)
- TCZ 8 mg/kg IV to TCZ 162 mg QW: 1/186 (0.5%)
- TCZ PFS Q2W to TCZ AI Q2W: 2/168 (1.2%)

SC GCA (Week 52)

Grade 2 Post-baseline Changes in ALT and/or AST
- PBO + 26-week prednisone taper:0/50 (0.0%)
- PBO + 52-week prednisone taper: 0/51 (0.0%)
- TCZ 162mg QW+ 26-week prednisone taper: 2/100 (2.0%)
- TCZ 162mg Q2W+ 26-week prednisone taper: 1/49 (2.0%)

Grade 3 Post-baseline Changes in ALT and/or AST

	• PBO + 26-week prednisone taper:0/50 (0.0%) • PBO + 52-week prednisone taper: 1/51 (2.0%) • TCZ 162mg QW+ 26-week prednisone taper: 2/100 (2.0%) • TCZ 162 mg Q2W+ 26-week prednisone taper: 1/49 (2.0%) Grade 4 Post-baseline Changes in ALT and/or AST • No patient experienced a shift from normal to Grade 4 for ALT or AST post-baseline.	
IV pJIA (Week 104)	• n=187 • Grade 2: 11 (5.9%) • Grade 3: 4 (2.1%) • Grade 4: 0 (0%) • Source: WA19977 Final Week 104 CSR Table 41 (p.157-158)	• n=187 • Grade 2: 3 (1.6%) • Grade 3: 4 (2.1%) • Grade 4: 0 (0%) • Source: WA19977 Final Week 104 CSR Table 41 (p.157-158)
SC pJIA (Week 52)	• >3x ULN- 5x ULN: All TCZ SC: 3/52 (5.8%) • > 5xULN: All TCZ SC: 2/52 (3.8%)	• > 3xULN- 5xULN: All TCZ SC: 0 • > 5xULN: All TCZ SC: 2/52 (3.8%)
IV sJIA (Week 12)	• > 2.5xULN to 5xULN (Grade 2) • PBO 0 • All TCZ 5/75 (6.7%) • > 5xULN to 20xULN (Grade 3) • PBO 0 • All TCZ 1/75 (1.3%) • No Grade 4 elevations • Source: WA18221 Week 12 Final CSR Table 60	• > 2.5xULN to 5xULN (Grade 2) • PBO 0 • All TCZ 2/75 (2.7%) • No Grade 3 or 4 elevations Source: WA18221 Week 12 Final CSR Table 60
IV sJIA (Week 260)	• n=112 • Grade 2 (> 2.5 - 5xULN): 17 (15.2%) • Grade 3 (> 5 -20 x ULN): 13 (11.6%) • Grade 4 (> 20 ULN): 1 (0.9%) • Source: WA18221 Week 260 Final CSR Table 52 (p.150)	• n=112 • Grade 2 (> 2.5 - 5xULN): 11 (11.6%) • Grade 3 (> 5 -20 x ULN): 5 (4.5%) • Grade 4 (> 20 ULN): 1 (0.9%) • Source: WA18221 Week 260 Final CSR Table 52 (p.150)
IV sJIA <2 Years (Week 52)	• n=11 • Grade 2: 2 (18.2%) • Grade 3: 1 (9.1%) • Grade 4: 2 (18.2%) • Source: NP25737 Final CSR, data output: outputt_lb_shift_SE	• n=11 • Grade 2: 0 (0%) • Grade 3: 4 (36.4%) • Grade 4: 0 (0%)

		• Source: NP25737 Final CSR, data output: output t_lb_shift_SE
SC sJIA (Week 52)	• n=51 • Grade 2: 3 (5.9%) • Grade 3: 1 (2.0%) • Grade 4: 1 (2.0%) Source: WA 28118 Final CSR data output:t_lb_shift_SE_LIVER.out	• n=51 • Grade 2: 1 (2.0%) • Grade 3: 1 (2.0%) • Grade 4: 0 (0%) Source: WA 28118 Final CSR data output:t_lb_shift_SE_LIVER.out

TCZ indications with acute dosing regimen:

COVID-19 (Day 60) [14]	• ***ALT shift from baseline***		• ***AST shift from baseline***	
➢ WA42380	• PBO: (n=141) • Grade 1: 48 (34.0%) • Grade 2: 15 (10.6%) • Grade 3:5 (3.5%) • Grade 4:1 (0.7%) • Source: WA42380 Final CSR	• TCZ 8 mg/kg: (n=288) • Grade 1: 122 (42.4%) • Grade 2:24 (8.3%) • Grade 3: 13 (4.5%) • Grade 4: 4 (1.4%) • Source: WA42380 Final CSR	• PBO: (n=135) • Grade 1: 35 (25.9%) • Grade 2: 9 (6.7%) • Grade 3:3 (2.2%) • Grade 4:3 (2.2%) • Source: WA42380 Final CSR	• TCZ 8 mg/kg: (n=265) • Grade 1: 94 (35.5%) • Grade 2:21 (7.9%) • Grade 3: 7 (2.6%) • Grade 4: 5 (1.9%) • Source: WA42380 Final CSR
➢ ML42528	• PBO: (n=125) • Grade 1: 36 (28.8%) • Grade 2: 1 (0.8%) • Grade 3: 3 (2.4%) Grade 4: 0 Source: ML42528 Final CSR	• TCZ: (n=247) • Grade 1: 84 (34%) • Grade 2: 18 (7.3%) • Grade 3: 2 (0.8%) Grade 4: 3 (1.2%) Source: ML42528 Final CSR	• PBO: (n=125) • Grade 1: 26 (20.8%) • Grade 2: 0 • Grade 3: 2 (1.6%) • Grade 4: 0 • Source: ML42528 Final CSR	• TCZ: (n=247) • Grade 1: 61 (24.7%) • Grade 2: 3 (1.2%) • Grade 3: 2 (0.8%) Grade 4: 2 (0.8%) Source: ML42528 Final CSR

[14] Data are limited to those that were “not high” at baseline from the shift table. A pooled assessment was not conducted as the frequency and timing of scheduled laboratory measurements was different. Individual study data are presented.

➢ WA42511	• PBO+RDV: (n= 210) • Grade 1: 74 (35.2%) • Grade 2: 15 (7.1%) • Grade 3: 9 (4.3%) • Grade 4: 4 (1.9%) • Source: WA42511 Final CSR	• TCZ+RDV: (n=417) • Grade 1: 217 (52%) • Grade 2: 44 (10.6%) • Grade 3: 21 (5%) • Grade 4: 3 (0.7%) • Source: WA42511 Final CSR	• PBO+RDV: (n= 210) • Grade 1: 66 (31.4%) • Grade 2: 8 (3.8%) • Grade 3: 10 (4.8%) • Grade 4: 5 (2.4%) • Source: WA42511 Final CSR	• TCZ+RDV: (n=417) • Grade 1: 182 (43.6%) • Grade 2: 23 (5.5%) • Grade 3: 12 (2.9%) • Grade 4: 3 (0.7%) • Source: WA42511 Final CSR

Bilirubin shift from baseline

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population

Placebo + DMARD (n=1009)
- > ULN to 3 x ULN: 9 (0.9%)
- > 3×ULN: 1 (0.1%)

- All TCZ (n=2009)
  - > ULN to 3xULN: 172 (8.6%)
  - > 3×ULN: 1 (0.05%)

Source: Summary of Clinical Safety RA (IV), Table 46 (p.149)

IV RA All Exposure (02 May 2012)

(n=4149)
- >ULN: 673 (16.2%)
- > 3× ULN: 3

IV Early RA WA19926 (Week 52)

<u>>ULN and ≤ 3xULN:</u>
- PBO + MTX: 2.8%
- TCZ 8 mg/kg + PBO: 8.9%
- TCZ 4 mg/kg + MTX: 6.2%
- TCZ 8 mg/kg + MTX: 13.8%

• ***SC RA (Week 24)***	10% of patients in each arm experienced a shift from normal at baseline to a worst post-baseline value between >than the ULN and < 3×ULN (10% SC vs. 11% IV). One patient in the SC arm experienced a shift from normal to between >3×ULN and ≤ 5×ULN. No patient experienced a shift from normal to >5×ULN.
SC RA all exposure population (4MSU Data Cut October 2012)	Two patients experienced a worst post-baseline total bilirubin elevation of ≤ 3 × ULN in the SC arm. • No patients experienced a shift to >3x ULN in the IV, IV-to-SC, and SC-to-IV arms
SC GCA (Week 52)	Bilirubin (shift from normal to Grade 1 post-baseline) • PBO + 26-week prednisone taper: 1/50 (2.0%) • PBO+ 52-week prednisone taper: 3/51 (5.9%) • TCZ 162 mg QW+ 26-week prednisone taper: 9/100 (9.0%) • TCZ 162 mg Q2W+ 26-week prednisone taper: 6/49 (12.2%) Bilirubin (shift from normal to Grade 2 post-baseline) • PBO + 26-week prednisone taper: 0/50 (0.0%) • PBO + 52-week prednisone taper: 0/51 (0.0%) • TCZ 162 mg QW+ 26-week prednisone taper: 4/100 (4.0%) • TCZ 162 mg Q2W+ 26-week prednisone taper: 1/49 (2.0%) Bilirubin (shift from normal to Grade 3 or 4 post-baseline) • None
IV pJIA (Week 104)	>ULN-1.5XULN (Grade 1) • All TCZ 18/187 (9.6%) >1.5-3XULN (Grade 2) • All TCZ 14/187 (7.5%) >3-10XULN (Grade 3) • All TCZ 1/187 (0.5%) >10XULN (Grade 4) • All TCZ 1/187 (0.5%) Source: WA 19977 Week 104 Final CSR Table 43 (p.159)

