THE EU RISK MANAGEMENT PLAN FOR ROACTEMRA®(TOCILIZUMAB)

RMP version to be assessed as part of this application:

RMP Version number: 27.1

Data lock point for this RMP: June 2021

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

Date and Time (UTC)	Reason for Signing	Name
21-Oct-2021 09:02:01	Company Signatory (PV)	PPD
21-Oct-2021 10:23:11	Deputy QPPV	PPD

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EU RMP FOR ROACTEMRA®

Rationale for Submitting an Updated RMP:

This RMP version 27.1 is submitted in support of a line extension application for the use of tocilizumab in COVID-19 (procedure EMEA/H/C/000955/II/0101) and in response to the CHMP and PRAC Rapporteur's preliminary assessment report.

Summary of Significant Changes in This RMP:

Part II: Module SVII and Module SVIII were updated to note that 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. The important identified risk "severe hypersensitivity reactions" has been removed from the list of safety concerns.

Parts III and V were updated to reflect the changes in the list of safety concerns.

Annex 2 was updated to reflect the removal from the list of safety concerns of the important identified risk "severe hypersensitivity reactions".

Annex 3 was updated to remove the protocols for the studies WA22490 (ARTIS) and WA28029 (ARTHUR), post-approval commitments removed from the RMP within previous RMP update procedures. The study WA29358 protocol version 5.0 was replaced with version 6.0.

Annex 4 was updated to remove the guided questionnaire associated with the risk "severe hypersensitivity reactions".

Annex 6 was updated to remove wording related to the risk of severe hypersensitivity reactions from both the physician information pack and the patient information pack.

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: 26.0

Approved with Procedure Number: EMEA/H/C/000955/II/0097

Date of approval (opinion date): 23 July 2020 (CHMP Opinion)

See Page 1 for e-signature and date

Dr. Birgitt Gellert (QPPV) Date
(Delegate: 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. <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: **Intravenous (IV) Formulation:** 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.
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.

	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:** **Intravenous (IV) Formulation:** *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.

Pharmaceutical form(s) and strengths	**Current**: **<u>IV Formulation:</u>** <u>*Concentrate for Solution for Infusion*</u> 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. **<u>SC Formulation:</u>** 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%.

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)

The Main Existing Treatment Options:

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

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

[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)

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	17 July 2016
sJIA	WA28118	Final CSR (Week 52)
	WA29231	11 August 2017

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
4- ≤ 6 months	1	0.5
7 - ≤ 9 months	4	2.3
10 - ≤ 12 months	2	1.8
13 - ≤ 15 months	6	5.9
16 - ≤ 18 months	4	5.1
19 - ≤ 21 months	5	7.5
22 - ≤ 24 months	6	9.9
25 - ≤ 27 months	1	2
28 - ≤ 30 months	2	4.3
31 - ≤ 33 months	5	11.9
34 - ≤ 36 months	13	34
37 - ≤ 39 months	3	8.4
Total	**52**	**93.6**

Duration of Exposure	Number of Patients	Person Years of Exposure (PY)
sJIA		
≤ 3 months	4	0.4
4- ≤ 6 months	1	0.2
7 - ≤ 9 months	3	1.8
10 - ≤ 12 months	1	0.8
13 - ≤ 15 months	11	11.2
16 - ≤ 18 months	5	6.3
19 - ≤ 21 months	2	3.2
22 - ≤ 24 months	7	11.8
25 - ≤ 27 months	0	0
28 - ≤ 30 months	1	2.3
31 - ≤ 33 months	0	0
34 - ≤ 36 months	1	2.6
37 - ≤ 39 months	2	5.6
40 - ≤ 42 months	4	12.4
43 - ≤ 45 months	3	10.1
46 - ≤ 48 months	3	10.6
49 - ≤ 51 months	3	11.3
Total	**51**	**90.5**

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 WA28117 + WA29231/STmt_exp_rmp_dur.out, WA28118 + WA29231/STmt_exp_rmp_dur.out _SE.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	132	50.7
7 - ≤ 9 months	122	71.5
10 - ≤ 12 months	156	128.2
13 - ≤ 15 months	453	461.5
16 - ≤ 18 months	306	386.3
19 - ≤ 21 months	185	275.8
22 - ≤ 24 months	98	168.1
25 - ≤ 27 months	1	2
28 - ≤ 30 months	3	6.6
31 - ≤ 33 months	5	11.9
34 - ≤ 36 months	14	36.6
37 - ≤ 39 months	5	14
40 - ≤ 42 months	4	12.4
43 - ≤ 45 months	3	10.1
46 - ≤ 48 months	3	10.6
49 - ≤ 51 months	3	11.3
Total	**1630**	**1678.4**

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.

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	29	49.2
TCZ SC 162 mg Q3W	27	44.4
Total	**52***	**93.6**
sJIA		
TCZ SC 162 mg QW	**30**	**58.6**
TCZ SC 162 mg Q10D	**8**	**11.3**
TCZ SC 162 mg Q2W	**22**	**20.6**
Total	**51**	**90.5**

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, WA28117 + WA29231/STmt_exp_rmp_dur.out, WA28118 + WA29231/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	950	1053.7
TCZ SC 162 mg Q10D	8	11.3
TCZ SC 162 mg Q2W	658	569
TCZ SC 162 mg Q3W	27	44.4
Total	**1630***	**1678.4**

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

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

i28119a/STmt_exp_rmp_dur_all_ah128_SE.out, WA28117 + WA29231/STmt_exp_rmp_dur.out, WA28118 + WA29231/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	2.8
≥ 2 < 5	2	5	1.6	8.6
≥ 5 < 12	8	15	14.4	28.9
≥ 12 < 18	6	15	11.3	26.0
Total	**16**	**36**	**27.3**	**66.3**
sJIA				
< 2	1	2	2.3	2.7
≥ 2 < 5	3	**5**	3.3	8.2
≥ 5 < 12	10	10	16.6	16.5
≥ 12 < 18	8	12	14.0	26.9
Total	**22**	**29**	**36.2**	**54.3**

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, WA28117 + WA29231/STmt_exp_rmp_age.out, WA28118 + WA29231/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	2.3	5.5
≥ 2 < 5	5	10	4.9	16.8
≥ 5 < 12	18	25	31	45.4
≥ 12 < 18	14	27	25.3	52.9
≥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**	**319.3**	**1359.3**

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
WA28119/STmt_exp_rmp_age_all_ah128_SE.out, WA28117 + WA29231/STmt_exp_rmp_age.out, WA28118 + WA29231/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
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

Ethnic/Racial Origin	Persons (n)	Person Time (PY)
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
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	85.9
Asian	0	0
American Indian or Alaska Native	0	0
Black	0	0
Other	5	7.7
Total	**52**	**93.6**
sJIA		
White	41	73.1
Asian	1	3.3
American Indian or Alaska Native	1	1.6
Black	1	2.6
Other	7	9.8
Total	**51**	**90.5**

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, WA28117 + WA29231/STmt_exp_rmp_race.out, WA28118 + WA29231/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	1307.3
Asian	56	70.9
American Indian or Alaska Native	35	41.5
Black	68	66.2
Other	204	191.1
Unknown	2	1.2
Total	**1630**	**1678.2**

SC = subcutaneous

Source: WA22762/Stmt_exp_rmp_race.out, NA25220/STmt_exp_rmp_race.out, W28119/STmt_exp_rmp_rac_all_ah128_SE.out, WA28117 + WA29231/STmt_exp_rmp_race.out, WA28118 + WA29231/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**
COVID-19		
Elderly (≥ 75 years old)	125	7.7
Pregnant women	0	0
Renal impairment	152	9.6

Special Population	Persons (n)	Person Time (PY)
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
Liver impairment	0	0
Total	**35**	**35**
GCA		
Pregnant women	0	0
Elderly (≥ 75 years old)	44	35.7
Renal impairment	0	0
Liver impairment	0	0
Total	**44**	**35.7**
pJIA		
Pregnant women	**0**	**0**
Renal impairment	**0**	**0**
Liver impairment	**0**	**0**
Total	**0**	**0**
sJIA		
Pregnant women	**0**	**0**
Renal impairment	**0**	**0**
Liver impairment	**0**	**0**
Total	**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.
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 werer 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); please refer to the current PSUR/PBRER for this information.

SV.1.2 Exposure

The estimated cumulative post-authorization exposure to tocilizumab from the International Birth Date (11 April 2005) to 10 April 2021 (inclusive) are presented in the PBRER (data lock point 10 April 2021). The estimated cumulative market exposure to TCZ until 10 April 2021 is 2,567,502 patients (2,213,381 PY) of which 932,120 patients (874,999 PY) were estimated to have received TCZ during the reporting interval (from 11 April 2020 to 10 April 2021).

IV Formulation

The combined cumulative post-marketing exposure of patients to IV tocilizumab is estimated to be 1,815,406 patients (1,600,447 PY).

SC Formulation

The combined cumulative post-marketing exposure of patients to SC tocilizumab is 752,096 (612,933 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

The following safety concerns have been reclassified within this submission of an updated RMP:

- The safety concern “serious infection”, considered as important identified risks for chronic TCZ dosing, was assessed as important potential risk for the indication of COVID-19.
- The safety concern “complications of diverticulitis”, considered as important identified risks for chronic TCZ dosing, was assessed as important potential risk for the indication of COVID-19.
- The important identified risk “serious hypersensitivity reactions” has been removed from the list of safety concerns. “Serious hypersensitivity reactions” is considered a well known risk due to the widespread knowledge on the part of the healthcare professionals administering and managing the patients. Therefore, routine risk minimization measures are considered adequate to minimize this risk, and the risk is removed from the RMP.

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
IV pJIA (Week 104)	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

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]

[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.

- 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

- 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:

	ALT shift from baseline		***AST shift from baseline***	
COVID-19 (Day 60) [14]				
➢ 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
➢ 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

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[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.

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)	>ULN and ≤ 3xULN: • 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%)

	TCZ 4 mg/kg + MTX (n= 289) Grade 1: 19 (6.6%) Grade 2: 1 (0.3%) Grade 3: 1 (0.3%) Grade 4: 0 (0.0%) TCZ 8 mg/kg + MTX (n=290) Grade 1: 25 (8.6%) Grade 2: 0 (0.0%) Grade 3: 0 (0.0%) Grade 4: 1 (0.3%) TCZ 8 mg/kg +PBO (n=292) Grade 1: 24 (8.2%) Grade 2: 3 (1.0%) Grade 3-4: 0 (0.0%)
SC RA (Week 24)	Grade 3 and 4 TCZ 162 mg QW + DMARD: 0 TCZ 162 mg Q2W + DMARD: 0
SC RA all exposure population (4MSU Data Cut October 2012)	Grade 3 and 4 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 Grade 3: 0 Grade 4: 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.

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%) – No patient experienced serious myocardial infarction during study
IV pJIA (Week 104)	Marked Laboratory Abnormalities: 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)
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

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

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:

<u>COVID-19 (Day 60)</u>

➢ 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
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

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

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.

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.

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).

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

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
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 1:

EUDRAVIGILANCE INTERFACE

ANNEX 1 – EUDRAVIGILANCE INTERFACE

Not applicable.

ANNEX 2:

TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

ANNEX 2:

TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table 1 Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
ML28664 (formerly tracked as GA28719) [1] (RABBIT) *Category 3*	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	First Patient First Visit: Q1 2009 Final CSR: Q4 2022
WA29358 (Pediatric Registry) *Category 3*	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) and to evaluate for the risk of malignancies, serious infections, and gastrointestinal perforation	First Patient First Visit: Q1 2009 Final Report Submission Q1 2026

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

Table 2 Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission
NA25220	To assess: • Efficacy of treatment with tocilizumab (TCZ) 162 mg SC versus placebo given every other week (q2w), in combination with DMARDs, at Week 24 using ACR20. • Safety of treatment with TCZ 162 mg SC versus placebo given every other week (q2w), in combination with DMARDs, with regard to adverse events (AEs) and laboratory assessments. Secondary • Prevention of progression of structural joint damage at Week 24 and Week 48 • Improvement of physical function • Long-term safety and efficacy • Pharmacokinetics (PK) and pharmacodynamics	Safety will be assessed using reporting of AEs, clinical laboratory results (hematology, chemistry, lipid profiles, liver function, immunogenicity [including IgE data], etc.), physical examination and vital signs.	September 2014

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission
MA21488 RA	Evaluation of three treatment strategies based on TCZ and/or methotrexate in patients with active RA who have inadequately responded to prior DMARD treatment.	Immunogenicity	Final CSR February 2014
WA22762	To assess: • The efficacy of treatment with 162 mg tocilizumab (TCZ) given subcutaneously (SC) weekly versus 8 mg/kg TCZ given intravenously (IV) every 4 weeks with regard to non-inferiority of the proportion of patients who achieve ACR20 at Week 24. • The safety of treatment with 162 mg TCZ given SC weekly versus 8 mg/kg TCZ given IV every 4 weeks, with regard to AEs and laboratory assessments. Secondary Objectives: • Long-term safety and efficacy • Pharmacokinetics (PK) and pharmacodynamics (PD) of TCZ following SC administration • Immunogenicity of TCZ following SC administration Effect of IV to SC switch on the safety, efficacy, PK and PD of TCZ	Safety will be assessed using reporting of AEs, clinical laboratory results (hematology, chemistry, lipid profiles, liver function, immunogenicity [including IgE data], etc.), physical examination and vital signs	Q2 2014

