GEDEON RICHTER PLC.

RISK MANAGEMENT PLAN

FOR

Tuyory (tocilizumab)

20 mg/mL concentrate for solution for infusion;
162 mg solution for injection in pre-filled syringe;
162 mg solution for injection in pre-filled pen

EU Risk Management Plan for Tuyory (tocilizumab)

RMP version to be assessed as part of this application:

RMP Version number	0.2
Data lock point for this RMP:	30 July 2025
Rationale for submitting an updated RMP	RMP is updated with changes requested in the D120 List of Questions and 52 weeks safety data from the final CSR of RGB19101 clinical trial.
Summary of significant changes in this RMP	Clinical trial exposure has been updated in Part II Module III with 52 weeks data from the final CSR of RGB19101. Part SVII has been updated with 52 weeks data from RGB19101 related to each safety concern (Adverse Events of Special Interest). The naming of the educational tools has been changed according to GVP XVI Rev 3 (EMA/204715/2012; effective date, 06 August 2024). Risk factors and risk groups for thrombocytopenia and elevated lipid levels have been revised according to the request in Question 102 of the D120 List of Questions. Targeted Follow-up Questionnaire Forms have been amended according to the request in Question 103 of the D120 List of Questions, typing errors have been corrected.
QPPV name	**Attila Oláh MD**
[redacted]	[redacted]
[redacted]	[redacted]

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	tocilizumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, Interleukin inhibitors; L04AC07
Marketing Authorisation Applicant	Gedeon Richter Plc.
Medicinal products to which this RMP refers	#1
Invented name(s) in the European Economic Area (EEA)	Tuyory
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody of the immunoglobulin $G1_k$ subclass
	Summary of mode of action Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.
	Important information about its composition Tocilizumab is a humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.
Hyperlink to the Product Information	Please see eCTD Module 1.3.1.
Indication(s) in the EEA	Current: Intravenous (IV) Formulation: Tuyory (tocilizumab) 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 tumour necrosis factor (TNF) antagonists. In these patients, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate. Tuyory 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. Tuyory 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. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. Tuyory in combination with MTX is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tuyory 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) Formulations:</u> Tuyory 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, Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

	Tuyory is indicated for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 1 year of age and older (12 years and older in case of using the pre-filled pen), who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Tuyory can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. Tuyory in combination with MTX is indicated for the treatment of juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older (12 years and older in case of using the pre-filled pen), who have responded inadequately to previous therapy with MTX. Tuyory can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tuyory is indicated for the treatment of Giant Cell Arteritis (GCA) in adult patients.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: <u>Intravenous (IV) Formulation:</u> RA: The recommended posology is 8 mg/kg body weight, given once every four weeks. For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended. 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 Tuyory 8 mg/kg may be administered. There should be an interval of at least 8 hours between these two infusions. sJIA: 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: 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 (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. Tuyory 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 Tuyory 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. <u>Subcutaneous (SC) Formulations:</u> RA: The recommended posology is subcutaneous 162 mg once every week. 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 Tuyory subcutaneously. 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. GCA: The recommended posology is subcutaneous 162 mg once every week in combination with a tapering course of glucocorticoids. Tuyory can be used alone following discontinuation of glucocorticoids. Tuyory 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. Method of administration: After proper training in injection technique, patients may self-inject with tocilizumab if their physician determines that it is appropriate. The total content (0.9 mL) of the pre-filled syringe should be administered as a subcutaneous injection.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: <u>Intravenous formulation:</u> Concentrate for solution for infusion; 20 mg/mL Tuyory IV is available in 4 mL, 10 mL, and 20 mL vials, containing 80 mg, 200 mg, and 400 mg of tocilizumab, respectively.

	Subcutaneous formulation: Solution for injection in pre-filled syringe; 162 mg Solution for injection in pre-filled pen; 162 mg
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

According to the Guideline on good pharmacovigilance practices (GVP) Module V (EMA/838713/2011 Rev 2) this part of the RMP could be omitted.

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

In line with the current regulatory guiding principles of both EMA (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues- EMEA/CHMP/BMWP/42832/2005 Rev1 and Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues- EMA/CHMP/BMWP/403543/2010) and following the EMA and MHRA regulatory interactions (EMA 2017, MHRA 2023), comparative *in vivo* pharmacokinetic and toxicological studies of the biosimilar tocilizumab (Tuyory) and its reference product, RoActemra have not been performed.

Part II: Module SIII - Clinical trial exposure

The biosimilar comparability programme contained a Phase I comparative pharmacokinetic/pharmacodynamic cross-over clinical trial conducted in healthy subjects (RGB192101) and a Phase III comparative clinical efficacy and safety trial conducted in subjects with active rheumatoid arthritis (RGB19101), against the reference product RoActemra.

In these completed clinical trials, 290 subjects have been exposed to Tuyory (tocilizumab) (see Table SIII.1). 108 of these subjects were exposed to a single-dose of Tuyory 162 mg solution for injection in pre-filled syringe and 182 subjects were exposed to 20 mg/mL concentrate for solution for infusion.

Table SIII.2, SIII.3 and SIII.4 show cumulative subject exposure by sex, product, age range, by race and by treatment duration.

Table SIII.1 – Cumulative subject exposure from clinical trials

Treatment Study No.	Number of subjects
Tuyory	**290**
RGB192101*	108
RGB19101**	182
EU-RoActemra	**290**
RGB192101*	104
RGB19101**	186

**162 mg solution for injection in pre-filled syringe*
***20 mg/mL concentrate for solution for infusion*

Table SIII.2 - Cumulative subject exposure to Tuyory from completed clinical trials by sex and age group

Study No. Sex Age group	Number of subjects
RGB192101*	**108**
Male	108
20-29 years	62
30-40 years	46
RGB19101**	**182**
Male	41
20-29 years	1
30-39 years	2
40-49 years	6
50-59 years	8
60-69 years	15
≥70 years	9
Female	141
20-29 years	5
30-39 years	10
40-49 years	26
50-59 years	37
60-69 years	41
≥70 years	22
Total	**290**

**162 mg solution for injection in pre-filled syringe*
***20 mg/mL concentrate for solution for infusion*

Table SIII.3 - Cumulative subject exposure to investigational drug from completed trials by race

Race	Number of subjects
White	0
Black	0
Asian	290
Other	0
Total	**290**

Table SIII.4 – Extent of exposure to Tuyory IV drip infusion in clinical trial RGB19101

Characteristics	Tuyory
Number of administrations of IP (times)	
n	182
Mean (SD)	12.2 (2.5)
Median	13.0
Min–Max	1-13
25th percentile	13.0
75th percentile	13.0
Duration of administration of IP (days)[a]	

Characteristics	Tuyory
n	182
Mean (SD)	318.7 (70.4)
Median	337.0
Min–Max	1-344
25th percentile	335.0
75th percentile	337.0
Compliance rate of IP (%)[b]	
n	182
Mean (SD)	98.53 (5.06)
Median	100.00
Min–Max	50.0-100.0
25th percentile	100.00
75th percentile	100.00
n (%) <75	1 (0.5)
n (%) ≥75	181 (99.5)

FAS = full analysis set; IP = investigational product; Max = maximum; Min = minimum; n = number of subjects per category; SD = standard deviation

[a] Date of the last IP administration - Date of the first IP administration + 1.

[b] The number of times IP at the dose based on the protocol (times) / Planned number of administrations (times) × 100

Source: Table 12-1, Section 12.1 of the RGB19101 Clinical Study Report

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

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

Criterion: **Severe allergic or anaphylactic reactions**

Reason for exclusion: To ensure general safety of patients with known severe hypersensitivity to monoclonal antibodies when treated with Tuyory.

Is it to be included as missing information? (Yes/No): No

Rationale: Hypersensitivity is contraindicated in the SmPC.

Criterion: **Active severe infections**

Reason for exclusion: Patients with a history of recurring or chronic infections or with active underlying conditions, may potentially be predisposed to infections when exposed to Tuyory.

Is it to be included as missing information? (Yes/No): No

Rationale: 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.

Criterion: **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.**

Reason for exclusion: To ensure general safety of patients to be treated with Tuyory in the clinical trial setting.

Is it to be included as missing information? (Yes/No): No

Rationale: There is no data to suggest that tocilizumab has an effect on pulmonary, renal, or endocrine function. Active hepatic disease/hepatic impairment, neurological disorders, cardiovascular risk, and complications of diverticulitis are listed as special warnings and precautions in the SmPC.