SC pJIA (Week 52)	Bilirubin (shift from normal to Grade 1 post-baseline) • TCZ SC Q3W (<30kg): 1/27 (3.7%) • TCZ SC Q2W (>30kg): 3/25 (12.0%) • All TCZ SC: 4/52 (7.7%) Bilirubin (shift from normal to Grade 2 post-baseline) • TCZ SC Q3W (<30kg): 0 • TCZ SC Q2W (> 30kg): 0 • All TCZ SC: 0 Bilirubin (shift from normal to Grade 3 or 4 post-baseline) • TCZ SC Q3W (<30kg): 0 • TCZ SC Q2W (> 30kg): 0 • All TCZ SC: 0 • Source: Summary of Clinical Safety, Table 36 (pp.98-99)
IV sJIA (Week 12)	> ULN to 1.5xULN (Grade 1) • Placebo 0 • All TCZ 2/75 (2.7%) > 1.5xULN to 3xULN (Grade 2) • Placebo 0 • All TCZ 1/75 (1.3%) No Grade 3 or Grade 4 bilirubin elevations Source: WA 18221 Week 12 Final CSR, Table 60
IV sJIA Week 260	> ULN to 1.5xULN (Grade 1) • All TCZ 9/112 (8%) > 1.5xULN to 3xULN (Grade 2) • All TCZ 13/112 (11.6%) > 3xULN to 10xULN (Grade 3) • All TCZ 2/112 (1.8%) No Grade 4 elevations Source: Summary of Clinical Safety, Table 36 (pp.98-99)
IV *sJIA* <2 Years Week 52	Bilirubin (shift from normal to Grade 1 post-baseline) • TCZ 12 mg/kg: 0

Bilirubin (shift from normal to Grade 2 post-baseline)

- TCZ 12 mg/kg: 2/11 (18.2%)

Bilirubin (shift from normal to Grade 3 or 4 post-baseline)

- TCZ 12 mg/kg: 1/11 (9.1%)

Source: NP25737 CSR, data output: t_lb_shift_SE

SC sJIA Week 52

n=51

- Grade 1: 4 (7.8%)
- Grade 2: 3 (5.9%)
- Grade 3 or 4: 0 (0%)

Source: WA28118 Final CSR, data output

TCZ indications with acute dosing regimen:

COVID-19 (Day 60) [15]

- WA42380
  - PBO: (n=142)
  - Grade 1: 11 (7.7%)
  - Grade 2: 7 (4.9%)
  - Grade 3: 3 (2.1%)
  - Grade 4: 1 (0.7%)
  - TCZ: (n=283)
  - Grade 1: 23 (8.1%)
  - Grade 2: 2 (0.7%)
  - Grade 3: 6 (2.1%)
  - Grade 4: 0
  - Source: WA42380 Final CSR
- ML42528
  - PBO: (n=122)
  - Grade 1: 2 (1.6%)
  - Grade 2: 0
  - Grade 3: 0
  - Grade 4: 0
  - TCZ: (n=242)
  - Grade 1: 9 (3.7%)
  - Grade 2: 4 (1.7%)
  - Grade 3: 3 (1.2%)
  - Grade 4: 0
  - Source: ML42528 Final CSR
- WA42511
  - PBO+RDV: (n=206)
  - Grade 1: 20 (9.7%)
  - Grade 2: 10 (4.9%)
  - Grade 3: 0
  - Grade 4: 2 (1.0%)
  - TCZ+RDV: (n=413)
  - Grade 1: 46 (11.1%)
  - Grade 2: 19 (4.6%)
  - Grade 3: 5 (1.0%)
  - Grade 4: 1 (0.2%)
  - Source: WA42511 Final CSR

[15] Data are limited to those that were “not high” at baseline from the shift table. A pooled assessment was not conducted as the frequency and timing of scheduled laboratory measurements was different. Individual study data are presented.

Rates of Serious Hepatic AEs

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population	No serious hepatic AEs Source: Summary of Clinical Safety Table 32 (p.76)
IV RA All Exposure (02 May 2012)	0.04/100PY (95% CI: 0.02, 0.09)
IV Early RA (WA19926 Week 52)	No serious hepatic AEs
SC RA all exposure population (4MSU Data Cut October 2012)	• No serious hepatic AEs
IV pJIA Week 104	0.33/100PY (95% CI: 0.01, 1.81) Source: WA19977 Week 104 CSR, data output; slae1_hp_ah1005
SC pJIA Week 52	No serious hepatic AEs for Week 52 SC pJIA Source: Summary of Clinical Safety Table 36 (pg. 98/99)
IV sJIA Week 12	No serious hepatic AEs Source: WA18221 Week 12 Final CSR Table 60
IV sJIA Week 104	No serious hepatic AEs Source: WA18221 Week 104 Final CSR, Tables 76-78
IV sJIA Week 260	No serious hepatic AEs Source: WA18221 Week 104 Final CSR, Tables 76-78
IV *sJIA* <2 Years Week 52	No serious hepatic AEs Source: NP25737 CSR Section 7.10.2.1

No serious hepatic AEs
Source: WA28118 Final CSR, data output: t_lb_shift_SE_LIVER.out

SC sJIA Week 52

TCZ indications with acute dosing regimen:

COVID-19 (Day 60)

- Pooled data from WA42380, ML42528, and WA42511

-
- Pooled Safety-Evaluable Population:
- PBO: 1.2%
- TCZ: 1.7%
- Baseline Steroid Use subgroup:
- PBO: 1.0%
- TCZ: 1.5%
- Source: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_SE_HEPA.out
- root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_aesi_bsteroid_SE.out

Laboratory Abnormalities in the Post-Marketing Setting:
IV RA (WA25204 (ENTRACTE)) Open Label CV Outcome, No Fixed Duration

Of the 1538 patients with moderate to severe RA and treated with tocilizumab, elevations in ALT or AST >3 x ULN occurred in 5.3% and 2.2% patients, respectively (Clinical Study Report – Study WA25204 Addendum).

Rates of Serious Hepatic AEs in the Post-Marketing Setting:

IV RA (WA25204 (ENTRACTE)) Open label CV outcome, No fixed duration

Three serious hepatic events occurred on the TCZ arm (event rate 0.1, 95% CI [0.01, 0.21]). The events were:

• Hepatitis (2 cases) and Hepatic Encephalopathy (1 case).

In a post-marketing analysis of this study, an external adjudication panel assessed 1 case with the event of hepatitis as related to TCZ. The outcome, for this same case of hepatitis, was resolved.

Source: Clinical Study Report – Study WA25204 (Addendum)

Seriousness/outcomes

Mild and moderate elevations of hepatic transaminases have been observed with TCZ 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 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.
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 $\times$ ULN. In patients with elevated ALT or AST above 5 $\times$ 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, RoActemra 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 $\times$ ULN, initiation of treatment with tocilizumab is not recommended.

Impact on the Benefit-risk 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 favorable.

The risk of hepatotoxicity is described in the tocilizumab 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 TCZ and the known efficacy, the MAH concludes that the benefit-risk of TCZ in the indicated treatment populations remains positive.

Public Health Impact
None identified.

Information on Important Potential Risks

Thrombocytopenia and the Potential Risk of Bleeding

MedDRA terms: Haematopoietic thrombocytopenia (SMQ), Thrombocytopenia SMQ wide

Laboratory data analysis based on CTCAE grades:

- Grade 1: 75,000/mm^3 - < lower limit of normal (LLN)
- Grade 2: 50,000 - <75,000/mm^3
- Grade 3: 25,000 - <50,000/mm^3
- Grade 4: <25,000/mm^3

Potential mechanisms:
Thrombocytosis is among the most common extra-articular manifestations of RA and IL-6 administration results in substantial increase in platelets that could be explained by enhanced thrombopoiesis through induction of thrombopoietin. Thus, reduction (normalization) of platelet count may be expected with inhibition of the IL-6 receptors.

Evidence source(s) and strength of evidence:
Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.

Characterization of the risk:

Background incidence/prevalence
RA, sJIA, pJIA, GCA, and CAR T-cell CRS

Patients with RA are frequently on concomitant medications, including MTX and steroids that may reduce platelet count.

COVID-19
A meta-analysis of 22 studies (4889 patients) from China published between December 2019 and April 2020 showed that 10.9%; 95% CI (8.1-13.6) of COVID-19 patients had

thrombocytopenia. The platelet count in severe COVID-19 patients was 14.47 × 109/L; 95% CI (33.0-4.06), which was not significantly lower than that in non-severe patients (Jin et al. 2020). A study of 1,476 COVID-19 patients in Wuhan, China, reported 20.7% had thrombocytopenia during hospitalization. Compared with survivors, non-survivors were older, were more likely to have thrombocytopenia and had lower nadir platelet counts. The study concluded that thrombocytopenia is common in patients with COVID-19 and is associated with increased risk of in-hospital mortality (Yang et al. 2020a).

Among 191 COVID-19 patients, 7% had thrombocytopenia on admission (Zhou et al. 2020). 15 out of 21 non-survivors (8% of the total cohort) admitted to hospital in Wuhan developed overt disseminated intravascular coagulation (≥5points) according to the International Society on Thrombosis and Haemostasis diagnostic criteria (Tang et al. 2020a).

Risk factors and risk groups

Significantly lower platelet count has been associated with over 5-fold enhanced risk of severe COVID-19 (OR: 5.13; 95% CI: 1.81–14.58) (Lippi et al. 2020).

Mortality

A meta-analysis showed that there was a significant difference in platelet count between survivors and non-survivors COVID-19 patients. The mean difference of platelet count between survivors and non-survivors was 38.37 × 10^9/L; 95% CI (55.79-20.94) (Jin et al. 2020). Among 54 non-survivor COVID-19 patients, thrombocytopenia was present in 20% of the cases (Zhou et al. 2020). A study investigated the prognostic factors of 28-day mortality of severely affected COVID-19 patients and the association between mortality and the administration of low molecular weight heparin for at least 7 days. Elevated D-dimer, prolonged PT, increased age, and lower platelet count were associated with higher 28-day mortality (Tang et al. 2020b).