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission
WA19977 (pJIA)	To evaluate the efficacy and safety of TCZ in patients with active polyarticular juvenile rheumatoid arthritis	General safety profile of TCZ	Final CSR December 2013
WA18696 extension	Long term extension study of safety during treatment with TCZ in patients completing treatment in core studies	General safety profile of TCZ	Final CSR 31 March 2014
NP22775	To investigate the effect of TCZ on the pharmacokinetics and pharmacodynamics of an oral contraceptive in female patients with active rheumatoid arthritis	CYP450 enzyme normalisation	Final CSR August 2012
NA25256	To evaluate the humoral immune response 5 weeks after vaccination with 23-valent pneumococcal polysaccharide vaccine in patients with active RA treated with TCZ + MTX, compared with the humoral immune response in patients treated with MTX alone.	Safety profile of TCZ	Clinical study report completed in September 2012
WA17823	To assess the efficacy of treatment with MRA versus placebo, in combination with MTX, with regard to the reduction in signs and symptoms over 6 months, the prevention of structural joint damage and improvement in physical function over 12 months in patients with moderate to severe, active rheumatoid arthritis who have had an inadequate response to MTX.	Safety profile of TCZ	Final CSR February 2013
WA18695	To assess the long-term safety of 8 mg/kg TCZ as monotherapy or in combination with background DMARD therapy/therapies with regard to adverse events and laboratory result abnormalities	Safety profile of TCZ	Final CSR March 2013

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission
WA19923	A Mechanism of Action study to evaluate the effects of IL-6 receptor blockade with TCZ on lipids, arterial stiffness, and markers of atherogenic risk in patients with moderate to severe active rheumatoid arthritis	Lipid elevations and cardiovascular/cerebrovascular risks	Final CSR January 2012
WA19926	To assess: the efficacy of treatment with TCZ monotherapy and TCZ + MTX combination therapy, versus MTX monotherapy, with regard to the following primary endpoint in patients with early, moderate-to- severe rheumatoid arthritis (RA): • Proportion of patients who achieve DAS28 remission (DAS28 < 2.6) at 6 months. Secondary Objectives: • Prevention of structural joint damage over 12 months and maintenance of this effect at 24 months. • Improvement in physical function over 12 months and maintenance of this effect at 24 months. • Pharmacokinetics, immunogenicity and pharmacodynamics of TCZ in patients with early RA. Safety and efficacy of TCZ administration in patients with early RA.	Safety and efficacy in patients with early RA	Q4 2014

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission
WA29049	Pharmacodynamics study to evaluate neutrophil kinetics and function following tocilizumab treatment in healthy volunteers	Neutropenia and the potential risk of infection	Q2 2015
WA18221 (sJIA)	Part I: To evaluate the efficacy and safety of TCZ in patients with active systemic juvenile idiopathic arthritis (sJIA); Part II: To examine the effect (in completers of Part I) of long term use of TCZ on: • Safety (including immunogenicity); • Efficacy (including assessment of joint counts and objective measurements including hsCRP, fever, hemoglobin); • Ability to reduce corticosteroid dosage to clinically significant levels; Part III: • To assess the long-term safety of 8 mg/kg tocilizumab in children ≥ 30 kg and 12 mg/kg tocilizumab in children < 30 kg with regard to adverse events and laboratory result abnormalities	General safety profile of TCZ	Final CSR Q1 2015
WA25204 (ENTRACTE)	A clinical outcomes study to evaluate the effects of IL-6 receptor blockade with tocilizumab (TCZ) in comparison with etanercept (ETA) on the rate of cardiovascular events in patients with moderate to severe rheumatoid arthritis (RA).	Cardiovascular events	Q4 2016
WA22479 (British Society of Rheumatology Biologics Register [BSRBR])	Prospective observational cohort studies for safety data collection	Serious hypersensitivity reactions	Final Switcher Report: Completed on 30 November 2018

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission
WA22480 (ARTIS) registry study	To provide long term safety data from the use of TCZ in Sweden for RA patients	Serious infections, Complications of diverticulitis (including GI perforation), Serious hypersensitivity reactions, Neutropenia, Thrombocytopenia and the potential risk of bleeding, Hepatotoxicity, Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events, Malignancies, Demyelinating disorders	Final Report: Q4 2019
WA28029 (ARTHUR)	To investigate the use of less frequent dosing upon reinitiating treatment in patients who have achieved a high level of efficacy with TCZ but have experienced laboratory abnormalities (including thrombocytopenia, neutropenia, liver enzyme abnormalities) in sJIA patients.	Thrombocytopenia, neutropenia, liver enzyme abnormalities	Final CSR: May 2020

ANNEX 3:

PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

ANNEX 3

PROTOCOLS FOR PROPOSED, ONGOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

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1. PART A: REQUESTED PROTOCOLS OF STUDIES IN THE PHARMACOVIGILANCE PLAN, SUBMITTED FOR REGULATORY REVIEW WITH THIS UPDATED VERSION OF THE RMP

Not applicable

2. PART B: REQUESTED AMENDMENTS OF PREVIOUSLY APPROVED PROTOCOLS OF STUDIES IN THE PHARMACOVIGILANCE PLAN, SUBMITTED FOR REGULATORY REVIEW WITH THIS UPDATED VERSION OF THE RMP

Not applicable

3. PART C: PREVIOUSLY AGREED PROTOCOLS FOR ONGOING STUDIES AND FINAL PROTOCOLS NOT REVIEWED BY THE COMPETENT AUTHORITY

Approved Protocols

Study	Protocol Title	Protocol Number / Version	Protocol Date	Procedure Number
RABBIT ML28664 (formerly tracked as GA28719)	Long-term Observation of Treatment with Biologics in Rheumatoid Arthritis	Study Protocol According to the Fourth Amendment	1 January 2009	Approved with RMP v7 (EMEA-H-C-000955-II-007) on 22 April 2010
WA29358 (Pediatric Registry)	Observational Safety and Effectiveness Study of Patients with Polyarticular Juvenile Idiopathic Arthritis Treated with Tocilizumab	v6.0	28 April 2020	PAM MEA 041

Long-term Observation of Treatment with Biologics in Rheumatoid Arthritis

RABBIT

Study Protocol According to the Fourth Amendment

Updated version valid from January 1st 2009

Dated 20th November 2008

Type of study	Prospective cohort study
Principal Investigators	Prof. Dr. Angela Zink, Dr. Joachim Listing, Dr. Anja Strangfeld
Study coordination	Deutsches Rheuma-Forschungszentrum Berlin Forschungsbereich Epidemiologie Charitéplatz 1 10117 Berlin
Scientific advisory board	Prof. Dr. P. Herzer, Prof. Dr. J. Kekow, Prof. Dr. R. Rau, Prof. Dr. M. Schneider
Pharmaceutical companies	Abbott GmbH & Co. KG (since 2003) Amgen GmbH (since 2003) Bristol Myers Squibb GmbH (since 2007) Essex Pharma GmbH (since 2001) Roche Pharma AG (since 2007) Wyeth-Pharma GmbH (since 2001) UCB (from 2009)
Start of 2nd study extension	January 1st 2009
End of recruitment	December 2011
End of follow up cohort-1	December 2011
End of follow up cohort-2	5 years after inclusion of the last patient (December 2016)
End of study	1 year after end of follow up cohort-2 (December 2017)

The German Biologics Register RABBIT has been conducted since May 2001 under the auspices of the "Kompetenznetz entzündlich-rheumatische Systemerkrankungen"

("Competence Network Rheumatology"). The content of the original study protocol as well as the extension protocol was agreed with the Deutsche Gesellschaft für Rheumatologie (German Society for Rheumatology).

1. General remarks

The German biologics register RABBIT ("**R**heumatoide **A**rthritis - **B**eobachtung der **Bi**ologika-Therapie) is an independent long-term observational cohort study of the safety and effectiveness of biologic agents in rheumatoid arthritis (RA). The aim of the register is to provide safety and effectiveness data on all licensed biologic drugs available for the treatment of RA. The register was started with the pharmaceutical companies Wyeth Pharma and essex pharma after etanercept and infliximab had been licensed in early 2000. According to the first study protocol (dated 05.02.2001) RA patients treated with etanercept or infliximab in routine care should be compared to RA patients receiving conventional disease modifying antirheumatic drugs (DMARD). In 2003, the interleukin-1 receptor antagonist anakinra and the TNF inhibitor adalimumab were licensed and Amgen as well as Abbott joined the register (see 1st amendment 06.06.2003, 2nd amendment June 2005). The principles for including new biologic agents as index drugs which qualify for enrollment of patients are the following:

- the efficacy of the new agent has been proven in randomized controlled trials
- the drug is licensed in Germany for the treatment of RA,
- principal investigators, study physician, advisory board and the pharmaceutical companies already funding RABBIT agree to include the new substance as index drug,
- the pharmaceutical company which sells the new drug makes an appropriate contribution to the joint, unconditional grant for the study,
- the contracts between the companies and the German Rheumatism Research Centre are modified accordingly.

This pertained to rituximab and abatacept from 2007 (see 3rd amendment). According to this 4th amendment a new extension of RABBIT will be started in January 2009 (see below)..

In order to detect increased risks even for the occurrence of rare events, the goal for cohort-1 was to recruit 1,000 patients for each of the biologic agents adalimumab, anakinra, etanercept and infliximab. A control group of 2,000 conventionally treated patients was needed to put the results into perspective (see study protocol dated 05.02.2001, 1st amendment 06.06.2003, 2nd amendment June 2005). Recruitment for this first RABBIT

cohort was stopped by the end of 2006 when these recruitment goals were partially achieved.

Cohort-2, started in January 2007, recruits patients treated with rituximab or abatacept (see 3rd amendment).

From 1st January 2009, a new enrollment period will be started. RABBIT will then be open to recruit patients with a new start on abatacept, adalimumab etanercept, infliximab, or rituximab, as well as – after licensing – the new biologic agents certolizumab, golimumab, and tocilizumab. Again, a control group of patients with at least one DMARD failure and start of a new DMARD therapy will be recruited.

2. Reasons for the extension of RABBIT

Golimumab, certolizumab, and tocilizumab are effective biologic agents (1-4) and they will presumably be licensed in Germany for the treatment of RA in 2009. They will be included in RABBIT as soon as they fulfill all entry criteria listed above.

The availability of the first cytokine inhibitors in Germany in 2001 opened new and effective therapeutic options for patients with very severe RA refractory to standard therapies. These agents were prescribed to those patients with the highest needs due to disease activity and treatment history. With growing experience in the treatment with biologic DMARDs and with an increasing spectrum of licensed drugs there has been a shift to treat also patients with moderate disease activity and severity and less previous treatment failures. While the first patients treated with biologics had an average of 4 and up to 8 previous treatment failures, now patients have a mean of two to three previous conventional therapies (more than 3 DMARD failures: 65% of the anti-TNF patients in 2001/2002 versus 36% in 2005/2006). Therefore, in the next years the spectrum of patients treated with biologics (but also the spectrum of patients treated with conventional DMARDs) will be different from the "historical controls" enrolled between 2001 and 2006 into cohort-1. Furthermore, the decision to continue or stop a treatment depends on the availability of alternative treatment options. More treatment options will therefore influence treatment continuation rates. Patients receiving infliximab or etanercept in 2001 who remained on this drug for 2 years are likely different from those patients receiving a biologic in 2010 and continuing this treatment also for 2 years.

During the last years, results from the RABBIT database have increased the knowledge regarding the safety of biologic agents in RA (5-10). Most of the current concerns, however, refer to the risk of rare serious adverse events or safety aspects of possible interactions (e.g. between different drugs or between a drug and the activity of the disease, or the influence of

biologics on the outcome of a pregnancy). A better understanding of these interactions will have a direct influence on clinical practice and reduce the risk of a drug by enabling the physician to act in time. The number of patients already recruited to RABBIT is too low to allow for these analyses. Therefore, from 2009 RABBIT will be open not only for those drugs currently recruited to cohort-2 and those newly licensed after 2008, but also for those enrolled in cohort-1.

To harmonize the analysis of the data RABBIT collaborates closely with other European registers, namely the British register BSRBR (11) and the Swedish register ARTIS (12;13). Data have been provided to the pharmaceutical companies every six months and have been used by the companies to fulfill their responsibilities towards the EMEA.

3. Aims of the study

Major aims are:

1. To study the long-term safety of biologic agents

   This includes the observation of all adverse events (serious and non-serious) in order to assess the overall safety profile. Specific emphasis will be laid on "events of interest" (see 8.1.1 below).

2. To describe the long-term effectiveness of treatment with biologic agents (disease outcomes on therapy as well as after terminating therapy).

   Major outcomes are: DAS28 response, ACR 20/50/70 response, time under therapy, and functional status.

3. To describe selected direct and indirect costs of therapy with biologics compared to conventional DMARD therapy.

   This includes the description of health care consumption and work disability.

4. Study Design

RABBIT is a prospective observational cohort study. Physicians aiming at taking part in RABBIT must sign a contract with the DRFZ.

Patients enrolled into the cohort-1 have follow up visits at month 3, 6, 12, 18, 24, 30, 36, 48, and 60 according to the initial protocol. These patients will be followed up till December 2011 at month 72, 84, 96, 108, 120.

Patients enrolled into cohort-2 have follow up visits at month 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60.

There is no influence on any treatment decision from the principal investigators, scientific advisory board or pharmaceutical companies sponsoring the study. The type of the treatment administered, and the conduct of individual therapy including dosages is determined by the treating physician only.