Criterion: **Uncontrolled disease states, such as asthma or inflammatory bowel disease where flares are commonly treated with oral or parenteral corticosteroids.**

Reason for exclusion: Potential for patients to be unable to adhere to study protocol. Oral steroids had to remain stable and parenteral steroids were prohibited in Tuyory RA clinical trials to enable accurate assessment of Tuyory efficacy.

Is it to be included as missing information? (Yes/No): No

Rationale: This exclusion criterion was not related to the safety of the patient population.

Criterion: **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**

Reason for exclusion: To ensure general safety of patients to be treated with Tuyory in the clinical trial setting.

Is it to be included as missing information? (Yes/No): No

Rationale: Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with tocilizumab in RA patients. Complications of diverticulitis is listed as a special

warning and precaution in the SmPC and is included as an important identified risk in this RMP (refer to Module SVII.3.1).

Criterion: **Current liver disease as determined by the investigator.**

Reason for exclusion: To ensure general safety of patients to be treated with Tuyory in the clinical trial setting.

Is it to be included as missing information? (Yes/No): No

Rationale: Treatment with tocilizumab, 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)

Criterion: **Active TB requiring treatment within the previous 3 years and no evidence of active TB infection at enrollment.**

Reason for exclusion: To ensure general safety of patients to be treated with Tuyory in the clinical trial setting.

Is it to be included as missing information? (Yes/No): No

Rationale: Tuberculosis is listed as a special warning and precaution in the SmPC.

Criterion: **Primary or secondary immunodeficiency (history of or currently active).**

Reason for exclusion: To ensure general safety of patients to be treated with Tuyory in the clinical trial setting.

Is it to be included as missing information? (Yes/No): No

Rationale: These patients may be more prone to infections; infections are listed as a special warning and precaution in the SmPC.

Criterion: **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**

Reason for exclusion: To ensure general safety of patients to be treated with Tuyory in the clinical trial setting.

Is it to be included as missing information? (Yes/No): No

Rationale: 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).

Criterion: **Pregnant women or nursing (breast feeding) mothers.**

Reason for exclusion: To ensure the safety of pregnant women or nursing (breast feeding) mothers.

Is it to be included as missing information? (Yes/No): No

Rationale: Information on the use of tocilizumab in pregnant women or nursing (breast feeding) mothers is provided in the SmPC including guidance on contraceptive use and advice that tocilizumab should not be used during pregnancy unless necessary. Healthcare providers are advised to consider discontinuation of therapy in breastfeeding women, or discontinuation of treatment.

Criterion: **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.**

Reason for exclusion: Potential for patients to be unable to adhere to study protocol or have conditions that would affect efficacy assessments.

Is it to be included as missing information? (Yes/No): No

Rationale: This exclusion criterion was not related to the safety of the patient population.

Criterion: **Patients with lack of peripheral venous access**

Reason for exclusion: Potential for patients to be unable to adhere to study protocol/receive study medication.

Is it to be included as missing information? (Yes/No): No

Rationale: This exclusion criterion was not related to the safety of the patient population.

Criterion: **History of MAS within 3 months prior to the screening visit (Criteria specific to sJIA)**

Reason for exclusion: To ensure general safety of patients to be treated with tocilizumab in the clinical trial setting.

Is it to be included as missing information? (Yes/No): No

Rationale: There is no data to suggest that tocilizumab has any effect on MAS. MAS is listed in the special warnings and precautions for use section in the SmPC.

Criterion: **Active uveitis (absence of uveitis must be documented by a slitlamp ophthalmology examination within 12 weeks prior to baseline; Criteria specific to pJIA)**

Reason for exclusion: To ensure general safety of patients to be treated with tocilizumab in the clinical trial setting.

Is it to be included as missing information? (Yes/No): No

Rationale: There are insufficient data to suggest that tocilizumab has an effect on uveitis.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

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

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

Table SIV.1: Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure	
	Tuyory clinical development programme	**RoActemra clinical development programme (RMP v29.0)**
Pregnant or breastfeeding women	Not included in the Tuyory clinical development programme.	IV formulation: 55 patients SC formulation: 5 patients
Patients with Relevant comorbidities		

Patients with hepatic impairment	Not included in the Tuyory clinical development programme.	IV formulation: 24 patients
Patients with renal impairment	Not included in the Tuyory clinical development programme.	IV formulation: 152 patients
Patients with cardiovascular impairment	Not included in the Tuyory clinical development programme.	IV formulation: 221 patients
Patients with a disease severity different from inclusion criteria in clinical trials	RGB19101 clinical trial included RA patients with moderate to severe disease (DAS28-ESR≥3.2).	The clinical trial program for RoActemra in RA subjects recruited patients with moderate to severe disease.
Subpopulations carrying known and relevant genetic polymorphisms	There is no known association between the use of Tuyory and polymorphisms.	There is no known association between the use of RoActemra and polymorphisms.
Combination with other biologics	Not included in the Tuyory clinical development programme.	The use of tocilizumab (RoActemra) in combination with rituximab in RA patients was investigated in one trial (WX21956). However, the trial was terminated early for reasons unrelated to safety, and the number of patients recruited at the time of study termination was too small to determine the efficacy and safety of the combination therapy.
Other		
Paediatric patients	Not included in the Tuyory clinical development programme.	IV formulation: 311 patients SC formulation: 103 patients
Elderly patients (≥75 years)	IV formulation: Tuyory: 3 patients RoActemra: 1 patient	IV formulation: 286 patients SC formulation: 74 patients

Part II: Module SV - Post-authorisation experience

Not applicable. Tuyory (tocilizumab) is not yet marketed.

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

Potential for Misuse for Illegal Purposes

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

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

Erythropoietins have been associated with illegal use, primarily in athletes, in order to stimulate the bone marrow to increase red blood cell production thereby achieving the performance enhancement associated with training at high altitude. Results from clinical trials with tocilizumab have demonstrated improvement in anaemia of chronic disease, associated with chronic inflammatory conditions, but no increase in healthy volunteers or in patients with normal haemoglobin labels.

Additionally, supraphysiological levels of haemoglobin have not been recorded in patients receiving tocilizumab. Therefore, tocilizumab is not considered to be of use as a performance enhancing drug in this context.

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

Based on the information acquired during the clinical development programme, Tuyory has been demonstrated to be biosimilar, confirming a similar safety and tolerability profile to the reference medicinal product RoActemra (Roche), which has been authorised in the EU since 16 January 2009.

Therefore, the safety concern list for Tuyory is identical with the one included in the European Risk Management Plan of RoActemra (v29.0, date of sign off: 27 November 2023). The following risks are considered important for the inclusion in the safety concern list:

- 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

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

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

Not applicable.

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

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

Important identified risks:

SVII.3.1.1 Serious Infection (MedDRA terms: SOC Infections and Infestation)

This safety concern is considered as an important identified risk for chronic tocilizumab dosing, but is assessed as important potential risk for the indication of COVID-19. For ease of review, all data related to COVID-19 are included below under the Section Information on Important Identified Risks, together with data related to chronic tocilizumab dosing.

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 with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.

Characterisation of the risk

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).

In study RGB192101 (Phase I, healthy volunteers), 15 subjects (13.6%) across the two study arms experienced 17 treatment emergent adverse events (TEAEs) in the SOC of ”Infections and Infestations” (9 subjects [8.3%] after receiving Tuyory, 7 subjects [6.7%] after receiving RoActemra).

In study RGB19101 (Phase III, subjects with active RA), across the two study arms 199 subjects (54.1%) experienced 372 TEAEs in the SOC of “Infections and Infestations” (98 subjects [53.8%] in the Tuyory arm; 101 subjects [54.3%] in the RoActemra arm).

Severity and nature of risk

In the IV RA all exposure population, upper respiratory tract infection was the most commonly reported type of infection, 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.

In study RGB192101 (Phase I, healthy volunteers), 11 of all 17 TEAEs in the SOC “Infections and Infestations” were of mild severity (5 events after receiving Tuyory, 6 events after receiving RoActemra). 6 of the TEAEs were of moderate severity (5 events after receiving Tuyory, 1 event after receiving RoActemra). None of the TEAE were severe.

In study RGB19101 (Phase III, subjects with active RA), across the two study arms 168 of all 372 TEAEs in the SOC “Infections and Infestations” were classified as mild events (80 events in the Tuyory arm, 88 events in the RoActemra arm). 196 of the TEAEs were of moderate severity (106 events in the Tuyory arm, 90 events in the RoActemra arm). 8 of the TEAEs were severe in nature (1 event in the Tuyory arm [PT: Pneumocystis jirovecii pneumonia], 7 events in the RoActemra arm, [PTs: Pneumocystis jirovecii pneumonia, Pneumonia, Bacteraemia, Lung abscess, Infectious pleural effusion and Appendicitis]).

