Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

EUROPEAN UNION (EU) RISK MANAGEMENT PLAN (RMP) FOR TOFIDENCE (TOCILIZUMAB)

RMP version number:	0.5
Data lock point (DLP) for this RMP:	22 April 2021
Date of final sign off:	19 April 2024

QPPV name: Lucia Matejkinova

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

Template Version 4.0

Governed by DEV-SOP-3135

ADMINISTRATIVE INFORMATION

Other RMP versions under evaluation

Not applicable - no other versions of Tofidence EU RMP are currently under evaluation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
ADA	Anti-drug antibody
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aRMM	Additional risk minimisation measure
AST	Aspartate aminotransferase
CAR	Chimeric antigen receptor
CHMP	The Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
DHPC	Direct Healthcare Professional Communication
DMARD	Disease modifying anti-rheumatic drugs
DILI	Drug-induced liver injury
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GCP	Good Clinical Practice
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
ICU	Intensive care unit
IL-6	Interleukin 6
MTX	Methotrexate
NAb	Neutralising antibody
NSAID	Non-steroidal anti-inflammatory drugs
PAC	Patient alert card
pJIA	Juvenile idiopathic polyarthritis
PK	Pharmacokinetic
PT	Preferred Term (MedDRA)
QPPV	Qualified Person Responsible for Pharmacovigilance
RA	Rheumatoid arthritis
RBC	Red Blood Cell
RMP	Risk Management Plan
sJIA	Systemic juvenile idiopathic arthritis
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TB	Tuberculosis
TEAE	Treatment emergent adverse event

Abbreviation	Definition
TNF	Tumour necrosis factor

PART I: PRODUCT(S) OVERVIEW

Table 1: Product(s) Overview

Active substance(s) (INN or common name)	Tocilizumab
Pharmacotherapeutic group(s) (ATC Code)	Interleukin inhibitors (L04AC07)
Marketing Authorisation Applicant	Biogen Netherlands B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Tofidence
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Interleukin-6 inhibitor
	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, a humanised IgG1 monoclonal antibody against the human IL-6 receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.
Hyperlink to the Product Information	For product information, please refer to Module 1.3.1.

Indication(s) in the EEA	**Current:** Not applicable. **Proposed (if applicable):** Tofidence in combination with methotrexate (MTX), is indicated for: ▪ the treatment of severe, active and progressive rheumatoid arthritis (RA) in adults not previously treated with methotrexate. ▪ 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, Tofidence can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tofidence 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. Tofidence 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. Tofidence can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX. Tofidence 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. Tofidence can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Dosage in the EEA	**Current:** Not applicable. **Proposed (if applicable):** 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 COVID-19 is a single 60-minute intravenous infusion of 8 mg/kg in patients who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of 8 mg/kg may be administered. The interval between the two infusions should be at least 8 hours. For individuals whose body weight is more than 100 kg, doses exceeding 800 mg per infusion are not recommended. 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.

Pharmaceutical form(s) and strengths	**Current *(if applicable)*:** Not applicable. **Proposed *(if applicable)*:** Concentrate for solution for infusion. Tofidence is a clear to opalescent, colourless to pale yellow solution, supplied in type I clear glass vials with a butyl rubber stopper. Each milliliter concentrate contains 20 mg tocilizumab. ▪ 80 mg of tocilizumab in 4 mL (20 mg/mL) ▪ 200 mg of tocilizumab in 10 mL (20 mg/mL) ▪ 400 mg of tocilizumab in 20 mL (20 mg/mL)
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)

Part II Module SI is not required for new marketing authorisation applications in the EU for biosimilar medicinal products according to the guideline on Good Pharmacovigilance Practices (GVP) – Module V (Rev 2) (EMA/838713/2011 Rev 2).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Tofidence is a proposed biosimilar to RoActemra and has the same target antigen binding epitope and binding affinity as RoActemra. Tofidence has been shown to have the same in vitro and in vivo mechanism of action as RoActemra and the components of the mechanism of action have also been shown to have the same activity in vitro, and in vivo monkey models of RA. In summary, Tofidence has demonstrated analytical similarity in terms of structural, physicochemical and biological activity in vitro and in vivo.

Guidelines outlining the required biosimilar antibody therapeutic studies indicate that the developmental and reproductive toxicity, genotoxicity, carcinogenicity and drug interaction studies are not warranted when the proposed biosimilar product has been demonstrated to be highly similar to the reference medicinal product, through extensive structural and functional characterisation and animal toxicity studies (CHMP guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: nonclinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 Rev 1]). As Tofidence is a proposed biosimilar, the relevant evidence supporting reference product should apply equally. Nevertheless, due to regional regulatory requirements in other territories, the Applicant has conducted a number of non-clinical studies, including a repeat dose toxicity study in Cynomolgus Monkeys. This study confirmed the similarity between the toxicity profiles of Tofidence and Actemra.

Key safety findings from non-clinical studies with potential relevance to human usage are described in Table 2.

Table 2: Key safety findings from non-clinical studies and relevance to human usage

SAFETY FINDING	RELEVANCE TO HUMAN USE
Repeat-dose Toxicity	
Monkey (Cynomolgus Monkey): *5 animals/sex/group, doses of Tofidence at 10, 30, and 100 mg/kg, Actemra at 30 mg/kg i.v. or control on Day 0, Week 1, Week 2, Week 3, and Week 4, followed by a 4 week recovery period (Study No. 2017021).* <u>Clinical symptoms observed</u> In the high dose group, 10% of the animals presented with symptoms including lethargy, reduced activity, lying in cages, and cold limbs.	These findings were not thought to be related to investigational drug. This finding is of no toxicological significance to humans.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Changes in serum biochemistry results Serum levels of complements C3 and C4 declined for both the reference and certain investigational drug groups. Albumin/globulin ratio (A/G) increased for various dose groups of investigational drug, and total protein level (TP) declined for the high dose group.	Results suggest that animal immunity levels declined somewhat after multiple administrations. These indicators returned to normal during the recovery period. Given that tocilizumab is an immunosuppressive agent, the results are not unexpected and were observed in the RoActemra clinical development programme.
Changes in cytokine levels Levels of serum IL-6 and IL-6R in the reference drug group and various dose groups of investigational group increased significantly.	Given that tocilizumab is an anti-IL-6 compound, these results are not unexpected and have been observed in the RoActemra clinical development programme.
Formation of anti-drug antibodies Four weeks following dosing, 10% of animals in the low dose group developed anti-drug antibodies.	Since this result was only observed in the low dose group, it is thought that higher doses used in the investigational and high dose groups were able to produce drug immunosuppression. This finding is of no toxicological significance to humans.
Pathological changes Animals in both treatment groups displayed weight gain of the spleen and/or weight loss of the thymus. Histopathological change related to administration of the reference drug and the investigational drug was seen in the spleen, namely increased mitosis in the white pulp. Additionally, both treatments aggravated pathological increase of lymphocyte count in the white pulp of the spleen, as well as aggravated lesion severity of lymphocytopenia in the thymus cortex. Finally, dermal and/or subcutaneous bleeding at injection sites were observed for both reference drug and the investigational drug with lesion recovery observed in the recovery period.	Since the effects were observed following treatment with both the investigational and reference drug, the observations are unlikely to be relevant to the treatment of humans.
Reproductive/developmental toxicity	
Reproductive toxicology studies comparing Tofidence and RoActemra have not been performed because they are not required according to EU guidance on biosimilar products (CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).	Not applicable.

SAFETY FINDING	RELEVANCE TO HUMAN USE
Genotoxicity	
Genotixicity studies comparing Tofidence and RoActemra have not been performed because they are not required according to EU guidance on biosimilar products (CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).	Not applicable.
Carcinogenicity	
Carcinogenicity studies comparing Tofidence and RoActemra have not been performed because they are not required according to EU guidance on biosimilar products (CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010).	Not applicable.
Safety pharmacology	
No specific safety pharmacology studies were performed. Safety endpoints were incorporated into the monkey repeat-dose toxicity study (Study No. 2017021). This approach is compatible with CHMP guidance on similar biological medicinal products containing monoclonal antibodies, which states that safety pharmacology studies are not routinely required (CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues EMA/CHMP/BMWP/403543/2010).	Not applicable.
Other toxicity-related information or data – Local Tolerance Testing	
Rabbit (New Zealand White): *6 female animals/group, doses of Tofidence at 12.3 mg/kg, RoActemra at 12.3 mg/kg i.v. or control on Day 1 and Day 15 with a recovery period of up to 14 days (Study No. Q17-S136-IR).*	No local irritation was observed after intravenous administration of either the investigational or reference drug, therefore there is no safety concern relevant to human exposure.
Other toxicity-related information or data – Immunogenicity	

SAFETY FINDING	RELEVANCE TO HUMAN USE
Monkey (Cynomolgus Monkey): *4 animals/sex/group, doses of Tofidence at 10 and 30 mg/kg, Actemra at 10 and 30 mg/kg on Week 0, 2, 4, 6, 8, 10 and 12, followed by a 6 week recovery period (Study No. 2015045).*	The immunogenicity results after multiple intravenous administrations of BAT-1806 were similar to those of tocilizumab, with no abnormal irritation reactions and symptoms observed in either treatment groups. Anti-drug antibodies were detected in only one animal in the low-dose tocilizumab group, while no anti-drug antibodies were detected in any other animal. The results suggest that there is no safety concern relevant to human exposure.
Other toxicity-related information or data – In Vitro Haemolysis	
Defibrinated rabbit blood treated with Tofidence, Actemra, sodium chloride negative control, or sterile water positive control.	Following 3 hours of incubation, no haemolysis or haemagglutination was observed for Tofidence or Actemra treated samples. There is no safety concern relevant to human exposure.
Human red blood cells treated with Tofidence, Actemra, sodium chloride negative control, or sterile water positive control.	Following a 3 hour incubation with human red blood cells, neither test or reference article resulted in hemolysis or an aggregation effect.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Tocilizumab is a recombinant humanised monoclonal antibody that binds to human IL-6 receptor. 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.

In accordance with regulatory guidelines for a biosimilar development, following the demonstration of physicochemical and functional similarity of Tofidence and the reference medicinal product/reference product (RMP/RP), the applicant conducted a pharmacokinetic (PK) study in healthy subjects to support a claim for biosimilarity via a 3-way demonstration of bioequivalence between Tofidence, the United States-Reference Medicinal Product, and European Union-Reference Medicinal Product, as per EMA (EMA, 2014) and international regulatory guidelines (FDA, 2015; WHO, 2009) on the development of biosimilar drugs. This study was followed by a clinical efficacy and safety trial in a sensitive patient population i.e. RA. The latter was selected as the lead indication, due to the relatively high treatment effect observed in clinical trials with RoActemra for this indication and being a sensitive population for the comparative immunogenicity assessment thus, facilitating the detection of potential differences between Tofidence and the EU-Reference Medicinal Product.

According to the Guideline on similar biological medicinal products (EMA, 2014) comparable safety and efficacy of a biosimilar to its reference product has to be demonstrated or otherwise justified in accordance with the data requirements laid down in Directive 2001/83/EC. Further, if biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification. In accordance with this guidance extrapolation of the clinical results in RA to other approved indications for RoActemra will be sought to support approval of Tofidence in these other indications.

Tofidence has the same pharmaceutical form and the same dosage strength as RoActemra. Data from the two completed studies provide clinical evidence supporting the similarity of Tofidence to the reference medicinal product RoActemra. These studies include a single dose 3-way PK similarity study in healthy volunteers and a double blind randomised active comparator study in adult subjects with RA. The clinical trials were conducted in accordance with Good Clinical Practices.

Study BAT1806-001-CR was a randomised, double blind, single dose study that compared the pharmacokinetics (PK), safety, and immunogenicity of Tofidence with US-licensed Actemra and EU-approved RoActemra in 129 healthy male Chinese participants. Of these, 45 healthy participants were exposed to Tofidence. Results confirm the 3-way PK equivalence of Tofidence and the EU Reference medicinal product and US-reference product. The safety and immunogenicity data supported the assertion of clinical similarity between Tofidence and both the US-licensed Actemra and the EU-approved RoActemra (Zhang et al., 2021).

Study BAT1806-002-CR was a double-blind, parallel-group, active-control study in participants with RA with inadequate response to MTX. The primary objective of the study was to assess the similarity in efficacy between Tofidence and EU- and US-reference products based on ACR-20

response at Week 12 (EU) or Week 24 (US). In this pivotal study, a total of 312 participants were included in the safety set for Tofidence, which included 312 participants that received treatment with Tofidence up to Week 24, and 290 participants that received treatment up to Week 48. Results from this trial demonstrated that the safety and immunogenicity profile of Tofidence was similar to that of RoActemra.

A summary of Tofidence exposure is presented in the tables below:

Table 3: Duration of exposure

Duration of exposure (Safety Analysis Set)			
Study Identifier	**Treatment Group**	**Number of Patients**	**Person-time**
BAT1806-001-CR	Tofidence	45	-[1]
	Actemra US	42	-[1]
	RoActemra EU	42	-[1]
BAT1806-002-CR			
(T1 and T2 combined)	Tofidence	312	249.29
	RoActemra EU-> Tofidence	142	118.84
	RoActemra EU	167	126.21
1 to <3 m	Tofidence	9	1.62
	RoActemra EU-> Tofidence	0	0
	RoActemra EU	7	1.31
3 to <6 m	Tofidence	10	3.79
	RoActemra EU-> Tofidence	2	0.94
	RoActemra EU	5	1.71
≥6 m	Tofidence	288	243.64
	RoActemra EU-> Tofidence	140	117.90
	RoActemra EU	145	122.63
Total		621	494.34

[1] A single administration of investigational or reference product was given in Study BAT1806-001-CR.

T1 = treatment period 1; T2 = treatment period 2

Person-time is expressed in years.

Table 4: Age group and gender

Age group (Safety Analysis Set)	Study Identifier	Treatment group	Patients		Person-time	
			M (N, %)	F (N, %)	M	F
18-55 years	BAT1806-001-CR	Tofidence	45 (100%)	0	-[1]	0
		Actemra US	42 (100%)	0	-[1]	0
		RoActemra EU	42 (100%)	0	-[1]	0
18-64 years	BAT1806-002-CR	Tofidence	37 (13.3)	242 (86.7)	29.45	192.82
		RoActemra EU-> Tofidence	21 (16.3)	108 (83.7)	17.24	90.51
		RoActemra EU	19 (13.1)	126 (86.9)	15.24	94.24
65-74 years		Tofidence	6 (18.8)	26 (81.3)	4.05	22.12
		RoActemra EU-> Tofidence	2 (18.2)	9 (81.8)	1.71	7.67
		RoActemra EU	2 (9.1)	20 (90.9)	0.98	15.75
75-84 years		Tofidence	0	1 (100.0)		0.85
		RoActemra EU-> Tofidence	0	2 (100.0)		1.71
		RoActemra EU	0	0		
≥85 years		Tofidence	0	0		
		RoActemra EU-> Tofidence	0	0		
		RoActemra EU	0	0		
Total			87 (14.0)	534 (86.0)	68.67	425.67

[1] A single administration of investigational or reference product was given in Study BAT1806-001-CR.