5. Inclusion criteria

Inclusion criteria

- signed informed consent
  - for patients who switch between the cohort-1 and cohort-2 there is a need to sign a second informed consent form
  - a second informed consent will also be needed for the extension period of cohort-1 (years 6 to 10)
- diagnosis of RA according to the ACR criteria
- age at onset of RA >15 years
- starting treatment with a biologic agent or a conventional DMARD provided this start is in agreement with the following enrolment periods:
  - enrolment period I (May 1st 2001 to December 31st 2006) allowed the recruitment of patients with a new start of a treatment with
    - conventional DMARDs after a failure of at least one previous DMARD treatment (control group of cohort-1)
    - etanercept or infliximab (since 2001) or adalimumab or anakinra (since 2003).
  - enrollment period II (January 1st 2007 to December 31st 2008) allows the recruitment of patients with new starts of treatment with
    - rituximab or abatacept into cohort-2 irrespective whether the patients were already enrolled into cohort-1 or not.
  - enrollment period III (since January 1st 2009) opens cohort 2 for the recruitment of patients with a new start of
    - rituximab or abatacept similar as in enrollment period II
    - one of the biologic agents already recruited to cohort-1: etanercept, infliximab, adalimumab
    - agents newly available after January 2009: golimumab, tocilizumab, certolizumab
    - conventional DMARD treatment (without concomitant biologic therapy) after failure of at least one DMARD treatment (control group)

- patients who fulfill the criteria of the enrollment period III the recruitment is possible irrespectively whether they were already enrolled into cohort-1 or not.
- patients of cohort-1 who switch to anakinra remain in cohort-1.

- In the case of a switch between treatment A and treatment B no washout period is necessary, however, a previous treatment with the index drug under which the patient is enrolled in RABBIT is only allowed provided this drug was not prescribed during the last 3 months before enrollment.
- In the case of a combination therapy a stop of one combination partner alone does not qualify for recruitment. A new start of a treatment with a biologic or a new start of a conventional DMARD therapy without biologics is necessary.
- Glucocorticoids are not considered as DMARDs.

6. Assessments and evaluation methods

The following outcome measures have been and will be used:

A. Safety:

1. Occurrence of adverse events (serious/non-serious)
2. Outcome of pregnancy
3. Mortality

B. Effectiveness

1. Time on therapy
2. Reasons for change of treatment
3. CRP, ESR, swollen joint count, tender joint count, Disease Activity Index (DAS28)
4. ACR20, ACR50, ACR70 response criteria, DAS28 (EULAR) response criteria
5. Functional status (Hannover Functional Status Questionnaire FFbH)
6. Pain and fatigue, sleep disorders (0-10 rating scales)
7. Patient's assessment of general health (0-10 rating scale)
8. Quality of life (SF-36)
9. Working status (full time or part time employment, early retirement)
10. Time on sick leave

C. Costs

1. Days in hospital
2. Medication and joint prosthesis
3. Days off work in employed patients
4. Early retirement and return to work (working days gained)

Additionally, basic sociodemographic data, disease duration, co-morbidity, smoking habits, and co-medication will be documented.

Flow chart of parameters investigated

	t_0	t_1 3 M	t_2 6 M	t_3 12 M	t_4 18 M	t_5 24 M	t_6 30 M	t_7 36 M	t_8 42 M	t_9 48 M	t_{10} 54 M	t_{11} 60 M	t_{10} 72 M	t_{11} 84 M	t_{12} 96 M	t_{13} 108 M	t_{14} 120 M
			Cohort-1 initial phase										Cohort-1 extension period				
			Cohort-2														
Patient characteristics Duration of symptoms, RF, gender, prior therapy	x																
Start/end of biologic therapy	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Start/end of DMARD therapy	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Reasons for discontinuation of therapy	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Rheumatic co-medications	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Vaccination	x-2			x-2		x-2		x-2		x-2		x-2					
AEs (physician)	x-2	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Side effects (patient)		x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Co-morbidity (physician)	x						x					x-2	x-1		x-1		
Joint counts	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
ESR, CRP	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Morning stiffness	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Pain	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Fatigue	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
General health assessment (patient)	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Functional status (FFbH)	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Physician contacts	x	x	x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Sick leave	x		x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Hospitalizations	x		x	x	x	x	x	x	x-2	x	x-2	x	x-1	x-1	x-1	x-1	x-1
Pregnancy incl. outcome				x		x		x		x		x	x-1	x-1		x-1	x-1
Job situation	x			x		x		x		x		x	x-1	x-1	x-1	x-1	x-1
Smoking	x-2			x-2		x		x		x		x		x-1		x-1	x-1
SF-36	x-2			x-2		x-2		x-2		x-2		x		x-1		x-1	x-1
Patient satisfaction	x-2	x-2		x-2		x-2		x-2		x-2		x-2					

"x" assessed in both cohorts, "x-1" assessed only in cohort-1, "x-2" assessed only in the cohort-2 cohort.

7. Adverse event reporting

Adverse events and serious adverse events will be recorded according to the ICH guideline on clinical safety data management: definitions and standards CPMP/ICH/377/95/E2A. Therefore, any untoward medical occurrence observed in a patient has to be reported as adverse event (AE). The AE does not necessarily have to have a causal relationship to the treatment of the patient. Any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect has to be reported as serious adverse event (SAE). These definitions of AEs and SAEs are also provided in the CRFs. For

non-serious adverse events, severity grading will be performed according to the recommendations of the OMERACT Toxicity Working Group. For the coding of AE and SAE the Medical Dictionary MedDRA will be used on the preferred term level. It is intended to update the AE/SAE database with every update of MedDRA.

8. Statistical analysis

8.1. Safety endpoints

8.1.1. Events of interest

In agreement with all companies funding RABBIT, the British biologics register BSRBR (11) and the Swedish register ARTIS (12;13) the following "events of interest" which require specific attention were defined:

- tuberculosis,
- other serious infections (e.g. pneumonia, infections of the CNS, septicemia, bone or joint infections, opportunistic infections),
- congestive heart failure,
- myocardial infarction,
- central demyelination,
- serious hematologic disorders (e.g. bone marrow depression and hypoplastic anemia),
- neoplasms (lymphomas, solid malignancies, other neoplasms),
- deaths

On November 19, 2008 the following extension of the events of interest was agreed upon the scientific advisory board meeting with all pharmaceutical companies funding RABBIT:

- serious systemic hypersensitivity reactions / serious infusion reactions
- hepatic failure
- serious gastrointestinal ulcer/perforation
- stroke.

Furthermore the number of pregnancies and their outcome will be investigated.

Incidence rates of these events of interest are reported regularly (see 8.1.2). Changes of the list above have to be based on an agreement between the pharmaceutical companies

funding RABBIT and the principal investigators. They should be communicated to the British and Swedish register.

Additional information which is not part of the CRF is gathered from the treating physician in the case of events of interest. Additional information not part of the CRF is also gathered for all other SAEs which are according to the assignment of the treating rheumatologist possibly related to a biologic agent or a conventional DMARD. SAEs with missing assignment of the causal relationship are considered as possibly related. The results of these queries are sent out to every company marketing the possibly related biologic agent.

8.1.2. Six months reports

Every six months each pharmaceutical company receives a report which contains detailed records on each particular SAE (events of interest and other SAE) which occurred during the 6 months period and which were assigned to the biologic agent marketed by the company. The report comprised also all SAEs assigned to conventional non biologic treatment. Except for deaths and malignancies a SAE is assigned to all biologics a patient received during the last 3 month before the onset of the SAE (3-months risk window). For rituximab a 9 months risk window is applied. SAE which cannot be assigned to one of the biologic agents according to this rule are assigned to conventional treatment. This approach with equal risk windows for different SAEs is used for feasibility reasons. In contrast, malignancies and deaths are assigned to all biologic agents the patient was ever exposed to. The assignments are not connected with a conclusion about a causal relationship.

In addition to the detailed reports of SAEs the companies funding RABBIT receive three summary reports comprising crude cumulative incidence rates of events of interest and their 95% confidence intervals. The so called "Manchester template" is used to report the event rates. This "Manchester template" includes incidence rates of the total number of all observed SAEs. Each company receives one report on their own drug and two control group reports: one of biologics naïve patients and one of SAEs observed in patients under conventional treatment who were previously exposed to biologics. Copies of all summary reports are sent to the members of the scientific advisory board and the spokesman of the commission drug therapy of the German Society for Rheumatology (DGRh).

Detailed multivariate analyses cannot be provided every six months, but will be done in scientific investigations and published in international journals. These results will be reviewed and if necessary re-evaluated in the final study report.

8.1.3. Signal detection

Serious and non serious adverse events will be registered in the AE database continuously. Every 6 months the clinical database (containing clinical data and treatment data) will be updated, validated and merged with the AE database. The six months reports are based on these merged databases and are used for signal detection. A significant elevated crude incidence rate of a SAE (signal) may lead to a detailed statistical analysis (see below).

8.1.4 Detailed statistical analyses

The major aim of RABBIT is to protect future patients from harm caused by serious adverse events. It is impossible to achieve this aim by following a pre-specified list of primary hypotheses since the spectrum of possible SAEs is wide and every list would therefore be incomplete. New scientific results or new biologic agents may lead to extensions and/or changes in the list of "events of interest". Therefore, the principal investigators and the study physician are free to decide which safety concern will be investigated next.

There is no general statistical analysis plan which would be appropriate for the different scientific questions. For different AEs different confounders have to be considered. Patients follow up for several years likely will receive changing treatments. These changes have to be taken into account. Furthermore, the decision to prescribe, to stop or to continue a treatment depend on the availability of treatment options and experiences with these alternatives. For this reason the mix of patients receiving a particular treatment will likely change during follow-up. The risk of developing an AE may therefore change over time for various reasons (see below). Possible confounding factors or biases have to be taken into account very carefully to avoid any false conclusion. In RABBIT this will be done by considering the following principles of statistical safety analyses:

Principles of the statistical analysis

a) Confounding by indication will be taken into account

Treatment decisions are based on the needs of a particular patient. Patients treated with biologics are more severely ill and have more treatment failures than patients treated with conventional DMARDs. Furthermore, the decisions to prescribe, to stop or to continue a treatment are influenced by the spectrum of available drugs and the experience to treat patients with them. Some of the newer biologic agents (e.g. abatacept and rituximab) have been licensed for patients with previous failure of anti-TNF therapy. Patients in cohort-1 and cohort-2 and especially patients receiving biologics and those receiving conventional DMARDs are therefore not fully

comparable. For this reason comparisons based on crude unadjusted estimates cannot be interpreted but appropriate statistical methods that are able to account for confounding by indication have to be applied.

b) **Patient characteristics which likely influence the risk of developing a particular AE will be taken into account**

Examples for these patient characteristics are age, sex, body mass index (e.g. for cardiac disorders), co-morbid conditions (e.g. COPD), treatment history of specific drugs (e.g. azathioprine for malignancy risk). In the first step those risk factors for which the increased risk was shown in previous studies will be considered. Further patient characteristics which possibly influence the risk of developing the AE might be investigated in addition.

c) **The possible influence of co-medication has to be considered**

This applies especially, but not limited to, treatment with glucocorticoids, MTX, leflunomide, other DMARDs.

d) **Changing risks over time will be considered. They may result from:**

changes in treatment

selection processes caused by treatment decisions

Patients who remain on a drug for more than one year are likely different from the total sample of patients in whom the treatment with this drug was started.

the course of RA itself

The risk of developing an AE may be influenced by the inflammatory activity (e. g. the risk of developing arteriosclerosis)

an AE under investigation might be a sequelae of a previous AE

e.g. a septic shock as a sequelae of pneumonia.

e) **Multivariate statistical methods appropriate to deal with these challenges will be applied.**

Examples are (fields of application in parentheses):

- Propensity score methods (14) (confounding by indication)
- Cox regression (15) (confounders, changing risks)
- Generalized regression models for survival data (16-18) models (confounders, changing risks, recurrent AEs)
- Generalized estimation equations (19) (confounders, changing risks, recurrent AEs)

- Competing risk models (20) (competing risks, selection processes)
- Missing data models (21) (missing data).

f) **In the case of rare events the advantages of nested case control studies will be taken into account.**

With the availability of a very large number of possible controls (> 6,000) it should be possible to match cases who suffered from a particular SAE with controls who were similar to the cases according to a rather large number of possible confounders (up to 10).

g) **The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline (22) will be followed.**

Furthermore, the results will be presented in a comprehensible way to enable the reader to follow them in detail. Papers submitted or already published by the RABBIT team give examples how such analyses will be performed (5-7).

8.2 Effectiveness endpoints

Established endpoint measures in RA (DAS28 response, ACR 20/50/70 response, remission rates, treatment continuation, and functional outcome) will be used to describe the long-term effectiveness of biologic agents. The principles described above for the analysis of safety endpoints will also be followed in a similar manner regarding effectiveness endpoints (for examples see (23-25)).

8.3. Cost analyses

Because of the high costs of the biologic agents it is reasonable to compare direct and indirect costs. Indirect costs include the description of health care consumption and work disability. There are, however, limitations concerning the evaluation of cost-effectiveness: For feasibility reasons assessments of radiographic progression, a major outcome in rheumatoid arthritis, are not performed. Therefore, the analyses have to be done in a descriptive manner only. The limitations of the results will be mentioned. It is for the reasons mentioned not planned to perform direct cost-effectiveness comparisons among drugs.

8.4. Dropout analyses

In case patients are lost to follow-up, the reasons for study non-completion are determined and comparisons of drop-outs and non-drop outs are performed.