Seriousness

In study RGB192101 (Phase I, healthy volunteers) no Serious Adverse Events (SAEs) occurred in the SOC “Infections and infestations”.

In study RGB19101 (Phase III, subjects with active RA), 11 TEAEs (out of 372) in the SOC “Infections and infestations” were classified as SAEs in 9 subjects (2.4%) across the two study arms. 2 SAE in 2 subject (1.1%) occurred on the Tuyory arm (PT: Pneumocystis jirovecii pneumonia), 9 SAEs in 7 subjects (3.8%) occurred on the RoActemra arm (PTs: Pneumocystis

jirovecii pneumonia, Pneumonia, Bacteraemia, Lung abscess, Infectious pleural effusion, Appendicitis, Pyelonephritis and Biliary tract infection).

Impact on Quality of Life (QoL)

Tocilizumab may reduce resistance to infections; therefore, patients will be monitored for any signs or symptoms of infections. Patients may experience severe infections, which can sometimes be fatal. Vigilance for the timely detection of serious infection is recommended for patients receiving biologic treatments for moderate to severe RA, GCA, pJIA, or sJIA as signs and symptoms of acute inflammation may be lessened, associated with suppression of the acute-phase reaction. The effects of tocilizumab on C-reactive protein, neutrophils, and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Similar monitoring requirements and recommendations for vigilance apply for COVID-19 patients.

Risk factors and risk groups

Patients with diabetes reported a higher rate of serious infections compared to patients without diabetes. Patients treated with tocilizumab and taking background corticosteroids reported a higher rate of serious infections compared to patients not taking background corticosteroids. The rate of serious infections appears to increase with body weight.

Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions (e.g., diverticulitis, diabetes, or ILD which may predispose patients to infections).

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 tocilizumab.
- Exclusion of any possibility of an active infection before initiating therapy in RA, sJIA, pJIA, and CRS (including screening for latent TB). Interruption of tocilizumab if a patient develops a serious infection until the infection resolves in these indications.
- Exclusion of any possibility of any concurrent active serious infection before initiating therapy in COVID-19.
- In the prescribing information, patients with COVID-19 are recommended to contact a healthcare professional immediately should they identify symptoms suggesting infection emergence to assure rapid evaluation and appropriate treatment.

Impact on the benefit-risk balance of the product

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab. Patients may experience severe infection or frequent minor infections. There have been a number of serious infections reported including cellulitis (inflammation of the deep layers of skin), pneumonia, shingles (herpes zoster), sepsis (toxins in the blood or tissues), and reactivation of a viral infection (Epstein-Barr). Tuyory's 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.

SVII.3.1.2 Complications of Diverticulitis (MedDRA terms: GI Perforation Standardised MedDRA Query [SMQ] [narrow]; GI Perforation SMQ [wide])

This safety concern is considered an important identified risk for chronic tocilizumab dosing, but is assessed as important potential risk for the indication of COVID-19. For ease of review, all data related to COVID-19 are included below under the Section Information on Important Identified Risks, together with data related to chronic tocilizumab dosing.

Potential mechanisms

Potential infectious etiology (diverticulitis)

Evidence source(s) and strength of evidence
Adequate and well-controlled clinical trials and their long-term extensions with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.

Characterisation 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 1 patient (0.2%) (Bhayana et al. 2020). Zangrillo et al. (2020) reported a single case of GI perforation in a case series of 73 mechanically ventilated patients with confirmed COVID-19 admitted to the ICU in Milan, Italy (Zangrillo et al. 2020). A retrospective study included 81 adult COVID-19 patients with abdominal computed tomography performed from 1 April 2020 to 1 May 2020 in Brazil. A single case of intestinal perforation was observed on abdominal imaging accounting for the prevalence of 1% (Horvat et al. 2021).

In study RGB192101 (Phase I, healthy volunteers), no subject across the two study arms experienced TEAEs in the "Diverticulitis, Intestinal Perforation" Adverse Event of Special Interest (AESI) category (extraction criteria: Gastrointestinal perforation SMQ, Diverticulum inflammations HLT).

In study RGB19101 (Phase III, subjects with active RA), across the two study arms 1 subject (0.5%) experienced 1 TEAE in the "Diverticulitis, Intestinal Perforation" AESI category (extraction criteria: Gastrointestinal perforation SMQ, Diverticulum inflammations HLT) in the Tuyory arm (PT: Large intestine perforation).

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.

In study RGB19101 (Phase III, subjects with active RA), the 1 TEAE in the "Diverticulitis, Intestinal Perforation" AESI category was severe in nature (PT: Large intestine perforation).

Seriousness/Outcomes

Most events resolved without sequelae (23/33). Two events were fatal.

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

In study RGB19101 (Phase III, subjects with active RA), the 1 TEAE in the "Diverticulitis, Intestinal Perforation" AESI category was serious in nature (PT: Large intestine perforation).

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.

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

Preventability

Prescribing information warning that tocilizumab should be used with caution in patients with a history of intestinal ulceration or diverticulitis. Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, should be evaluated promptly for early identification of GI perforation. Patients to be alerted to seek care in case of symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage, and/or unexplained change in bowel habits with fever.

Impact on the risk-benefit balance of the product:

The rare event of perforation of the large bowel has been seen in subjects who had large bowel infections. Perforations may occur in the absence of clear symptoms or clinical signs. Tocilizumab should not be administered to patients with a history of complicated diverticulitis and should be used with caution in patients with a history of diverticulitis. Tuyory's 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:
There is no public health impact.

SVII.3.1.3 Neutropenia (MedDRA terms: Neutropenia High-Level Term (HLT), Neutrophil count decreased Preferred Term)

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 with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.

Characterisation of the risk:

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).

In study RGB192101 (Phase I, healthy volunteers), within the AESI category "Cytopenia, Thrombocytopenia" (extraction criteria: Haematopoietic leukopenia SMQ and Haematopoietic thrombocytopenia SMQ) the following TEAEs occurred which were relevant for the risk of "Neutropenia". 43 subjects (39.1%) across the two study arms experienced 64 TEAEs for the PT of "Neutrophil count decreased" (27 subjects [25%] after receiving Tuyory, 36 subjects [34.6%] after receiving RoActemra).

In study RGB19101 (Phase III, subjects with active RA), within the AESI category "Cytopenia, Thrombocytopenia" (extraction criteria: Haematopoietic leukopenia SMQ and Haematopoietic thrombocytopenia SMQ) the following TEAEs occurred which were relevant for the risk of "Neutropenia". Across the two study arms 16 subjects (4.3%) experienced 25 TEAEs for the PT of "Neutrophil count decreased" (3 subjects [1.6%] in the Tuyory arm, 13 subjects [7.0%] in the RoActemra arm). In addition, 2 subjects (0.5 %) experienced 3 TEAEs for the PT of "Neutropenia" (1 subject [0.5%] in the Tuyory arm, 1 subject [0.5%] in the RoActemra arm).

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 tocilizumab to date for all indications other than COVID-19.

In study RGB192101 (Phase I, healthy volunteers), all 64 TEAEs for the PT "Neutrophil count decreased" were of mild severity (28 events after receiving Tuyory, 36 events after receiving RoActemra).

In study RGB19101 (Phase III, subjects with active RA), all 25 TEAEs for the PT "Neutrophil count decreased" were mild in nature (3 events in the Tuyory arm, 22 events in the RoActemra arm), all 3 TEAEs for the PT "Neutropenia" were moderate in severity (1 event in the Tuyory, 2 events in the RoActemra arm).

Seriousness/outcomes

Grade 3 and 4 CTCAE Grade data are provided in RoActemra's RMP (v29.0) 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.

In study RGB192101 (Phase I, healthy volunteers) and RGB19101 (Phase III, subjects with active RA) no SAEs occurred which were relevant for the risk of "Neutropenia".

Impact on Quality of Life

Decreases in neutrophil counts have been observed in RA, GCA, pJIA, and sJIA patients following treatment with tocilizumab.

Preventability

In patients not previously treated with tocilizumab for all indications other than, COVID-19, initiation is not recommended in patients with an ANC below $2x10^9$/L. Monitoring during treatment is recommended and dose modification or treatment discontinuation is recommended based upon ANC. In patients who develop an ANC $<0.5x10^9$/L continued treatment is not recommended. For patients with COVID-19 who develop an ANC $<0.5x10^9$/L continued treatment is not recommended.

For patients with COVID-19 who develop an ANC $<1x10^9$/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 white blood cell counts have been associated with tocilizumab treatment. Tuyory's 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:

There is no public health impact.