Person-time is expressed in years.

Table 5: Ethnic origin

Ethnic origin	Study Identifier	Treatment group	Patients	Person-time
Asian	BAT1806-001-CR	Tofidence	45	-[1]
		Actemra US	42	-[1]

Ethnic origin	Study Identifier	Treatment group	Patients	Person-time
		RoActemra EU	42	-[1]
	BAT1806-002-CR	Tofidence	126	97.92
		RoActemra EU-> Tofidence	59	48.80
		RoActemra EU	68	49.63
White	BAT1806-002-CR	Tofidence	186	151.36
		RoActemra EU-> Tofidence	83	70.03
		RoActemra EU	99	76.58
Total			621	494.34

[1] A single administration of investigational or reference product was given in Study BAT1806-001-CR.

Person-time is expressed in years.

The totality of the evidence available from the complete biosimilarity assessment, including the analytical similarity assessment program, non-clinical, and clinical studies demonstrate that Tofidence has similar pharmaceutical quality, safety and efficacy when compared to the licenced reference medicinal product sourced from the EU and the US (RoActemra/Actemra respectively).

The data supports that Tofidence and RoActemra have a comparable safety profile.

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

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

The Tofidence clinical development programme has employed specific exclusion criteria which were either related to the evaluation of efficacy (to ensure that the appropriate target disease was studied, or to avoid confounding the efficacy evaluation), or were related to safety (in order to protect trial patients from potential risks associated with investigational product administration), or were related to good clinical practice (GCP) e.g., to ensure that proper follow-up was possible.

The majority of these criteria, which are outlined in the clinical study protocol, are not contraindications for therapy in the approved indications. Some of these criteria are mentioned in the summary of product characteristics for RoActemra as situations in which caution should be applied when using the product.

A review of the key exclusion criteria in pivotal studies, and an assessment of their relevance to be considered as areas of missing information are presented in Table 6.

Table 6: Discussion of exclusion criteria in relation to the assessment of missing information

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Severe allergic or anaphylactic reactions	To ensure general safety of patients with known severe hypersensitivity to monoclonal antibodies when treated with Tocilizumab	No	Hypersensitivity is contraindicated in the SmPC.
Active severe infections	Patients with a history of recurring or chronic infections or with active underlying conditions, may potentially be predisposed to infections when exposed to Tocilizumab.	No	For RA, sJIA, pJIA, 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	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Significant medical problems (such as uncontrolled hypertension, congestive heart failure, and history of unstable angina pectoris, myocardial infarction, or cerebrovascular accident within the past 12 months, uncontrolled diabetes, renal or liver disease)	To ensure general safety of patients to be treated with Tocilizumab in the clinical trial setting.	No	There is no data to suggest that Tocilizumab has an effect on pulmonary, renal, or endocrine function. Active hepatic disease/hepatic impairment, neurological disorders, cardiovascular risk, and complications of diverticulitis are listed as special warnings and precautions in the SmPC.
Intra-articular or parenteral corticosteroids ≤4 weeks before randomization	Parenteral steroids were prohibited in the Tocilizumab RA clinical trials to enable accurate assessment of Tocilizumab efficacy	No	This exclusion criterion was not related to the safety of the patient population.
Clinically significant laboratory abnormalities or other clinically indicated diseases	To avoid any confounding effect of laboratory abnormalities on efficacy or safety results	No	In the SmPC, dose adjustments are required in the case of laboratory abnormalities such as liver enzyme abnormalities, blood count etc.
Active TB within the previous 3 months and no evidence of active TB infection at enrollment.	To ensure general safety of patients to be treated with Tocilizumab in the clinical trial setting.	No	Tuberculosis is listed as a special warning and precaution in the SmPC.
Recurrent bacterial, fungal, or viral infection	To avoid any possible impact by tocilizumab, in relationship with its immunosuppressant effect, on the treatment of a current or recent infection	No	Guidance regarding infections is included in SmPC Section 4.4.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Current or history of diverticulitis, complications of diverticulitis, history of diverticulosis requiring antibiotic treatment, current or history of chronic ulcerative lower gastrointestinal tract diseases or any other lower gastrointestinal condition that may have predisposed to perforation	To ensure general safety of patients to be treated with Tocilizumab in the clinical trial setting	No	Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with Tocilizumab in RA patients. Complications of diverticulitis is listed as a special warning and precaution in the SmPC and is included as an important identified risk in this RMP (refer to Module SVII.3.1).
Current liver disease as determined by the investigator.	To ensure general safety of patients to be treated with Tocilizumab in the clinical trial setting	No	Treatment with Tocilizumab, particularly when administered concomitantly with MTX, may be associated with elevations in hepatic transaminases. This has been listed in the SmPC under Special Warnings and Precautions for use. Hepatotoxicity is classified as an important identified risk in this RMP (refer to Module SVII.3.1).
History of malignancy or lymphoproliferative disease	To ensure general safety of patients to be treated with Tocilizumab in the clinical trial setting	No	Malignancy is listed as a special warning and precaution in the SmPC. Malignancies are included as an important potential risk in this RMP (see Module SVII.3.1).

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of demyelinating disease	Tocilizumab use in patients with a history of or symptoms and/or diagnostic findings suggestive of demyelinating disease is not recommended due to the known association of anti-interleukin agents with demyelinating disorders	No	Wording concerning demyelinating disorders is currently included in SmPC Section 4.4.
Pregnant or lactating women	To ensure the safety of pregnant women or nursing (breast feeding) mothers.	No	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.
History of alcoholism or drug abuse	Potential for patients to be unable to adhere to study protocol	No	This exclusion criterion was not related to the safety of the patient population

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, as well as those caused by prolonged exposure to tocilizumab.

The clinical development program for Tofidence includes 2 studies, one which enrolled healthy volunteers and one efficacy and safety study in patients with RA.

The results from the completed clinical studies with Tofidence available to date demonstrate that the safety and immunogenicity profile is similar to that of RoActemra. Due to the small size of the safety database, (CHMP guideline on similar biological medicinal products containing

biotechnology-derived proteins as active substances: nonclinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 Rev 1) lack of precision for estimated differences in AE/ ADR are to be expected reflecting heterogeneity of the enrolled individuals and the properties of the underlying sampling distribution. The probability to detect uncommon or rare adverse events in this setting will also be limited. In addition, risks associated with prolonged latency until the onset of the adverse event (e.g., in case of a slow disease dynamic, effects requiring a prolonged treatment duration, or effects that depend on the slow accumulation of the medicinal product) are probably under-represented in the current data set.

Given the role of the clinical evidence in a biosimilar development program these limitations are not considered critical. It is the entirety of the evidence in support of a proposed biosimilar, i.e. the physico-chemical characterisation and performance in the functional assays plus the abbreviated clinical program that in aggregate provide the justification for the assertion that Tofidence and RoActemra are comparable versions of tocilizumab. The remaining residual uncertainty at this point is very small despite the noted limitations of the clinical data set.

Under the premise that Tofidence and RoActemra are comparable versions of tocilizumab, the accumulated safety data on RoActemra is considered integral to the safety profile of Tofidence. Given that RoActemra gained a marketing authorisation in the EU in 2009, the volume of patient exposure in the post marketing setting alone should allow the identification of rare events that appear in <1 in 10,000 exposed individuals.

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

The degree of exposure to populations typically under-represented in the clinical development programme is provided in Table 7.

Table 7: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant or Breastfeeding women	Studies with Tofidence have not been conducted in pregnant or breastfeeding women. Given the demonstrated analytical similarity, comparable performance in the functional assays and resemblance in the clinical profile between Tofidence and RoActemra, data generated using RoActemra inform of the benefit risk of Tofidence in this patient group. A single pregnancy in a subject exposed to Tofidence occurred in the BAT1806-002-CR study up to the data-lock point for this RMP (22 April 2021). The RoActemra SmPC advises that there are no adequate data from the use of RoActemra in pregnant women and that an animal study has shown an increased risk of spontaneous abortion/ embryo-foetal death at a high dose (RoActemra SmPC, 2021).

Type of special population	Exposure
Patients with relevant comorbidities: • Hepatic impairment • Renal impairment • Cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients with hepatic or renal impairment, those with cardiovascular disease, were not evaluated during clinical trials of Tofidence. The RoActemra label advises that RoActemra treatment may be associated with elevations in hepatic transaminases, therefore, caution should be exercised when considering treatment of patients with active hepatic disease or hepatic impairment. The RoActemra label advises that no dose adjustment is required in patients with mild or moderate renal impairment. Tofidence has been studied in two clinical trials, one in healthy volunteers, and one in subjects with RA. The RA population studied in the Phase 3 study is aligned with the RA indication in the label of RoActemra (i.e. severe, active and progressive RA). For other approved indications for RoActemra, the applicant will request to extrapolate to other indications of the reference product.
Patients with relevant different ethnic origin	The Phase 1 study was conducted in male Chinese subjects, while the Phase 3 study consisted of 59.3% white subjects and 40.7% Asian subjects. However, tocilizumab has been extensively studied in subject populations that included men and women of a variety of racial backgrounds and ages in clinical trials conducted by the reference product. The reference product, RoActemra was approved in the EU in 2009, and is approved worldwide in countries including the US, Australia, New Zealand, Canada, China, and Japan.
Subpopulations carrying relevant genetic polymorphisms	Single nucleotide polymorphisms in the IL6R have been associated with altered response to tocilizumab in patients with RA (Luxembourger et al., 2019). In the Tofidence clinical development programme, IL6R genotyping was not performed. It is noted that gene-typing is not performed in standard clinical practice when RoActemra is used in patients with RA.
Other: Children	No clinical studies have been conducted with Tofidence in the paediatric patient population. The reference product is indicated for the treatment of active sJIA in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. According to Regulation (EC) No 1901/2006 the requirement to submit a paediatric investigation plan does not apply to similar biological medicinal products. No paediatric investigation plan has been submitted for Tofidence.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

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 (RBC) 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

The overall benefit risk profile of Tofidence corresponds to that of RoActemra. All the established potential and identified risks are listed in the RoActemra Risk Management Plan and are considered equally applicable to Tofidence.

Important identified risks for patients treated with tocilizumab are listed in Section SVII.3.1.

Important potential risks for patients treated with tocilizumab are listed in Section SVII.3.2. These potential risks are based on information derived from use of other anti-IL6 therapies, including class effects, registries, spontaneous reports, and literature.

Important identified risks include the following:

- Serious infection
- Complications of diverticulitis
- Neutropenia
- Hepatotoxicity

Important potential risks include the following:

- Thrombocytopenia and the potential risk of bleeding
- Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events
- Malignancies
- Demyelinating disorders
- Immunogenicity

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

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

- **Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:**
  - Identified risk:
    - Macrophage activation syndrome: occurs with a low frequency.
- **Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered**

by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Identified risks:
  - Serious hypersensitivity reactions
  - Abdominal pain, mouth ulceration, gastritis, stomatitis, gastric ulcer, nausea, diarrhea: followed up by routine pharmacovigilance activities
  - Rash, pruritus, urticaria: followed up by routine pharmacovigilance activities
  - Headache, dizziness: followed up by routine pharmacovigilance activities
  - Weight increased, platelet count decreased, cholesterol increased: followed up by routine pharmacovigilance activities
  - Hypertension: followed up by routine pharmacovigilance activities
  - Leukopenia, Hypofibrinogenaemia: followed up by routine pharmacovigilance activities
  - Peripheral oedema, hypersensitivity reactions: followed up by routine pharmacovigilance activities
  - Conjunctivitis: followed up by routine pharmacovigilance activities
  - Cough, Dyspnoea: followed up by routine pharmacovigilance activities
  - Nephrolithiasis: followed up by routine pharmacovigilance activities
  - Hypothyroidism: followed up by routine pharmacovigilance activities

- **Other reasons for considering the risks not important:**
  - Identified risks:
    - Anaphylaxis: this is considered a well-known risk due to the widespread knowledge on the part of the healthcare professionals administering and managing the patients. Therefore, routine risk minimization measures are considered adequate to minimize this risk
    - Drug-induced liver injury, hepatitis, jaundice, hepatic failure: these hepatic related risk are covered under the identified risk of hepatotoxicity

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

The rationale for considering the remaining risks relevant for inclusion in the current list of safety concerns at the time of initial MAA is presented in Table 8. RoActemra is the reference product (tocilizumab) for Tofidence.

Table 8: Risks considered important for inclusion in the list of safety concerns in the RMP

Risk category	Benefit-risk impact
Important Identified Risk 1: • Serious Infections	This is an important identified risk as requested by the EMA for RoActemra. IL-6 is involved in diverse physiological processes including T-cell activation and induction of immunoglobulin secretion. Inhibition of IL-6 function may therefore increase susceptibility to infection. Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including RoActemra. Serious infections was one of the most common and severe ADRs reported in the RoActemra clinical development programme (RoActemra SmPC, 2021). Active, severe infections is included as a contraindication in SmPC Section 4.3. Serious infections may require medical intervention to be treated, often requiring hospitalisation. Serious infections are thus included as an important identified risk.
Important Identified Risk 2: • Complications of diverticulitis	This is an important identified risk as requested by the EMA for RoActemra. Events of diverticular perforations as complications of diverticulitis have been reported uncommonly with RoActemra in RA patients, but as a serious ADR (RoActemra SmPC, 2021). It is also reported that gastrointestinal perforations have been associated with use of anti-IL-6 drugs with most such events occurred in patients with pre-existing risk factors such as pre-existing diverticulitis or use of oral glucocorticoids) [Choy et al., 2020]. In controlled clinical trials in the RoActemra clinical development programme, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with tocilizumab therapy. In the long-term exposure population the overall rate of gastrointestinal perforation was 0.28 events per 100 patient years. Complications of diverticulitis may require medical intervention to be treated, often requiring hospitalisation. Complications of diverticulitis are thus included as an important identified risk.