Platelet Laboratory Data

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population

PBO+DMARD (n=1010)

- Grade 1: 12 (1.2%)
- Grade 2: 2 (<1%)
- Grade 3: 1 (<1%)
- Grade 4: 0

TCZ 4 mg/kg +MTX (n=611)

- Grade 1: 40 (6.5%)
- Grade 2: 2 (<1%)
- Grade 3-4: 0

TCZ 8 mg/kg +DMARD (n=1407)

- Grade 1: 133 (9.5%)
- Grade 2: 3 (<1%)
- Grade 3: 3 (<1%)
- Grade 4: 1 (<1%)

Summary of Clinical Safety RA (IV) (Table 86 p. 232)

IV RA All Exposure (02 May 2012)

(n= 4163)
Normal: 3371 (81.0%)
Grade 1: 711 (17.1%)
Grade 2: 53 (1.3%)
Grade 3: 18 (0.4%)
Grade 4: 10 (0.2%)
Source: Safety Update of IV TCZ Adult RA Studies (Data cutoff date 2 May 2012)

IV Early RA WA19926 (Week 52)

PBO + MTX (n= 282)

- Grade 1: 5 (1.8%)
- Grade 2: 0 (0.0%)
- Grade 3: 1 (0.4%)

	• Grade 4: 1 (0.4%) <u>TCZ 4 mg/kg + MTX (n= 289)</u> • Grade 1: 19 (6.6%) • Grade 2: 1 (0.3%) • Grade 3: 1 (0.3%) • Grade 4: 0 (0.0%) <u>TCZ 8 mg/kg + MTX (n=290)</u> • Grade 1: 25 (8.6%) • Grade 2: 0 (0.0%) • Grade 3: 0 (0.0%) • Grade 4: 1 (0.3%) <u>TCZ 8 mg/kg +PBO (n=292)</u> • Grade 1: 24 (8.2%) • Grade 2: 3 (1.0%) • Grade 3-4: 0 (0.0%)
<u>SC RA (Week 24)</u>	• <u>Grade 3 and 4</u> • TCZ 162 mg QW + DMARD: 0 • TCZ 162 mg Q2W + DMARD: 0
<u>SC RA all exposure population (4MSU Data Cut October 2012)</u>	• <u>Grade 3 and 4</u> • TCZ 8 mg/kg IV to TCZ 162 mg QW: 1/186 (0.54%) • TCZ PFS Q2W:1/170 (0.58%) • There were 0 events in all remaining treatment group

SC GCA (Week 52)	PBO + 26-week prednisone taper (n=50) • Grade 1-4: 0 (0%) • PBO + 52-week prednisone taper (n=51) • Grade 1: 1 (2.0%) • Grade 2-4: 0 (0%) • TCZ 162mg QW+ 26-week prednisone taper (n=100) • Grade 1: 7 (7%) • Grade 2-4: 0 (0%) • TCZ 162 mg Q2W + 26-week prednisone taper (n=49) • Grade 1: 5 (10.2%) • Grade 2-4: 0 (0%) • Source: WA28119 Week 52 CSR, pp1891
IV pJIA (Week 104)	• n=188 • Grade 1: 17 (9.0%) • Grade 2: 1 (0.5%) • Grade 3: 1 (0.5%) • Grade 4: 1 (0.5%) • Source: WA 19977 Week 104 Final CSR, Table 30 (p.155)
SC pJIA (Week 52)	• n=52 • Grade 3-4: 0 (0%) • Source: Summary of Clinical Safety pJIA (SC), Table 35 (p.95)
IV sJIA (Week 12)	• Placebo: • Grade 1: 1/34 (2.9%) • All TCZ: • Grade 1: 6/75 (8.0%) • All TCZ Thrombocytopenia AE rate: • Placebo: 0/100PY • All TCZ: 0/100PY • Source: WA 18221 Final CSR; data output: stlb22_btow
IV sJIA (Week 260)	• Grade 1: 34/112 (30.6 %) • Grade 2: 1/112 (0.9%)

- Grade 3: 3/112 (2.7%)
- All TCZ Thrombocytopenia AE rate: 10.7/100PY (95% CI: 7.59-14.59)
- Source: WA18221 Week 260 CSR Section 7.10.1.4 Table 46 (p. 143)

IV sJIA <2 Years (Week 52)

- Grade 1: 1/11 (10.0%)
- Grade 2: 1 (9.1%)
- Thrombocytopenia AE rate: 27.2/100PY (95% CI: 3.29, 98.10)
- Source: NP25737 CSR, data output: t_ae_rate_THROMBR_SE

SC sJIA (Week 52)

- n=51
- Grade 3 and 4: 0 (0%)

Source: WA28118 Final CSR

TCZ indications with acute dosing regimen:

COVID-19 (Day 60) [16]

-

➢ WA42380

- PBO: n=122
- Grade 1: 19 (15.6%)
- Grade 2: 3 (2.5%)
- Grade 3: 1 (0.8%)
- Grade 4: 0
- TCZ: n=258
- Grade 1: 49 (19.0%)
- Grade 2: 8 (3.1%)
- Grade 3: 7 (2.7%)
- Grade 4: 3 (1.2%)
- Source: WA42380 Final CSR

➢ ML42528

- PBO: n = 112
- Grade 1: 7 (6.3%)
- Grade 2: 0

[16] Data are limited to those that were “not low” at baseline from the shift table. A pooled assessment was not conducted as the frequency and timing of scheduled laboratory measurements was different. Individual study data are presented.

- Grade 3: 0
- Grade 4: 0
-

TCZ: n = 220
Grade 1: 13 (5.9%)
Grade 2: 1 (0.5%)
Grade 3: 0
Grade 4: 1 (0.5%)
Source: ML42528 Final CSR

➢ WA42511

-
- PBO: n=194
- Grade 1: 29 (14.9%)
- Grade 2: 2 (1.0%)
- Grade 3: 3 (1.5%)
- Grade 4: 0
- TCZ: n=386
- Grade 1: 98 (25.4%)
- Grade 2: 11 (2.8%)
- Grade 3: 10 (2.6%)
- Grade 4: 1 (0.3%)
-
- Source: WA42511 Final CSR

Seriousness/outcomes

IV RA all exposure population (2 May 2012)

No association between decreases in platelet counts and serious bleeding events has been reported.

SC RA all exposure population (4MSU Data Cut October 2012)

In the SC RA all exposure population (N=1465), no events of thrombocytopenia led to withdrawal and 20 events of thrombocytopenia or platelet count decreased led to dose modification.

No association between decreases in platelet counts and serious bleeding events were reported nor was there a relationship between body weight and the incidence of thrombocytopenia.

Severity and nature of risk

Please refer to seriousness/outcomes. For Thrombocytopenia severity grading see the frequency with 95% CI.

Impact on Quality of Life

There is a risk that a patient's platelet count may decrease when they are taking TCZ.

Risk factors and risk groups

None identified

Preventability

Caution is to be exercised when considering initiating treatment in patients with platelet count <100 x 10^9/L. Monitoring during treatment is recommended and dose modification or treatment discontinuation is recommended based upon platelet count. In patients who develop a platelet count $<$ 50 x 10^3/µL, continued treatment is not recommended.

In COVID-19 patients with platelet count $<50\times10^3/\mu L$, initiation of treatment is not recommended.

For patients with COVID-19, monitoring of platelet counts according to current standard clinical practices is recommended.

Impact on the Benefit-Risk Balance of the Product

Thrombocytopenia is a risk of TCZ treatment; however, the 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 identified.

Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events

MedDRA terms: Myocardial infarction SMQ narrow, Ischaemic Cerebrovascular or Hemorrhagic Cerebrovascular SMQ narrow, Roche Standard AEGT: lipid laboratory parameters

Potential mechanisms:
As has been observed with other biological DMARDs, increases in lipid parameters may reflect the pharmacodynamic effect of TCZ on suppression of inflammation in patients with RA.

Evidence source(s) and strength of evidence:
Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.

Characterization of the risk:

Background incidence/prevalence
RA, sJIA, pJIA, GCA, and CAR T-cell CRS

Myocardial infarction:

- 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 hyperlipidemia, dyslipidemia, 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).

Risk factors and risk groups

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).

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).

Myocardial Infarctions

Rates of Serious Myocardial Infarction

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population	• Control: 0.49/100 PY • TCZ 4 mg/kg + DMARD: 0.18/100 PY • TCZ 8 mg/kg + DMARD: 0.17/100 PY
IV RA all exposure population (2 May 2012)	• 0.27/100PY (95% CI: 0.20, 0.36) events per 100 PYs
IV Early RA (WA19926 Week 52)	• PBO + MTX: 0 • TCZ 4 mg/kg + MTX: 1.1/100PY (0.2, 3.3) • TCZ 8 mg/kg + MTX: 0.4/100PY (0.0, 2.1) • TCZ 8 mg/kg +PBO: 0.4/100PY (0.0, 2.1)
SC RA Week 24	• PBO + DMARD: 0/100 PY • TCZ 162 mg QW + DMARD: 0.35/ 100 PY (95% CI: 0.01, 1.92) • TCZ 162 mg QW + DMARD: 0/100 PY
• ***SC RA all exposure population (4MSU October 2012)***	• 0.19/100 PY (95% CI: 0.04, 0.55)

TCZ indications with acute dosing regimen:

COVID-19 (Day 60) [17]

- Pooled data from WA42380, ML42528, and WA42511

-
- Pooled Safety-Evaluable Population:
- PBO: 0.6%
- TCZ: 0.7%
- Baseline Steroid Use subgroup:
- PBO: 1.0%
- TCZ: 0.7%
- Source: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_SE_MI.out
- root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_aesi_bsteroid_SE.out

[17] Events include both serious and non-serious occurrences. The three COVID-19 studies use wide SMQ for the relevant outputs.