SVII.3.1.4 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, causal association between tocilizumab and serious hepatotoxicity has been established. The assessment was further validated by an independent drug-induced liver injury (DILI) expert panel on selected cases.

Characterisation of the risk:

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

The overall worldwide incidence rate of DILI variously specified in the general population is low (13.9-24.0 per 100,000 people). The incidence of acute and clinically significant DILI (requiring hospitalization or requiring specialist referral), however, is even lower (2.3-2.4 per 100,000 persons per year). At the more severe end of the spectrum, the occurrence of all-cause acute liver failure in the developed world is considered very rare (1 to 6 cases per 1,000,000 people every year). There is wide variability in the incidence rates of DILI in populations. This is due to the following reasons:

- Difficulty in recognizing and diagnosing DILI (e.g., there are no widely accepted criteria for diagnosis of DILI, instead it is a diagnosis of exclusion)
- Difficulty in attribution of the event to a drug. There are multiple drug agents commonly in use among the general population, and in particular among patients with RA, where many DMARDs as well as over-the-counter drugs frequently used (e.g., anti-inflammatories) are recognized to have hepatotoxic effects.
- Under-ascertained predisposing factors (such as heavy alcohol consumption, use of herbal agents), as well as other factors prevalent in the RA population, such as obesity, diabetes, etc., that may impact individual background risk.
- Trade-offs in undertaking population-level studies that of necessity cover less detail on larger numbers of individuals, versus undertaking small studies with comprehensive data detail on more circumscribed populations but with multiple exclusions, which by default are less representative of patients receiving medical care under real-world conditions or of target populations.

Thus, the epidemiology data presented contains limitations which make the generalizability of these results, including extrapolation to the RA population challenging. This was further compounded by inconsistent definition of DILI across different publications examined, and reporting of results for only a single drug comparator, further limiting the generalization of the results for the RA population with or without biological DMARD.

As MTX is used as background therapy in a large number of RA patients, the observations with this agent are relevant in this context. In the MTX SmPC, 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.

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 of RoActemra

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.

In study RGB192101 (Phase I, healthy volunteers), 6 subjects (5.5%) across the two study arms experienced 9 TEAEs in the “Hepatic Function Disorder” AESI category (extraction criteria: Hepatic disorders SMQ, excluding Congenital, familial, neonatal and genetic disorders of the liver

SMQ narrow and Hepatic disorders specifically reported as alcohol-related SMQ narrow), 4 subjects (3.7%) after receiving Tuyory, 5 subjects (4.8%) after receiving RoActemra.

In study RGB19101 (Phase III, subjects with active RA), across the two study arms 122 subjects (33.2%) experienced 152 TEAEs in the AESI category of "Hepatic Function Disorder" (extraction criteria: Hepatic disorders SMQ, excluding Congenital, familial, neonatal and genetic disorders of the liver SMQ narrow and Hepatic disorders specifically reported as alcohol-related SMQ narrow), 56 subjects (30.8%) in the Tuyory arm, 66 subjects (35.5%) in the RoActemra arm.

Severity and nature of risk

Eight cases were assessed as tocilizumab 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 tocilizumab-related DILI cases represent a small proportion of the estimated 1,066,849 patients exposed to tocilizumab to date, resulting in a crude rate of ~8 cases/1,000,000 patients, representing a rare event frequency.

In study RGB192101 (Phase I, healthy volunteers), all 9 TEAEs in the "Hepatic Function Disorder" AESI category were of mild severity (4 events after receiving Tuyory, 5 events after receiving RoActemra).

In study RGB19101 (Phase III, subjects with active RA), across the two study arms 120 of all 152 TEAEs in the "Hepatic Function Disorder" AESI category were classified as mild events (55 events in the Tuyory arm, 65 events in the RoActemra arm). 32 of the TEAEs were of moderate severity (15 events in the Tuyory arm, 17 events in the RoActemra arm). None of the TEAEs were severe in nature.

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.

In study RGB192101 (Phase I, healthy volunteers) and RGB19101 (Phase III, subjects with active RA) no SAEs occurred in the "Hepatic Function Disorder" AESI category.

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, tocilizumab 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 ×ULN. In patients with elevated ALT or AST above 5× ULN, treatment is not recommended.

In RA, GCA, pJIA, and sJIA, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. The recommended dose modifications, including tocilizumab discontinuation, based on transaminases levels, in line with SmPC Section 4.2. For ALT or AST elevations > 3–5 x ULN, 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× 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 Tuyory's 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) is already mentioned in the approved labels. Given the well-described and managed safety profile of tocilizumab and the known efficacy, the benefit-risk of tocilizumab in the indicated treatment populations remains positive.

Public Health Impact

There is no public health impact.

Important potential risks:

SVII.3.1.5 Thrombocytopenia and the Potential Risk of Bleeding (MedDRA terms: Haematopoietic thrombocytopenia [SMQ], Thrombocytopenia SMQ wide)

Potential mechanisms

Thrombocytosis is among the most common extra-articular manifestations of RA and IL6 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 with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.

Characterisation 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. 2020).

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).

In study RGB192101 (Phase I, healthy volunteers), within the AESI category "Cytopenia, Thrombocytopenia" (extraction criteria: Haematopoietic leukopenia SMQ and Haematopoietic thrombocytopenia SMQ) no subject across the two study arms experienced TEAEs which were relevant for the risk of "Thrombocytopenia and the Potential Risk of Bleeding".

In study RGB19101 (Phase III, subjects with active RA), within the AESI category "Cytopenia, Thrombocytopenia" (extraction criteria: Haematopoietic leukopenia SMQ and Haematopoietic thrombocytopenia SMQ) the following TEAEs occurred which were relevant for the risk of "Thrombocytopenia and the Potential Risk of Bleeding". Across the two study arms 10 subjects (2.7%) experienced 14 TEAEs for the PT of "Platelet count decreased" (7 subjects [3.8%] in the Tuyory arm, 3 subjects [1.6%] in the RoActemra arm).

Risk factors and risk groups

In a single-cohort retrospective study conducted by Lee et al. (2019), advanced patient age and a low platelet count prior to tocilizumab treatment were associated with the development of thrombocytopenia after treatment.

Severity and nature of risk

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

In study RGB19101 (Phase III, subjects with active RA), across the two study arms all 14 TEAEs for the PT of "Platelet count decreased" were classified as mild events (10 events in the Tuyory arm, 4 events in the RoActemra arm).

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.

COVID-19

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 × 109 /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).

In study RGB192101 (Phase I, healthy volunteers) and RGB19101 (Phase III, subjects with active RA) no SAEs occurred which were relevant for the risk of "Thrombocytopenia and the Potential Risk of Bleeding".

Impact on Quality of Life

There is a risk that a patient's platelet count may decrease when they are taking tocilizumab. Risk factors and risk groups.

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 <50×10^3 /μL, 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 tocilizumab treatment; however, Tuyory's 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

There is no public health impact.

SVII.3.1.6 Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events (MedDRA terms: Myocardial infarction SMQ narrow, Ischaemic Cerebrovascular or Hemorrhagic Cerebrovascular SMQ narrow)

Potential mechanisms

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

Evidence source(s) and strength of evidence

Adequate and well-controlled clinical trials and their long-term extensions with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.

Characterisation of the risk

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 hyperlipidaemia, dyslipidaemia, and hypercholesterolemia in patients with COVID-19 ranged from 5% to 46.2% (Zhang et al. 2020b; Grasselli et al. 2020; Lodigiani et al. 2020; Petrilli et al. 2020). The low prevalence of 5% for hyperlipidaemia 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 dyslipidaemia (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).

In study RGB192101 (Phase I, healthy volunteers) the following TEAEs occurred which were relevant for the risk of "Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events" (AESI category of Abnormal lipid levels in tests, extraction criteria: Dyslipidaemia SMQ; AESI category of Cerebrovascular disorder, extraction criteria: Central nervous system vascular disorders SMQ; extraction criteria: Myocardial infarction SMQ narrow). 1 subject (0.9%) across the two study arms experienced 1 TEAE relevant for

“Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events” risk after receiving RoActemra (PT: Blood triglycerides increased).

In study RGB19101 (Phase III, subjects with active RA), the following TEAEs occurred which were relevant for the risk of “Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events” (AESI category of Abnormal lipid levels in tests, extraction criteria: Dyslipidaemia SMQ; AESI category of Cerebrovascular disorder, extraction criteria: Central nervous system vascular disorders SMQ; extraction criteria: Myocardial infarction SMQ narrow). Across the two study arms 52 subjects (12.5%) experienced 63 TEAEs relevant for the risk of “Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events” (23 subjects [12.6%] in the Tuyory arm, 29 subjects [15.5%] in the RoActemra arm).