Risk category	Benefit-risk impact
Important Identified Risk 3: • Neutropenia	This is an important identified risk as requested by the EMA for RoActemra. In the SmPC (Section 4.4) a warning is included stating that decreases in neutrophil count have been observed following treatment with tocilizumab in combination with methotrexate. As severe neutropenia may be associated with an increased risk of serious infection (RoActemra SmPC, 2021), neutropenia is therefore considered an important identified risk with Tofidence.
Important Identified Risk 4: • Hepatotoxicity	This is an important identified risk as requested by the EMA for RoActemra. Transient or intermittent mild and moderate elevations of hepatic transaminases have been reported commonly with RoActemra treatment, and with increased frequency when used concomitantly with potentially hepatotoxic drugs (e.g., methotrexate) (RoActemra SmPC, 2021). In addition, serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have been observed with RoActemra, as well as cases of liver failure resulting in liver transplantation. Given the serious nature of such events, hepatoxicity is therefore considered an important identified risk with Tofidence.
Important Potential Risk 1: • Thrombocytopenia and the potential risk of bleeding	This is an important potential risk as requested by the EMA for RoActemra. In the RoActemra clinical development programme in the 6-month controlled trials decreases in platelet counts below 100 x 10^3/ µL occurred in 1.7% of patients on tocilizumab 8 mg/kg plus DMARDs compared to <1% on placebo plus DMARDs. These decreases occurred without associated bleeding events. During the double-blind controlled period and with long-term exposure, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical trials. Very rare reports of pancytopenia have occurred in the post marketing setting (RoActemra SmPC, 2021). Thrombocytopenia and the potential risk of bleeding is therefore considered an important potential risk with Tofidence.

Risk category	Benefit-risk impact
Important Potential Risk 2: • Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events	This is an important potential risk as requested by the EMA for RoActemra. In the RoActemra clinical development programme, elevations in lipid parameters including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were observed in patients treated with tocilizumab. In the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents. Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events is therefore considered an important potential risk with Tofidence.
Important Potential Risk 3: • Malignancies	This is an important potential risk as requested by the EMA for RoActemra. Immunosuppressors such as IL-6 inhibitors can increase the risk for some forms of cancer (Bugelsk et al., 2010). In the RoActemra clinical development programme, the clinical data were insufficient to assess the potential incidence of malignancy following exposure to tocilizumab. Long-term safety evaluations are ongoing. Malignancies are often serious, needing chronic medical intervention. Hospitalisation is often required in order to provide appropriate treatment (medication and/or procedure). Malignancies have a potential for a severe outcome and death. Malignancies is therefore considered an important potential risk with Tofidence.

Risk category	Benefit-risk impact
Important Potential Risk 4: • Demyelinating disorders	This is an important potential risk as requested by the EMA for RoActemra. Secondary auto-immunity affecting the central nervous system (CNS) is well described with some biologic agents, mainly tumour necrosis factor (TNF)-alpha inhibitors (Beauchemin and Carruthers., 2016), and there has been isolated case reports of auto-immunity in CNS following tocilizumab therapy (Beauchemin and Carruthers., 2016; RoActemra EPAR, 2009). With the reference product RoActemra, the potential for central demyelination is currently unknown (RoActemra SmPC, 2021). Given the potential for persistent or significant disability or incapacity, demyelinating disorders is therefore considered an important potential risk with Tofidence.
Important Potential Risk 5: • Immunogenicity	This is an important potential risk as requested by the EMA for RoActemra. In the RoActemra clinical development programme, a total of 2,876 patients were tested for anti-tocilizumab antibodies in the 6-month controlled clinical trials. Of the 46 patients (1.6%) who developed anti-tocilizumab antibodies, 6 had an associated medically significant hypersensitivity reaction, of which 5 led to permanent discontinuation of treatment. Thirty patients (1.1%) developed neutralising antibodies (RoActemra SmPC, 2021). Immunogenicity is therefore considered an important potential risk with Tofidence.

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

SVII.2.1 Newly identified safety concerns

Not applicable for initial marketing authorisation application submission.

SVII.2.2 Reclassification of existing safety concerns

Not applicable for initial marketing authorisation application submission.

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 Risk 1: Serious Infections

The safety concern "serious infection" is considered an important identified risk for chronic Tocilizumab dosing, and 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.

Relevant MedDRA terms: No MedDRA term adequately captures the given term. Verbatim term of 'Serious Infections' used.

Potential mechanisms

Tocilizumab is a recombinant humanised IgG1 mAb that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). A potential risk of infections is associated with any immunomodulatory biologic agent. IL-6 plays a role in a variety of immune-related functions including T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. Inhibition of IL-6 has been observed to increase risk of serious infection during the period of exposure (RoActemra SmPC, 2021).

Patients with RA, 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

Serious infections are a potential risk due to mechanism of action of tocilizumab (immunosuppression) and are also seen with molecules with similar mechanism of action (other IL-6 inhibitors). Adequate and well-controlled clinical trials and their long-term extensions, provide the strongest evidence.

Characterisation of the risk

This risk is characterised in Table 9.

Table 9: Characterisation of important identified risk: Serious Infections

Frequency	**RA, sJIA, pJIA** 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., 2020; 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., 2020; 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 BAT-1806-001-CR (healthy volunteers study), 5 subjects (3.9%) across the three study arms experienced treatment-related treatment emergent adverse events (TEAEs) in the SOC of 'Infections and Infestations' [2.2% in the Tofidence arm; 7.1% in the RoActemra-EU arm; 2.4% in the Actemra-US arm]. In study BAT-1806-002-CR (Rheumatoid arthritis), across all study arms 135 subjects (21.7%) experienced treatment-related TEAEs in the SOC of 'Infections and Infestations' [19.6% in the Tofidence arm; 28.1% in the RoActemra arm; 19.0% in the RoActemra to Tofidence switch arm].

Absolute risk and relative risk	The overall risk of serious infection following treatment with tocilizumab is considered low, from the data generated during the Tofidence clinical development programme, as well as that observed for the innovator product RoActemra. Given that RoActemra is approved for concomitant use with methotrexate, also an immunosuppressant, combination therapy is associated with an increased risk of serious infection. For patients initiating tocilizumab therapy for RA, the overall risk of serious infection is not significantly different to that of TNF inhibitors, but was associated with an increased risk of serious bacterial infection (Pawar et al., 2019).
Seriousness and severity	In study BAT-1806-001-CR, all events in the SOC 'Infections and Infestations' were of mild severity, none of which were serious. In study BAT-1806-002-CR, across all study arms, 2.3% of AEs in the SOC 'Infections and Infestations' were classified as serious in nature.
Reversibility and long-term outcomes	In study BAT-1806-002-CR, infections generally resolved upon stopping or interrupting the study drug. No long-term outcome is expected after resolution of hypersensitivity reactions.
Impact on quality of life (QoL)	Serious infections may require medical intervention to be treated, often requiring hospitalisation. No long-term effect is expected after resolution of the serious infection. 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, 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 by 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 and interstitial lung disease 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 Tofidence 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 (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). The Tocilizumab 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.

The majority of TEAEs of infections observed with tocilizumab were mild to moderate and were resolved with standard of care treatment. Risk of serious infections has been considered in the overall benefit-risk assessment with benefit-risk balance remaining positive.

Routine pharmacovigilance activities will be implemented to monitor this risk (see Part III). Risk of infection is included in the warnings and precautions for use (SmPC Section 4.4).

Risk minimisation activities are discussed in Part V.

Public health impact

No significant public health impact is expected.

Per real world evidence data, patients with diabetes or increased body weight are associated with an increased risk of serious infection.

Important Identified Risk 2: Complications of diverticulitis

The safety concern "complications of diverticulitis" 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.

Relevant MedDRA terms: Diverticulitis (PT) or GI Perforation Standardised MedDRA Query (SMQ) (narrow); GI Perforation SMQ (wide)

Potential mechanisms

The mechanism for intestinal perforation as a complication of diverticulitis in patients receiving tocilizumab is not fully understood, but prior diverticulitis has been noted as a risk factor (Strangfeld et al., 2017).

Evidence source(s) and strength of evidence

Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.

Characterisation of the risk

This risk is characterised in Table 10.

Table 10: Characterisation of important identified risk: Complications of diverticulitis

Frequency	**RA, sJIA, pJIA** Myllykangas-Luosujärvi found a 6-fold excess mortality in patients with RA as a result of diverticular disease, and postulated a link to medications used to treat RA (Myllykangas-Luosujarvi et al.,1995). As corticosteroids are known to be associated with abscess development, and since both corticosteroids and NSAIDs have been implicated in perforated diverticular disease, Mpofu et al. undertook a case control study to investigate their association with the development of sigmoid diverticular abscess perforation in patients with and without RA (Mpofu et al., 2004). This demonstrated a strong association between corticosteroid treatment in the development of sigmoid diverticular abscess perforation in both rheumatic and non-rheumatic patients. Data from claims databases suggest that treatment with corticosteroids may be associated with an increased risk of gastrointestinal (GI) perforations with rates of 0.19 for biologics administered concomitantly with corticosteroids, and 0.3 for corticosteroids (Curtis et al., 2012) **COVID-19** Limited information is available for GI perforation in patients with COVID-19. Associations between GI symptoms and COVID-19 have been evidenced but restricted to diarrhea (CDC 2020a; WHO 2020a; WHO 2020b). In a retrospective cross-sectional study of 412 COVID-19 patients in Boston, United States, bowel wall perforation was observed in 1patient (0.2%) (Bhayana et al., 2020). Zangrillo et al. (2020) reported a single case of GI perforation in a case series of 73 mechanically ventilated patients with confirmed COVID-19 admitted to the ICU in Milan, Italy (Zangrillo et al. 2020). A retrospective study included 81 adult COVID-19 patients with abdominal computed tomography performed from 1 April 2020 to 1 May 2020 in Brazil. A single case of intestinal perforation was observed on abdominal imaging accounting for the prevalence of 1% (Horvat et al., 2021). In study BAT-1806-001-CR (healthy volunteers study), no instances of complications of diverticulitis were observed, including intestinal perforations etc. In study BAT-1806-002-CR (Rheumatoid arthritis), a single subject experienced a single event of diverticular perforation (RoActemra arm).

Absolute risk and relative risk	Several studies have reported an increased risk of complications of diverticulitis following treatment with tocilizumab. Data from the German biologics register RABBIT revealed a that the crude rate of lower intestinal perforations was significantly increased in tocilizumab treated RA patients (2.7/1000 PYs) as compared with all other treatments (0.2−0.6/1000 PYs) (Strangfeld et al., 2017). The overall risk of complications of diverticulitis following treatment with tocilizumab is still considered low however, from the data generated during the Tofidence clinical development programme, as well as that observed for the innovator product RoActemra.
Seriousness and severity	For the single event of diverticular perforation that occurred in study BAT-1806-002-CR, the event was classified as serious (and severe), as the subject required in-patient hospitalisation. The event was judged as possibly related to study treatment.
Reversibility and long-term outcomes	In study BAT-1806-002-CR, the event resolved with sequalae. Long-term outcomes following complications of diverticulitis such as intestinal perforation are generally good and respond well to conservative management. Patients requiring colonic resection however have mortality rates >10% (Sarin and Boulos, 1994).
Impact on quality of life (QoL)	Complications of diverticulitis such as intestinal perforation may have a substantial impact on patients' lives and quality of life, potentially requiring hospitalisation or surgical intervention (Sarin and Boulos, 1994). Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation.

Risk factors and risk groups

Tocilizumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis.

Preventability

Prescribing information warning that 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 gastrointestinal 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 benefit-risk balance of the product

The rare event of perforation of the large bowel has been seen in subjects who had large bowel infections. Perforations may occur in the absence of clear symptoms or clinical signs. Tocilizumab should not be administered to patients with a history of complicated diverticulitis and should be

used with caution in patients with a history of diverticulitis. The Tocilizumab 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

Because of low overall incidence of complications of diverticulitis, the potential public health impact is considered low.

Important Identified Risk 3: Neutropenia

Relevant MedDRA terms: Neutropenia (PT) / Neutrophil count decreased (PT)

Potential mechanisms

IL-6 plays a role in a variety of immune-related functions including T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. The molecular underpinning of why neutrophil levels are reduced following tocilizumab therapy are unknown. In vitro studies suggest that IL-6 increases circulating neutrophils by releasing them from marginated pools in bone marrow (Suwa et al., 2000), and tocilizumab may therefore potentially reverse this effect. Furthermore, neutrophil counts were elevated in a monkey model of arthritis and were rapidly increased by the administration of IL-6, a kinetic effect suggestive of migration of neutrophils from the marginal pool to the circulation. The increase in neutrophils was inhibited by tocilizumab (Hashizume et al., 2011).

Evidence source(s) and strength of evidence

Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.

Characterisation of the risk

This risk is characterised in Table 11.

Table 11: Characterisation of important identified risk: Neutropenia

Frequency	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 BAT-1806-001-CR (healthy volunteers study), 57 subjects (44.2%) across the three study arms experienced treatment-related TEAEs of the PT 'Neutrophil Count Decreased' [26.7% in the Tofidence arm; 47.6% in the RoActemra-EU arm; 59.5% in the Actemra-US arm]. In study BAT-1806-002-CR (Rheumatoid arthritis), across all study arms 51 subjects (8.2%) experienced treatment-related TEAEs in PT 'Neutropenia' [7.7%% in the Tofidence arm; 9.0% in the RoActemra arm; 8.5% in the RoActemra to Tofidence switch arm].
Absolute risk and relative risk	The overall risk of neutropenia across all indications approved for Tocilizumab is considered relatively high (i.e. 'common' frequency per RoActemra SmPC section 4.8). The clinical development programme of Tofidence as well as that of RoActemra show these events are non-serious in nature.
Seriousness and severity	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 BAT-1806-001-CR, over 80% (46/57) of decreased neutrophil counts were mild to moderate in nature. None of the events were considered serious in nature. In study BAT-1806-002-CR, no cases of neutropenia were considered SAEs, and the majority were mild to moderate in nature.
Reversibility and long-term outcomes	Discontinuation of treatment is expected to lead to recovery of neutrophil counts. The SmPC (Section 4.2) recommends that for RA patients, neutrophils should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice. Long-term neutropenia may be associated with increased risk of infection.
Impact on quality of life (QoL)	The impact on individual patients is difficult to predict. The morbidity associated with neutropenia derives from the increased susceptibility to infection that is causes. The specific impact will depend on the infection involved.