Lipids (baseline to last observation)

TCZ indications with a periodic chronic dosing regimen:

SC RA (Week 24)	• Increase in LDL from < 100 to ³ 160 mg/dL (4.1 mmol/L): • TCZ 162mg QW + DMARD: 5/631 (0.8%) • TCZ 162mg Q2W + DMARD: 4/437 (0.9%) • Placebo + DMARD: 0/218
• ***SC RA all exposure population (4MSU October 2012)***	• PBO PFS Q2W to TCZ AI Q2W: 0 • TCZ PBO PFS Q2W to TCZ PFS Q2W: 0 • 162mg QW + DMARD: 6/521 (1.2%) • TCZ 8 mg/kg IV to TCZ 162 mg QW: 4/186 (2.2%) • TCZ 162 mg QW to TCZ 8 mg/kg IV: 0 • TCZ PFS Q2W: 1/170 (0.6%) • TCZ PFS Q2W to TCZ AI Q2W: 3/168 (1.8%)
IV RA DMARD-IR all control population •	• Lipid Elevations from <130 mg/dL at baseline to ≥ 130 mg/dL at the last observation: • PBO+DMARD: 4% (89/653) • Source: Clinical summary RA IV, p. 185
IV RA all exposure population (2 May 2012)	• Lipid Elevations ≥ 130 mg/dL and < 160 mg/dL: • 150/4171 patients (3.6%) with baseline LDL cholesterol values < 100 mg/dL • Lipid Elevations ≥ 160 mg/dL: • 43/4171 patients (1.0%) • 169/4171 patients (4.1%) • 241/4171 patients (5.8%)
IV Early RA WA19926 (Week 52)	• At baseline, majority of patients had LDL cholesterol levels < 160 mg/dL. • Shifts from levels < 160 mg/dL at baseline to ≥ 160 mg/dL at the last observation, more frequent in the TCZ treatment groups than in the placebo + MTX group. • Highest incidence of shifts to ³ 160 mg/dL in the TCZ 8 mg/kg + placebo groups followed by the TCZ 8 mg/kg + MTX and then the TCZ 4 mg/kg + MTX groups.

- **Rates of Serious Stroke (combined ischemic, hemorrhagic including transient ischemic attacks) and marked laboratory abnormalities**

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population

- Control: 0.24/100 PYs
- 4 mg/kg + DMARD: 0//100 PYs
- TCZ 8 mg/kg + DMARD: 0.33/100 PYs

IV RA all exposure population (2 May 2012)

- 0.32/100 PY (95% CI: 0.24, 0.42)

IV Early RA WA19926 (Week 52)

- PBO + MTX: 0.8/100PY (0.1, 2.8)
- TCZ 4 mg/kg + MTX: 0.8/100PY (0.1, 2.8)
- TCZ 8 mg/kg + MTX: 0/100PY
- TCZ 8 mg/kg +PBO: 0/100PY

SC RA (Week 24)

- TCZ 162 mg QW + DMARD: 0/100PY
- TCZ 162 mg Q2W + DMARD: 0/100PY
- Placebo + DMARD: 0/100PY

- ***SC RA all exposure population (4MSU October 2012)***

- 0.25 events per 100 PYs (95% CI: 0.07, 0.64)

SC GCA (Week 52)

Marked Laboratory Abnormalities:

Total Cholesterol (> 18.30 mmol/L and ≥ 30% increase):

- PBO + 26-week prednisone taper: 1/50 (2.0%)
- PBO + 52-week prednisone taper: 2/51 (3.9%)
- TCZ 162mg QW+ 26-week prednisone taper: 2/100 (2.0%)
- TCZ 162mg Q2W+ 26-week prednisone taper: 2/49 (4.1%)

High LDL Cholesterol (> 5.4mmol/L and ≥ 30% increase):

- PBO + 26-week prednisone taper: 1/50 (2.0%)
- PBO + 52-week prednisone taper: 0/51 (0.0%)
- TCZ 162mg QW+ 26-week prednisone taper: 2/100 (2.0%)

- TCZ 162 mg Q2W+ 26-week prednisone taper: 1/49 (2.0%)

- ***<u>IV pJIA (Week 104)</u>***

- – No patient experienced serious myocardial infarction during study
- <u>Marked Laboratory Abnormalities:</u>
- Total Cholesterol >=170 mg/dL:
- All TCZ 78/185 (42.2%)
- High LDL Cholesterol (>=130 mg/dL):
- All TCZ 10/185 (5.4%)
- Source: WA19977 Week 104 CSR Tables 44- 45; data output: stdm1_elv_ldl

- ***SC pJIA (Week 52)***
  - Rates of serious myocardial infarction:
  - TCZ SC Q3W (<30kg): 0
  - TCZ SC Q2W (> 30kg): 0
  - All TCZ SC: 0
  - Marked Laboratory Abnormalities:
  - Total Cholesterol (>= 200md/dL post-baseline) (patients with baseline elevations are excluded):
  - All TCZ SC: 6/47 (12.8%)
  - High LDL Cholesterol (>=130 mg/dL post-baseline) (patients with baseline elevations are excluded):
  - All TCZ SC: 7/49 (14.3%)
  - Source: SCS pJIA SC Table 37 (p.103); data output: t_lb_elev_SE
- ***IV sJIA (Week 12)***
  - Rates of serious myocardial infarction:
  - No events of serious myocardial infarction
  - Marked Laboratory Abnormalities:
  - Total Cholesterol (>=240 md/dL post-baseline):
  - Placebo: 1/37 (3.0%)
  - All TCZ: 6/75 (8.0%)
  - High LDL Cholesterol (>=160 mg/dL post-baseline):
  - Placebo: 1/37 (3.0%)
  - All TCZ: 3/69 (4.3%)
  - Source: WA18221 Week 12 Final CSR Tables 64-65
- ***IV sJIA (Week 260)***
  - Rates of serious myocardial infarction:
  - Not Assessed[18]
  - Marked Laboratory Abnormalities:
  - Total Cholesterol (³ 200 mg/dL post-baseline):
  - All TCZ: 37/110 (33.6%)
  - High LDL Cholesterol (>=130 mg/dL post-baseline):
  - All TCZ IV: 18/105 (17.1%)
  - Source: WA18221 Week 260 CSR, (p.26)

[18] Serious myocardial infarction was not assessed since it is not generally applicable to the paediatric population.

• ***sJIA IV < 2 Years (Week 52)***	• Rates of serious myocardial infarction: • Not assessed • Marked Laboratory Abnormalities: • Total Cholesterol (>=200 md/dL post-baseline): • All TCZ: 5/11 (45.5%) • High LDL Cholesterol (>=130 mg/dL post-baseline): • All TCZ: 3/11 (27.3%) • Source: CSR NP25737 Section 6.8.8; data outputs: t_lb_elve_SE; t_lb_shift_SE
• ***SC sJIA (Week 52)***	• Rates of serious myocardial infarction: • All TCZ 0 • Marked Laboratory Abnormalities: • Total cholesterol (>=200 md/dL post-baseline) (patients with baseline elevations are excluded): • All TCZ 17/48 (35.4%) • High LDL Cholesterol (>=130 mg/dL post-baseline) (patients with baseline elevations are excluded): • All TCZ 11/47 (23.4%) • Source: Final CSR WA28118 Section 6.8.7; data output: SA996_t_lb_elev_chol1_SCS_SE

TCZ indications with acute dosing regimen:

COVID-19 (Day 60) [19]

- Pooled data from WA42380, ML42528, WA42511

- Pooled Safety-Evaluable Population:
- PBO: 3.3%
- TCZ: 2.0%
- Baseline Steroid Use subgroup:
- PBO: 3.5%
- TCZ: 2.2%
- Source: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_SE_STROKE.out
- root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_aesi_bsteroid_SE.out

[19] Events include both serious and non-serious occurrences. The three COVID-19 studies use wide SMQ for relevant outputs.

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 factors and risk groups
None identified

Preventability:
Lipid parameters such as total cholesterol, triglycerides, and/or low LDL should be monitored during the first 4-8 weeks of TCZ treatment. Patients should be managed according to local clinical guidelines for management of hyperlipidemia.

Impact on the benefit-risk balance of the product:
Increases in total cholesterol, LDL, and triglycerides have been observed following TCZ treatment. The TCZ SmPC, Patient Information Leaflet, 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.

Malignancies

MedDRA terms: Malignancies SMQ narrow

Potential mechanisms:
TCZ is an immunosuppressive agent and may therefore result in an increased risk of malignancy.

Evidence source(s) and strength of evidence:
Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.

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).

Rates of Medically Confirmed Malignancy including NMSC[20]

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population	• PBO: 1.48/100PY (0.74, 2.65) • TCZ 4 mg/kg + DMARD: 1.6/100 PY • TCZ 8 mg/kg + DMARD: 0.7/100 PY Source: Summary of Clinical Safety RA (IV) Table 90 (p.242)
IV RA all exposure population (2 May 2012)	• 1.26 (95% CI: 1.09, 1.44) events per 100 PY
IV Early RA WA19926 (Week 52)	All malignancies • PBO + MTX: 1.2 (0.2, 3.4) per 100 PY • TCZ 4 mg/kg + MTX: 1.5 (0.4, 3.9) per 100 PY • TCZ 8 mg/kg + MTX: 1.1 (0.2, 3.3) per 100 PY • TCZ 8 mg/kg +PBO: 1.1 (0.2, 3.3) per 100 PY
SC RA (Week 24)	All malignancies • PBO + DMARD: 0 per 100 PYs • TCZ 162 mg QW + DMARD: 1.38/100PY (0.38, 3.53) • TCZ 162 mg Q2W + DMARD: 1.64/100PY (0.34, 4.80) Source: Summary of Clinical Safety RA (SC), Table 37, (p.89)
• ***SC RA all exposure population (4MSU October 2012)***	All malignancies • 1.24 events per 100 PY (95% CI: 0.76, 1.92
SC GCA (Week 52)	• PBO + 26-week prednisone taper: 4.2/100PY (95% CI 0.5-15.3) • PBO + 52-week prednisone taper: 2.1/100PY (95% CI 0.1-11.6) • TCZ 162 mg QW+ 26-week prednisone taper: 1.1/100PY (95% CI 0.0-6.0) • TCZ 162 mg Q2W+ 26-week prednisone taper: 0.0/100PY (95% CI 0.0-8.1)

[20] Medically Confirmed Malignancies: A medical review of all reported events from the Malignancy SMQ was performed to identify malignant lesions. Review was undertaken to ensure that the terms were consistent with malignancy, regardless of histological confirmation.