9. Power considerations

To achieve the aims of RABBIT the team at the DRFZ will continue to motivate rheumatologists to enroll patients into RABBIT. However, since RABBIT is an observational study of routine rheumatologic care in Germany the number of patients under a particular drug who will be enrolled is not manageable by the study centre. Nevertheless from our previous experience we assume that it should be possible to enroll 500 to 1,000 RA patients under each of the biologic agents abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab into cohort-2 until the end of 2011. In addition we aim to recruit 1,000-1,500 RA patients with at least one DMARD failure who will be enrolled at the start of a new DMARD therapy (control group of cohort-2).

Number of patients enrolled	Expected number of patient years
500	~2,000
750	~3,000
1,000	~4,000
1,500	~6,000

Tab. 1: Expected number of patient years available in 2011 by the number of patients enrolled

At the end of a five years follow-up period we expect to have observed roughly 3,000 patient years (pyrs) each under abatacept, certolizumab, golimumab, tocilizumab and approximately 4,000 patient years under rituximab. This estimate may vary because of the actual number of enrolled patients or because of lower or higher treatment continuation rates (see tab. 2). A large proportion of the patients of cohort-2 will be new patients (40-50%) the others will be switchers from cohort-1. Taking both cohorts together, we expect to have roughly 8,000 pyrs under adalimumab or etanercept, 3,500 – 4,000 pyrs under infliximab and approximately 15,000 pyrs under conventional DMARD treatment which split in ~7,500 pyrs in biologics naïve patients and ~7,500 pyrs of conventional DMARD treatment after a stop of a treatment with biologics.

Large sample sizes are needed to estimate the incidence rates of rare serious adverse events and to estimate the possible influence of treatment, disease, and SAE specific confounders on the occurrence of the SAEs. And vice versa the power to detect risk factors of rare SAEs is considerably lower than the power to detect the risk of frequent events or to

find clinically important changes in disease activity. The following power considerations therefore centre on risk factors for infrequent or even rare events. The power to detect such risk factors usually depends on patient numbers, number of AEs/SAEs under consideration, number, nature and magnitude of the influence of confounding factors, and the statistical model that will be applied. The power is further influenced by the dissimilarity of the group sizes. In the case of an observational study like RABBIT, power calculations can therefore only be considered as approximate estimates.

The most important factor for the power calculation (for Cox regression, Poisson regression GEE models) is the number of AEs/SAEs observed. Assuming firstly an overall incidence rate > 2/100 patient years (e.g. serious infections [May 2008 on average: 3.4/100 pyrs]) then the power of RABBIT is sufficient (>=80%) for detection of moderate increases (Hazard ratios of 1.5 or larger) in the comparison of one of the biologic agents with the remaining sample or more importantly for the comparison of one of the new biologic agents with "TNF blockers of the first generation" (with patients receiving TNFα antibodies (adalimumab, infliximab) or with patients receiving etanercept) (see Tab. 2). A similarly high power would be achievable for the comparison with patients treated with conventional DMARD. Even the analysis of trends in the risk of serious infections caused by changes in the case mix should have a sufficient power if this analysis is made for patients receiving adalimumab, etanercept, or infliximab. Obviously the power is lower if only 500 patients under a new biologic could be recruited or if the treatment termination rates under a particular agent are higher and only 2,000 pyrs instead of 3,000 pyrs are therefore available at the end of follow up (for further details see Tab. 2).

1. Aim to detect a hazard ratio of 1.5			
Patient years biologic	Patient years comparator group	Incidence rate comparator /1,000 pyrs	Power
2,000§	8,000#	20 / 30	~60% / ~80%
3,000*	8,000#	20 / 30	~70% / ~90%
4,000‡	8,000#	20 / 30	~80% / ~95%
3,000*	3,000*	25 / 30	~70% / ~80%
4,000‡	3,000*	25 / 30	~75% / ~80%
2. Aim to detect a hazard ratio of 2.0			
3,000*	8,000#	3 / 5	<50% / ~65%
4,000‡	8,000#	3 / 5	~55% / ~75%
8,000#	8,000#	3 / 5	~75% / ~90%
Aim to detect a hazard ratio of 2.5			
2,000§	8,000#	3 / 5	~50% / ~75%
3,000*	8,000#	3 / 5	~70% / ~90%
4,000‡	8,000#	3 / 5	~80% / ~95%
3,000*	3,000*	3 / 5	~65% / ~80%
4,000‡	3,000*	3 / 5	~70% / ~90%

Tab. 2: Power calculations to detect an increase in the risk of developing an AE in patients exposed to one biologic agent compared to patients receiving other biologic drugs or conventional DMARDs

e.g. etanercept, or adalimumab, or "comparable conventional DMARD episodes"

* assumed for abatacept, certolizumab, golimumab, tocilizumab

‡ assumed for infliximab, rituximab

§ if only 500 cases receiving drug xx were recruited

To detect a clear increase of an uncommon SAE with an overall incidence rate of 3 to 5/1000 patient years (e.g. myocardial infarction, heart failure, septicemia) is possible if this increase corresponds to an hazard ratio of 2.5 or larger (see tab. 2).

However, previous analyses have shown that important risk factors are identifiable also in the case of uncommon SAEs (risk of developing heart failure (6), herpes zoster (7), or an incident malignancy (10)). This was possible by the application of (generalized) Cox regression models or nested case controlled designs. Nevertheless these results also underline the need to increase the sample size of RABBIT to improve the ability to generalize results.

10. Study procedures

All physicians already participating in RABBIT will be asked to enroll patients in the expanded cohort-2. Patients already enrolled in cohort-1 will be switched to cohort-2 at start of treatment with abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, or tocilizumab or at start of a new DMARD treatment (see 5.). A stop of a biologic treatment and continuation of treatment with one or two DMARDs does not qualify for the enrollment into cohort-2. For the enrollment into the control group of cohort-2 a new treatment with conventional DMARDs (without concomitant biologic drugs) as a combination therapy or as mono therapy has to be started after failure of at least one DMARD treatment. Physicians who did not enroll patients into cohort-1 may start to participate in RABBIT and enroll patients into cohort-2.

Participating physicians are provided with the study protocol, precise instructions how to fill out the various forms, copies of the patient information leaflet and consent form, and a suitable supply of questionnaires.

The completed case report forms (physician and patient questionnaires) for cases and controls are sent by fax to the DRFZ as soon as they have been completed. To avoid misrouting, fax numbers have to be stored electronically in the fax machine.

Forms arriving in the central coordinating office are reviewed daily. Each sponsor will receive biannual reports on adverse events for the patients under his own product as well as for the control groups (see 8.1.2).

Documenting serious adverse events on the physician report form does not release the treating physician from his/her responsibility to notify the Bundesamt für Arzneimittel und Medizinprodukte (BfArM) (German regulatory authority) or the Paul-Ehrlich-Institut, or the relevant pharmaceutical company in case of an unexpected serious adverse event. The study coordinating office cannot discharge this duty on the physician's behalf as it cannot guarantee that it will meet the 24-hour deadline.

Staff: A study physician is responsible for the study supervision, coding adverse events and compiling reports. Two statisticians are responsible for the data analysis and statistical testing. Medical data managers are responsible for study monitoring of cohort-1 and cohort-2 (organization of schedules, coding, dropout research, etc.). The medical data managers continuously monitor receipt of completed forms and issue timely reminders to call patients for follow-up visits. If a patient is more than six weeks overdue, the physician's office or the patient himself or herself are contacted. If a patient has switched doctors, the patient's new physician will be asked (with the patient's consent) to complete the remaining forms and to continue to follow-up this patient. If a study patient dies the physician is asked to report the date and cause of death to the study coordinating office. If this information cannot be provided the team at the DRFZ tries to ascertain it from the authorities.

11. Dropouts

Patients have the right to leave the study at any time. The study coordinating office reserves the right to contact these patients by letter or phone to ask their reasons for discontinuing their participation.

A patient switching from cohort-1 to cohort-2 will not be counted as drop out from cohort-1 as long as he/she is under observation within cohort-2. Data from the time points he/she is observed in cohort-2 closest to the missing time points in cohort-1 are used as replacement of that data for long-term observation.

12. Ethical considerations / data protection

The sponsors do not influence the treatment decisions taken by the physicians documenting the patients. To underline the importance of this, the same fee will be paid for scheduled visits in cohort-2 as for the visits of patients treated with biologics or conventional DMARDs in cohort-1.

Patients will be informed about the purpose of the study by their treating physician and will receive a study information leaflet. They will be asked for their written informed consent to take part in the study and have their personal data disclosed to the study coordinating office (see attachment). Patients' names, addresses and phone numbers will be disclosed to the study coordinating office for study monitoring purposes. Personal data such as names, addresses and phone numbers will be kept strictly separate from the questionnaire data. A statement of obligation is signed to ensure that the two data sets are not matched up. The personal details entered in the computer are protected by two passwords. The questionnaires contain a serial patient number that is already entered in the DRFZ. The

physicians are instructed to keep lists (in addition to the study coordinating office) showing the names with the matching anonymous numbers.

The study protocol for cohort-1, dated February 5th, 2001 was submitted for review to the Ethics Committee of the Charité Medical School in Berlin. The Ethics Committee approved it at March 1st, 2001. Three amendments (dated February 2003, June 2005, and November 2006) were also approved by the Ethics Committee of the Charité. This study protocol will be sent to the Ethics Committee of the Charité University Medicine Berlin as an amendment to the previous protocols. The previous protocol and its three amendments remain valid till the end of 2008 and will be replaced by this protocol by January 2009.

Data will be archived for at least ten years after the end of the study at the DRFZ in Berlin. No selected data or entire data sets will be disclosed without authorization to third parties, including the sponsors, but the sponsors will receive upon request additional analyses on their own products separate from the joint evaluations. The study management, advisory board and sponsors will decide jointly whether data may be passed on for pooling (international studies).

13. Cooperation between study management, advisory board and sponsors

The study management team is supported by a scientific advisory board comprising four experienced community and hospital rheumatologists. The scientific advisory board was appointed by the governing board of the German Society for Rheumatology in agreement with the Professional Association of German Rheumatologists. The advisory board's duties are: regular review of reports, consultation in case of serious events, discussion of the research agenda and the statistical analysis plans. The advisory board members meet personally at least once annually with the principal investigators and the study physicians and otherwise communicate by telephone conferences and e-mail.

The sponsors are entitled to have two delegates with no voting rights present at the meetings of the scientific advisory board.

14. Cost sharing among companies

All companies participating in RABBIT support the register with joint, unconditional grants. In principle, each company has an equal share of the personnel and overhead costs at the DRFZ. In case of very low recruitment, in consensus with all other companies, the share of an individual company can be lowered. Those companies who have two different drugs under observation in RABBIT have a share of 150% of the usual share. The budget is set up in advance for one or more years by the DRFZ and agreed in the meetings with the

companies. Identical contracts are then sent out by the DRFZ to all companies and signed bilaterally. The contracts are only effective after all companies have signed.

The documentation fees for the participating rheumatologists are 30 Euros (plus VAT if applicable) for all measurement points with the exception of the baseline visit in cohort 2 from 01.01.2009. The fee for this first visit is 50 Euros (plus VAT, if applicable) due to the higher work load of this first CRF.

The documentation fees are calculated in the beginning of each year for the previous year. Each company covers the documentation fee for patients enrolled under their own drug plus an equal share of the fees for the control group. The queries sent out in case of serious adverse events are covered by the company who received the report. If more than one drug was given in the considered time span, all companies involved receive the report. The costs are then splitted among these companies.

The documentation fees are paid to the physicians by the Rheumatologische Fortbildungsakademie (RhAK). The participating rheumatologists will receive payment once a year for the preceding year. In order to enable the RhAK to pay the documentation fees to the participating rheumatologists on time in the beginning of each year, the Companies perform payment in advance of 90% of the expected sum by January 15th of each year for the preceding year.

The RhAK receives a handling fee which is agreed upon among all companies.

15. Cooperation between the DRFZ and the companies funding RABBIT

15.1. Reporting of Adverse Events

The study leadership undertakes to pass on to the manufacturer concerned all relevant information on important events, including in particular serious adverse events, that comes to its attention regarding the patients being treated with one of the biologic drugs observed in RABBIT. Concerning the reporting of serious adverse events, the doctors responsible for carrying out the treatment will be notified of their obligation to advise the manufacturer in question within a maximum period of 24 hours by fax with a copy of the fax to the DRFZ for information. The manufacturers will collect all such notifications concerning serious adverse events.

Every six months the DRFZ provides the companies with updated reports about incidence rates of serious adverse events (see 8.1.2). These reports may be included conveniently into the periodic safety update reports (PSUR) of the companies. Upon request the team at the DRFZ will investigate whether or not unexpected signals known to a pharmaceutical company participating in RABBIT were also observed in RABBIT. The SAEs and crude

incidence rates observed in patients receiving the biologic agent which is marketed by this company will be provided as soon as possible. Corresponding incidence rates under conventional DMARD treatment may additionally be provided.

15.2. Publications

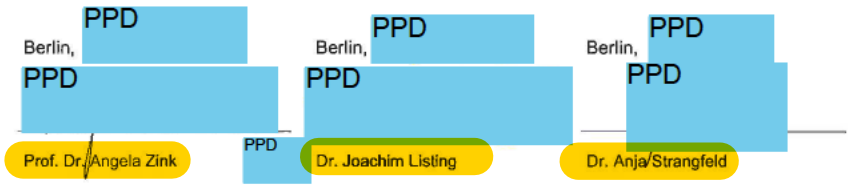
The intermediary and final results will be evaluated and published by the study leadership. The names of all participating doctors who have brought in at least 1% of the number of cases will appear in the footnotes of the publications of the study leadership. The heads of institutions with a particularly high involvement can be invited as co-authors. On an individual basis, the study leadership and the Advisory Committee will together decide on the question of co-authorship. The financial support of the manufacturers is also acknowledged in publications.