Risk factors and risk groups

None identified.

Severity and nature of risk

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

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

In study RGB192101 (Phase I, healthy volunteers), the 1 TEAE relevant for “Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events” risk experienced by 1 subject was of mild severity.

In study RGB19101 (Phase III, subjects with active RA), across the two study arms 55 of all 63 TEAEs relevant for the risk of “Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events” were classified as mild events (27 events in the Tuyory arm, 28 events in the RoActemra arm). 7 of the TEAEs were of moderate severity (3 events in the Tuyory arm, 4 events in the RoActemra arm). 1 TEAE in the RoActemra arm was severe in nature (PT: Acute coronary syndrome).

Seriousness/outcomes

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

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).

In study RGB192101 (Phase I, healthy volunteers) no SAEs occurred which were relevant for “Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events” risk.

In study RGB19101 (Phase III, subjects with active RA) 1 SAE occurred in 1 subject (0.5%) of the RoActemra arm relevant for the “Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events” risk (PT: Acute coronary syndrome).

Impact on Quality of Life

Increases in total cholesterol, LDL, and triglyceride levels have been observed in patients following treatment with tocilizumab. 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 tocilizumab treatment. Tuyory's 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.

SVII.3.1.7 Malignancies (MedDRA terms: Malignancies SMQ narrow)

Potential mechanisms:
Tocilizumab 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 with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.

Characterisation of the risk:

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).

In study RGB192101 (Phase I, healthy volunteers), no subject across the two study arms experienced TEAEs in the AESI category of "Malignant tumors and unspecified tumors" (extraction criteria: Malignant or unspecified tumours SMQ).

In study RGB19101 (Phase III, subjects with active RA), across the two study arms 1 subject (0.3%) experienced 1 TEAE in the "Malignant tumors and unspecified tumors" AESI category (extraction criteria: Malignant or unspecified tumours SMQ) in the RoActemra arm (PT: "Colon cancer").

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.

In study RGB19101 (Phase III, subjects with active RA), the 1 TEAE in the "Malignant tumors and unspecified tumors" AESI category was severe in nature (PT: "Colon cancer").

Seriousness/outcomes

In study RGB19101 (Phase III, subjects with active RA), the 1 TEAE in the "Malignant tumors and unspecified tumors" AESI category was serious in nature (PT: "Colon cancer").

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. Tocilizumab treatment should not be started in subjects with cancer. Tuyory's 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.

SVII.3.1.8 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 with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.

Characterisation of the risk:

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 et al. 2021).

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

In study RGB192101 (Phase I, healthy volunteers), no subject across the two study arms experienced TEAEs in the AESI category "Demyelinating Disorders" (extraction criteria: Demyelinating disorders NEC HLT, Chronic inflammatory demyelinating polyradiculoneuropathy PT, Demyelinating polyneuropathy PT).

In study RGB19101 (Phase III, subjects with active RA), no subject across the two study arms experienced TEAEs in the AESI category "Demyelinating Disorders" (extraction criteria: Demyelinating disorders NEC HLT, Chronic inflammatory demyelinating polyradiculoneuropathy PT, Demyelinating polyneuropathy PT).

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 tocilizumab 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 tocilizumab, although the risk is unknown. Tuyory's 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.

SVII.3.1.9 Immunogenicity (MedDRA terms: Not applicable)

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 with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0), Tuyory's clinical development programme and scientific literature.

Characterisation of the risk:
Not applicable

Seriousness/outcomes

Not Applicable

Severity and nature of risk

Neither ADA status nor period appeared to influence frequency of hypersensitivity or anaphylaxis events in clinical trial RGB192101.

There was no evidence of a relationship between ADA status, TEAEs or adverse events corresponding to MedDRA SMQs of hypersensitivity or anaphylaxis (regardless of relatedness to the study drug) during clinical trial RGB19101.

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 tocilizumab is low in patients with adult RA, pJIA, GCA, or sJIA.

Neither ADA nor NAb positive status had an impact on efficacy (i.e., change in DAS28-ESR from baseline) at Week 12, Week 24 or Week 52 during clinical trial RGB19101.

Public health impact

Not applicable

SVII.3.2. Presentation of the missing information

Not applicable since no missing information has been identified for Tuyory.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: 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-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

According to the reference product's (RoActemra, Roche GmbH) RMP version: 29.0, eight specific adverse reaction follow-up questionnaires are utilized to collect information in a standardized manner and monitor the frequency and nature of AEs emerging during post-marketing use. These targeted follow-up questionnaires are related to the following safety concerns:

- Serious infections (including Neutropenia)
- Complications of diverticulitis (including GI perforation)
- Thrombocytopenia and the potential risk of bleeding
- Hepatotoxicity
- Elevated Lipid Levels and potential risk of Cardiovascular/Cerebrovascular Events (2)
- Malignancies
- Demyelinating disorders

These specific targeted follow-up questionnaires are used to acquire the details of the event description, performed diagnostic tests, patient history, concomitant medications taken by the patient and for the collection of relevant data of spontaneously reported individual case safety reports related to the above-mentioned safety concerns.

Please see Annex 4 of the RMP for details.

Other forms of routine pharmacovigilance activities

Not applicable, since no such activities are conducted or planned.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance studies/activities are planned.

III.3 Summary Table of additional Pharmacovigilance activities

No additional pharmacovigilance studies/activities are planned.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk	
Serious infections *	**Routine risk communication:** **SmPC** 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:** Section 2 Warnings and precautions Section 4 Possible serious side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
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 minimisation activities recommending specific clinical measures to address the risk:** None

Safety concern	Routine risk minimisation activities
	Other risk minimisation measures beyond the Product Information: Pack size: None Medicine's legal status: Tuyory 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 minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory 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 **Patient Information Leaflet** Section 2 Warning and precautions Section 4 Possible Side Effects **Routine risk minimisation 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 minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.

Safety concern	Routine risk minimisation activities
Important potential risk	
Thrombocytopenia and the potential risk of bleeding	**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 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory 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 minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine
Malignancies	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet** Section 2 Warnings and precautions **Routine risk minimisation activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimisation activities
	None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine
Demyelinating Disorders	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.
Immunogenicity	**Routine risk communication:** **SmPC** Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine

* 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 Minimisation Measures

Additional risk minimisation 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 minimisation measure is required for treatment of CRS. Use of tocilizumab for CRS and its risk profile are specified in the SmPC. The additional risk minimisation measures listed in Table Part V.2 are not applicable for the COVID-19 indication.

Table Part V.2: Additional risk minimisation measures

Important identified risk	
Serious Infections *	
Additional Risk Minimisation Measure	Patient Card; Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (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 minimisation activity	**Patient Card** To inform both the patient and health care providers that tocilizumab increases the risk of getting infections which can become serious if not treated and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of infections. **Guide for risk minimisation for patients** To inform the patient of the risk of serious infections and provide additional guidance beyond that provided in the PIL. **Guide for risk minimisation for healthcare professionals – Brochure** To inform and provide more detailed guidance to healthcare providers on the risk of serious infections. **Guide for risk minimisation for healthcare professionals - Dosing Guide** To inform and provide more detailed dosing guidance, administration instructions, and risks to healthcare providers
Target audience and planned distribution path	Patients and Healthcare professionals
Plans for evaluating the effectiveness of the interventions and criteria for success	Performing periodic benefit-risk evaluation in compliance with GVP Module VII (EMA/816292/2011 Rev.1*) and submitting the report (PBRER) in accordance with the EURD list.
Complications of Diverticulitis *	
Additional Risk Minimisation Measure	Patient Card; Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (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 minimisation activity	**Patient Card** To inform both the patient and health care providers that patients using tocilizumab may develop complications of diverticulitis which can become serious if not treated and of the need for timely and appropriate diagnostic and therapeutic measures in case of the early signs of such events. **Guide for risk minimisation for patients** To inform the patient of the risk of complications of diverticulitis and provide additional guidance beyond that provided in the PIL. **Guide for risk minimisation for healthcare professionals – Brochure** To inform and provide more detailed guidance to healthcare providers on the risk of complications of diverticulitis. **Guide for risk minimisation for healthcare professionals - Dosing Guide** To inform and provide more detailed dosing guidance, administration instructions, and risks to healthcare providers
Target audience and planned distribution path	Patients and Healthcare professionals
Plans for evaluating the effectiveness of the interventions and criteria for success	Performing periodic benefit-risk evaluation in compliance with GVP Module VII (EMA/816292/2011 Rev.1*) and submitting the report (PBRER) in accordance with the EURD list.
Neutropenia	
Additional Risk Minimisation Measure	Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (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 minimisation activity	**Guide for risk minimisation for patients** To inform the patient of the risk of neutropenia and provide additional guidance beyond that provided in the PIL. **Guide for risk minimisation for healthcare professionals - Brochure** To inform and provide guidance to healthcare providers on the risk of neutropenia. **Guide for risk minimisation for healthcare professionals - Dosing Guide** To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patients and Healthcare professionals
Plans for evaluating the effectiveness of the interventions and criteria for success	Performing periodic benefit-risk evaluation in compliance with GVP Module VII (EMA/816292/2011 Rev.1*) and submitting the report (PBRER) in accordance with the EURD list.
Hepatotoxicity	
Additional Risk Minimisation Measure	Guide for risk minimisation for patients; Guide for risk minimisation for healthcare professionals (Brochure); Patient Card
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 minimisation activity	**Guide for risk minimisation for patients** To inform the patient of the risk of hepatotoxicity and provide additional guidance beyond that provided in the PIL. **Guide for risk minimisation for healthcare professionals - Brochure** To inform and provide guidance to healthcare providers on the risk of hepatotoxicity. **Patient Card** To inform both the patient and health care providers that patients using tocilizumab may develop hepatotoxicity, and on rare occasions, patients have experience serious life-threatening liver problems, some of which have required liver transplant. Patients will be monitored