TCZ indications with acute dosing regimen:

COVID-19 (Day 60)

- Pooled data from WA42380, ML42528, WA42511

-
- Pooled Safety-Evaluable Population:
- PBO: 0
- TCZ: 0.1%
- Baseline Steroid Use subgroup:
- PBO: 0
- TCZ: 0
- Source: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_SE_MCMALIG.out
- root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_aesi_bsteroid_SE.out

Rates of serious malignancies

TCZ indications with a periodic chronic dosing regimen:

IV RA all exposure population (2 May 2012)	• 0.96 (95% CI: 0.82, 1.13) events per 100 PY
IV Early RA WA19926 (Week 52)	PBO + MTX: 1.2 (0.2 - 3.4) / 100 PY TCZ 4 mg/kg + MTX: 1.5 (0.4 - 3.9) / 100 PY TCZ 8 mg/kg + MTX: 0.4 (0.0 – 2.1) / 100 PY TCZ 8 mg/kg +PBO: 0.7 (0.1 – 2.7) / 100 PY
SC RA (Week 24)	TCZ 162 mg QW + DMARD: 1.04 per 100 PY TCZ 162 mg Q2W + DMARD: 1.09 per 100 PY Placebo + DMARD: 0 per 100 PY
• ***SC RA all exposure population (4MSU October 2012)***	• 0.87 events per 100 PY (95% CI: 0.48, 1.46)
SC GCA (Week 52)	• PBO + 26-week prednisone taper: 2.2/100PY (95% CI 0.1-12.2) • PBO + 52-week prednisone taper: 2.1/100PY (95% CI 0.1-11.6) • TCZ 162 mg QW+ 26-week prednisone taper: 0.0/100PY (95% CI 0.0-4.0) • TCZ 162 mg Q2W+ 26-week prednisone taper: 0.0/100PY (95% CI 0.0-8.1)
• ***IV pJIA (Week 104)***	• 0 events • Source: WA19977 Final Week 104 CSR Section 1.2.4 (p. 182)
• ***SC pJIA (Week 52)***	• 0 events • Source: SCS pJIA SC Section 2.1.5.1
• ***IV sJIA (Week 12)***	• 0 events • Source: SCS pJIA SC Section 2.1.5.1
• ***IV sJIA (Week 260)***	• Not Assessed Source: WA18221 Week 260 final CSR Section 3.6.7.1 (p.45)

- ***IV <2 Years (Week 52)***
  - 0 events
  - Source: Final CSR NP25737 Section 7.9.6
- ***SC sJIA (Week 52)***
  - 0 events
  - Source: Final CSR WA28118 Section 6.8.7

Seriousness/outcomes
Not Applicable

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 factors and risk groups:
None identified

Preventability:
Not applicable

Impact on the benefit-risk balance of the product:
There have been very few reports of cancer, and no individual tumor type predominates. Despite the low event rate, a potential risk cannot be excluded. TCZ treatment should not be started in subjects with cancer. The TCZ SmPC, Patient Information Leaflet, Educational Materials for Healthcare professionals and patients, mitigate the risk severity and also provide information regarding managing 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. EMEA 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.

Demyelinating Disorders

MedDRA terms: Demyelination (narrow SMQ)

Potential mechanisms:
None identified

Evidence source(s) and strength of evidence:
Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.

Characterization of the risk:

Background incidence/prevalence

RA, sJIA, pJIA, GCA, and CAR T-cell CRS

Incidence rates of demyelination events in RA patients exposed to traditional or biologic DMARDs were calculated based on data in subjects with no demyelination events before cohort entry (n=82), the calculated incidence rate of demyelinating events was 0.041 per 100 PY (Benatsky S et al. 2010).

COVID-19
Evidence on demyelinating disorders such as Guillian-Barre syndrome in COVID-19 patients is scarce in the literature. Fragiel et al. (2021) reported that the frequency of Guillain-Barre syndrome in patients attending 61 Spanish emergency departments during the first 2 months of the pandemic was 0.15% in patients with evidence of COVID-19 infection and 0.02% in those without COVID-19 (Fragiel 2021).

No risk factors or data on mortality due to Guillain-Barre syndrome in COVID-19 patients were available in the literature.

Rates of Demyelination

TCZ indications with a periodic chronic dosing regimen:

IV RA DMARD-IR all control population	• No cases identified
IV RA all exposure population (2 May 2012)	• 0.02 (95% CI: 0.00, 0.05) events per 100 PY
IV Early RA WA19926 (Week 52)	• No cases identified
SC RA (Week 24)	• TCZ 162 mg QW + DMARD: 0 • TCZ 162 mg Q2W + DMARD: 0 • Placebo + DMARD: 0
• ***SC RA all exposure population (4MSU October 2012)***	• 0 events per 100 PY (95% CI: 0.00, 0.23)
SC GCA (Week 52)	• PBO + 26-week prednisone taper: 0.0/100PY (95% CI 0.0-7.8) • PBO + 52-week prednisone taper: 0.0/100PY (95% CI 0.0-7.7) • TCZ 162 mg QW+ 26-week prednisone taper: 0.0/100PY (95% CI 0.0-4.0) • TCZ 162 mg Q2W+ 26-week prednisone taper: 0.0/100PY (95% CI 0.0-8.1)
IV pJIA (Week 104)	• 0 events Source: WA19977 Final Week 104 CSR Section 1.2.9 (p. 183)
SC pJIA (Week 52)	• 0 events • Source : SCS pJIA SC Section 2.1.5.1
IV sJIA (Week 12)	• 0 events • Source: sJIA SCS 7.4.7.5 (p. 179)

IV sJIA (Week 260)	• Not Assessed • Source: WA18221 Week 260 final CSR Section 3.6.7.1 (p.45)
IV sJIA <2 Years (Week 52)	• 0 events • Source: Final CSR NP25737 Section 7.9.6
SC sJIA (Week 52)	• 0 events Source: Final CSR WA28118 Section 6.8.7
TCZ indications with acute dosing regimen:	
COVID-19 (Day 60)	•
Pooled data from WA42380, ML42528, WA42511	• Pooled Safety-Evaluable Population: • 0 events • Baseline Steroid Use subgroup: • 0 events • Source: root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_SE_DEMY.out • root/clinical_studies/RO4877533/share/pool_MA_REM_CSR/prod/output/t_ae_aesi_bsteroid_SE.out

Seriousness/outcomes
By its nature, such events would be expected to be serious.

Severity and nature of risk
Refer to frequency with 95%CI and seriousness/outcomes

Impact on Quality of Life:
The risk of demyelination with TCZ is unknown

Risk factors and risk groups:
None identified

Preventability:
Not applicable

Impact on the benefit-risk balance of the product:
There have been very few reports of nerve damage (demyelination) in patients treated with TCZ, although the risk is unknown. The TCZ 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:
Not applicable

Immunogenicity

MedDRA terms: Not applicable

Positive anti-TCZ antibodies were detected using confirmation assay
Potential mechanisms:
Immune response to the infusion or injection of a protein (IgG)

Evidence source(s) and strength of evidence:
Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.

Characterization of the risk:

Background incidence/prevalence
Not applicable

Rates of Immunogenicity (anti-TCZ antibodies)

TCZ indications with a periodic chronic dosing regimen:

IV RA all exposure population (2 May 2012)	A total of 44/3945 patients tested positive for anti-TCZ antibodies, 5 of whom also experienced an anaphylactic reaction, while 39 did not.
IV Early RA WA19926 (Week 52)	• Placebo + MTX: 10/282 (3.5%) [259 tested] • TCZ 4 mg/kg + MTX: 8/289 (2.8%) [259 tested] • TCZ 8 mg/kg + MTX: 5/290 (1.7%) [267 tested] • TCZ 8 mg/kg + Placebo: 4/292 (1.4%) [269 tested] No correlation of anti-TCZ antibody development to clinical response or AEs was observed.
• ***SC RA all exposure population (4MSU October 2012)***	• Of the 1462 patients in the SC all exposure population who were tested for anti-TCZ antibodies, 20 (1.4%) patients developed anti-TCZ antibodies, and 6 (0.4%) patients were positive for IgE isotype. None experienced anaphylaxis.
SC GCA (Week 52)	• PBO + 26-week prednisone taper: 1/49 (2.0%) • PBO + 52-week prednisone taper: 1/47 (2.1%) • TCZ 162 mg QW+ 26-week prednisone taper: 1/95 (1.1%) • TCZ 162 mg Q2W+ 26-week prednisone taper: 3/46 (6.5%)
IV pJIA (Week 104)	• ALL TCZ: 1/187 (0.5%) • Source: WA19977 final CSR Week 104 (p.529)
SC pJIA (Week 52)	• All TCZ SC: 3/52 (5.8%) • Source: SCS pJIA SC Table 46 (pg. 115)
IV sJIA (Week 12)	• Placebo: 0 • All TCZ SC: 1 • Source: WA18221 CSR
IV sJIA (Week 260)	• All TCZ: 2/112 (1.8%) • Source: WA18221 Week 260 CSR Section 6.2.3 (p.100)

IV sJIA <2 Years (Week 52)

- All TCZ: 3/11 (27.3%)
- Source: CSR NP25737 data output: l_ada_PK

SC sJIA (Week 52)

- All TCZ: 0/46

Source: CSR WA28118 Section 5.4

Seriousness/outcomes
Not Applicable

Severity and nature of risk
No correlation between the development of anti-TCZ antibodies and serious hypersensitivity or anaphylaxis has been observed in clinical trials with TCZ.