Provided that they include the names of the authors, the manufacturers are entitled to publish the results of all product-related reports in their entirety or in the form of extracts and/or to include these in their own publications.

Before being submitted for publication (to a publishing house or to any other form of media), all publications must be approved by the parties. All publications will require the agreement of the parties. Each party has a period of 30 days, in which it can object, starting on the date on which the proposed publication is received from another party. If the parties are unable to agree on the contents of a publication within further 30 days, the party raising the objection has the right to add a written statement in the form of a footnote or some other suitable form to the publication in question. If this written statement is not received within 60 days after the proposed publication has been received by the other party, the party planning the publication shall be entitled to proceed with the publication without the statement.

16. Additional Investigations

In principle, it is possible for sub samples of subjects to be included in supplementary investigations (e.g. basic scientific blood and tissue tests). Besides a separate clarification of any ethical and data protection issues, and besides the patients' informed consent, any such inclusion in supplementary investigations shall require the prior agreement of the study leadership and the advisory committee. All such supplementary studies shall require independent organisation and financing.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NI PASS PROTOCOL

TITLE:	**OBSERVATIONAL SAFETY AND EFFECTIVENESS STUDY OF PATIENTS WITH POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH TOCILIZUMAB**
PROTOCOL NUMBER:	WA29358
VERSION NUMBER:	6
REGISTRIES:	May include, but not limited to, the following: • Childhood Arthritis and Rheumatology Research Alliance (CARRA) • Juvenile arthritis Methotrexate/Biologics long-term Observation (JuMBO) • Biologika in der Kinderrheumatologie-Register (Biologics in Pediatric Rheumatology Registry) (BiKeR)
TEST PRODUCT:	Tocilizumab (RO4877533)
DATE FINAL:	Version 1: 24 August 2015
DATES AMENDED:	Version 2: 18 November 2015 Version 3: 20 July 2016 Version 4: 27 July 2017 Version 5: 17 August 2018 Version 6: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
23-Apr-2020 18:58:49	Deputy EU QPPV	PPD
24-Apr-2020 16:46:04	Company Signatory	

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Due to significant enrollment challenges, protocol WA29358 has been amended to complete this post-marketing requirement with a smaller number of registry patients, as agreed with the FDA and EMA.

Changes to the protocol, along with a rationale for the change, are summarized below:

- The proposed number of patients has been reduced. The original protocol proposed evaluating 800 patients (400 patients newly initiating tocilizumab (TCZ), 400 patients newly initiating a comparator biologic). In the amended protocol, enrollment will be stopped in June 2020, after the study has been open to enrollment for 5 years, and patients will then be followed for up to 5 years. It is expected that approximately 600 patients will have been enrolled (300 patients newly initiating TCZ, 300 patients newly initiating a comparator biologic) by June 2020. These changes are outlined in Section 5.1 “Study Design” and in Section 5.11 “Study Size”.
- The initial projected timeline of last patient enrolled has been revised accordingly throughout.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
BiKeR	Biologika in der Kinderrheumatologie-Register (Biologics in Pediatric Rheumatology Registry)
CARRA	Childhood Arthritis and Rheumatology Research Alliance
CRF	Case Report Form
CSR	clinical study report
DMARD	disease-modifying antirheumatic drug
DSUR	*development safety update report.*
EC	Ethics Committee
EMA	European Medicines Agency
eoJIA	extended oligoarticular juvenile idiopathic arthritis
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiological Practice
ICF	Informed Consent Form
IL-6	interleukin 6
IRB	Institutional Review Board
IV	intravenous
JADAS-10	Juvenile Arthritis Disease Activity Score in 10 joints
JADAS-71	*Juvenile Arthritis Disease Activity Score in 71 joints*
JIA	juvenile idiopathic arthritis
JuMBO	Juvenile arthritis Methotrexate/Biologics long-term Observation
PBRER	periodic benefit-risk evaluation report
pJIA	polyarticular juvenile idiopathic arthritis
Q3W	every 3 weeks
Q4W	every 4 weeks
RA	rheumatoid arthritis
RF	rheumatoid factor
SC	subcutaneous
sJIA	systemic juvenile idiopathic arthritis
TCZ	tocilizumab

1. RESPONSIBLE PARTIES

This protocol has been developed by Roche for submission to the health authorities and to identify the data that will be collected in response to postmarketing requirements. It will not be implemented as a protocol at registry sites. Rather, individual registries have implemented their own registry-specific protocols, which include collection of the specific data indicated in this protocol. To satisfy the postmarketing requirements, data will be collected from patients who are enrolled in national disease or treatment registries (hereafter referred to as "feeder registries"), which may include, but are not limited to, the following:

- Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry
- Juvenile arthritis Methotrexate/Biologics long-term Observation (JuMBO) registry
- Biologika in der Kinderrheumatologie-Register (Biologics in Pediatric Rheumatology Registry) (BiKeR)

The feeder registry protocols will be implemented at registry sites.

2. AMENDMENTS AND UPDATES

Any revisions to the protocol will be prepared by Roche or a designee to provide updated information to health authorities. The revised protocol will not be implemented at registry sites. Rather, individual registries will implement their own registry-specific protocols, which will include collection of the specific data indicated in this protocol.

Amendments to the feeder registry protocols will be prepared and submitted by the feeder registries to the Institutional Review Boards (IRBs)/Ethics Committees (ECs). Amendments to the feeder registry protocols may be submitted by Roche or the feeder registries directly to regulatory authorities, in accordance with local regulatory requirements.

3. MILESTONES

Study milestones are as follows:

Study Milestone	Estimated Date [a]
Start of data receipt from feeder registries	October 2015
End of receipt of data collection from feeder registries	*June 2025*
Annual reports of data from each individual feeder registry*, which are summarized in the PBRER/DSUR*	Annually *for feeder registry data, and summarized in the PBRER/DSUR following nationally agreed reporting periods*

PBRER = periodic benefit–risk evaluation report; *DSUR = development* safety update report.

[a] The dates for the milestones are estimated dates and may be revised by the individual feeder registries.

4. RATIONALE AND BACKGROUND

4.1 BACKGROUND ON POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

Polyarticular juvenile idiopathic arthritis (pJIA), as defined by the International League of Associations of Rheumatology (ILAR; Petty et al. 2004) is composed of several subsets of juvenile idiopathic arthritis (JIA). For the purposes of this study, pJIA will include the following subsets of patients as per the licensed indications in the United States and the European Union:

- Patients with rheumatoid factor (RF)-positive pJIA
- Patients with RF-negative pJIA
- Patients with extended oligoarticular JIA (eoJIA)

4.2 BACKGROUND ON TOCILIZUMAB

Interleukin 6 (IL-6) is a pleiotropic pro-inflammatory multifunctional cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. It was originally identified as B-cell stimulatory factor 2 because of its role in inducing the final maturation of B cells into antibody-producing cells. IL-6 has been shown to be involved in such diverse processes as T-cell activation, initiation of acute-phase response, and stimulation of hematopoietic precursor cell growth and differentiation. IL-6 is also produced by synovial and endothelial cells, leading to local production in joints affected by inflammatory processes such as JIA.

Tocilizumab (TCZ) is a recombinant humanized anti-human monoclonal antibody of the IgG1 subclass directed against the IL-6 receptor that inhibits the function of IL-6. Intravenous (IV) TCZ is currently being studied or has been studied in a variety of diseases, including Castleman's disease, multiple myeloma, systemic lupus erythematosus, Crohn's disease, ankylosing spondylitis, adult rheumatoid arthritis (RA), systemic JIA (sJIA), and pJIA. Subcutaneous TCZ has been studied in adult RA and is currently being studied in both sJIA and pJIA, as well as in giant cell arteritis, systemic sclerosis, and Takayasu arteritis.

Data from Study WA19977 (CHERISH; pivotal trial) and two Japanese studies (MRA318JP and MRA319JP) enabled the approval of TCZ IV in patients with pJIA in the United States in April 2013 and in the European Union in June 2013. TCZ SC administration was approved for the treatment of pJIA in the European Union in April 2018 and in the United States in May 2018 based on the results from the Phase Ib trial WA28117 (JIGSAW 117).

Following the approvals, separate postmarketing registry requirements were requested by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

4.3 STUDY RATIONALE

This protocol has been developed by Roche to meet the following requirements by the FDA and EMA.

The FDA requested "a long-term safety study in X pediatric patients 2−17 years of age with polyarticular JIA (pJIA) treated with tocilizumab to evaluate for the risk of malignancies, serious infections, gastrointestinal perforation, and effects on growth. The study should include a control group of pediatric pJIA patients. Patients should be followed for X years."

The EMA requested "a submission of the draft protocol of the registry as proposed by the MAH, collecting long-term efficacy and safety data in pJIA treatment. The registry will address, but not limited to, efficacy of 10 mg/kg for patients $<$30 kg; impact of the RF status on the 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 of TCZ therapy on the occurrence/treatment of uveitis."

The EMA request for the study to address the impact of TCZ therapy on the "increased risk of atherosclerosis in RA patients" will be satisfied by the evaluation of cardiovascular events in patients with pJIA. In a previous communication on 17 January 2013 to the EMA, the rationale for evaluating cardiovascular events as a surrogate for atherosclerosis was accepted.

This protocol describes the collection, analysis, and reporting of aggregate and some patient data from the feeder registries to satisfy these postmarketing requirements to examine the long-term safety and effectiveness profile of TCZ in patients with pJIA in an observational setting, outside of a controlled clinical trial.

4.4 OBJECTIVES

The overall objective for the study is to assess the long-term safety and effectiveness of TCZ (IV or SC) in relation to comparator biologic in the treatment of pJIA in a real-world setting for 5 years.

The safety objectives for the study are as follows:

- To assess in routine clinical practice the rate of serious adverse events and the rates of adverse events in predefined categories of special interest (infections [serious], cardiovascular events [serious], malignancies [serious and non-serious], gastrointestinal perforations [serious], and uveitis events [serious and non-serious]) in pJIA patients treated with TCZ (IV or SC) or a comparator biologic
- To assess in routine clinical practice the rate and treatment outcome of uveitis in pJIA patients treated with TCZ (IV or SC) or a comparator biologic on the basis of available data from the feeder registries

- To assess in routine clinical practice the growth (relative to age-specific standards for height and weight) of pJIA patients treated with TCZ (IV or SC) or a comparator biologic
- To assess in routine clinical practice the development (via self-reported or examined Tanner staging) of pJIA patients treated with TCZ (IV or SC) or a comparator biologic on the basis of available data from the feeder registries

The effectiveness objectives for the study are as follows:

- To assess in routine clinical practice the effectiveness of TCZ (IV or SC) in patients with RF-positive and RF-negative pJIA, as determined on the basis of Juvenile Arthritis Disease Activity Score in 10 joints (JADAS-10)
- To assess in routine clinical practice the effectiveness of 10 mg/kg TCZ in pJIA patients weighing $<$ 30 kg at treatment initiation, as determined on the basis of JADAS-10

5. RESEARCH METHODS

5.1 STUDY DESIGN

This is an international, multicenter, prospective, observational-cohort study to examine long-term safety and effectiveness data from patients with pJIA treated with TCZ IV 8 mg/kg (10 mg/kg in patients weighing <30 kg) Q4W or TCZ SC 162 mg Q2W (Q3W in patients weighing <30 kg) or a comparator biologic. Roche will obtain aggregate and some patient data from active feeder registries in the United States and the European Union, conduct periodic analyses, and report the associated results to the appropriate health authorities. Roche has confirmed that the feeder registries will collect all data points required to support the study endpoints. This protocol will not be implemented at the feeder registry sites and will not be approved by local IRBs/ECs. Rather, individual registries will implement their own registry-specific protocols, which will include collection of the specific data indicated in this protocol.