Risk factors and risk groups

A number of risk factors have been identified that lead to increased risk of neutropenia. Many medications used to treat RA can induce neutropenia, such as methotrexate (due to folic acid deficiency) [Lazaro and Morel., 2015]), rituximab (Salmon et al., 2015), as well as anti-TNF agents (e.g., adalimumab, etanercept, and infliximab; Rajakulendran et al., 2006). A less common cause of neutropenia is an RA-related autoimmune reaction (Lazaro and Morel., 2015). Other risk factors include female gender, and lower baseline neutrophil counts (Fragoulis et al., 2018).

Preventability

Neutropenia may be prevented by administration of granulocyte colony stimulating factor.

In patients not previously treated with Tocilizumab for all indications other than, COVID-19, initiation is not recommended in patients with an ANC below 2 x 10^9/L. Monitoring during treatment is recommended and dose modification or treatment discontinuation is recommended based upon ANC. In patients who develop an ANC < 0.5 x 10^9/L continued treatment is not recommended.

For patients with COVID-19 who develop an ANC <1 x 10^9/L, administration of treatment is not recommended.

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

Impact on the benefit-risk balance of the product

Risk of neutropenia has been considered in the overall benefit-risk assessment with benefit-risk balance remaining positive.

Routine pharmacovigilance will be implemented for neutropenia (see Part III). Dose adjustment in relation to low neutrophil count is included in the Posology and method of administration (SmPC Section 4.2) and Warnings and Precautions (SmPC Section 4.4).

Risk minimisation activities are discussed in Part V.

Public health impact

The public health impact of neutropenia is expected to be minimal. In a pooled analysis of data from phase 3 and 4 trials, infection rates within 30 days of neutrophil count changes were calculated per 100 patient-years of Tocilizumab exposure. The analysis found that while more Tocilizumab-treated than placebo-treated patients had grade 1/2 or 3/4 neutrophil counts (Tocilizumab: 28.2%/3.1%; placebo: 8.9%/0.2%), rates (95% CI) of serious infections within 30 days of normal [4.66 (4.31, 5.03)], grade 1/2 [2.48 (1.79, 3.34)] and 3/4 [2.77 (0.34, 10.01)] neutrophil counts were similar. Furthermore, patients who stopped Tocilizumab in response to decreased neutrophil count returned more quickly to normal levels than patients who reduced or continued their dose. Decreases in neutrophil counts in patients taking Tocilizumab do not therefore appear to be associated with serious infections and are normalized by current risk mitigation guidelines as outlined in the SmPC (Moots et al., 2017).

Important Identified Risk 4: Hepatotoxicity

Relevant MedDRA terms: Drug related hepatic disorders - comprehensive search (SMQ)/ 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).

Potential mechanisms

The mechanism by which tocilizumab causes hepatotoxicity unknown, but may be the result of its effects on the immune system or on the IL-6 pathway which is important in liver regeneration.

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

Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.

Characterisation of the risk

This risk is characterised in Table 12.

Table 12: Characterisation of important identified risk: Hepatotoxicity

Frequency	The overall worldwide incidence rate of drug-induced liver injury (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. 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/litre) (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). In study BAT-1806-001-CR (healthy volunteers study), 23 subjects (17.8%) and 18 subjects (14.0%) across the three study arms experienced treatment-related TEAEs of the PTs increased ALT and increased AST, respectively. In the Tofidence arm, increased ALT was recorded in 6 subjects (13.3%), while increased AST was recorded in 7 subjects (15.6%). In study BAT-1806-002-CR (Rheumatoid arthritis), across all study arms 71 subjects (11.4%) experienced treatment-related TEAEs in the PT 'ALT increased', while 36 subjects (5.8%) experienced treatment-related 'AST increases'. Considering the Tofidence arm, 29 subjects (9.3%) and 17 subjects (5.4%) experienced treatment-related increases in ALT and AST, respectively.
Absolute risk and relative risk	The overall risk of liver enzyme abnormalities across all indications approved for Tocilizumab is considered relatively high (i.e. 'common' frequency per RoActemra SmPC section 4.8). The clinical development programme of Tofidence as well as that of RoActemra show these events are non-serious in nature.

Seriousness and severity	Mild and moderate elevations of hepatic transaminases have been observed with Tocilizumab treatment. Increased frequency of these elevations was observed when drugs, which are known to cause hepatotoxicity (e.g., MTX), were used in combination with Tocilizumab. Serious DILI, including acute liver failure, hepatitis, and jaundice, have been observed with Tocilizumab. Cases of liver failure resulting in liver transplantation have been reported. In study BAT-1806-001-CR, all treatment-related cases of ALT and AST increases were mild in nature. None of the events were considered serious in nature. In study BAT-1806-002-CR, no cases of ALT or AST increases were considered SAEs, and the majority were mild to moderate in nature.
Reversibility and long-term outcomes	The mild liver injury caused by tocilizumab is generally short lived and resolves within 2 to 6 weeks. The majority of patients can continue the 4 weekly infusions, although dose reduction may be warranted (SmPC Section 4.2). There are normally no long-term consequences following recovery from transient increases in liver enzymes.
Impact on quality of life (QoL)	The typical transient or intermittent mild and moderate elevations of hepatic transaminases that are commonly observed with Tofidence treatment are not expected to significantly affect quality of life. Serious drug-induced liver injury, including acute liver failure, hepatitis and jaundice, have however been observed with RoActemra. Cases of liver failure resulting in liver transplantation have been reported. (RoActemra SmPC 2021). Such events may have a substantial impact on patients' lives and quality of life, any may require medical intervention or hospitalisation.

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

The SmPC recommends that for RA, pJIA and sJIA patients, ALT/AST should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter (SmPC Section 4.4). Criteria for treatment modification or discontinuation are also included in the SmPC (SmPC Section 4.2).

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 COVID-19 patients with elevated ALT or AST above 10 x ULN, administration of RoActemra treatment is not recommended. In COVID-19 patients, ALT /AST should be monitored according to current standard clinical practices.

Impact on the benefit-risk balance of the product

Risk of hepatotoxicity has been considered in the overall benefit-risk assessment with benefit-risk balance remaining positive, given the rare frequency of serious hepatotoxicity events.

Routine pharmacovigilance will be implemented for hepatoxicity (see Part III). Dose adjustment in relation to elevations in live enzyme levels is included in the Posology and method of administration (SmPC Section 4.2) and Warnings and Precautions (SmPC Section 4.4).

Risk minimisation activities are discussed in Part V.

Public health impact

The public health impact of hepatotoxicity is not known.

Important Potential Risk 1: Thrombocytopenia and the potential risk of bleeding

Relevant MedDRA terms: Thrombocytopenia (PT) / Haematopoietic thrombocytopenia (SMQ), Thrombocytopenia SMQ wide

Potential mechanisms

IL-6 is involved in diverse physiological processes including the stimulation of haemopoiesis. IL-6 increases platelet count during inflammation (Lee et al., 2019), and its inhibition therefore may lead to reduced platelet counts.

Evidence source(s) and strength of evidence

Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.

Characterisation of the risk

This risk is characterised in Table 13.

Table 13: Characterisation of important potential risk: Thrombocytopenia and the potential risk of bleeding

Frequency	**RA, sJIA, pJIA** 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 × 10^9/L; 95% CI (33.0-4.06), which was not significantly lower than that in non-severe patients (Jin et al., 2020). A study of 1,476 COVID-19 patients in Wuhan, China, reported 20.7% had thrombocytopenia during hospitalization. Compared with survivors, non-survivors were older, were more likely to have thrombocytopenia and had lower nadir platelet counts. The study concluded that thrombocytopenia is common in patients with COVID-19 and is associated with increased risk of in-hospital mortality (Yang et al., 2020a). Among 191 COVID-19 patients, 7% had thrombocytopenia on admission (Zhou et al., 2020). 15 out of 21 non-survivors (8% of the total cohort) admitted to hospital in Wuhan developed overt disseminated intravascular coagulation (≥5points) according to the International Society on Thrombosis and Haemostasis diagnostic criteria (Tang et al., 2020a). In study BAT-1806-001-CR (healthy volunteers study), a single subject (0.8%) across all 3 treatment arms experienced treatment-related TEAE of the PT Thrombocytopenia. No events of bleeding were recorded during the study. In study BAT-1806-002-CR (Rheumatoid arthritis), across all study arms 16 subjects (2.6%) experienced treatment-related TEAEs in the PT 'Thrombocytopenia' [1.9% in the Tofidence arm; 3.6% in the RoActemra arm; 2.8% in the RoActemra to Tofidence switch arm].
Absolute risk and relative risk	As can be seen above, tocilizumab treatment is associated with a low risk of thrombocytopenia. While a risk of bleeding is theoretically associated with lowered platelet levels, bleeding events were not observed in either the Tofidence or RoActemra clinical development programmes.
Seriousness and severity	In study BAT-1806-001-CR, the event occurred in the RoActemra treatment arm, and was considered mild in severity and non-serious in nature. In study BAT-1806-002-CR, all cases of Thrombocytopenia were non-serious in nature, and of mild or moderate severity.

Reversibility and long-term outcomes	Discontinuation of treatment is expected to lead to recovery of platelet counts. Long-term thrombocytopenia may be associated with increased risk of bleeding events.
Impact on quality of life (QoL)	Thrombocytopenia by itself in the absence of bleeding events is not expected to impact 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

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

Immune thrombocytopenia (ITP) is an autoimmune disease defined by low platelet counts which presents with an increased bleeding risk. Several genetic risk factors (e.g., polymorphisms in immunity-related genes) predispose to IT. Autoantibodies and cytotoxic CD8+ T cells (Tc) mediate the anti-platelet response leading to thrombocytopenia (Swinkels et al., 2018). Other studies have found increased risk of Thrombocytopenia in patients with RA associated with coadministration of MTX and NSAID or multiple drug interactions (Franck et al., 1996). Drug-induced ITP is also associated with use of drugs including DMARDs and NSAIDSs (van den Bemt et al., 2004).

Preventability

The SmPC recommends that for RA patients, platelets should be monitored every 4 to 8 weeks after the start of therapy and thereafter according to standard clinical practice. In sJIA and pJIA patients, platelets should be monitored at the time of second infusion and thereafter according to good clinical practice (SmPC Section 4.4).

Criteria for treatment modification, interruption or discontinuation are also included in the SmPC (SmPC Section 4.2).

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

Risk of thrombocytopenia and bleeding events has been considered in the overall benefit-risk assessment with benefit-risk balance remaining positive.

Routine pharmacovigilance will be implemented for this potential risk (see Part III). Dose adjustment/interruption/discontinuation in relation to this potential risk is included in the Posology and method of administration (SmPC Section 4.2) and Warnings and Precautions (SmPC Section 4.4).

Risk minimisation activities are discussed in Part V.

Public health impact

Since all events of thrombocytopenia reported with Tofidence were non-serious and did not lead to bleeding events, the potential public health impact is considered low.

Important Potential Risk 2: Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events

Relevant MedDRA terms: Hyperlipidaemia (PT) / Myocardial infarction SMQ narrow, Ischaemic Cerebrovascular or Hemorrhagic Cerebrovascular SMQ narrow

Potential mechanisms

Potential mechanisms for hyperlipidemia and increased risk of cardiovascular and cerebrovascular events following treatment with tocilizumab may involve the inhibition of IL-6 induced expression of aapolipoproteins in the liver (Kawashiri et al., 2011; Müller et al., 2015) which function in lipoprotein clearance.

Additionally, 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 of the innovator product provide the strongest evidence.

Characterisation of the risk

This risk is characterised in Table 14.

Table 14: Characterisation of important potential risk: Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events

Frequency	**RA, sJIA, pJIA** **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) **<u>COVID-19</u>** The prevalence of elevated lipid levels such as hyperlipidemia, dyslipidemia, and hypercholesterolemia in patients with COVID-19 ranged from 5% to 46.2% (Zhang et al., 2020b; Grasselli et al., 2020; Lodigiani et al., 2020; Petrilli et al., 2020). The low prevalence of 5% for hyperlipidemia was observed from a study of 140 hospitalized COVID-19 patients in China (Zhang et al., 2020b). In Europe, a retrospective case series of 1,591 Italian ICU patients with laboratory-confirmed COVID-19 found 18% had hypercholesterolemia (Grasselli et al., 2020). Among 388 Italian COVID-19 patients admitted to either ICU or general ward, 19.6% had dyslipidemia (Lodigiani et al., 2020). Studies from the United States found relatively higher prevalence of elevated lipid profiles compared to studies from Europe and China: of 5,279 COVID-19 patients identified between 1 March 2020 and 8 April 2020 in New York, 32.5% had hyperlipidemia (Petrilli et al., 2020). The COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) estimated that as of 30 November 2021, in the United States, the prevalence of CVD was 36.8% in adults and 8.7% 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 BAT-1806-001-CR (healthy volunteers study), 26 subjects (20.2%) across the three study arms experienced treatment-related TEAEs of the PT Hypertriglyceridaemia [20.0% in the Tofidence arm; 26.2% in the RoActemra-EU arm; 14.3% in the Actemra-US arm]. 5 subjects experienced related AEs in the SOC 'Cardiac Disorders' across all three study arms, but events were not related to lipid parameters as expected given the single administration of tocilizumab used in the study (3 subjects experienced Arrhythmia Supraventricular, 1 subject experienced Sinus Tachycardia, 1 subject experienced Supraventricular Extrasystoles). In study BAT-1806-002-CR (Rheumatoid arthritis), across all study arms 36 subjects (5.8%) experienced treatment-related TEAEs in the PT 'Hyperlipidaemia' [6.7% in the Tofidence arm; 4.2% in the RoActemra arm; 5.6% in the RoActemra to Tofidence switch arm]. For the PT 'Hypertriglyceridaemia', 29 subjects (4.7%) experienced treatment-related TEAEs overall [5.8% in the Tofidence arm; 4.2% in the RoActemra arm; 2.8% in the RoActemra to Tofidence switch arm].