Impact on Quality of Life:
Not applicable

Risk factors and risk groups:
None identified

Preventability:
Not known

Impact on the benefit-risk 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

Information on Missing Information

There is no missing information for tocilizumab requiring further characterization.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 21 Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Serious infection * • Complications of diverticulitis * • Neutropenia • Hepatotoxicity

Table 21 Summary of Safety Concerns (Cont.)

Important potential risks	• Thrombocytopenia and the potential risk of bleeding • Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events • Malignancies • Demyelinating disorders • Immunogenicity
Missing information	None

COVID = coronavirus disease 19; TCZ = tocilizumab.

* The safety concerns “serious infection” and “complications of diverticulitis” are considered important identified risks for chronic TCZ dosing, but are assessed as important potential risks for the indication of COVID-19.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities beyond Adverse Reactions Reporting and Signal Detection:

Specific adverse reaction follow-up forms (guided questionnaires [GQs]) for:

- Serious infections[21]
- Complications of diverticulitis (including GI perforation)
- Thrombocytopenia and the potential risk of bleeding
- Hepatotoxicity
- Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events
- Malignancies
- Demyelinating disorders

The purpose of these guided questionnaires is to collect information in a standardized manner and monitor the frequency and nature of AEs emerging during clinical trials and post-marketing use.

Please see Annex 4 of the RMP for details.

Other forms of routine pharmacovigilance activities

- *Serious infections*: Collect and analyze information on hematogenous bacterial arthritis in the sJIA population < 18 years of age.

[21] Routine pharmacovigilance GQ for events of special interest will collect neutrophil data in cases of serious infection.

- *Immunogenicity*: Collect and analyze anti-TCZ antibodies in all patients treated with TCZ (routine sampling) and in patients who experience hypersensitivity that lead to study withdrawn (event driven sampling), in ongoing clinical trials and assess whether there is any correlation between the development of anti-TCZ antibodies and hypersensitivity or clinical response. This is specific to the ongoing clinical trials and does not apply to spontaneous post-marketing cases.
- The ZUMA-8 study added to the safety profile on the use of TCZ for the treatment of CAR-T induced CRS in patients taking Kite's brexucabtagene autoleucel drug. No AEs were observed as being related to TCZ in ZUMA-8, and no new safety signals were detected. The MAH sees this as further confirmation that the benefit-risk balance of TCZ administration in this setting is positive. The MAH concludes to continue the monitoring with routine Pharmacovigilance activities that are already in place..

III.2 Additional Pharmacovigilance Activities

The safety concerns of serious infections, complications of diverticulitis (including GI perforation), neutropenia, thrombocytopenia and the potential risk of bleeding, hepatotoxicity, elevated lipid levels and potential risk of cardiovascular/cerebrovascular events, malignancies and demyelinating disorders in RA patients are being investigated in ongoing Study RABBIT (ML28664, formerly tracked as GA28719[22]). These safety concerns were also investigated in the completed Study WA22480 (ARTIS; now complete). Both are EU registries for epidemiological data Table 22). Study WA28029 (ARTHUR) investigated the possibility of dose reduction for laboratory abnormalities (low platelets, low neutrophil, and elevated liver transaminase levels), in sJIA patients.

The ongoing paediatric registry (WA29358) investigates long-term safety and efficacy data in pJIA patients (Table 23).

Table 22 ML28664 (formerly tracked as GA28719) - (RABBIT)

Study/activity short name and title: Long-term observation of treatment with biologics in rheumatoid arthritis
Rationale and study objectives: To provide safety and effectiveness data on all licensed biologic drugs available for the treatment of RA
Study design: Phase IV – 2nd study extension; prospective observational cohort study
Study populations: Patients with rheumatoid arthritis

[22] ML28664 (formerly tracked as GA28719) was a study code duplication which has been corrected.

Milestones: First Patient First Visit: Q1 2009 Annual updates will be provided in the PSUR Last Patient Last Visit: ongoing Final CSR Q4 2022
CSR=clinical study report; PSUR= Periodic Safety Update Report; Q = quarter; RA=rheumatoid arthritis.

Table 23 WA29358 (Paediatric Registry)

Study/activity short name and title: Observational safety and effectiveness study of patients with polyarticular juvenile idiopathic arthritis treated with TCZ
Rationale and study objectives: Collecting long-term efficacy and safety data in pJIA treatment. The registry will address, but is not limited to, efficacy of 10 mg/kg for patients < 30 kg; impact of the RF status on efficacy of TCZ therapy; impact of TCZ therapy on the increased risk of atherosclerosis in RA patients, impact of TCZ therapy on growth development, influence on the occurrence and treatment of uveitis, and to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation
Study design: An international, multicenter, prospective, observational cohort study.
Study populations: Patients with pJIA aged ≤ 17 years at the time of newly initiating treatment with TCZ or comparator biologic
Milestones: First Patient First Visit: Q1 2009 Annual updates will be provided in the PSUR Recruitment End: June 2020 Study Completion: June 2025 Final Report Submission: January 2026
pJIA=polyarticular juvenile idiopathic arthritis; PSUR = Periodic Safety Update Report; Q = quarter; RA=rheumatoid arthritis; RF = rheumatoid factor; TCZ=tocilizumab.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 24 Planned and Ongoing Pharmacovigilance Studies

Study	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3- Required additional pharmacovigilance studies conducted to evaluate the effectiveness of risk minimisation activities				
ML28664 (formerly tracked as GA28719) (RABBIT) registry study Ongoing	To provide safety and effectiveness data on all licensed biologic drugs available for the treatment of RA	Serious infections, Complications of diverticulitis (including GI perforation), Neutropenia, Thrombocytopenia and the potential risk of bleeding, Hepatotoxicity, Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events, Malignancies, Demyelinating disorders	Routine updates to be provided in the scheduled PSURs Final CSR	Q4 2022
WA29358 (Paediatrics registry study) Ongoing	Collecting long-term efficacy and safety data for TCZ in the treatment of pJIA	Impact of TCZ therapy on the increased risk of atherosclerosis (cardiovascular events) growth and development, influence on the occurrence/treatment of uveitis and to evaluate the risk of malignancies, serious infections, and gastrointestinal perforation, and the efficacy of the 10 mg/kg IV Q4W regimen, and the impact of RF status on efficacy	Routine updates to be provided in the scheduled PSURs Recruitment End: June 2020 Study Completion: June 2025 Final Report Submission: January 2026	Q1 2026

CSR=Clinical Study Report; GI = gastrointestinal; IV = intravenous; NA = not applicable; pJIA=polyarticular juvenile idiopathic arthritis; PSUR = Periodic Safety Update Report; Q = quarter; Q4W = once every 4 weeks; RA=rheumatoid arthritis; RF=rheumatoid factor; TCZ=tocilizumab.

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 TCZ for IV or SC administration for RA, early RA, GCA, pJIA, sJIA, or COVID-19.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN
V.1 Routine Risk Minimization Measures

Table 25 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Serious Infections *	**Routine risk communication:** **SmPC** **IV and SC formulation**: 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 Formulation** Section 2 Warnings and precautions. What you need to know before you are given TCZ Section 4 Possible serious 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: RoActemra is a prescription only medicine.

Safety concern	Routine risk minimization activities
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 **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: RoActemra is a prescription only medicine.
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: RoActemra is a prescription only medicine
Hepatotoxicity	**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

Safety concern	Routine risk minimization activities
	Patient Information Leaflet (IV/SC formulation) Section 2 Warning 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: RoActemra is a prescription only medicine
Thrombocytopenia and the potential risk of bleeding	**Routine risk communication:** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use 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: RoActemra is a prescription only medicine
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:**

Safety concern	Routine risk minimization activities
	None **Other risk minimization measures beyond the Product Information:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine
Malignancies	**Routine risk communication:** 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: RoActemra is a prescription only medicine
Demyelinating Disorders	**Routine risk communication:** Section 4.4 Special warnings and precautions for use **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: RoActemra is a prescription only medicine
Immunogenicity	**Routine risk communication:** 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

Safety concern	Routine risk minimization activities
	Medicine's legal status: RoActemra is a prescription only medicine

IV=Intravenous ; SC=Subcutaneous ; SmPC=Summary of Product Characteristics.

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic TCZ 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. CRS, 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 tocilizumab for CRS and its risk profile are specified in the SmPC. The additional risk minimization measures listed in Table 26 are not applicable for the COVID-19 indication.