The study will allow for analysis of aggregate and some patient-level data from approximately 600 patients with pJIA (defined as RF-positive pJIA, RF-negative pJIA, or eoJIA per ILAR classification (Petty et al. 2004) who are enrolled in national disease or treatment registries (i.e., feeder registries) in the United States and Germany, at approximately 100 sites. The feeder registries may include, but are not limited to, the CARRA, JuMBO, and BiKeR registries. Data may also be collected from patients in other countries, including Canada, Puerto Rico, and Israel, at sites affiliated with these registries. Approximately 300 patients will be initiating treatment with TCZ (IV or SC), with or without a non-biologic disease-modifying antirheumatic drug (DMARD), and approximately 300 patients will be initiating treatment with a comparator biologic, with or without a non-biologic DMARD. The decision to prescribe TCZ (IV or SC) or a comparator biologic should be made by a physician and patient without regard to potential participation in any of the feeder registries, and there is no protocol-mandated

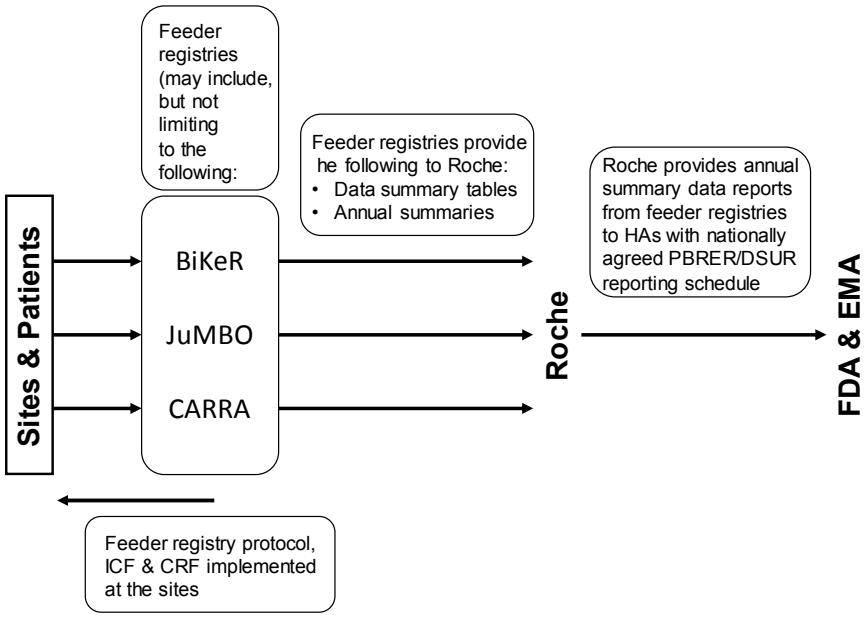
treatment assignment in the feeder registries. Patients will be evaluated and treated according to their physician's standard practice and discretion.

The observation period for this study is defined as a maximum of 5 years for patients initiating treatment with TCZ (IV or SC) or a comparator biologic. Data for the study will be collected directly from the feeder registries. Patients who switch therapy or discontinue therapy during the observation period will continue to be followed in accordance with the feeder registry protocols to allow for long-term safety assessment up to the maximum period of 5 years.

This study will start with the receipt of aggregate data from the feeder registries, estimated to be October 2015, and will end with the receipt of the last aggregate data, estimated to be *June 2025*. Some patient-level data will be received only upon study completion. During the study period, the feeder registries will produce annual reports *based on summary data reports. This information will be supplied to the Agencies in alignment with the nationally agreed* TCZ periodic benefit-risk evaluation report (PBRER)/*development* safety update report (*DSUR*) periods *and will be* based on summary data reports.

The study design is summarized in Figure 1.

Figure 1 Study Design



BiKeR = Biologika in der Kinderrheumatologie-Register (Biologics in Pediatric Rheumatology Registry); CARRA = Childhood Arthritis and Rheumatology Research Alliance; CRF = Case Report Form; *DSUR=development safety update report; HA=Health Authority;* ICF = Informed Consent Form; JuMBO = Juvenile arthritis Methotrexate/Biologics long-term Observation; *PBRER= periodic benefit-risk evaluation report.*

5.2 RATIONALE FOR STUDY DESIGN

TCZ (IV or SC) alone or in combination with methotrexate has been approved for the treatment of patients 2 years of age or older with active pJIA in the United States and the European Union. This study is designed to allow for collection and analysis of aggregate and some patient-level safety and effectiveness data from patients with pJIA in a real-world setting. The international setting will allow for a geographically diverse population, including the United States and the European Union. The data collection period of a maximum of 5 years for patients receiving TCZ (IV or SC) will allow for long-term efficacy and safety assessment and collection of data on growth and development in patients enrolled in the feeder registries.

5.3 PATIENT POPULATION

Patients enrolled in the feeder registries must meet all of the following criteria for inclusion in this study:

- Diagnosis of pJIA, defined according to ILAR classification (Petty et al. 2004), and in line with the licensed indications in the United States and the European Union:

  Patients with RF-positive pJIA

  Patients with RF-negative pJIA

  Patients with eoJIA

- Initiation of treatment with TCZ (IV or SC) or a comparator biologic

  The TCZ group will include patients with no previous exposure to TCZ (IV or SC). The comparator biologic group will include patients with no previous exposure to that specific comparator biologic.

- Age ≤17 years at the time of initiation of treatment with TCZ (IV or SC) or a comparator biologic

5.4 DOSAGE, ADMINISTRATION, AND COMPLIANCE

Dosing and treatment duration for TCZ IV or SC and the comparator biologic are at the discretion of the patient's physician in accordance with local clinical practice and local labeling.

5.5 PATIENT ENROLLMENT AND COHORT ASSIGNMENT

There is no protocol-mandated treatment assignment in the feeder registries, and the decision to prescribe TCZ (IV or SC) or a non-TCZ biologic comparator will be made by a physician and patient without regard to potential participation. Patients meeting the inclusion criteria and providing consent to the registry will be allocated to one of the two groups, TCZ or non-TCZ comparator, based on physician-assigned treatment.

As agreed with the FDA, to ensure the two treatment cohorts are balanced with respect to geographic region and timing of enrollment, patients will only be enrolled if a TCZ (IV or SC) patient can be matched to a non-TCZ comparator patient based firstly on

geographical region and then on calendar period (must have newly initiated therapy with TCZ [IV or SC] and non-TCZ comparator within a period of 3 months on either side of the treatment initiation date). This will ensure that matched patients are enrolled into their respective treatment cohorts during a defined period where prescribing practices will not differ.

Patients enrolled in the comparator cohort who subsequently switch to treatment with TCZ (IV or SC) can be re-enrolled in the TCZ cohort provided the TCZ cohort is still open for enrollment, they meet all the inclusion criteria, and they can be matched to a comparator cohort patient in the same manner as all other patients being enrolled into the TCZ cohort. Hence, a patient can contribute data to both cohorts. However, if the patient subsequently switches treatment back to the original comparator biologic or a different comparator biologic, they will not be re-enrolled into the comparator cohort.

Similarly, patients enrolled into the TCZ cohort who subsequently switch to a comparator biologic can be re-enrolled into the comparator cohort provided the cohort is still open for enrollment, they meet all the inclusion criteria, and they are the best match for an enrolling TCZ cohort patient. Otherwise, they will only contribute to the TCZ cohort. Patients originally enrolling into the TCZ cohort, then enrolling into the comparator cohort, who then switch treatment back to TCZ (IV or SC), cannot re-enroll into the TCZ cohort.

Patients can only enroll into each cohort once. Details of the geographic regions used for each registry are described in the Statistical Analysis Plan.

Note that for the CARRA registry, over-enrollment occurred within the non-TCZ comparator arm during the first year of enrollment. To adjust for this disparate enrollment rate, the TCZ patients already enrolled during this period will be retrospectively matched at random (if greater than one match exists) to non-TCZ comparator patients firstly by geographical region and time period (newly initiated therapy with non-TCZ comparator within a period of 3 months on either side of the treatment initiation date). Any non-TCZ comparator patients without a match will not participate in this study, unless a match is obtained at a later date.

The 5-year report will state that the concurrent enrollment model was applied retrospectively for patients from the CARRA registry (where comparator patients were initially recruited faster than TCZ patients), and prospectively for all patients enrolled into the study from all participating registries.

Data handling conventions for patients who switch, discontinue, or interrupt treatment with the TCZ (IV or SC) or a non-TCZ comparator are described in the Statistical Analysis Plan.

5.6 PRIMARY OUTCOME MEASURES

The outcome measures for the study are as follows.

- Rate of serious adverse events
- Rates of adverse events in the following categories of special interest:
  - Serious infections
  - Serious cardiovascular events
  - Serious and non-serious malignancies
  - Serious gastrointestinal perforations
  - Serious and non-serious uveitis events
- Rate and treatment outcome of uveitis
- Growth patterns (relative to age-specific standards for height and weight)
- Development patterns (via self-reported or examined Tanner staging)
- JADAS-10

Further details on the data collection, data analysis, and reporting can be found in the Statistical Analysis Plan.

5.7 ADVERSE EVENT REPORTING

The study utilizes secondary data collection, therefore there is no requirement to collect or report Individual Case Safety Reports. However, safety reporting responsibilities will be documented in agreements with the feeder registries.

Roche has confirmed that the feeder registries will report the following adverse events:

- Infections [serious], cardiovascular events [serious], malignancies [serious and non-serious], gastrointestinal perforations [serious], and uveitis events [serious and non-serious])

5.8 DATA COLLECTION AND MANAGEMENT

The observation period for this study is defined as a maximum of 5 years for all patients.

All data included in this study will be obtained from active feeder registries. Patient data will be collected by the feeder registries via paper or electronic Case Report Forms. The data collection for this study is suggested to start at baseline and continue every 6 months thereafter or according to local practice and upon completion of the study or upon early termination from the feeder registry. Data collection may be supplemented by extracting data recorded prior to baseline and between patient visits, according to feeder registry practices.

The feeder registries will be responsible for management of the data they collect, including quality checking of the individual data points. Accurate and reliable data

collection will be ensured by each feeder registry's standard processes for data collection and verification.

Aggregate data reports will be transferred to Roche at annual intervals by the feeder registries, and some patient-level data will be transferred at the 5-year time point, as specified in the Statistical Analysis Plan.

5.9 MONITORING OF FEEDER REGISTRY PROCESSES

Roche will monitor the processes at the feeder registries on a periodic basis to ensure the collection and reporting of data to Roche meets international standards for data quality and patient safety.

5.10 FEEDER REGISTRY REPLACEMENT

Roche has the right to replace a feeder registry at any time. Reasons for replacing a feeder registry and respective sites may include, but are not limited to, the following:

- Excessively slow recruitment
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiological Practices (GPPs) or any other pertinent local laws or guidelines

5.11 STUDY SIZE

Aggregate and some patient-level data will be collected from a sample size of *approximately 300* patients with pJIA receiving TCZ (IV or SC), and another *approximately 300* patients with pJIA receiving a comparator biologic. Patients receiving TCZ (IV or SC) or a comparator biologic will be enrolled in the feeder registries and followed for 5 years to allow for detection of serious adverse events (and events of special interest) over long-term observation and to enable observation of efficacy, growth and development patterns over this extended period of time.

Based on data snapshots for the CARRA (15 July 2019) and BiKeR (3 June 2019) registries, it is estimated that approximately 30% of the patients will discontinue TCZ (IV or SC) in their first year of treatment, with approximately 15% of the remaining patients discontinuing TCZ (IV or SC) treatment in each subsequent year, and with 2% of patients per year lost to follow up. These revised assumptions, along with an enrollment of approximately 300 patients treated with TCZ (IV or SC), provides a revised estimate of 99 patients treated with TCZ (33%) with data for 5 years of TCZ (IV or SC) therapy, and 270 patients treated with TCZ (90%) with 5 years of follow-up in the study (either on or off TCZ). Hence, the total number of patients with 5 years of follow-up will be higher than previously predicted (270 vs. 237 patients); however, a lower number of patients will have been exposed to TCZ for over 1 year (206 vs. 324 patients). The reduced number of patients exposed to TCZ (IV or SC) is due mainly to a higher rate of TCZ withdrawal than previously expected.

With approximately 300 TCZ-treated (IV or SC) patients enrolled, the estimate of total exposure in patient years for the TCZ arm is predicted to be 840 patient years exposure to TCZ, with a total exposure of 1425 patient years, assuming patients contribute half a year of exposure on average in the year they are lost to follow-up/discontinue TCZ (IV or SC) treatment. This compares favorably to the figures stated in the previous versions of the protocol (where a sample size of 400 patients in the TCZ group *would* result in *approximately* 240 patients at the end of 5 years, and up to approximately 1200 patient years in total for the study).

For the evaluation of growth *and development, previous versions of the protocol expected to* include approximately 240 patients *treated with* TCZ *(IV or SC)* aged ≤11 years, *with approximately* 100 of these patients expected to complete the 5-year study, allowing for assessment of long-term growth patterns through adulthood. *In the CARRA and BiKeR data snapshots, 114 (50%) of the 230 patients treated with TCZ enrolled to date were <11 years. Therefore, it is now predicted that approximately 150 patients will be <11 years. With 90% of these patients completing the 5-year follow-up, this would provide approximately 135 patients for the long-term evaluation of growth and development. This compares favorably to the previously estimated figure of 100 patients.*

In order to evaluate of the effectiveness of the 10 mg/kg IV TCZ Q4W regimen for patients *who weigh <*30 kg, *the study was originally expected to* include approximately 150 patients in the TCZ group *weighing <*30 kg. However, as a consequence of the subsequent approval of TCZ SC for the treatment of pJIA in the European Union and United States in 2018, the number of patients on TCZ IV was expected to be reduced by 30% to 50%. *Consequently, the expected number of patients on the 10 mg/kg IV TCZ Q4W regimen was expected to be reduced from 150 patients to 50–75 patients. Based on the CARRA and BiKeR data snapshots, of the 230 patients enrolled, 45 patients (20%) weighed <30 kg at enrollment, and 40 of these 45 patients (89%) were on the 10 mg/kg IV Q4W regimen. Therefore, of the next 70 patients enrolled (to give 300 in total in the TCZ group as expected under the current version of the protocol), approximately 14 patients (20%) are expected to weigh <30 kg. Based on the snapshot data, the majority of these patients are expected to be on IV rather than SC, providing at least 50 of 300 patients treated with TCZ on the 10 mg/kg IV Q4W regimen with this protocol amendment. Although this is lower than initially predicted with the original protocol, it is considered adequate, given the longer-term efficacy reported for Study WA19977 (CHERISH), which showed that in general, patients weighing <30 kg on the 10 mg/kg IV Q4W regimen had a trend toward better efficacy responses through the end of the study at Week 104 than those on the 8 mg/kg IV Q4W regimen, including JIA ACR 30/50/70/90, JADAS-71, inactive disease, and clinical remission (WA19977 Week 104 Clinical Study Report; available upon request).*

5.12 ANALYSIS OF OUTCOME MEASURES

Descriptive summary analyses will be used to characterize baseline demographics (which may include, but are not limited to, family income, geographic region, sex, race, ethnicity, and age), medical history (which may include, but is not limited to, comorbidities, disease phenotype, previous biologic treatment, disease activity, severity, and duration), medications (which may include, but are not limited to, methotrexate, corticosteroids, and growth hormone), growth (height and weight), development (self-reported or examined Tanner staging).