	closely for changes in blood liver enzyme level.
Target audience and planned distribution path	Patients and Healthcare professionals
Plans for evaluating the effectiveness of the interventions and criteria for success	Performing periodic benefit-risk evaluation in compliance with GVP Module VII (EMA/816292/2011 Rev.1*) and submitting the report (PBRER) in accordance with the EURD list.
Important potential risk	
Thrombocytopenia and the potential risk of bleeding	
Additional Risk Minimisation Measure	Guide for risk minimisation for patients; Guide for risk minimisation for healthcare professionals (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 minimisation activity	**Guide for risk minimisation for healthcare professionals - Brochure** To inform and provide guidance to healthcare providers on the risk of thrombocytopenia. **Guide for risk minimisation for patients** To inform the patient of the risk of thrombocytopenia beyond that provided in the PIL
Target audience and planned distribution path	Patients and Healthcare professionals
Plans for evaluating the effectiveness of the interventions and criteria for success	Performing periodic benefit-risk evaluation in compliance with GVP Module VII (EMA/816292/2011 Rev.1*) and submitting the report (PBRER) in accordance with the EURD list.
Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events	
Additional Risk Minimisation Measure	Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (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 minimisation activity	**Guide for risk minimisation for patients** To inform the patient of the risk of elevated lipid levels and provide additional guidance beyond that provided in the PIL **Guide for risk minimisation for healthcare professionals - Brochure** To inform and provide guidance to healthcare providers on the risk of elevated lipid levels. **Guide for risk minimisation for healthcare professionals - Dosing Guide** To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patients and Healthcare professionals
Plans for evaluating the effectiveness of the interventions and criteria for success	Performing periodic benefit-risk evaluation in compliance with GVP Module VII (EMA/816292/2011 Rev.1*) and submitting the report (PBRER) in accordance with the EURD list.
Malignancies	
Additional Risk Minimisation Measure	Guide for risk minimisation for patients; Guides for risk minimisation for healthcare professionals (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 minimisation activity	**Guide for risk minimisation for patients** To inform the patient of the risk of malignancies and provide additional guidance beyond that provided in the PIL. **Guide for risk minimisation for healthcare professionals - Brochure** To inform and provide guidance to healthcare providers on the risk of malignancies. **Guide for risk minimisation for healthcare professionals - Dosing Guide** To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patients and Healthcare professionals

Plans for evaluating the effectiveness of the interventions and criteria for success	Performing periodic benefit-risk evaluation in compliance with GVP Module VII (EMA/816292/2011 Rev.1*) and submitting the report (PBRER) in accordance with the EURD list.
Demyelinating Disorders	
Additional Risk Minimisation Measure	Guide for risk minimisation for healthcare professionals (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 minimisation activity	**Guide for risk minimisation for healthcare professionals - Brochure** To inform and provide guidance to healthcare providers on the risk of demyelinating disorders
Target audience and planned distribution path	Healthcare professionals
Plans for evaluating the effectiveness of the interventions and criteria for success	Performing periodic benefit-risk evaluation in compliance with GVP Module VII (EMA/816292/2011 Rev.1*) and submitting the report (PBRER) in accordance with the EURD list.

PIL=Patient Information leaflet; PBRER=Periodic Benefit-Risk Evaluation 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 minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Serious infections *	**Routine risk communication:** **SmPC** 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:** Section 2 What you need to know before you	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	are given TCZ Section 4 Possible serious side effects: tell a doctor straightaway. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine. **Additional risk minimisation measures:** Patient Card Guide for risk minimisation for patients Guides for risk minimisation for healthcare professionals (Brochure, Dosing Guide)	**pharmacovigilance activities:** None
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 minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine. **Additional risk minimisation measures:** Patient Card Guide for risk minimisation for patients Guides for risk minimisation for healthcare professionals (Brochure, Dosing Guide)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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 2 What you need to know before you used Tuyory Section 4 Possible Side Effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine **Additional risk minimisation measures:** Guide for risk minimisation for patients Guides for risk minimisation for healthcare professionals (Brochure, Dosing Guide)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** None
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** Section 2 Warning and precautions Section 4 Possible side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** In patients with RA, GCA, pJIA, sJIA, ALT	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	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 minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine **Additional risk minimisation measures:** Guide for risk minimisation for patients Guide for risk minimisation for healthcare professionals (Brochure) Patient Card	
Important potential risk		
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 minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine **Additional risk minimisation measures:** Guide for risk minimisation for patients Guide for risk minimisation for healthcare professionals (Brochure)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** None
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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Section 4 Possible side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine **Additional risk minimisation measures:** Guide for risk minimisation for patients Guides for risk minimisation for healthcare professionals (Brochure, Dosing Guide)	questionnaire **Additional pharmacovigilance activities:** None
Malignancies	**Routine risk communication:** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine **Additional risk minimisation measures:** Guide for risk minimisation for patients Guide for risk minimisation for healthcare professionals (Brochure, Dosing Guide)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire **Additional pharmacovigilance activities:** None
Demyelinating Disorders	**Routine risk communication:** Section 4.4 Special warnings and precautions for use **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Other risk minimisation measures beyond the Product Information: Pack size: None Medicine's legal status: Tuyory is a prescription only medicine **Additional risk minimisation measures:** Guide for risk minimisation for healthcare professionals (Brochure)	questionnaire **Additional pharmacovigilance activities:** None
Immunogenicity	**Routine risk communication: SmPC** Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine No Additional Risk Minimisation Measure.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **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

Part VI: Summary of the risk management plan

Summary of risk management plan for Tuyory (tocilizumab)

This is a summary of the risk management plan (RMP) for Tuyory. The RMP details important risks of Tuyory, how these risks can be minimised, and how more information will be obtained about Tuyory's risks and uncertainties (missing information).
Tuyory's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tuyory should be used.
This summary of the RMP for Tuyory 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 Tuyory's RMP.

I. The medicine and what it is used for

Tuyory is authorised for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, giant cell arteritis, chimeric antigen receptor T cell-induced cytokine release syndrome and COVID-19 infection. (see SmPC for the full indication). It contains tocilizumab the active substance and it is given by subcutaneous injection or intravenous infusion.
Further information about the evaluation of Tuyory's benefits can be found in Tuyory's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage. [Link to the website]

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

Important risks of Tuyory, together with measures to minimise such risks and the proposed studies for learning more about Tuyory's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

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

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

In the case of Tuyory, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.
If important information that may affect the safe use of Tuyory is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Tuyory are risks that need special risk management activities to further investigate or minimise 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 Tuyory. 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

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

II.B Summary of important risks

Important identified risk: Serious infection *	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.
Risk factors and risk groups	Patients with diabetes reported a higher rate of serious infections compared to patients without diabetes. Patients treated with tocilizumab and taking background corticosteroids reported a higher rate of serious infections compared to patients not taking background corticosteroids. The rate of serious infections appears to increase with body weight. Healthcare professionals should exercise caution when considering the use of tocilizumab in patients with a history of recurring or chronic infections or with underlying conditions

	(e.g., diverticulitis, diabetes, or ILD which may predispose patients to infections). 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.
Risk minimisation measures	**Routine risk communication:** **SmPC** 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:** Section 2 What you need to know before you are given TCZ Section 4 Possible serious side effects: tell a doctor straightaway. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine. **Additional risk minimisation measures:** Patient Card Guide for risk minimisation for patients Guides for risk minimisation for healthcare professionals (Brochure, Dosing Guide)

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 with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.
Risk factors and risk groups	Tocilizumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis. No study described the risk factors associated with GI perforation in COVID-19 patients.
Risk minimisation measures	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects

	<u>Patient Information Leaflet</u>: Section 2 Warnings and precautions Section 4 Possible side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine. **Additional risk minimisation measures:** Patient Card Guide for risk minimisation for patients Guides for risk minimisation for healthcare professionals (Brochure, Dosing Guide)

Important identified risk: Neutropenia	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.
Risk factors and risk groups	None identified.
Risk minimisation measures	**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 Tuyory Section 4 Possible Side Effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine.