Table 26 Additional Risk Minimization Measures

Safety Concern	Serious Infections *
Additional Risk Minimization Measure	Patient Alert Card; Patient Brochure; Healthcare Provider Brochure; Dosing Guide
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that health care providers are aware of the need for timely and appropriate measures to diagnose and treat infections
Rationale for the additional risk minimization activity	**Patient Alert Card** To inform both the patient and health care providers that TCZ 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 **Patient Brochure** To inform the patient of the risk of serious infections and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide more detailed guidance to healthcare providers on the risk of serious infections **Dosing Guide** To inform and provide more detailed dosing guidance, administration instructions, and risks to healthcare providers
Target audience and planned distribution path	Patient and Healthcare providers

Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. **EMEA/H/C/PSUSA/00002980/201704** the commitment of the MAH to present evaluations of effectiveness of additional Risk Minimization Measure metrics is considered fulfilled as of PSUR 17.
Safety Concern	**Complications of Diverticulitis ***
Additional Risk Minimization Measure	Patient Alert Card; Patient Brochure; Healthcare Provider Brochure; Dosing Guide
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat complications of diverticulitis
Rationale for the additional risk minimization activity	**Patient Alert Card** To inform both the patient and health care providers that patients using TCZ 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 **Patient Brochure** To inform the patient of the risk of complications of diverticulitis and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide more detailed guidance to healthcare providers on the risk of complications of diverticulitis **Dosing Guide** To inform and provide more detailed dosing guidance, administration instructions, and risks to healthcare providers
Target audience and planned distribution path	Patient and Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. **EMEA/H/C/PSUSA/00002980/201704,** the commitment of the MAH to present evaluations of effectiveness of additional Risk Minimization Measure metrics is considered fulfilled as of PSUR 17.
Safety Concern	**Neutropenia**
Additional Risk Minimization Measure	Patient Brochure; Healthcare Provider Brochure; Dosing Guide
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to

	diagnose and treat neutropenia
Rationale for the additional risk minimization activity	**Patient Brochure** To inform the patient of the risk of neutropenia and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of neutropenia **Dosing Guide** To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patient and health care providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. **EMEA/H/C/PSUSA/00002980/201704,** the commitment of the MAH to present evaluations of effectiveness of additional Risk Minimization Measure metrics is considered fulfilled as of PSUR 17.
Safety Concern	**Hepatotoxicity**
Additional Risk Minimization Measure	Patient Brochure; Healthcare Provider Brochure; Patient Alert Card, Direct Healthcare Professional Communication (DHPC)
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that health care providers are aware of the risk of hepatotoxicity and the need for timely and appropriate measures to detect hepatotoxicity
Rationale for the additional risk minimization activity	**Patient Brochure** To inform the patient of the risk of hepatotoxicity and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of hepatotoxicity **Patient Alert Card** To inform both the patient and health care providers that patients using TCZ 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. **DHPC (one time only RMM activity)** To inform healthcare professionals of serious DILI, including acute liver failure, hepatitis, and jaundice, in some cases requiring liver transplant, that have been observed with the administration of Actemra/RoActemra® (tocilizumab). The frequency of serious hepatotoxicity is considered rare. Healthcare professionals should

	follow the guidance including dose modification and tocilizumab discontinuation as per the approved label.
Target audience and planned distribution path	Patient and healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	• Metrics of distribution channels of educational materials to patients and health care professionals. • Comparison of exposure-adjusted reporting rates for the relevant events by PSUR period as proxy for comprehension/readability evaluation of patients and healthcare professions on the content of the educational materials and compliance with recommendations. The intervention will be assessed as effective, if no indication of sustained or increasing trend in exposure-adjusted response rate for serious hepatic events over time per PSUR interval
Safety Concern	**Thrombocytopenia and the potential risk of bleeding**
Additional Risk Minimization Measure	Healthcare Provider Brochure; Patient Brochure
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat thrombocytopenia
Rationale for the additional risk minimization activity	**Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of thrombocytopenia **Patient Brochure** To inform the patient of the risk of thrombocytopenia beyond that provided in the PIL
Target audience and planned distribution path	Patient and health care providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. **EMEA/H/C/PSUSA/00002980/201704** the commitment of the MAH to present evaluations of effectiveness of additional Risk Minimization Measure metrics is considered fulfilled as of PSUR 17.
Safety Concern	**Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events**
Additional Risk Minimization Measure	Patient Brochure; Healthcare Provider Brochure; Dosing Guide

Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to detect elevated lipid levels and evaluate further.
Rationale for the additional risk minimization activity	**Patient Brochure** To inform the patient of the risk of elevated lipid levels and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of elevated lipid levels **Dosing Guide** To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patient and Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. **EMEA/H/C/PSUSA/00002980/201704** the commitment of the MAH to present evaluations of effectiveness of additional Risk Minimization Measure metrics is considered fulfilled as of PSUR 17.
Safety Concern	**Malignancies**
Additional Risk Minimization Measure	Patient Brochure; Healthcare Provider Brochure; Dosing Guide
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat malignancies.
Rationale for the additional risk minimization activity	**Patient Brochure** To inform the patient of the risk of malignancies and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of malignancies **Dosing Guide** To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patient and Healthcare providers

Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. **EMEA/H/C/PSUSA/00002980/201704** the commitment of the MAH to present evaluations of effectiveness of additional Risk Minimization Measure metrics is considered fulfilled as of PSUR 17.
Safety Concern	**Demyelinating Disorders**
Additional Risk Minimization Measure	Healthcare Provider Brochure
Objectives	The objective of the measure is to ensure that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat demyelinating disorders
Rationale for the additional risk minimization activity	**Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of demyelinating disorders
Target audience and planned distribution path	Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Per procedure No. **EMEA/H/C/PSUSA/00002980/201704** the commitment of the MAH to present evaluations of effectiveness of additional Risk Minimization Measure metrics is considered fulfilled as of PSUR 17.

PIL=Patient Information leaflet; PSUR=Periodic Safety Update Report; TCZ=tocilizumab.

* The safety concerns “serious infection” and “complications of diverticulitis” are considered important identified risks for chronic TCZ dosing, but are assessed as important potential risks for the indication of COVID-19.

V.3 Summary of Risk Minimization Measures

Table 27 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections *	**Routine risk communication:** **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. What you need to know before you are given TCZ Section 4 Possible serious 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:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine. **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions • Collect and analyze information on hematogenous bacterial arthritis in the sJIA population < 18 years of age **Additional pharmacovigilance activities:** Epidemiology data • EU registries • (Ongoing: RABBIT, WA29358) •
Complications of Diverticulitis *	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions

Safety concern	Risk minimization measures	Pharmacovigilance activities
	<u>Patient Information Leaflet</u>: 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: RoActemra is a prescription only medicine. **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	**Additional pharmacovigilance activities:** Epidemiology data • EU registries • (Ongoing: RABBIT, WA29358)
Neutropenia	**Routine risk communication:** **<u>SmPC</u>** Section 4.2 Posology and method of administration Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects/Laboratory evaluations **<u>Patient Information Leaflet</u>** Section 2 What you need to know before you used RoActemra Section 4 Possible Side Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions, i.e. for events of special interest will collect neutrophil data in cases of serious infection **Additional pharmacovigilance activities:** Epidemiology data • EU registries • (Ongoing: RABBIT, WA29358)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other risk minimization measures beyond the Product Information: Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure Dosing Guide	
Hepatotoxicity	**Routine risk communication:** **SmPC** Section 4.2 Posology and method of administration (IV formulation) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet** (IV/SC formulation) Section 2 Warning 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: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure Patient Alert Card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • EU registries: (Ongoing: RABBIT)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	DHPC	
Thrombocytopenia and the potential risk of bleeding	**Routine risk communication:** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Section 4.2 Posology and method of administration (IV formulation) **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: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • EU registries • (Ongoing: RABBIT)
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:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • EU registries • (Ongoing: RABBIT, WA29358)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure Dosing Guide	
Malignancies	**Routine risk communication:** Section 4.4 Special warnings and precautions for use 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: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure Dosing Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • EU registries • (Ongoing: RABBIT, WA29358)
Demyelinating Disorders	**Routine risk communication:** Section 4.4 Special warnings and precautions for use **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:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Guided questionnaire for specific adverse reactions **Additional pharmacovigilance activities:** Epidemiology data • EU registries • (Ongoing: RABBIT)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	RoActemra is a prescription only medicine **Additional risk minimization measures:** Healthcare Provider Brochure	
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: RoActemra is a prescription only medicine No Additional Risk Minimization Measure.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Collect and analyze anti-TCZ antibodies in patients who experience hypersensitivity reactions that led to study withdrawal in ongoing clinical trials and investigate the risk of developing anti-TCZ antibodies at re-administration, when TCZ treatment had been interrupted. This is specific to the ongoing clinical trials and does not apply to spontaneous post-marketing cases **Additional pharmacovigilance activities:** None

IV=intravenous; SC=subcutaneous; sJIA = systemic juvenile idiopathic arthritis; SmPC=Summary of Product Characteristics; TCZ=tocilizumab.

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic TCZ dosing, but are assessed as important potential risks for the indication of COVID-19.

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN FOR ROACTEMRA (TOCILIZUMAB)

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

RoActemra Summary of Product Characteristics and its package leaflet give essential information to healthcare professionals and patients on how RoActemra should be used.

This summary of the RMP for RoActemra 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 RoActemra RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

RoActemra 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 (see SmPC for the full indication). It contains tocilizumab as the active substance and it is given by intravenous infusion or subcutaneous injection.