Incidence rates, with 95% confidence intervals, will be provided for serious adverse events. In addition, the number of serious adverse events and percentage of patients with at least one event will be summarized by Medical Dictionary for Regulatory Affairs System Organ Class and Preferred Term. Rates of all serious adverse events and rates of adverse events in predefined categories of special interest (infections [serious], cardiovascular events [serious], malignancies [serious and non-serious], gastrointestinal perforations [serious], and uveitis events [serious and non-serious]) will be calculated on the basis of the drug exposure period for both the TCZ group and the comparator group (i.e., patients receiving a comparator biologic). Rates of selected events that could be potentially associated with prior drug exposure (including cardiovascular events and malignancies) will also be calculated for both the TCZ group and the comparator group; events occurring any time during follow-up (including the period after treatment discontinuation) would be included in incidence rate calculations. Incidence rates of serious adverse events and 95% confidence intervals will be presented for the TCZ group and the comparator group at 5 years.

The height standard deviation scores will be summarized descriptively over time by treatment group. The data for development patterns will be summarized by gender for each treatment group. The rate of uveitis and description of treatment outcome will be summarized. JADAS-10 will be summarized over time. The Statistical Analysis Plan outlines which analyses will be performed for all patients enrolled in the study, the TCZ group, the comparator group, the subgroups of patients with a baseline body weight of <30 kg or ≥ 30 kg, and the subgroups of RF-positive and RF-negative patients. JADAS-10 will also be summarized for patients in the TCZ group with a baseline bodyweight of <30 kg.

Patients who switch therapy or discontinue therapy during the observation period will continue to be followed to allow for long-term safety assessment of serious adverse events and adverse events in predefined categories of special interest (infections [serious], cardiovascular events [serious], malignancies [serious and non-serious], gastrointestinal perforations [serious], and uveitis events [serious and non-serious]). These data will be included in the calculation of incidence rates of events associated with prior treatment exposure. After all patients have completed up to 5 years of treatment, data from the TCZ group will be presented with data from the comparator group.

Annual reports based on summary reports provided by each individual feeder registry will be produced. A 5-year report of the overall summary data combining data from the feeder registries will also be produced. No formal hypothesis tests will be conducted.

A model-based approach using combined individual patient data from all registries adjusting for confounders will be applied to estimate the risk of adverse events for selected events.

Full details of planned statistical summaries will be specified in a separate Statistical Analysis Plan.

5.13 LIMITATIONS OF THE RESEARCH METHOD

Because patients are not randomized to treatment, patients in the TCZ group and patients in the comparator group may differ with regard to baseline characteristics. Data on treatment outcome for uveitis and self-reported or examined Tanner staging may not be available for all patients. Comparison of the safety and efficacy between the two groups may be subject to bias. The long duration of study follow-up may result in a sizable loss of study participants, which could result in under-reporting of safety events. To minimize loss of study participants, the feeder registries will be advised to instruct their sites to encourage all patients, including those who discontinue TCZ or the comparator biologic or switch to other therapies during the study, to remain in the feeder registry to maximize data collection.

6. PROTECTION OF HUMAN SUBJECTS

6.1 COMPLIANCE WITH LAWS AND REGULATIONS

The feeder registries will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted (see European Union guideline on Good Pharmacovigilance Practices).

The feeder registries will comply with national, international, and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

6.2 CONFIDENTIALITY

Roche will receive aggregate and some patient data from each feeder registry. Only anonymized patient data will be transmitted.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study may be published or presented at scientific meetings. If this is foreseen, the feeder registries and feeder registry investigators agree to submit all

manuscripts or abstracts to Roche prior to submission. This allows Roche to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the feeder registry investigators.

Roche will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the feeder registry investigator and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from the study will become and remain the exclusive and unburdened property of Roche, except when agreed otherwise.

8. REFERENCES

Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.

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)	See table below

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): (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
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
Ant biotic 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: .....

Roche

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 5

PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

ANNEX 5: PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

Not applicable for this EU RMP.

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.

ANNEX 7:

OTHER SUPPORTING DATA

(INCLUDING REFERENCED MATERIAL)

ANNEX 7: OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

Literature References

Literature cited as a new reference within RMP version 27.0 includes the following:

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 Final report. N Engl J Med 2020;383:1813-26.

Center for Disease Prevention and Control (CDC). Groups at Higher Risk for Severe Illness. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html. Accessed on 1 March 2021.CDC 2021a

Centre for Disease Prevention and Control. COVID-19 Treatment Guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/. Accessed on 22 February 2021.CDC 2021b

COVID-NET. Weekly Summary of Covid-19 related hospitalization. Available from: https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html. Accessed on 28 February 2021.

EMA Webpage 2020. https://www.ema.europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation

European Centre for Disease Prevention and Control (ECDC). Coronavirus disease 2019 (COVID-19) Surveillance Report. Available from: https://covid19-surveillance-report.ecdc.europa.eu/ Accessed on 27 June 2021. ECDC 2021

Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021; 384:693-704.

Lilly and Incyte Press Release 2021. https://investor.lilly.com/news-releases/news-release-details/lilly-and-incyte-announce-results-phase-3-cov-barrier-study

NIH Press Release 2021. https://www.nih.gov/news-events/news-releases/nih-closes-enrollment-trial-comparing-covid-19-treatment-regimens

Oualha M, Bendavid M, Berteloot L, et al. Severe and fatal forms of COVID-19 in children. Arch Pediatr. 2020;27(5):235–8.

RECOVERY Collaborative Group, Horby P, Pessoa-Amorim G, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021 May 1;397(10285):1637-1645.

WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data Available from: https://covid19.who.int/. Accessed on 19 May 2021. WHO 2020a.

WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021;384(6):497-511.

Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239–42.

Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. ChinaXiv preprint [resource on the Internet]. 2020 [updated 5 March 2020; cited 17 March 2020]. Available from: http://www.chinaxiv.org/abs/202003.00026.

ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

ANNEX 8: SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval date[1] Procedure	Change
27.1	Current submission	• Part II: Module SVII and Module SVIII were updated to note that 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. The important identified risk “severe hypersensitivity reactions” has been removed from the list of safety concerns. • Parts III and V were updated to reflect the changes in the list of safety concerns. • Annex 2 was updated to reflect the removal from the list of safety concerns of the important identified risk “severe hypersensitivity reactions”. • Annex 3 was updated to remove the protocols for the studies WA22490 (ARTIS) and WA28029 (ARTHUR), post-approval commitments removed from the RMP within previous RMP update procedures. The study WA29358 protocol version 5.0 was replaced with version 6.0. • Annex 4 was updated to remove the guided questionnaire associated with the risk “severe hypersensitivity reactions”. • Annex 6 was updated to remove wording related to the risk of severe hypersensitivity reactions from both the physician information pack and the patient information pack.

[1] CHMP Opinion for the RMP

Version	Approval date[1] Procedure	Change
27.0	-	• Part I: Product Overview updated to reflect proposed indication and dosage in COVID-19. • Part II: • Module SI updated to reflect pertinent epidemiological literature on COVID-19. • Part II: Module SIII updated to include exposure in COVID-19 patients from the WA42380 (COVACTA), ML42528 (EMPACTA) and WA42511 (REMDACTA) trials. • Part II: Module SIV updated to include key exclusion criteria from WA42380, ML42528 and WA42511. • Part II: Module SV updated to include latest post-authorization experience. • Part II: Module SVI updated to note that all risks related to COVID-19 are considered potential. • Part II: Module SVII updated with investigator-reported adverse event terms from Studies WA42380, ML42528, and WA42511 that met the search terms specified for each safety concern in the COVID-19 patient population. • Part II: Module SVIII updated to note that all the risks related to COVID-19 are all considered potential, and milestone dates updated. • Parts III and V: Pharmacovigilance activities related to ZUMA-8 included in previous RMP in error. These activities now removed. • Annex 2 – Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme updated with milestones for WA29358. • Annex 7 - Other Supporting DATA (Including Referenced Material) updated to include new references.

Version	Approval date[1] Procedure	Change
26.0	23 July 2020 EMEA/H/C/000955/II/0097	• Updated study status from 'Ongoing' to 'Completed' for PASS Category 3 studies WA28029 (ARTHUR) and WA22480 (ARTIS) in the following Sections: o Section III.2 – Additional PV activities; o Section III.3 – Summary Table of Additional Pharmacovigilance Activities; o Section V.3 – Summary of Risk Minimization Measures o Annex 2 – Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme. • Inclusion of key results from studies WA28029 (ARTHUR) and WA22480 (ARTIS) in Section III.2 – Additional PV activities. • Post-marketing exposure in the RMP was updated to align with information presented in the 2019 RoActemra PSUR/PBRER (Report No. 1093173; reporting interval 11 April 2018 to 10 April 2019).
25.4	10 January 2020 EMEA/H/C/000955/II/0092	• The RoActemra EU RMP Version 25.4 was updated to consolidate the approved EU RMP versions 25.3 and 25.2, which were reviewed by EMA in separate, parallel procedures.

25.2	17 Oct 2019 EMEA/H/C/000955/II/0086	• Conclusion on the completed post-marketing commitment PAM MEA-045, evaluating hypersensitivity (or anaphylaxis) in patients who switched between TCZ IV and SC routes of administration, thus mandating the removal of study BSRBR from Part III.2 Additional Pharmacovigilance Activities section, since the MAH are no longer participating in the BSRBR registry. Furthermore, the removal of BSRBR from Annex 2 ongoing studies and moving it to completed studies. • Removal of OTIS registry from additional pharmacovigilance (PV) activities – 'effects during pregnancy' has been removed from missing information in EU RMP Version 24.1. Version 24.1 included a reclassification of safety concerns in line with the updated definition of safety concerns introduced in GVP Module V Revision 2. As a result of this reclassification 'effects during pregnancy' was removed from missing information. This, therefore, no longer mandates the requirement of the inclusion of the OTIS registry in the RMP. • Inclusion of information from the ZUMA-8 (KTE-X19-108) study, on the collection of additional safety data on the use of RoActemra in the treatment of cytokine release syndrome (CRS) post treatment, with chimeric antigen receptor (CAR) T therapies, with respect to the agreement the MAH has made with EMA. • Administrative changes, including: – updates to product overview, made in line with updates to the reference safety information; – addition of updated protocol for ML28664 (RABBIT) in Annex 3; – updates and corrections to the pharmacovigilance plan including the removal of guided questionnaire (GQ) for neutropenia since neutropenia data is captured in the GQ for the risk of serious infections, and removal of US Claims database from additional pharmacovigilance activity as the threshold to use US Claims data has never been met for identified or potential risks and thus proposing its removal; – administrative updates made to additional pharmacovigilance activities in Part III.2 – correction made to additional risk minimization activities for important identified risks of thrombocytopenia and potential risk of bleeding and to liver enzyme and bilirubin elevations and potential risk of hepatotoxicity, – correction to an error made to the rate of serious hypersensitivity reactions – correction made to additional PV activities with respect to study WA29358. During the EU RMP update from v23 to v24.1, study WA29358 was added erroneously as an additional PV activity to some of the safety concerns, such that WA29358 does not address those safety concerns. Therefore, WA29358 has been removed as an additional PV activity from the following safety concerns: 'Serious Hypersensitivity Reactions', 'Neutropenia', 'Liver Enzyme and Bilirubin Elevations and Potential Risk of Hepatotoxicity', 'Thrombocytopenia and the risk of potential bleeding' and 'Demyelinating Disorders'.

Version	Approval date[1] Procedure	Change
25.3	01 Oct 2019 EMEA/H/C/000955/IB/0090	• The LPLV and Final CSR dates for Study WA28029 are updated in Section III.2 – Additional Pharmacovigilance Activities; in Section III.3 – Summary Table of Additional Pharmacovigilance Activities; and in Annex 2 – Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme
25.1	23 Aug 2019 EMEA/H/C/000955/IB/0088/G	• Upgraded the risk of hepatotoxicity from an important potential risk to an important identified risk along with the characterization of risk, related risk minimization activities and educational materials (Patient/Healthcare provide brochure, PAC, DHPC) Administrative changes, including: Annex 2: removal of duplication of text 'complication of diverticulitis (including GI perforation); Annex 3: update to EMA approved protocol versioning of study WA29358
24.1	EMEA/H/C/000955/II/0076	Consolidation of sJIA specific information from RMP 24.0 with the Autoinjector and pJIA specific information from RMP 22.0 and 23.1 respectively. Introduction of lower body weight limit for patients with sJIA between 1 and 2 years of age when receiving subcutaneous administration of RoActemra Update to the Post-Marketing exposure consistent with the current PBRER Update to Part V.2 - 'Plans for evaluating the effectiveness of the interventions and criteria for success' in line with the EMEA/H/C/PSUSA/00002980/201704 procedure Inclusion of CRS indication to the Product Profile and epidemiology section (in partial response to the Comment 27 of the sJIA Assessment Report) Update to Annex 3 and Annex 6.
24.0		Updated data in support of the proposed indication of use of tocilizumab (TCZ) in the subcutaneous treatment of systemic juvenile idiopathic arthritis (sJIA) in patients aged 1-17 years. Transition of RMP contents to the revised GVP Module V (R2) template. Reclassification of all safety concerns in alignment with the current guidance in the GVP Module V (R2) regulation. Updates to the ongoing studies in the Pharmacovigilance Plan. Updates to the Characterization of risks frequencies (95% CI) and format change to ensure consistency in data presentation across all indications. Educational material updates, specific to the sJIA (SC) indication. Updates to Annex 2, 3, 6, 7 and 8 respectively.
23.1		This version was consolidated with the approved RMP version 21.1 for GCA, in response to PRAC feedback on RMP version 23.0 for pJIA (sc).