	Additional risk minimisation measures: Guide for risk minimisation for patients Guides for risk minimisation for healthcare professionals (Brochure, Dosing Guide)

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.
Risk factors and risk groups	Treatment with other hepatotoxic drugs (e.g., MTX).
Risk minimisation 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** Section 2 Warning and precautions Section 4 Possible side effects **Routine risk minimisation 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 minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine. **Additional risk minimisation measures:** Guide for risk minimisation for patients Guide for risk minimisation for healthcare professionals (Brochure) Patient Card

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 with the reference product (RoActemra, Roche) as

	described within the originator's RMP (v29.0) and scientific literature.
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).
Risk minimisation measures	**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 minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine **Additional risk minimisation measures:** Guide for risk minimisation for patients Guide for risk minimisation for healthcare professionals (Brochure)

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 with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.
Risk factors and risk groups	Patients with underlying CVD are at higher risk for severe illness from COVID-19. 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.
Risk minimisation measures	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Patient Information Leaflet** Section 2 Warnings and precautions Section 4 Possible side effects

	Routine risk minimisation activities recommending specific clinical measures to address the risk: None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine **Additional risk minimisation measures:** Guide for risk minimisation for patients Guides for risk minimisation for healthcare professionals (Brochure, Dosing Guide)

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.
Risk factors and risk groups	None identified.
Risk minimisation measures	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine. **Additional risk minimisation measures:** Guide for risk minimisation for patients Guides for risk minimisation for healthcare professionals (Brochure, Dosing Guide)

Important potential risk: Demyelinating Disorders	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0) and scientific literature.
Risk factors and risk groups	None identified.

Risk minimisation measures	**Routine risk communication:** **SmPC** Section 4.4 Special warnings and precautions for use **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine. **Additional risk minimisation measures:** Guide for risk minimisation for healthcare professionals (Brochure)

Important potential risk: Immunogenicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions with the reference product (RoActemra, Roche) as described within the originator's RMP (v29.0), Tuyory's clinical development programme and scientific literature.
Risk factors and risk groups	None identified.
Risk minimisation measures	**Routine risk communication: SmPC** Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** Pack size: None Medicine's legal status: Tuyory is a prescription only medicine **Additional risk minimisation measures:** None

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

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Tuyory.

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

There are no studies planned for Tuyory.

Annex 4 - Specific adverse drug reaction follow-up forms

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TOCILIZUMAB TARGETED FOLLOW-UP FORM

for

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 DD/MM/YYYY): (Discharge Date DD/MM/YYYY):			☐No
Onset Date (DD/MM/YYYY)				
Stop Date (DD/MM/YYYY)				
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐**Death** Date of Death (DD/MM/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 a sequalae	
	☐Resolved	☐Unknown	☐Worsened	☐Death
Was the patient neutropenic at the current time of the	☐No			☐Unknown

serious or opportunistic infectious event?	☐Yes: Provide lab results including Date of abnormal labs if available (DD/MM/YYYY):
Was the infection associated with an ANC of <1000/mm^3 (10^9/L)	☐No ☐Yes: Provide Date of abnormal labs (DD/MM/YYYY): ☐Unknown
Did dose modification occur in association with lab abnormality?	☐No ☐Yes: Provide Date of dose modification (DD/MM/YYYY): ☐Unknown

Drug therapy details - Tocilizumab				
Indication:				
Start Date (DD/MM/YYYY)				
Starting Dose	_____ mg/kg _____ Total monthly dose (mg)			
Frequency	☐Monthly ☐Other please specify:			
History of 4 most recent infusions/injections prior to Adverse Event (AE)	Date (DD/MM/YYYY)	Dose	Route (IV or SC)	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 (DD/MM/YYYY to DD/MM/YYYY)

Please attach all the 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

	Baseline Value (Prior to TCZ use)	Date of Baseline Test (DD/MM/ YYYY)	Lab results at time of event including Date of Test (DD/MM/ YYYY)	Test Results (include units)		Reference Range (If applicable)	Pending?
				Value	Unit		
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, spenomegaly, 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?	☐History	☐Concurrent	☐Not present

[redacted]

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

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

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 TARGETED FOLLOW-UP FORM

for

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 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 DD/MM/YYYY): (Discharge Date DD/MM/YYYY): ☐No
Onset Date (DD/MM/YYYY)
Stop Date (DD/MM/YYYY)
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐**Death** Date of Death (DD/MM/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 a sequalae ☐Resolved ☐Unknown ☐Worsened ☐Death

Drug therapy details - Tocilizumab				
Indication:				
Start Date (DD/MM/YYYY)				
Starting Dose	mg/kg		Total monthly dose (mg)	
Frequency	☐Monthly ☐Other please specify:			
History of 4 most recent infusions/injections prior to Adverse Event (AE)	Date (DD/MM/YYYY)	Dose	Route (IV or SC)	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 (DD/MM/YYYY to DD/MM/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 benne performed, and the results:

	Baseline Value (Prior to TCZ use)	Date of Baseline Test (DD/MM/ YYYY)	Date of Test (DD/MM/ YYYY)	Test Results (include units)		Reference Range (If applicable)	Pending ?
				Value	Unit		
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: _____

[redacted]

TOCILIZUMAB TARGETED FOLLOW-UP FORM

for

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 DD/MM/YYYY): (Discharge Date DD/MM/YYYY):			☐No
Onset Date (DD/MM/YYYY)				
Stop Date (DD/MM/YYYY)				
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐**Death** Date of Death (DD/MM/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 ☐Resolved	☐Improved ☐Unknown	☐Recovered with a sequalae ☐Worsened	☐Death
Was the hepatic event associated	☐No			

[redacted]

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

Drug therapy details - Tocilizumab				
Indication:				
Start Date (DD/MM/YYYY)				
Starting Dose	_____ mg/kg _____ Total monthly dose (mg)			
Frequency	☐Monthly ☐Other please specify:			
History of 4 most recent infusions/injections prior to Adverse Event (AE)	Date (DD/MM/YYYY)	Dose	Route (IV or SC)	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)

[redacted]

Treatment	Dosing Regimen	Dates of Therapy (DD/MM/YYYY to DD/MM/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 the laboratory results (ALT, AST, Indirect bilirubin, INR, Alkaline phosphatase, albumin, CBC, CRP, eosinophils etc) and imaging tests. Please provide SI (International System of Units) if available. Otherwise, as reported.
☐Labs Attached

	Baseline Value (Prior to TCZ use)	Date of Baseline Test (DD/MM/YYYY)	Date of Test (DD/MM/YYYY)	Test Results (include units)		Reference Range (If applicable)	Pending?
				Value	Unit		
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 benne performed, and the result:

Test	**Conducted?**	**Results (include units)**		**Date (DD/MM/YYYY)**
		Value	**Unit**	
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

[redacted]

Statins Specify:	☐Yes ☐No				☐Past	☐Concomitant	☐N/A
Acetaminophen	☐Yes ☐No				☐Past	☐Concomitant	☐N/A
Antibiotic Specify:	☐Yes ☐No				☐Past	☐Concomitant	☐N/A
Other Please specify:	☐Yes ☐No				☐Past	☐Concomitant	☐N/A

Thank you for completing this form.