	For the PT 'Hypercholesterolemia', 30 subjects (4.8%) experienced treatment-related TEAEs overall [4.5% in the Tofidence arm; 7.2% in the RoActemra arm; 2.8% in the RoActemra to Tofidence switch arm].
Absolute risk and relative risk	The overall risk of elevations in lipid levels (hypercholesteremia, Hypertriglyceridemia) can range from very common to uncommon (RoActemra SmPC section 4.8). The clinical development programme of Tofidence as well as that of RoActemra show these events are non-serious in nature. Elevations in LDL cholesterol responded to treatment with lipid-lowering.
Seriousness and severity	In study BAT-1806-001-CR, the majority of subjects experienced Hypertriglyceridaemia events that were mild to moderate in nature, with only 1 subject experiencing a Grade II event. One (1) subject experienced a CTCAE grade IV event of hypertriglyceridaemia with no clinical symptoms and was classed as non-serious. In study BAT-1806-002-CR, all cases of Hyperlipidaemia, Hypertriglyceridaemia, and Hypercholesterolemia were non-serious in nature, and mostly mild-to-moderate in nature.
Reversibility and long-term outcomes	Discontinuation of treatment is expected to lead to reversal of elevations in lipid levels. The SmPC (Section 4.4) recommends that for In sJIA, pJIA and RA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia. Long-term elevations in lipids are associated with increased risk of cardiovascular events.
Impact on quality of life (QoL)	The impact of the cardiovascular or cerebrovascular event will vary according to the nature and severity of the specific event. This could for example be associated with mild inconvenience to the patient for less severe events, while cardiovascular events such as myocardial infarction or stroke may have severe long-standing consequences and may be fatal. The relationship between elevations seen in total cholesterol, LDL, and triglycerides and the risk for cardiovascular/cerebrovascular disease is unknown.

Risk factors and risk groups

Patients with underlying cardiovascular are at higher risk for severe illness from COVID-19 (CDC 2022). Of 41 Chinese COVID-19 patients admitted to hospital, 6 (15%) had underlying CVD; patients with CVD comprised 23% of those requiring ICU care and 11% of those who did not (Huang et al., 2020).

Preventability

The SmPC recommends that for sJIA, pJIA and RA patients, assessment of lipid parameters should be performed 4 to 8 weeks following initiation of therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia (SmPC Section 4.4).

In the RoActemra clinical development programme, in the majority of patients, there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents.

Impact on the benefit-risk balance of the product

Risk of elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events have been considered in the overall benefit-risk assessment with benefit-risk balance remaining positive. The SmPC, Patient Information Leaflet, Educational Materials for Healthcare professionals and patients, mitigate the risk severity and also provide information regarding managing the risk.

Routine pharmacovigilance will be implemented for this potential risk (see Part III).

Risk minimisation activities are discussed in Part V.

Public health impact

The incidence of lipid elevations following tocilizumab treatment is within expected range for the population treated with other biologics (e.g., Sarilumab), thereby no additional impact to public health is foreseen.

Since for the majority of patients there was no increase in atherogenic indices, and elevations in total cholesterol responded to treatment with lipid lowering agents, the potential public health impact is considered low.

Important Potential Risk 3: Malignancies

Relevant MedDRA terms: Malignant tumours (SMQ narrow)

Potential mechanisms

Many immunosuppressive agents are associated with an increased risk of malignancy (Gallagher et al., 2010; Beyaert et al., 2013). IL-6 is thought to play a dual role in cancer. , IL-6 with its pro-inflammatory properties is over-expressed in almost all types of tumours. The strong association between inflammation and cancer is reflected by the high IL-6 levels in the tumour microenvironment, where it promotes tumorigenesis by regulating all hallmarks of cancer and multiple signalling pathways, including apoptosis, survival, proliferation, angiogenesis, invasiveness and metastasis (Kumari et al., 2016). Meanwhile, animal studies have shown that IL-6 is instrumental in tumor regression (Mulé et al., 1990).

Evidence source(s) and strength of evidence

Risk of malignancies is a potential risk due to the mechanism of action of tocilizumab (immunosuppression) and are also seen with molecules with similar mechanism of action (other IL-6 inhibitors).

Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.

Characterisation of the risk

This risk is characterised in Table 15.

Table 15: Characterisation of important potential risk: Malignancies

Frequency	**RA, sJIA, pJIA** 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 BAT-1806-001-CR (healthy volunteers study), no subject experienced an adverse event related to malignancy. In study BAT-1806-002-CR (Rheumatoid arthritis), across all study arms 1 subject (0.2%) experienced a malignancy, a case of Stage III ovarian cancer.
Absolute risk and relative risk	Several studies have reported an increased risk of malignancy among patients with RA (Simon et al, 2015). In the RoActemra clinical development programme, there was no overall trend in the type or incidence of malignancies observed with tocilizumab that might indicate an increased risk compared to the background rate in the study population.

Seriousness and severity	In study BAT-1806-002-CR, the case of ovarian cancer occurred in the Tofidence treatment arm and was considered possibly related to study treatment. The event was considered to be a serious AE and was of severe intensity.
Reversibility and long-term outcomes	The single case of Ovarian cancer that occurred in study BAT-1806-002-CR resulted in patient death. Malignancies have a potential for a severe outcome and death.
Impact on quality of life (QoL)	There have been reports of cancer in patients treated with Tocilizumab; no individual type of tumour was more common than expected in this population. The impact for a reduced quality of life is high in many cases.

Risk factors and risk groups

None identified.

Preventability

Early detection and prompt treatment has a significant impact on progression of disease and treatment success.

Impact on the benefit-risk balance of the product

Despite the low event rate, a potential risk cannot be excluded. Tocilizumab treatment should not be started in subjects with cancer. The SmPC, Patient Information Leaflet, Educational Materials for Healthcare professionals and patients, mitigate the risk severity and also provide information regarding managing the risk.

Malignancy has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Routine pharmacovigilance activities are in place to monitor this risk (see Part III).

Public health impact

Concern is high because of the seriousness of the risk; however because of low overall incidence of malignancies and related adverse events (which was in line with the background rate of malignancies in RA and other indications), the potential public health impact is considered low.

It is also noted that a 2011 meta-analysis and systematic review of randomised clinical trials found that tocilizumab does not significantly increase the rate of malignancies (Campbell et al., 2011).

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.

Important Potential Risk 4: Demyelinating disorders

Relevant MedDRA terms: Demyelination (narrow SMQ)

Potential mechanisms

Several isolated case reports have suggested an associated between demyelinating disorders such as multiple sclerosis and tocilizumab therapy. The molecular mechanism behind this remains unclear.

Evidence source(s) and strength of evidence

Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.

Characterisation of the risk

This risk is characterised in Table 16.

Table 16: Characterisation of important potential risk: Demyelinating disorders

Frequency	**RA, sJIA, pJIA** 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 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 BAT-1806-001-CR (healthy volunteers study) or study BAT-1806-002-CR (Rheumatoid arthritis), no subject experienced an adverse event related to Demyelinating disorders.

Absolute risk and relative risk	The overall risk of demyelinating disorders following treatment with Tofidence is considered very low. No events were noted in the Tofidence clinical development programme. In the RoActemra clinical development programme, 2 cases were described as optic neuritis and chronic brain ischemia most likely secondary to polycythemia. After completion of the original filing dossier, there was one report of drug-induced leukoencephalopathy (possibly drug-related), one cranial neuropathy, one abnormal nuclear magnetic resonance imaging and one peripheral demyelination. Isolated case studies have also been reported in the literature (Beauchemin and Carruthers., 2016)
Seriousness and severity	Not applicable, no cases arose during the Tofidence clinical development programme.
Reversibility and long-term outcomes	Demyelinating disorders are associated with poor long-term outcomes and significant disability, and are in many cases not reversible.
Impact on quality of life (QoL)	The impact for a reduced quality of life is high, given the potential for persistent or significant disability or incapacity associated with demyelinating disorders.

Risk factors and risk groups

None identified.

Preventability

Not known

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. The Tocilizumab 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.

Demyelinating disorders has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Routine pharmacovigilance activities are in place to monitor this risk (see Part III).

Public health impact

Because of low overall incidence of demyelinating disorders the potential public health impact is considered low.

Important Potential Risk 5: Immunogenicity

Relevant MedDRA terms: Drug Specific Antibody (PT)

Potential mechanisms

Any exogenous biologic has the potential for an immune response, which may lead to anti-drug antibodies and/or neutralising antibodies.

Evidence source(s) and strength of evidence

Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.

Characterisation of the risk

This risk is characterised in Table 17.

Table 17: Characterisation of important potential risk: Immunogenicity

Frequency	In study BAT-1806-001-CR (healthy volunteers study), across all study arms a total of 9 (7.0%), 29 (22.5%), and 41(31.8%) subjects reported antidrug antibody (ADA)-positive results on Day 15, Day 43 and Day 57, respectively. Similar ADA incidence rate was observed among 3 groups on Day 15 and Day 43. The ADA -positive results on Day 57 (Final Visit) was reported by 19 (42.2%), 10 (23.8%), and 12 (28.6%) subjects in Tofidence arm, RoActemra-EU arm, and Actemra-US arm, respectively. Across all study arms, neutralising antibodies (nAb) positivity was observed in a total of 9 (7.0%), 24 (18.6%), and 35 (27.1%) subjects on Day 15, Day 43, and Day 57, respectively. The nAb-positive results on Day 57 (Final Visit) was reported by 14 (31.1%), 9 (21.4%), and 12 (28.6%) subjects in the Tofidence arm, RoActemra-EU arm, and Actemra-US arm, respectively. In study BAT-1806-002-CR (Rheumatoid arthritis), a total of 91 (29.2%), 41 (24.6%), and 31 (21.8%) of subjects in the Tofidence arm, RoActemra-arm, and RoActemra switch arm, respectively, experienced ADAs at any point in the study. Over the whole study, all ADA positive subjects all tested positive for NAbs, except for 1 subject in each group. The majority of ADA responses were of low titer and transient.
Absolute risk and relative risk	Tocilizumab is considered to have a low risk of immunogenicity as it is a humanised mAb with an immunosuppressive mode of action. The development of ADAs and nAbs was not associated with safety concerns in the Tofidence clinical development programme.

Seriousness and severity	In studies BAT-1806-001-CR and BAT-1806-002-CR, there was no apparent effect of ADA development on safety and ADA were not associated with an increase in TEAEs, infusion related reactions, or hypersensitivity reactions. For the reference product, no correlation between the development of anti-Tocilizumab antibodies and serious hypersensitivity or anaphylaxis has been observed in clinical trials.
Reversibility and long-term outcomes	In study BAT-1806-001-CR, ADA and nAb levels were recorded up to Day 57, and levels were seen to persist at this timepoint. In study BAT-1806-002-CR, ADA and nAb levels were recorded up to the end of treatment period 2 (52 weeks total). Most patients reported transient ADAs of low titerwhich is in line with published data for the reference product (Burmester et al., 2017). The long-term outcome of sustained immunogenicity against tocilizumab is not known.
Impact on quality of life (QoL)	Impact on quality of life is expected to be minimal.

Risk factors and risk groups

Not identified.

Preventability

Not known.

Impact on the benefit-risk balance of the product

Immunogenicity has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive.

Routine pharmacovigilance activities are in place to monitor this risk (see Part III).

Public health impact

Because of the limited clinical relevance of immunogenicity and absence of associated safety concerns, the potential public health impact is considered low.

SVII.3.2 Presentation of the missing information

Not applicable.

PART II: MODULE SVIII - SUMMARY OF SAFETY CONCERNS

The Tofidence safety specification includes the following important identified risks, important potential risks and areas of missing information (Table 18).

Table 18: 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

* The safety concerns “serious infection” and “complications of diverticulitis” are considered important identified risks for chronic Tocilizumab dosing, and 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

The Sponsor employs routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline in order to further characterise all of the safety concerns discussed in this EU RMP. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

In addition to adverse reactions reporting and signal detection activities, the following routine pharmacovigilance activities are also employed in order to provide further characterisation data for specific safety concerns:

Specific adverse reaction follow-up questionnaires for malignancies: The Sponsor has a standardised global process for the use of follow-up questionnaires within the pharmacovigilance system as part of post-marketing surveillance. This process includes contact to the healthcare professional (HCP) or reporter using the questionnaire via phone, fax or send letter/form. The follow-up to consumer will include an attempt to obtain consent to contact the HCP. A minimum number of queries are made depending on the seriousness of the case; medical judgment or local regulations are applied to determine if further attempts (above the minimum) should be made. Data collection will occur using the questionnaire listed in Annex 4.

III. 2 Additional pharmacovigilance activities

Not applicable.

III. 3 Summary table of additional pharmacovigilance activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable - there are no imposed post-authorisation efficacy studies.

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

V. 1 Routine risk minimisation measures

A description of the routine risk minimisation measures per safety concern are discussed in Table 19.

Table 19: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Serious infection	***Routine risk communication:*** Active severe infections are included as a contraindication in SmPC Section 4.3 (Contraindications). Risk of serious infection is discussed in SmPC Section 4.4 (Special warnings and precautions for use). Infections are listed in SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Recommendation for action required in case of infection as well as monitoring of infections are included in SmPC Section 4.4 (Special warnings and precautions for use). Instructions to look out for signs of infections are included in PL Section 2 (What you need to know before you are given Tofidence). Signs of serious infection and instruction to alert doctor immediately are included in PL Section 4 (Possible side effects). ***Other routine risk minimisation measures beyond the Product Information:*** Pack size: None Legal status: Tofidence is a prescription only medicine.
Complications of diverticulitis	***Routine risk communication:*** Risk of complications of diverticulitis is discussed in SmPC Section 4.4 (Special warnings and precautions for use). Complications of diverticulitis are listed in SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects).