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

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

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

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

In the case of RoActemra, these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of RoActemra 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 RoActemra. 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 infection * • Complications of diverticulitis * • Neutropenia • Hepatotoxicity
Important potential risks	• Thrombocytopenia and the potential risk of bleeding • Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events • Malignancies • Demyelinating disorders • Immunogenicity
Missing information	None

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic TCZ 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	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Patients with diabetes reported a higher rate of serious infections compared to patients without diabetes. Patients treated with TCZ 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 by body weight. Healthcare professionals should exercise caution when considering the use of TCZ 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).
Risk minimization measures	**Routine risk measure:** **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. What you need to know before you are given TCZ Section 4 Possible serious 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:** Pack size: None Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • EU registries (Ongoing: RABBIT, WA29358) See Section II.C of this summary for an overview of the post-authorization development plan.
Important Identified Risk: Complications of Diverticulitis *	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	TCZ should be used with caution in patients with previous history of intestinal ulceration or diverticulitis.
Risk minimization measures	**Routine risk minimization measure:** **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: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Alert Card Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • EU registries (Ongoing: RABBIT, WA29358) See Section II.C of this summary for an overview of the post-authorization development plan.
Important Identified Risk: Neutropenia	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	None identified

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: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • EU registries (Ongoing: RABBIT) See Section II.C of this summary for an overview of the post-authorization development plan.
Important Identified Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Treatment with other hepatotoxic drugs (e.g., MTX).
Risk minimization measures	**Routine risk communication:** **SmPC** Section 4.2 Posology and method of administration (IV formulation) Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet** (IV/SC formulation) Section 2 Warning 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: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure Patient Alert Card DHPC
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • EU registries (Ongoing: RABBIT) See Section II.C of this summary for an overview of the post-authorization development plan.
Important Potential Risk : Thrombocytopenia and the potential risk of bleeding	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**Routine risk minimization measures:** **SmPC:** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Section 4.2 Posology and method of administration (IV formulation) **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: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • EU registries (Ongoing: RABBIT) See Section II.C of this summary for an overview of the post-authorization development plan.
Important Potential Risk : Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**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 Medicine's legal status: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data EU registries (Ongoing: RABBIT, WA29358) See Section II.C of this summary for an overview of the post-authorization development plan.
Important Potential Risk: Malignancies	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
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 **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: RoActemra is a prescription only medicine **Additional risk minimization measures:** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data • EU registries (Ongoing : RABBIT, WA29358) See Section II.C of this summary for an overview of the post-authorization development plan.
Important Potential Risk: Demyelinating Disorders	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Treatment with other hepatotoxic drugs (e.g., MTX).
Risk minimization measures	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use **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: RoActemra is a prescription only medicine **Additional risk minimization measures:** Healthcare Provider Brochure

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Epidemiology data EU registries (Ongoing: RABBIT) See Section II.C of this summary for an overview of the post-authorization development plan.
Important Potential Risk : Immunogenicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions, as described within this RMP, provide the strongest evidence.
Risk factors and risk groups	Not identified
Risk minimization measures	**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 Medicine's legal status: RoActemra is a prescription only medicine No Additional Risk Minimization Measure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorization development plan.

IV=Intravenous; SC=Subcutaneous; SmPC=Summary of Product Characteristics; TCZ=Tocilizumab.

* The safety concerns "serious infection" and "complications of diverticulitis" are considered important identified risks for chronic TCZ 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 RoActemra.

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

Study short name: ML28664 (formerly tracked as GA28719) (RABBIT)
Purpose of the study: The long-term observation of treatment with biologics in RA (RABBIT) in German biologics registry.

Study short name: WA29358
Purpose of the study: To provide long-term safety and efficacy data from the use of TCZ in pJIA patients.

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Tocilizumab Guided Questionnaire
Spontaneous or Serious/Non Serious Bleeding 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

Bleeding events have been observed in some patients treated with Tocilizumab. This guided questionnaire is intended to be used with both internal and external haemorrhagic events including haemorrhagic strokes. By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Thank you for your assistance. We look forward to your reply.

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) ☐ **Non-Serious**	
Related to Tocilizumab?	☐ Yes ☐ No
Outcome of the event:	☐ Persisting ☐ Improved ☐ Recovered with sequelae ☐ Resolved ☐ Unknown ☐ Worsened ☐ Death
Was the bleeding event associated with a platelet count of <100,000/mm^3?	☐ 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

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

Please attach all laboratory results (haemoglobin, hematocrit, platelet count, 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?**
Fecal Occult Blood Test						☐Yes
Urinalysis						☐Yes
INR						☐Yes
CT Scan						☐Yes
MRI						☐Yes
Colonoscopy						☐Yes
Endoscopy						☐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.			
Haemophilia	☐History	☐Concurrent	☐Not present
Von Willebrand's disease	☐History	☐Concurrent	☐Not present
Previous Event of Haemorrhage Specify:	☐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
Aspirin/ anti-platelet Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
NSAIDs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Coumarin/Coumadin	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Heparin	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
SSRIs Specify:	☐Yes ☐No				☐Past ☐Concomitant ☐N/A
Ginkgo Biloba	☐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.

Thank you for completing this form.

Completed by:

Name: ..... Position: .....

Signature: ..... Date: .....

E-mail: .....

Tocilizumab Guided Questionnaire
Demyelination 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

Demyelination 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): (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) ☐ **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

Treatment for the event		
Treatment	Dosing Regimen	Dates of Therapy (MM/DD/YYYY to MM/DD/YYYY)

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/ Differential WBC Count						☐ Yes
CRP						☐ Yes
CSF analysis (Please include protein, glucose, cell count, IgG, virus results)						☐ Yes
Brain and Spine CT Scan Number of lesions in white matter: Location of the lesions: Size of the lesions:						☐ Yes
MRI						☐Yes
Evoked potentials/ Electro-diagnostic studies Please specify if auditory, visual, or somatosensory						☐ 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.

Immunodeficiency Specify:	☐History	☐Concurrent	☐Not present
Viral infection Specify:	☐History	☐Concurrent	☐Not present
JC Virus	☐History	☐Concurrent	☐Not present
Lyme Disease	☐History	☐Concurrent	☐Not present
Other opportunistic infections Specify:	☐History	☐Concurrent	☐Not present
Other infections Specify:	☐History	☐Concurrent	☐Not present
SLE	☐History	☐Concurrent	☐Not present
Collagen vascular disease	☐History	☐Concurrent	☐Not present
Complications from previous immunosuppressive medication/conditions Specify:	☐History	☐Concurrent	☐Not present
Diabetes mellitus	☐History	☐Concurrent	☐Not present
Arteriosclerosis Specify:	☐History	☐Concurrent	☐Not present
Multiple Sclerosis	☐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
Aspirin Specify:	☐ Yes ☐ No				☐Past ☐Concomitant ☐N/A
NSAIDs 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.

Thank you for completing this form.

Completed by:

Name: ..... **Position:** .....

Signature: ..... **Date:** .....

E-mail: .....

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

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 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.			
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

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

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: .....

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

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

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

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		

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: .....

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): ☐ 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
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

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

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

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: .....

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:

☐ **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

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

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.

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Roche

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:

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

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

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: .....

Tocilizumab Guided Questionnaire
Stroke

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

Stroke 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

Description of the event
Type of Stroke: ☐ Ischemic: ☐ Hemorrhagic ☐ Other/unknown—please specify
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
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 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?
CT Scan						☐ Yes
MRI						☐ Yes
Carotid Doppler						☐ Yes
MRA (Magnetic Resonance Angiogram)						☐ Yes
Cerebral Arteriogram						☐ 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.			
Prior Stroke Specify:	☐ History	☐ Concurrent	☐ Not present
Prior TIA Specify:	☐ History	☐ Concurrent	☐ Not present
Prior Heart Attack Specify:	☐ History	☐ Concurrent	☐ Not present
Hypertension	☐ History	☐ Concurrent	☐ Not present
Smoking	☐ History	☐ Concurrent	☐ Not present

Specify:			
Diabetes Mellitus	☐History	☐Concurrent	☐Not present
Coronary artery Disease Specify:	☐History	☐Concurrent	☐Not present
Atrial Fibrillation	☐History	☐Concurrent	☐Not present
Sickle Cell Anemia	☐History	☐Concurrent	☐Not present
Hypercholesterolemia	☐History	☐Concurrent	☐Not present
Physical Inactivity	☐History	☐Concurrent	☐Not present
Obesity	☐History	☐Concurrent	☐Not present
Low platelet count	☐History	☐Concurrent	☐Not present
Cardiac valvular disease	☐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 medications 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.

Thank you for completing this form.

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

The Educational Materials for all the RoActemra indications include indication-specific Patient Brochures, a Patient Alert Card, a Dosing Guide and an HCP Brochure.

The Marketing Authorisation Holder (MAH) shall provide an educational pack covering the therapeutic indications RA, sJIA, pJIA and GCA, targeting all physicians who are expected to prescribe/use RoActemra containing the following:

- Physician Information Pack
- Nurse Information Pack
- Patient Information Pack

The MAH must agree with the national competent authority on the content and format of the educational material, as well as a communication plan, prior to distribution of the educational material.

The Physician Information pack should contain the following key elements:

- The Summary of Product Characteristics
- Dose calculation (RA, sJIA and pJIA patients), preparation of infusion and infusion rate
- Risk of serious infections
  - The product must not be given to patients with active or suspected infection
  - The product may lessen signs and symptoms of acute infection delaying the diagnosis
- Risk of Hepatotoxicity
  - Caution should be exercised when considering initiation of tocilizumab treatment in patients with elevated transaminases ALT or AST above 1.5x ULN. In patients with elevated ALT or AST above 5x 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.
- Risk of gastrointestinal perforations especially in patients with history of diverticulitis or intestinal ulcerations
- Reporting of serious adverse drug reactions
- The Patient Information Packs (to be given to patients by healthcare professionals)
- Diagnosis of Macrophage Activation Syndrome in sJIA patients

- Recommendations for dose interruptions in sJIA and pJIA patients

The Nurse Information Pack should contain the following key elements:

- Prevention of medical errors and injection/infusion reactions
  - Preparation of injection/infusion
  - Infusion rate
- Monitoring of the patient for injection/infusion reactions
- Reporting of serious adverse reactions

The Patient Information Pack should contain the following key elements:

- Package leaflet covering all approved indications (with instructions for use for SC formulation)
- Patient alert card
  - To address the risk of getting infections which can become serious if not treated. In addition, some previous infections may reappear.
  - To address the risk that patients using RoActemra may develop complications of diverticulitis which can become serious if not treated.
  - To address the risk that patients using RoActemra may develop serious hepatic injury. Patients would be monitored for liver function tests. Patients should inform their doctor immediately if they experience signs and symptoms of liver toxicity including tiredness, abdominal pain and jaundice.