Version	Approval date[1] Procedure	Change
23.0	CHMP Opinion: Feb 23, 2018 EMEA/H/C/000 955/II/0072	The RMP was updated to support pJIA indication in the SC route of administration. Results from Study WA28117 are summarized in Part II (SVII.2) to support the proposed SC indication. Additionally, Study results for Study WA25204 (ENTRACTE) were summarized. Annex 4 accordingly updated. Updates from the SmPC were included in the relevant sections of this RMP (Proposed Annex 2 is appended). Educational Materials were updated to include information regarding indication of use in the pJIA patient population (Annex 11). Post-authorization exposure information was updated (Updated Annex 3 appended). Clinical exposure for subcutaneous use was updated to include exposure in pJIA patients Risk frequencies were accordingly updated to include information from SC pJIA use Updates made to milestones for post authorization pharmacovigilance studies. Annex 5 updated to include ongoing Study WA29358.
22.0	CHMP Opinion: Feb 23, 2018 EMEA/H/C/000 955/II/0074/G	The RMP was updated to support the Autoinjector Filing. Study results for Study WA30003 and WA29917 were summarized. Non-clinical section for SC formulation was updated to include statement on PK study comparing PFS and AI. Section on Potential for Medication Errors was updated with relevant information when using ACTpen. Updates from the SmPC were included in the relevant sections of this RMP. Educational Materials were updated to include information regarding the autoinjector device
21.2		No changes made to the RMP information, except to Annex 11with updated Educational materials This version was prepared to provide EMA in the closing-sequence of the GCA Variation, after receipt of the EC Decision of approval for the GCA indication.
21.1	CHMP Opinion: Jul 21, 2017 EC Decision:	Proposed posology was updated. Proposed indication was added to section SIII.1, updates made to the incidence of adverse events related to lipid parameters, information related to CYP450 metabolism added. No new safety concerns added. Version prepared to include updates made to the label (SPC) in response to questionnaire from the Regulatory Agency for the initial filing for the proposed indication for Giant Cell Arteritis.

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21.0	Sept 20, 2017 Procedure: II066	The RMP is updated to support the GCA Filing. Results of study WA28119 are summarized. Exposure to patients in this trial (WA28119) is also updated and the relative risk frequencies are updated in the individual risk tables. Epidemiology for the indication of GCA is included. Updates from the current SmPC (related to GCA information) incorporated in relevant sections of this RMP. Additionally the information for breast-feeding and fertility from SmPC were also included in the RMP Updated SmPC is provided in Annex 2 Annex 4 for ongoing and clinical trial programme is updated to reflect the current status of each of the trials. No new trials were added to this Annex. Annex 11 is updated to provide updated Educational Materials that include information related to GCA. No new safety concerns added. Version prepared to support the proposed indication for Giant Cell Arteritis
20.0		Collation of approved v18.1 and 19.0 of the RoActemra/Actemra/TCZ EU RMP. PRAC feedback for v19.0 of the RoActemra/Actemra/TCZ EU RMP and PRAC endorsement for removal of potential risk of 'neutropenia and the potential risk of infections' is incorporated to this version. Additionally, the missing information for IgE data following TCZ SC treatment is removed from this RMP based on the results of the NA25220 (Brevacta) and WA22762 (Summacta) CSRs. No new safety concerns added. Important potential risk of 'neutorpeina and the potential for infection' has been removed. The missing information for IgE data following TCZ SC treatment has been removed.
19.0		The RMP is updated to summarize results of the WA29049 study No new safety concerns
18.1		PRAC feedback for v18.0 of the RoActemra/Actemra/TCZ EU RMP incorporated to this version No new safety concerns
18.0		The RMP was updated for the Early RA SC filing. Safety comparision between SUMMACTA and FUNCTION studies. The Roche current template was used for this version. Information on off-label use was added; exposure tables for SC use were updated; Additional PV activities to assess effectiveness of risk minimization measures were added. No new safety concerns
17.0		Regulatory request to combine all approved versions (16.3-16.6) No new safety concerns

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16.7		TENDER update prepared in Response to assessment fromPRAC (initial RMP version was 16.4 but by the time we received the preliminary report for further information 16.5, 16.6 had been prepared) No new safety concerns
16.6		Module SIII: Clinical trial exposure, Module SVII: Identified and potential risks Non-ATMP version, Part III: Pharmacovigilance Plan, Part IV: Plans for post-authorisation efficacy studies – sections Pharmacovigilance plan Plans for post-authorisation efficacy studies IV.1 Applicability of efficacy to all patients in the target population No new safety concerns
16.5		Module SIII: Clinical trial exposure, Module SVII: Identified and potential risks Non-ATMP version, Part III: Pharmacovigilance Plan, Part IV: Plans for post-authorisation efficacy studies – sections Pharmacovigilance plan Plans for post-authorisation efficacy studies IV.1 Applicability of efficacy to all patients in the target population No new safety concerns
16.4		TENDER (WA18221) study update with week 104 and 260 data. Module SIII: Clinical trial exposure, Module SIV: Populations not studied in clinical trials Modle SVI: Additional EU requirements for the safety specification Module SVII: Identified and potential risks Non-ATMP version, Module SVIII: Summary of the safety concerns Part III: Pharmacovigilance Plan Module V : Risk Minimization Measures Module VI: Summary of RMP Annex 4 No new safety concerns

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16.3		Function study update and also RMP versión 14.6 : Module SIII: Clinical trial exposure, Module SVII: Identified and potential risks Non-ATMP version, Part III: Pharmacovigilance Plan, Part IV: Plans for post-authorisation efficacy studies – sections updated with conclusions of the final SUMMACTA (WA22762) CSR. Part II: Module SIV: Populations not studied in Clinical trials – minor update for PIP5 modification. Part II: Module SVI: Additional EU requirements for the safety specification – updates to preventing medication error by visually impaired patients and accidental ingestion by children. Table of Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan updated for completed studies. No new safety concerns
16.2	No new safety concerns.	Update for NA25220 (BREVACTA) final CSR. No new safety concerns
16.1	No new safety concerns	Administrative and typographical updates to align RMP with version 14.4 and 15.1 No new safety concerns
16.0	.	Collation of EU RMP versions 14.4 and 15.1 at the request of the PRAC Paediatric and Elderly missing information removed by MAH. Collation of EU RMP versions 14.4 and 15.1. No new safety concerns were added Educational materials updated. Paediatric patients and Elderly patients removed from missing information category
15.1		At the request of the PRAC Neutropenia added as identified risk. Revision of tables/sections for the potential risk of skeletal development in paediatrics Phenprocoumon added in addition to warfarin for sections on CYP450 drug-drug interactions Deletion to references of the now disbanded Pharmacoepidemiology Board Addition of studies WA19926, WA22762, NA25220 to the Table of On-Going and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan Addition of protocols NP22775, WA29049, WA19926, WA22762, NA25220 to Annex 6
15.0		Version 15.0 was transferred to the new EU RMP format and updated to support an indication extension for use in patients with early rheumatoid arthritis No new safety concerns were added

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14.4		References to the autoinjector removed from Part I (Product Overview) and Part II (SI, SVI). Revised Educational Materials to remove references to the autoinjector (RA dose administration guide, HCP Brochure and Patient Brochure) added to Annex 11. Annex 2 updated with revised SmPC.
14.3		References to safety concerns previously classified as “Important Missing Information” were updated to refer to the class as “Missing Information.”
14.2		Rapporteur requests for correction of errors in wording were addressed. In response to rapporteur comments, the safety concern of Neutropenia was categorized as an Important Identified Risk rather than an Important Potential Risk. Wording was added to reflect data on IgE antibodies under the existing Important Potential Risk of Immunogenicity. Safety concerns regarding patients whose treatment route for TCZ changed were combined into a single entry under Important Missing Information.
14.1		Version 14.0 was updated to the new EU RMP format. Content was changed throughout to reflect updates to non-submission-specific sections such as Modules SII, SIII, and SVII. In response to rapporteur comments, the following safety concerns were added as items of Important Missing Information: Safety in patients <60 kg in switcher population New PV actions were added for the important potential risk of skeletal development in children
14.0		Additions associated with the proposed use of the SC formulation in the EU including: Additions to Section 1.1 Additions to Section 1.2, Section 1.3, Section 1.4, and Section 1.5 to include results from SC studies WA22762 and NA25220 Additions to Section 3, Section 4, and Section 5 Updates to IV all exposure population using a cutoff date of 02 May 2012 Updates to epidemiology sections (Section 1.7) for GI perforations, Infections, and Malignancies Updates to studies from Pharmacovigilance Plan in Section 2.
13.2		Update of paediatric registry information and WA19977 (pJIA) milestone date to Table 76 Outstanding Actions to be Completed, Including Milestones. Update of paediatric registry information to Table 92 Summary of the EU Risk Management Plan.
13.1		Addition of age distribution and disease type summary table (Table 9) for WA19977 and text to Section 1.2.1.5. Addition of pJIA, sJIA, RA safety comparison to Section 1.5.7 and addition of AE Table 22 Update of Adverse Events of Special Interest from Study WA19977 (infections and infestations rates by dosing group for WA1997; infusion-related reactions; immunogenicity; thrombocytopenia) in Section 1.5.8.

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		Update to studies WA18221 (sJIA) and WA19977 (pJIA) to Section 1.5.11 (Details of Important Identified and Potential Risks).
13.0		Update to brief description of product for pJIA Updates to Section 1.2, Section 1.2.1.5, Section 1.2.1.6, Section 1.3, Section 1.5, Section 1.5.1.2, Section 1.5.2, Section 1.5.5, Section 1.5.6, Section 1.5.7, Section 1.5.11.6, Table 84, Table 87, Table 88, Table 90, Table 91, Table 92 Table 95, Section 3.2, Table 96, Table 98, Table 99 for pJIA and pediatric studies. Updates to Section 1.4.1, Section 1.4.2, Section 1.4.3, Section 1.5.11.2, Section 1.5.11.3, Section 1.5.11.7, Section 1.3, Section 1.4, Section 1.5.1.2, Section 1.5.2, Section 1.5.5, and Section 1.5.6 Updates to the epidemiology sections: Section 1.7.7, Section 1.7.8, and Section 1.7.9 for pJIA. Update to Registry Section 2.3.4.4 Table 77
12.2		Addition of epidemiology data for congestive heart failure (section 1.7.2, Table 29, and Table 43). Addition of warning for false negative TB testing from SPC and PIL to Table 84, Table 96, and Table 99.
12.1		Addition of proposed SPC (section 4.4 and 4.8) text for interstitial lung disease to the following tables; Table 84, Table 96, Table 99.
12.0		Administrative update of RMP to incorporate changes from Versions 8.0, 9.0, 10.0 and 11.0.
11.0		Update of ADR table and text to reflect updates to the SPC Update of Japanese Postmarketing Surveillance data Addition of interstitial lung disease to Section 1.7.2 (Important Co-morbidities in the RA Population) Inclusion of an updated Guided Questionnaire for Serious Infections
10.0		Addition of pediatric data to support sJIA filing including: • New text in section 1.1.2 • New sections 1.7.4 to 8 on sJIA Incidence, Prevalence, Mortality and Demographic Profile • New protocols for patient registry studies appended in Annex 5. • Updated in response to questions received from EMEA regarding the sJIA filing (February 2011). Addition of pediatric data to support sJIA filing including: Summary of ADRs occurring in Paediatric patients with sJIA receiving tocilizumab treatment in Study WA18221 added. New tables (26 to 30) detailing risks associated with the proposed use of tocilizumab in paediatric patients with sJIA. New text regarding MAS presented in Annex 8 , Educational Material.
9.0:		Update of ADR table, plus update regarding SPC text on serious infections, hypercholesterolaemia and elevated bilirubin. Update of information on anaphylaxis and serious hypersensitivity reactions
8.0		Addition of minor updates on Japanese postmarketing data, long-term data for serious infections, myocardial infarctions, strokes, GI perforation, hepatic

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		events and malignancies, plus addition of incidences for adverse drug reactions
7.0		Update of ADR table. Addition of information on dose cap (maximum of 800 mg per infusion) for patients whose body weight is > 100 kg Minor correction on rates of neutropenia in clinical trials. Addition of information on study to elucidate the mechanism of reduction in neutrophil counts (ML25243). Removal of pharmacovigilance action plan for patients with a body mass index (BMI) of ≤18.5 kg/m2
6.0		Addition of data from preclinical fertility and milk excretion studies Updates to clinical trial information using a cut-off date of 6 February 2009 and two analysis populations: All Control and All Exposure. Update of ADR table: Addition of warning regarding viral reactivation. Hyperbilirubinemia and planned pharmacogenomic evaluation.