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for action required in case of patients presenting with symptoms potentially indicative of complicated diverticulitis are included in SmPC Section 4.4 (Special warnings and precautions for use). Instructions to look out for signs of diverticulitis are included in PL Section 2 (What you need to know before you are given Tofidence). ***Other routine risk minimisation measures beyond the Product Information:*** Pack size: None. Legal status: Tofidence is a prescription only medicine.
Neutropenia	***Routine risk communication:*** Dose adjustment in cases of low absolute neutrophil count are included in SmPC Section 4.2 (Posology and method of administration). Risk of neutropenia is included in SmPC Section 4.4 (Special warnings and precautions for use). Neutropenia is listed in SmPC Section 4.8 (Undesirable effects). PL Section 4 (Possible side effects). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Recommendations for management of patients with low absolute neutrophil counts are included in SmPC Section 4.2 (Posology and method of administration). Monitoring of neutrophil levels is recommend in SmPC Section 4.4 (Special warnings and precautions for use). ***Other routine risk minimisation measures beyond the Product Information:*** Pack size: None. Legal status: Tofidence is a prescription only medicine.
Hepatotoxicity	***Routine risk communication:*** Dose adjustment in cases of abnormal liver enzyme levels are included in SmPC Section 4.2 (Posology and method of administration). Risk of hepatotoxicity is included in SmPC Section 4.4 (Special warnings and precautions for use). Increased hepatic transaminases is listed in SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:***

Safety concern	Routine risk minimisation activities
	Recommendations for management of patients with liver enzyme abnormalities are included in SmPC Section 4.2 (Posology and method of administration). Monitoring of ALT and AST levels is recommend in SmPC Section 4.4 (Special warnings and precautions for use). ***Other routine risk minimisation measures beyond the Product Information:*** Pack size: None. Legal status: Tofidence is a prescription only medicine.
Important Potential Risks	
Thrombocytopenia and the potential risk of bleeding	***Routine risk communication:*** Dose adjustment in cases of low platelet count are included in SmPC Section 4.2 (Posology and method of administration). Risk of decreased platelet count is included in SmPC Section 4.4 (Special warnings and precautions for use). Decreased platelet count is listed in SmPC Section 4.8 (Undesirable effects). PL Section 4 (Possible side effects). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Recommendations for management of patients with low platelet count are included in SmPC Section 4.2 (Posology and method of administration). Monitoring of platelet counts is recommend in SmPC Section 4.4 (Special warnings and precautions for use). ***Other routine risk minimisation measures beyond the Product Information:*** Pack size: None. Legal status: Tofidence is a prescription only medicine.
Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events	***Routine risk communication:*** Risk of elevations in lipid parameters and cardiovascular risk are included in SmPC Section 4.4 (Special warnings and precautions for use). Hypercholesterolaemia is listed in SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** Recommendations for management of patients presenting with elevations in lipid parameters, including monitoring of lipids levels, are

Safety concern	Routine risk minimisation activities
	included in SmPC Section 4.4 (Special warnings and precautions for use). ***Other routine risk minimisation measures beyond the Product Information:*** Pack size: None. Legal status: Tofidence is a prescription only medicine.
Malignancies	***Routine risk communication:*** An increased risk of malignancy in RA is included in SmPC Section 4.4 (Special warnings and precautions for use). A potential risk of malignancy is included in SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None. ***Other routine risk minimisation measures beyond the Product Information:*** Pack size: None Legal status: Tofidence is a prescription only medicine.
Demyelinating disorders	***Routine risk communication:*** The potential risk of central demyelinating disorders is included in SmPC Section 4.4 (Special warnings and precautions for use). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None. ***Other routine risk minimisation measures beyond the Product Information:*** Pack size: None. Legal status: Tofidence is a prescription only medicine.
Immunogenicity	***Routine risk communication:*** A potential risk of immunogenicity is included in SmPC Section 4.8 (Undesirable effects). ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** None. ***Other routine risk minimisation measures beyond the Product Information:***

Safety concern	Routine risk minimisation activities
	Pack size: None. Legal status: Tofidence is a prescription only medicine.
Missing Information	
Not applicable.	

V. 2 Additional risk minimisation measures

Additional risk minimization measures are targeted for the indications of RA, pJIA, and sJIA. The additional risk minimization measures listed in Table 20 are not applicable for the COVID-19 indication.

Table 20: Additional risk minimization measures

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

Plans for evaluating the effectiveness of the interventions and criteria for success	Not applicable.
Safety Concern	**Complications of Diverticulitis ***
Additional Risk Minimization Measure	Patient Alert Card; Patient Brochure; Healthcare Provider Brochure; Dosing Guide
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat complications of diverticulitis
Rationale for the additional risk minimization activity	**Patient Alert Card** To inform both the patient and health care providers that patients using 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 **Patient Brochure** To inform the patient of the risk of complications of diverticulitis and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide more detailed guidance to healthcare providers on the risk of complications of diverticulitis **Dosing Guide** To inform and provide more detailed dosing guidance, administration instructions, and risks to healthcare providers
Target audience and planned distribution path	Patient and Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Not applicable
Safety Concern	**Neutropenia**

Additional Risk Minimization Measure	Patient Brochure; Healthcare Provider Brochure; Dosing Guide
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat neutropenia.
Rationale for the additional risk minimization activity	**Patient Brochure** To inform the patient of the risk of neutropenia and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of neutropenia **Dosing Guide** To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patient and health care providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Not applicable
Safety Concern	**Hepatotoxicity**
Additional Risk Minimization Measure	Patient Brochure; Healthcare Provider Brochure; Patient Alert Card, Direct Healthcare Professional Communication (DHPC)
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that health care providers are aware of the risk of hepatotoxicity and the need for timely and appropriate measures to detect hepatotoxicity

Rationale for the additional risk minimization activity	**Patient Brochure** To inform the patient of the risk of hepatotoxicity and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of hepatotoxicity **Patient Alert Card** To inform both the patient and health care providers that patients using 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. **DHPC (one time only RMM activity)** To inform healthcare professionals of serious DILI, including acute liver failure, hepatitis, and jaundice, in some cases requiring liver transplant, that have been observed with the administration of Tocilizumab. The
Target audience and planned distribution path	Patient and healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Not applicable
Safety Concern	**Thrombocytopenia and the potential risk of bleeding**
Additional Risk Minimization Measure	Healthcare Provider Brochure; Patient Brochure
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat thrombocytopenia
Rationale for the additional risk minimization activity	**Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of thrombocytopenia **Patient Brochure** To inform the patient of the risk of thrombocytopenia beyond that provided in the PIL
Target audience and planned distribution path	Patient and health care providers

Plans for evaluating the effectiveness of the interventions and criteria for success	Not applicable
Safety Concern	**Elevated Lipid Levels and Potential Risk of Cardiovascular/Cerebrovascular Events**
Additional Risk Minimization Measure	Patient Brochure; Healthcare Provider Brochure; Dosing Guide

Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to detect elevated lipid levels and evaluate further.
Rationale for the additional risk minimization activity	**Patient Brochure** To inform the patient of the risk of elevated lipid levels and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of elevated lipid levels **Dosing Guide** To provide support to the healthcare provider regarding dosing and administration instructions and the risks.
Target audience and planned distribution path	Patient and Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for success	Not applicable
Safety Concern	**Malignancies**
Additional Risk Minimization Measure	Patient Brochure; Healthcare Provider Brochure; Dosing Guide
Objectives	The objective of the measure is to ensure that patients seek medical attention early, and that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat malignancies.
Rationale for the additional risk minimization activity	**Patient Brochure** To inform the patient of the risk of malignancies and provide additional guidance beyond that provided in the PIL **Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of malignancies **Dosing Guide**

Target audience and planned distribution path	Patient and Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for	Not applicable
Safety Concern	**Demyelinating Disorders**
Additional Risk Minimization Measure	Healthcare Provider Brochure
Objectives	The objective of the measure is to ensure that the health care providers are aware of the need for timely and appropriate measures to diagnose and treat demyelinating disorders
Rationale for the additional risk minimization activity	**Healthcare Provider Brochure** To inform and provide guidance to healthcare providers on the risk of demyelinating disorders
Target audience and planned distribution path	Healthcare providers
Plans for evaluating the effectiveness of the interventions and criteria for	Not applicable

PIL=Patient Information leaflet.

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

V 2.1 Removal of additional risk minimisation activities

Not applicable.

V.3 Summary of risk minimisation measures

Table 21: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Serious infections *	***Routine risk minimisation measures:*** SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Complications of diverticulitis *	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects) Legal status: Tofidence is a prescription only medicine ***Additional risk minimisation measures:*** Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Neutropenia	***Routine risk minimisation measures:***	***Routine pharmacovigilance activities beyond adverse***

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Dosing Guide	***reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Hepatotoxicity	***Routine risk minimisation measures:*** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Patient Alert Card DHPC	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Important potential risks		
Thrombocytopenia and the potential risk of bleeding	***Routine risk minimisation measures:*** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Healthcare Provider Brochure	
Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Dosing Guide	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Malignancies	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given [Tofidence]). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Dosing Guide	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** AE follow-up form for malignancy ***Additional pharmacovigilance activities:*** None
Demyelinating disorders	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Healthcare Provider Brochure	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None ***Additional pharmacovigilance activities:*** None
Immunogenicity	***Routine risk minimisation measures:*** SmPC Section 4.8 (Undesirable effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:***	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	No additional risk minimisation activities.	***Additional pharmacovigilance activities:*** None
Missing information		
Not applicable.		

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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR TOFIDENCE

This is a summary of the risk management plan (RMP) for Tofidence. The RMP details important risks of Tofidence, how these risks can be minimised, and how more information will be obtained about Tofidence's risks and uncertainties (missing information).

Tofidence's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tofidence should be used.

This summary of the RMP for Tofidence should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of 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 the Tofidence's RMP.

I. The medicine and what it is used for

Tofidence is authorised for rheumatoid arthritis, systemic juvenile idiopathic arthritis, juvenile idiopathic polyarthritis, and COVID-19 (see SmPC for the full indication). It contains tocilizumab as the active substance, and it is given by intravenous infusion.

Further information about the evaluation of Tofidence 's benefits can be found in Tofidence's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: <link to the EPAR summary landing page>.

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

Important risks of Tofidence, together with measures to minimise such risks and the proposed studies for learning more about Tofidence'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 Tofidence, 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*.

II.A List of important risks and missing information

Important risks of Tofidence 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 Tofidence. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine):

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

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

II.B Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information.

Important Identified Risk(s)	
***Serious Infection** *	
Evidence for linking the risk to the medicine	Serious infections are a potential risk due to mechanism of action of tocilizumab (immunosuppression) and are also seen with molecules with similar mechanism of action (other IL-6 inhibitors). Adequate and well-controlled clinical trials and their long-term extensions, provide the strongest evidence.

Important Identified Risk(s)	
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 by 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 and interstitial lung disease 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 minimisation measures:*** SmPC Section 4.3 (Contraindications). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Alert Card Patient Brochure Healthcare Provider Brochure Dosing Guide
Additional pharmacovigilance activities	None
Complications of diverticulitis *	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.
Risk factors and risk groups	Tocilizumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects) Legal status: Tofidence is a prescription only medicine ***Additional risk minimisation measures:*** Patient Alert Card

Important Identified Risk(s)	
	Patient Brochure Healthcare Provider Brochure Dosing Guide
Additional pharmacovigilance activities	None
Neutropenia	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.
Risk factors and risk groups	A number of risk factors have been identified that lead to increased risk of neutropenia. Many medications used to treat RA can induce neutropenia, such as methotrexate (due to folic acid deficiency) [Lazaro and Morel., 2015], rituximab (Salmon et al., 2015), as well as anti-TNF agents (e.g., adalimumab, etanercept, and infliximab; Rajakulendran et al., 2006). A less common cause of neutropenia is an RA-related autoimmune reaction (Lazaro and Morel., 2015). Other risk factors include female gender, and lower baseline neutrophil counts (Fragoulis et al., 2018).
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Dosing Guide
Additional pharmacovigilance activities	None
Hepatotoxicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.
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.

Important Identified Risk(s)	
	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).
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.2 (Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Patient Alert Card Direct Healthcare Professional Communication (DHPC)
Additional pharmacovigilance activities	None

Important Potential Risk(s)	
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 of the innovator product provide the strongest evidence.
Risk factors and risk groups	Significantly lower platelet count has been associated with over 5-fold enhanced risk of severe COVID-19 (OR: 5.13; 95% CI: 1.81–14.58) (Lippi et al., 2020). Immune thrombocytopenia (ITP) is an autoimmune disease defined by low platelet counts which presents with an increased bleeding risk. Several genetic risk factors (e.g., polymorphisms in immunity-related genes) predispose to IT. Autoantibodies and cytotoxic CD8+ T cells (Tc) mediate the anti-platelet response leading to thrombocytopenia (Swinkels et al., 2018). Other studies have found increased risk of Thrombocytopenia in patients with RA associated with coadministration of MTX and NSAID or multiple drug interactions (Franck et al., 1996). Drug-induced ITP is also associated with use of drugs including DMARDs and NSAIDSs (van den Bemt et al., 2004).
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.2 (Posology and method of administration).

Important Potential Risk(s)	
	SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure
Additional pharmacovigilance activities	None
Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.
Risk factors and risk groups	Patients with underlying CVD are at higher risk for severe illness from COVID-19 (CDC 2022). Of 41 Chinese COVID-19 patients admitted to hospital, 6 (15%) had underlying CVD; patients with CVD comprised 23% of those requiring ICU care and 11% of those who did not (Huang et al., 2020).
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). PL Section 4 (Possible side effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Dosing Guide
Additional pharmacovigilance activities	None
Malignancies	
Evidence for linking the risk to the medicine	Risk of malignancies is a potential risk due to the mechanism of action of tocilizumab (immunosuppression) and are also seen with molecules with similar mechanism of action (other IL-6 inhibitors). Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.
Risk factors and risk groups	None identified.

Important Potential Risk(s)	
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8 (Undesirable effects). PL Section 2 (What you need to know before you are given Tofidence). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Patient Brochure Healthcare Provider Brochure Dosing Guide
Additional pharmacovigilance activities	None
Demyelinating disorders	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.
Risk factors and risk groups	None identified.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.4 (Special warnings and precautions for use). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** Healthcare Provider Brochure
Additional pharmacovigilance activities	None
Immunogenicity	
Evidence for linking the risk to the medicine	Adequate and well-controlled clinical trials and their long-term extensions of the innovator product provide the strongest evidence.
Risk factors and risk groups	None identified.
Risk minimisation measures	***Routine risk minimisation measures:*** SmPC Section 4.8 (Undesirable effects). Legal status: Tofidence is a prescription only medicine. ***Additional risk minimisation measures:*** No additional risk minimisation activities
Additional pharmacovigilance activities	None

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

Missing Information
None

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 Tofidence.

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

There are no studies required for Tofidence.

PART VII - ANNEXES

ANNEX 1 - EUDRAVIGILANCE INTERFACE

Not applicable.

ANNEX 2 - TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

A summary of completed clinical studies that were included in the Pharmacovigilance Plan of the Tofidence EU RMP (current or in previously approved RMP versions) is provided in the table below.

A completed clinical trial is defined as an interventional trial for which a full clinical study report (describing the results of the primary analysis, where relevant) is available. For purposes of the EU RMP, any clinical trial for which enrolment has begun but for which a full clinical study report is not available is considered ongoing.

Table 1: Annex II. Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
BAT1806-001-CR (NCT03606876) A randomised, double-blinded, single-dose, 3-arm parallel, comparative study to evaluate the pharmacokinetics and safety of Tofidence Injection vs Actemra® (US and EU) in Healthy Chinese Male Subjects	*Primary objective:* To establish pairwise PK biosimilarity between Tofidence vs EU-licensed Actemra, Tofidence vs US-licensed Actemra, US-licensed Actemra vs EU-licensed Actemra in healthy Chinese male subjects *Secondary Objectives:* To evaluate the clinical safety, tolerability, and immunogenicity of Tofidence Injection and Actemra (EU-licensed and US-licensed) in healthy male Chinese subjects.	Safety and tolerability in healthy male volunteers	Final CSR dated 06 June 2018. CSR corrigendum dated 21 June 2022.