Completed by:

Name: _____ **Position: _____**

Signature: _____ **Date: _____**

E-mail: _____

TOCILIZUMAB TARGETED FOLLOW-UP FORM

for

Spontaneous 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 Targeted Follow-up questionnaire is intended to be used with both internal and external haemorrhagic events including haemorrhagic strokes. By filling 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 DD/MM/YYYY): ☐No (Discharge Date DD/MM/YYYY):
Onset Date (DD/MM/YYYY)
Stop Date (DD/MM/YYYY)
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐**Death** Date of Death (DD/MM/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

[redacted]

Outcome of the event:	☐Persisting ☐Improved ☐Recovered with a sequalae ☐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 (DD/MM/YYYY): ☐Unknown
Did dose modification occur in association with lab abnormality?	☐No ☐Yes: Provide Date of dose modification (DD/MM/YYYY): ☐Unknown

Drug therapy details - Tocilizumab				
Indication:				
Start Date (DD/MM/YYYY)				
Starting Dose	mg/kg		Total monthly dose (mg)	
Frequency	☐Monthly ☐Other please specify:			
History of 4 most recent infusions/injections prior to Adverse Event (AE)	Date (DD/MM/YYYY)	Dose	Route (IV or SC)	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 (DD/MM/YYYY to DD/MM/YYYY)**

[redacted]

Please attach all the 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 benne performed, and the results:

	Baseline Value (Prior to TCZ use)	Date of Baseline Test (DD/MM/YYYY)	Date of Test (DD/MM/YYYY)	Test Results (include units)		Reference Range (If applicable)	Pending?
				Value	Unit		
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 Willerbrand'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	☐Yes				☐Past ☐Concomitant ☐N/A

[redacted]

Specify:	☐No				
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: _____

[redacted]

TOCILIZUMAB TARGETED FOLLOW-UP FORM

for

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 DD/MM/YYYY): (Discharge Date DD/MM/YYYY):			☐No
Onset Date (DD/MM/YYYY)				
Stop Date (DD/MM/YYYY)				
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐**Death** Date of Death (DD/MM/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 a sequalae	
	☐Resolved	☐Unknown	☐Worsened	☐Death

Drug therapy details - Tocilizumab				
Indication:				
Start Date (DD/MM/YYYY)				
Starting Dose	_____ mg/kg _____ Total monthly dose (mg)			
Frequency	☐Monthly ☐Other please specify:			
History of 4 most recent infusions/injections prior to Adverse Event (AE)	Date (DD/MM/YYYY)	Dose	Route (IV or SC)	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 (DD/MM/YYYY to DD/MM/YYYY)

Please attach all the 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 results:

	Baseline Value (Prior to TCZ use)	Date of Baseline Test (DD/MM/YYYY)	Date of Test (DD/MM/YYYY)	Test Results (include units)		Reference Range (If applicable)	Pending?
				Value	Unit		
Coronary Angiography							☐Yes

[redacted]

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: _____

[redacted]

TOCILIZUMAB TARGETED FOLLOW-UP FORM

for

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 DD/MM/YYYY): ☐No (Discharge Date DD/MM/YYYY):
Onset Date (DD/MM/YYYY)
Stop Date (DD/MM/YYYY)
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐**Death** Date of Death (DD/MM/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

[redacted]

Outcome of the event:	☐Persisting ☐Improved ☐Recovered with a sequalae ☐Resolved ☐Unknown ☐Worsened ☐Death

Drug therapy details - Tocilizumab				
Indication:				
Start Date (DD/MM/YYYY)				
Starting Dose	_____ mg/kg _____ Total monthly dose (mg)			
Frequency	☐Monthly ☐Other please specify:			
History of 4 most recent infusions/injections prior to Adverse Event (AE)	Date (DD/MM/YYYY)	Dose	Route (IV or SC)	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 (DD/MM/YYYY to DD/MM/YYYY)

Please attach all the 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

	Baseline Value (Prior to TCZ use)	Date of Baseline Test (DD/MM/ YYYY)	Date of Test (DD/MM/ YYYY)	Test Results (include units)		Reference Range (If applicable)	Pending ?
				Value	Unit		
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 Specify:	☐History	☐Concurrent	☐Not present
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

[redacted]

☐**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: _____

[redacted]

TOCILIZUMAB TARGETED FOLLOW-UP FORM

for

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 side (Please provide biopsy, pathology, and biomarker results if applicable)	

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

Select all that apply:

SERIOUSNESS CRITERIA CLASSIFICATION

☐**Death** Date of Death (DD/MM/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**

[redacted]

☐**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 ☐Resolved	☐Improved ☐Unknown	☐Recovered with a sequalae ☐Worsened	☐Death

Drug therapy details - Tocilizumab				
Indication:				
Start Date (DD/MM/YYYY)				
Starting Dose	_____ mg/kg _____ Total monthly dose (mg)			
Frequency	☐Monthly ☐Other please specify:			
History of 4 most recent infusions/injections prior to Adverse Event (AE)	Date (DD/MM/YYYY)	Dose	Route (IV or SC)	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 (DD/MM/YYYY to DD/MM/YYYY)

Risk factors

[redacted]

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 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 TARGETED FOLLOW-UP FORM

for

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 DD/MM/YYYY): (Discharge Date DD/MM/YYYY):			☐No
Onset Date (DD/MM/YYYY)				
Stop Date (DD/MM/YYYY)				
Select all that apply: **SERIOUSNESS CRITERIA CLASSIFICATION** ☐**Death** Date of Death (DD/MM/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 a sequalae	
	☐Resolved	☐Unknown	☐Worsened	☐Death

Drug therapy details - Tocilizumab				
Indication:				
Start Date (DD/MM/YYYY)				
Starting Dose	_____ mg/kg _____ Total monthly dose (mg)			
Frequency	☐Monthly ☐Other please specify:			
History of 4 most recent infusions/injections prior to Adverse Event (AE)	Date (DD/MM/YYYY)	Dose	Route (IV or SC)	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 (DD/MM/YYYY to DD/MM/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 results:

	Baseline Value (Prior to TCZ use)	Date of Baseline Test (DD/MM/YYYY)	Date of Test (DD/MM/YYYY)	Test Results (include units)		Reference Range (If applicable)	Pending?
				Value	Unit		
CBC/ Differential WBC Count							☐Yes
CRP							☐Yes
CSF analysis							☐Yes

[redacted]

(Please include protein, glucose, cell count, IgG, virus results)							
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	☐History	☐Concurrent	☐Not present

[redacted]

Please specify:	

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: _____

[redacted]

Annex 6 - Details of proposed additional risk minimisation activities

Key messages of the additional risk minimisation measures

Patient Card

- Additional guidance beyond that provided in the Patient Information Leaflet for patients.
- Addressing the risk that Tuyory may make an existing infection worse or increase the chance of getting a new infection.
- Information that patients using Tuyory may develop complications of diverticulitis, which can become serious if not treated.
- Addressing the risk that patients using Tuyory 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.
- Contact details of reporting side effects.

Guide for risk minimisation for patients

- Additional guidance beyond that provided in the Patient Information Leaflet for patients.
- Information on the formulations, indications of Tuyory, how it is given and what actions are required before starting treatment with Tuyory.
- Information on the blood tests (e.g., neutrophil, platelet count, liver enzymes, cholesterol level) which patients may receive during Tuyory treatment.
- Information on the important side effects of Tuyory treatment (e.g., infections, abdominal pain, hepatotoxicity, malignancies, side effects in children and adolescents).
- Contact details of reporting side effects.

Guide for risk minimisation for healthcare professionals - Brochure

- Additional guidance beyond that provided in the Patient Information Leaflet for treating physicians.
- Information on the formulations, indications of Tuyory and how it is given.
- Recommendations on how to minimise or prevent important risks of Tuyory in patients with RA, GCA, pJIA, sJIA, and CAR T cell-induced severe or life-threatening CRS. These include serious infections, complication of diverticulitis (including gastrointestinal perforation), IL-6 inhibition and MAS, haematological abnormalities: thrombocytopenia and the potential risk of bleeding and/or neutropenia, hepatotoxicity, elevated lipid levels and potential risk of cardiovascular/cerebrovascular events, malignancies, demyelinating disorders, infusion/injection reactions.
- Guidance on how to diagnose Macrophage Activation Syndrome in sJIA patients.
- Recommendation on dose adjustments due to liver enzyme abnormalities.
- Guidance on dosage and administration of Tuyory (including in paediatric patients), and dose interruption in sJIA and pJIA patients.
- Contact details of reporting side effects.

- General recommendations (including advice for pregnant or breast-feeding women).

Guide for risk minimisation for healthcare professionals - Dosing Guide

- Guidance for healthcare professionals for the dose preparation and IV or SC administration of Tuyory in patients with RA, GCA, pJIA, sJIA, CAR T cell-induced severe or life-threatening CRS and COVID-19.
- Information on the formulations, indications of Tuyory and what actions are required before starting treatment with Tuyory.
- Weight-based dosing calculation tables to guide health care professionals for the correct administration of intravenous Tuyory. Step-by step guidance on the process of infusion/injection (including both subcutaneous devices).
- Important safety information that healthcare professionals need to be aware of when administering Tuyory.
- Contact details of reporting side effects.