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
BAT1806-002-CR (NCT03830203) A randomised, double-blind, parallel-group, active-control study to compare the efficacy and safety of Tofidence to RoActemra® in rheumatoid arthritis patients with inadequate response to methotrexate	*Primary objective:* To demonstrate equivalent efficacy of BAT1806 and RoActemra in subjects with rheumatoid arthritis (RA) that is inadequately controlled by methotrexate (MTX). *Secondary Objectives:* To evaluate the efficacy profile of Tofidence compared with RoActemra over time based on secondary efficacy endpoints. To evaluate the safety and tolerability profile of Tofidence compared with RoActemra over the entire study period. To evaluate the immunogenicity profile of Tofidence in terms of anti-drug antibody (ADAs) production compared with RoActemra. To evaluate the steady-state pharmacokinetics (PK) of Tofidence compared with RoActemra. To assess safety and immunogenicity following transition from RoActemra to Tofidence.	Safety and tolerability in RA patients	CSR version 1.0 dated 13 October 2021. CSR version 2.0 dated 27 May 2022.

ANNEX 3 - PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority

Not applicable.

ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Adverse event follow-up forms will be distributed for potential events of malignancy (see Part III [*Pharmacovigilance Plan*] of the EU RMP for details).

The follow up forms for distribution are provided in this Annex below:

- Malignancy Follow-up Questionnaire

Biogen	Tocilizumab Data Collection Form – Malignancies (Governed by DEV-SOP-2771)	RD-FORM-2815 Version 1.0 Page 1 of 9

MCN (Case id) #: MFR Control #

I. Patient Information:

Patient Initials: _____
DOB: _____
Gender: _____
Race: _____
Height: _____
Weight _____

II. Tocilizumab Dosing Information:

Dose: _____
Start Date: _____
Stop Date: _____
Duration: _____
Frequency: _____
Every 4 weeks

Batch/Lot #: _____

Route of administration: _____

Indication for use: _____

Compliant with regimen: ☐ Yes ☐ No ☐ Unknown

Date of malignancy diagnosis: _____

Action taken regarding Tocilizumab: ☐ Dose not changed
☐ Dose reduced If yes, date: _____
☐ Stopped If yes, date: _____
Other: _____

Re-administration of Tocilizumab: ☐ Yes ☐ No ☐ Unknown
If yes, date: _____

Recurrence/relapse of malignancy: ☐ Yes ☐ No ☐ Unknown
If yes, date: _____

MCN (Case id) #: MFR Control #

III. Diagnosis

Type of malignancy:

IV. Seriousness:

Was the event classed as serious: ☐ Yes ☐ No ☐ Unknown

- ☐ Death *(see section VIII)*
- ☐ Life-threatening
- ☐ Disability / Incapacity
- ☐ Hospitalised / Prolonged hospitalisation
  - Date of admission: _____
  - Date of discharge: _____
- ☐ Medically significant
- ☐ Other (please specify) _____
- ☐ Surgery (please specify): _____

V. Causality assessment:

- ☐ Related to Tocilizumab
- ☐ Not related to Tocilizumab
- ☐ Other contributing factors (please specify):_____

VI. Clinical Findings:

A. Constitutional Signs/ Symptoms:

	Symptoms/Signs	Date(s)		Symptoms/Signs	Date(s)
☐	Asthenia		☐	Malaise	
☐	Weight Loss		☐	Weight Gain	
☐	Fatigue		☐	Oedema	
☐	Skin Colouring		☐	Skin Deformities	

MCN (Case id) #: MFR Control #

☐	Respiratory Distress			☐	Swollen Lymph Node		
☐	Somnolence			☐	Confusion		
☐	Anorexia			☐	Pruritus		
☐	Other			☐	Other		
☐	Other			☐	Other		

B. Laboratory results:

☐ Unavailable

{Please provide any available baseline laboratory data}

Laboratory Test	Normal Ranges	Date	Result	Date	Result	Date	Result
Complete Blood Count (CBC) with differential							
RBC							
Hgb							
Hct							
MCV							
MCH							
MCHC							
Reticulocyte count							
MPV							
Platelets							
WBC							
%Neutrophils							
%Bands							
%Lymphocytes							
%Monocytes							
%Eosinophils							
Tumour marker							
AFP							
Bence-Jones-Protein							
Beta-hCG							
CA 15-3							
CA 19-9							
CA 50							

Biogen	Tocilizumab Data Collection Form - Malignancies (Governed by DEV-SOP-2771)	RD-FORM-2815 Version 1.0 Page 4 of 9

MCN (Case id) #: MFR Control #

Laboratory Test	Normal Ranges	Date	Result	Date	Result	Date	Result
CA 72-4							
CA 125							
Calcitonin							
CEA							
Chromogranin							
CYFRA 21-1							
Serpin B4							
Homovanillic acid							
Catecholamines							

Laboratory Test	Normal Ranges	Date	Result	Date	Result	Date	Result
Tumour marker (Cont.)							
Vanillylmandelic acid							
LDH							
LDH-1							
MUC1							
NSE							
PLAP							
PSA							
Tumour M2-PK							
Other Tests							

C. Diagnostic procedures:

☐ None performed ☐ Unavailable

{Please provide a copy of the report}

Procedure	Date	Result
Ultrasonography		
CT		
MRI		
X-Ray		
Biopsy Specify:		
Other:		

D. Clinical-pathologic characteristics:

☐ Anatomic site _____

☐ Size of primary tumour _____

☐ Stage – TNM or AJCC _____

☐ Histologic type: _____

Biogen	Tocilizumab Data Collection Form - Malignancies (Governed by DEV-SOP-2771)	RD-FORM-2815 Version 1.0 Page 6 of 9

MCN (Case id) #: MFR Control #

VII. Management/Treatment:

- ☐ None
- ☐ Surgery (please specify): _____
- ☐ Chemotherapy
- ☐ Radiotherapy
- ☐ Hormonal therapy
- ☐ Other (please specify) _____
- ☐ Hospitalised
  - Admitting diagnosis: _____
  - Discharge diagnosis: _____
  - Please briefly describe hospital course: _____

VIII. Outcome:

- ☐ Resolved without sequelae
- ☐ Resolved with sequelae
  - Please describe: _____
- ☐ Not Resolved
- ☐ Death {Please provide a copy of the death certificate}
  - Date of death:
  - Cause of death:
- ☐ Unknown
- ☐ Autopsy {Please provide a copy of the autopsy report}

Biogen	Tocilizumab Data Collection Form - Malignancies (Governed by DEV-SOP-2771)	RD-FORM-2815 Version 1.0 Page 7 of 9

MCN (Case id) #: MFR Control #

IX. Past Medical History (PMH):

Risk Factor	Date Ongoing?	Risk Factor	Date Ongoing?
☐ Prior history of cancer Specify: _____		☐ Family history of cancer Specify: _____ Degree of relative: _____	
☐ Smoking		☐ Alcohol abuse	
☐ Underlying autoimmune disorder Specify: _____		☐ Serious infections Specify: _____	
☐ Prior radiation exposure		☐ Excessive sun exposure	

X. Other PMH:

☐ Yes ☐ No Please describe:

XI. Medication History:

Medication	Date	Medication	Date
☐ Therapy with chemotherapeutic agents Specify: _____		☐ Therapy with immunosuppressant drugs Specify: _____	
☐ Other: _____		☐ Other: _____	
☐ Other: _____		☐ Other: _____	

Biogen	Tocilizumab Data Collection Form - Malignancies (Governed by DEV-SOP-2771)	RD-FORM-2815 Version 1.0 Page 8 of 9

MCN (Case id) #: MFR Control #

XII. Current Medications:

{Please provide prescription, Over-the-counter (OTC), herbal, and vitamins used in the last 6 months.}

Medication	Dose/Schedule	Indication	Start Date	Stop Date	Reason for Discontinuing

XIII. Allergies:

☐ Yes ☐ No ☐ Unknown

Please describe: _____

MCN (Case id) #: MFR Control #

XIV. Other:

Please provide any additional information or attach any supporting documentation that will assist us in our evaluation of this report.

Print name/title: _____

Signature: _____ Date: _____

Please send the completed form to BBUsafetyreporting@biogen.com

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

Not applicable.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Draft key messages of the additional risk minimisation measures

Prior to the launch of Tofidence in each Member State, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at ensuring that the important identified risks associated with tocilizumab are made know to patients and healthcare providers, and to promote prevention, early diagnosis and adequate management of these events.

The MAH shall ensure that in each Member State where Tofidence is marketed, all healthcare professionals and patients/carers who are expected to prescribe or use Tofidence have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

Physician educational material

- The Summary of Product Characteristics
- Healthcare provider brochure
- Patient alert card
- Dosing guide

Healthcare provider brochure

- Relevant information of the identified risks associated with Tofidence
- Details of the population at higher risk for the safety concern addressed by the additional risk minimisation measures (aRMM) (e.g., risk factors).
- Details on how to minimise the safety concern addressed by the aRMM through appropriate monitoring and management (e.g., what to do, what not do, and who is most likely to be impacted according to different scenarios, like when to limit or stop prescribing/ingestion, how to administer the medicine, when to increase/decrease the dosage according to laboratory measurements, signs and symptoms)
- Instructions on how to handle possible adverse events
- Remarks on the importance of reporting reactions
- Recommendations on pregnancy and breast-feeding.

Patient alert card

- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Tofidence
- That Tofidence treatment may increase the risk of: of serious infection, complications of diverticulitis, and hepatotoxicity.
- Signs or symptoms of the safety concern and when to seek attention from a healthcare professional
- Contact details of the Tofidence prescriber

Dosing guide

- Information on weight based dosing and calculation of dose and vial number for each indication.
- Information on necessary supplies required for dosing.
- Information related to performing baseline assessments.
- Information related to management of allergic reactions.

The patient information pack

- Patient information leaflet
- A patient brochure
- **Patient brochure**
  - A description of the correct use of Tofidence and the risks associated with its use, namely risks of serious infection, complications of diverticulitis, hepatotoxicity, and malignancies.
  - A description of the sign and symptoms of infection, allergic reactions, complications of diverticulitis, and hepatotoxicity.
  - A description of the best course of action if sign and symptoms of those risks present themselves (e.g., How to reach your doctors).
  - Remarks on the importance of reporting adverse reactions, namely: infections, allergic reactions, complications of diverticulitis, and hepatotoxicity.
  - Information on the way the medicine will be administered.
  - Information on laboratory tests that may need to be performed during treatment.

ANNEX 7 - OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

Ahmed MH. Rheumatoid arthritis induced-fatty liver theory: One reason for global increase in prevalence of diabetes. Medical Hypotheses 2006;66(4):862-863.

Benatsky S et al. Demyelinating events in rheumatoid arthritis after drug exposures. Ann Rheum Obs. 2010; 69:1691-1693.

Beyaert R, Beaugerie L, Van Assche G, et al. Cancer risk in immune-mediated inflammatory diseases (IMID). *Mol Cancer.* 2013;12(1):98. Published 2013 Aug 29. doi:10.1186/1476-4598-12-98.

Beauchemin P, Carruthers R. MS arising during Tocilizumab therapy for rheumatoid arthritis. *Mult Scler*. 2016;22(2):254-256. doi:10.1177/1352458515623862.

Bhayana R, Som A, Li MD, et al. Abdominal Imaging Findings in COVID-19: Preliminary Observations [published online ahead of print, 2020 May 11]. Radiology. 2020;201908.

Bugelski PJ, Volk A, Walker MR, Krayer JH, Martin P, Descotes J. Critical review of preclinical approaches to evaluate the potential of immunosuppressive drugs to influence human neoplasia. *Int J Toxicol.* 2010;29(5):435-466. doi:10.1177/1091581810374654.

Burmester GR, Choy E, Kivitz A, et al. Low immunogenicity of tocilizumab in patients with rheumatoid arthritis. Ann Rheum Dis. 2017;76(6):1078-1085. doi:10.1136/annrheumdis-2016-210297.

Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests [published online ahead of print, 2020 Apr 13]. J Hepatol. 2020;S0168-8278(20)30218-X.

Campbell L, Chen C, Bhagat SS, Parker RA, Östör AJ. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatology (Oxford*). 2011;50(3):552-562. doi:10.1093/rheumatology/keq343.

Carmona L, Descalzo MA, Perez-Pampin E, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis. 2007;66(7):880-885. doi:10.1136/ard.2006.067660.

Centre for Disease Prevention and Control. Symptoms of Coronavirus [resource on the Internet]. 2020 [reviewed 13 May 2020; accessed 19 May 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.htm CDC 2020a

Centers for Disease Prevention and Control. Provisional Death Counts for Coronavirus Disease (COVID-19). Available from https://www.cdc.gov/nchs/nvss/vsrr/covid19/index.htm. Accessed on 27 January 2022. CDC 2022.

Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.

Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. *Nat Rev Rheumatol. 2020*;16(6):335-345. doi:10.1038/s41584-020-0419-z.

COVID-NET. A Weekly Summary of U.S. COVID-19 Hospitalization Data. Available from: https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html. Accessed on 26 January 2022.

Cressman DE, Greenbaum L, DeAngelis R, Cilbertom G, Furth E, Poli E, L. Liver failure and defective hepatocyte regeneration in interleukin-6 deficient mice. Science 1996; 274:1379–1383.

Curtis JR, Lanas A, John A, Johnson DA, Schulman KL. Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012 Jun 21. doi: 10.1002/acr.21764. [Epub ahead of print].

Czaja MJ, Xu J and Alt E. Prevention of carbon tetrachloride-induced rat liver injury by soluble tumor necrosis factor receptor. Gastroenterology 1995;108:1849–1854.

Dai M, Liu D, Liu M, et al. Patients with Cancer Appear More Vulnerable to SARS-COV-2: A Multicenter Study during the COVID-19 Outbreak [published online ahead of print, 2020 Apr 28]. Cancer Discov. 2020;10.1158/2159-8290.CD-20-0422.

Desai A, Sachdeva S, Parekh T, Desai R. COVID-19 and Cancer: Lessons from a Pooled Meta-Analysis. JCO Glob Oncol. 2020;6:557-559.

Du Pan SM, Dehler S, Ciurea A, Ziswiler HR, Gabay C, Finckh A, et al. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum. 2009;61:560–568.

Erdal GS, Polat O, Erdem GU, Korkusuz R, Hindilerden F, Yilmaz M, Yasar KK, Isiksacan N, Tural D. The mortality rate of COVID-19 was high in cancer patients: a retrospective single-center study. Int J Clin Oncol. 2021 May;26(5):826-834.

European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products (CHMP/437/04 Rev 1.) 23 October 2014.

Fragoulis GE, Paterson C, Gilmour A, et al. Neutropaenia in early rheumatoid arthritis: frequency, predicting factors, natural history and outcome. RMD Open. 2018;4(2):e000739. Published 2018 Oct 8. doi:10.1136/rmdopen-2018-000739.

Fragiel M, Miró Ò, Llorens P, Jiménez S, Piñera P, Burillo G, et al., SIESTA (Spanish Investigators in Emergency Situations Team) network. Incidence, clinical, risk factors and outcomes of Guillain-Barré in Covid-19. Ann Neurol. 2021 Mar;89(3):598-603.

Franck H, Rau R, Herborn G. Thrombocytopenia in patients with rheumatoid arthritis on long-term treatment with low dose methotrexate. Clin Rheumatol. 1996;15(3):266-270. doi:10.1007/BF02229705.

Fu Y, Yang Q, Xu M, et al. Secondary Bacterial Infections in Critical Ill Patients With Coronavirus Disease 2019. Open Forum Infect Dis. 2020;7(6):ofaa220. Published 2020 Jun 5.

Gallagher MP, Kelly PJ, Jardine M, et al. Long-term cancer risk of immunosuppressive regimens after kidney transplantation. *J Am Soc Nephrol*. 2010;21(5):852-858. doi:10.1681/ASN.2009101043.

Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med. 2020 Jun 11;382(24):2372-74.

Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy [published online ahead of print, 2020 Apr 6]. JAMA. 2020;323(16):1574-1581.

Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382(18):1708-1720.

Hashizume M, Higuchi Y, Uchiyama Y, Mihara M. IL-6 plays an essential role in neutrophilia under inflammation. *Cytokine.* 2011;54(1):92-99. doi:10.1016/j.cyto.2011.01.007.

Henry BM, Lippi G, Plebani M. Laboratory abnormalities in children with novel coronavirus disease 2019. Clin Chem Lab Med. 2020;58(7):1135-1138. doi:10.1515/cclm-2020-0272.

Hill DB, Marsano L, Cohen D, Allen J, Shedlofsky S and McClain C. Increased plasma interleukin-6 concentrations in alcoholic hepatitis. J Lab Clin Med 1992;119:547–552.

Horvat N, Pinto PVA, Araujo-Filho JAB, Santos JMMM, Dias AB, Miranda JA, de Oliveira CV, Barbosa CS, Morais TC, N Assuncao-Jr A, Nomura CH, Viana PCC. Abdominal gastrointestinal imaging findings on computed tomography in patients with COVID-19 and correlation with clinical outcomes. Eur J Radiol Open. 2021;8:100326.

Hu X, Hu C, Yang Y, et al. Clinical characteristics and risk factors for severity of COVID-19 outside Wuhan: a double-center retrospective cohort study of 213 cases in Hunan, China. Ther Adv Respir Dis. 2020;14:1753466620963035. doi:10.1177/1753466620963035.

Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30]. Lancet. 2020;395(10223):497-506.

Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study [published online ahead of print, 2020 Apr 8]. J Hepatol. 2020;S0168-8278(20)30206-3.

Jin S, Jin Y, Xu B, Hong J, Yang X. Prevalence and Impact of Coagulation Dysfunction in COVID-19 in China: A Meta-Analysis. Thromb Haemost. 2020 Nov;120(11):1524-1535.

Johnston S, Turpcu A, Shi N, Moawad D, Alexander K. Incidence and hazard of infections in rheumatoid arthritis patients treated with subsequent-line biologic disease modifying antirheumatic drugs after switching from first-line anti-tumor necrosis factor agents. Pharmacoepidemiol Drug Saf. 2011;20:S71.

Kawashiri SY, Kawakami A, Yamasaki S, et al. Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. *Rheumatol Int*. 2011;31(4):451-456. doi:10.1007/s00296-009-1303-y.

Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens [published online ahead of print, 2020 Apr 15]. JAMA. 2020;323(20):2085-2086.

Kumari N, Dwarakanath BS, Das A, Bhatt AN. Role of interleukin-6 in cancer progression and therapeutic resistance. *Tumour Biol.* 2016;37(9):11553-11572. doi:10.1007/s13277-016-5098-7.

Lazaro E, Morel J. Management of neutropenia in patients with rheumatoid arthritis. Joint Bone Spine. 2015;82(4):235-239. doi:10.1016/j.jbspin.2015.01.005.

Lee JS, Oh JS, Hong S, Lee CK, Yoo B, Kim YG. Tocilizumab-induced Thrombocytopenia in Patients with Rheumatoid Arthritis. *J Rheum Dis* 2019;26:186-190. https://doi.org/10.4078/jrd.2019.26.3.186.

Lin D, Liu L, Zhang M, et al. Co-infections of SARS-CoV-2 with multiple common respiratory pathogens in infected patients. Sci China Life Sci. 2020;63(4):606-609.

Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020;506:145-148.

Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy [published online ahead of print, 2020 Apr 23]. Thromb Res. 2020;191:9-14.

Lunt M, Watson KD, Dixon WG; British Society for Rheumatology Biologics Register Control Centre Consortium, Symmons DP, Hyrich KL; British Society for Rheumatology Biologics Register. No evidence of association between anti-tumor necrosis factor treatment and mortality in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2010;62:3145-3153.

Luxembourger C, Ruyssen-Witrand A, Ladhari C, et al. A single nucleotide polymorphism of IL6-receptor is associated with response to tocilizumab in rheumatoid arthritis patients. *Pharmacogenomics J*. 2019;19(4):368-374. doi:10.1038/s41397-019-0072-6.

Mellemkjaer L et al. Rheumatoid arthritis and cancer risk. Eur J Cancer 1996; 32A (10) :1753-1757.

Mendizabal M, Piñero F, Ridruejo E, Anders M, Silveyra MD, Torre A, et al. Prospective Latin American cohort evaluating outcomes of patients with COVID-19 and abnormal liver tests on admission. Ann Hepatol. 2021 Mar-Apr;21:100298.

Moots RJ, Sebba A, Rigby W, et al. Effect of tocilizumab on neutrophils in adult patients with rheumatoid arthritis: pooled analysis of data from phase 3 and 4 clinical trials. Rheumatology (Oxford). 2017;56(4):541-549. doi:10.1093/rheumatology/kew370.

Mpofu S, Mpofu CMA, Hutchinson D, et al. Steroids, non-steroidal anti-inflammatory drugs, and sigmoid diverticular abscess perforation in rheumatic conditions. Ann Rheum Dis 2004;63:588-590.

Müller N, Schulte DM, Türk K, et al. IL-6 blockade by monoclonal antibodies inhibits apolipoprotein (a) expression and lipoprotein (a) synthesis in humans. *J Lipid Res*. 2015;56(5):1034-1042. doi:10.1194/jlr.P052209.

Mulé JJ, McIntosh JK, Jablons DM, Rosenberg SA. Antitumor activity of recombinant interleukin 6 in mice. *J Exp Med.* 1990;171(3):629-636. doi:10.1084/jem.171.3.629.

Murray-Thomas and Cowie. Epidemiology and clinical aspects of congestive heart failure. JRAAS 2003;4:131–6.

Myllykangas-Luosujärvi R, et al. Shortening of life span and causes of excess mortality in a population-based series of subjects with rheumatoid arthritis. Clin Exp Rheumatol 1995;13:149-153.

Nguyen-Khoa B, Goehring E, Alexander K, Dong W, Napalkov P, Jones JK. Serious infections in rheumatoid arthritis patients switching anti-tumor necrosis factor drugs. [abstract]. Arthritis Rheum. 2010;62 Suppl 10:698 doi: 10.1002/art.28466.

Nicola et al. The Risk of Congestive Heart Failure in Rheumatoid Arthritis. Arthritis Rheum Vol. 52, No. 2, 2005, pp 412–420.

Ofori-Asenso Richard, Ogundipe Oyepeju, Adom Agyeman Akosua, Chin Ken Lee, Mazidi Mohsen, Ademi Zanfina, De Bruin Marie Louise, Liew Danny (2020) Cancer is associated with severe disease in COVID-19 patients: a systematic review and meta-analysis. Ecancer. 2020; 14:1047.

RoActemra summary of product characteristics 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf. Last accessed 13 October 2021.

Pawar A, Desai RJ, Solomon DH, et al. Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis: a multidatabase cohort study. *Ann Rheum Dis*. 2019;78(4):456-464. doi:10.1136/annrheumdis-2018-214367.

Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966. Published 2020 May 22.

Prior P. Cancer and rheumatoid arthritis: Epidemiologic considerations. Am J Med 1985;78:15-21.

Rajakulendran S, Gadsby K, Allen D, O'Reilly S, Deighton C. Neutropenia while receiving anti-tumour necrosis factor treatment for rheumatoid arthritis. Ann Rheum Dis. 2006;65(12):1678-1679. doi:10.1136/ard.2006.056176.

Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area [published online ahead of print, 2020 Apr 22]. JAMA. 2020;e206775.

RoActemra European Public Assessment Report 2009. Available at: https://www.ema.europa.eu/en/documents/assessment-report/roactemra-epar-public-assessment-report_en.pdf Last accessed 13 October 2021.

Salmon JH, Cacoub P, Combe B, et al. Late-onset neutropenia after treatment with rituximab for rheumatoid arthritis and other autoimmune diseases: data from the AutoImmunity and Rituximab registry. RMD Open. 2015;1(1):e000034. Published 2015 Jun 30. doi:10.1136/rmdopen-2014-000034.

Sarin S, Boulos PB. Long-term outcome of patients presenting with acute complications of diverticular disease. *Ann R Coll Surg Engl*. 1994;76(2):117-120.

Setoguchi S, Solomon DH, Weinblatt ME, Katz JN, Avorn J, Glynn RJ, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum. 2006;54:2757-2764.

Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis [published correction appears in Arthritis Res Ther. 2016;18(1):100]. *Arthritis Res Ther*. 2015;17(1):212. Published 2015 Aug 15. doi:10.1186/s13075-015-0728-9.

Solomon DH, et al. Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis 2006;65:1608-1612.

Solomon DH, Mercer E, Kavanaugh A. Observational studies on the risk of cancer associated with tumor necrosis factor inhibitors in rheumatoid arthritis: a review of their methodologies and results. Arthritis Rheum. 2012;64:21–32.

Strangfeld A, Richter A, Siegmund B, et al. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. *Ann Rheum Dis*. 2017;76(3):504-510. doi:10.1136/annrheumdis-2016-209773.

Suissa S, Bernatsky S, and Hudson, M. Anti-rheumatic drug use and the risk of acute myocardial infarction. Arthritis and Rheumatism. 2006:55(4):531-536.

Suwa T, Hogg JC, English D, Van Eeden SF. Interleukin-6 induces demargination of intravascular neutrophils and shortens their transit in marrow. *Am J Physiol Heart Circ Physiol*. 2000;279(6):H2954-H2960. doi:10.1152/ajpheart.2000.279.6.H2954.

Swinkels M, Rijkers M, Voorberg J, Vidarsson G, Leebeek FWG, Jansen AJG. Emerging Concepts in Immune Thrombocytopenia. Front Immunol. 2018;9:880. Published 2018 Apr 30. doi:10.3389/fimmu.2018.00880.

Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847. Tang et al. 2020a.

Taub R. Hepatoprotection via the IL-6/Stat3 pathway. J Clin Invest 2003 ;112 :978-980.

Thyagarajan V, Norman H, Alexander KA, Napalkov P, Enger C. Risk of mortality, fatal infection, and fatal malignancy related to use of anti-tumor necrosis factor-α biologics by rheumatoid arthritis patients. Semin Arthritis Rheum. 2012;42(3):223-233. doi:10.1016/j.semarthrit.2012.05.004.

US FDA Food and Drug Administration, Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Apr 2015.

van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. Drug Saf. 2004;27(15):1243-1252. doi:10.2165/00002018-200427150-00007.

Watson DJ, et al. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol 2003;30:1196-1202.

World Health Organization, Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). 2009.

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

World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19---final-report-1100hr-28feb2020-11mar-update.pdf?sfvrsn=1a13fda0_2&download=true. Accessed on 7 May 2020. WHO 2020b

Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40(5):998-1004.

Yang X, Yang Q, Wang Y, et al. Thrombocytopenia and its association with mortality in patients with COVID-19 [published online ahead of print, 2020 Apr 17]. J Thromb Haemost. 2020;10.1111/jth.14848. Yang 2020a.

Zangrillo A, Beretta L, Scandroglio AM, et al. Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy [published online ahead of print, 2020 Apr 23]. Crit Care Resusc. 2020.

Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428-430 (Zhang 2020a).

Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China [published online ahead of print, 2020 Feb 19]. Allergy. 2020;10.1111/all.14238 (Zhang 2020b).

Zhang H, Wang H, Wei H, Chen H, Liu J, Li C, Zhu X, Li X, Yu J, Zhou Y, Yang X, Wang Z, Wu M, Ding Y. A Phase I Clinical Study Comparing the Tolerance, Immunogenicity, and Pharmacokinetics of Proposed Biosimilar BAT1806 and Reference Tocilizumab in Healthy Chinese Men. Front Pharmacol. 2021 Jan 25;11:609522. doi: 10.3389/fphar.2020.609522. PMID: 33569002; PMCID: PMC7868548.

Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in Lancet. 2020 Mar 28;395(10229):1038] [published correction appears in Lancet. 2020 Mar 28;395(10229):1038]. Lancet. 2020;395(10229):1054-1062.

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

Summary of changes to the RMP over time

Version	Approval date Procedure	Change
Version 0.1	Date of sign-off: 26-August-2022 (internal approval before marketing authorisation)	This is the first version of the risk management plan (initial marketing authorisation application).
Version 0.2	Date of sign-off: 8-Sep-2022 (internal approval before marketing authorisation)	Minor editorial corrections in preparation for dossier publishing.
Version 0.3	Date of sign-off: 22-Feb-2023 (internal approval before marketing authorisation)	Minor changes (addition of additional monitoring, correction of typographical errors in Annex IV) to address CHMP Day 120 comments.
Version 0.4	Date of sign-off: 17-Apr-2024 (internal approval before marketing authorisation)	Removal of references to Cytokine Release Syndrome (CRS), as this indication is not claimed in the Product Information. Request from EMA before issuing CHMP Opinion.
Version 0.5	Date of sign-off: 19-Apr-2024 (internal approval before marketing authorisation)	Removal of references to Giant Cell Arteritis (GCA), as this indication is not claimed in the Product Information. Request from EMA before issuing CHMP Opinion.